



# Contributions and achievements on schistosomiasis control and elimination in China by NIPD-CTDR

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## Abstract

Being a zoonotic parasitic disease, schistosomiasis was widely spread in 12 provinces of Southern China in the 1950s, severely harming human health and hindering economic development. The National Institute of Parasitic Diseases at the Chinese Center for Diseases Control and Prevention, and Chinese Center for Tropical Diseases Research (NIPD-CTDR), as the only professional institution focussing on parasitic diseases at the national level, has played an important role in schistosomiasis control in the country. In this article, we look back at the changes of schistosomiasis endemicity and the contribution of NIPD-CTDR to the national schistosomiasis control programme. We review NIPD-CTDR's activities, including field investigations, design of control strategies and measures, development of diagnostics and drugs, surveillance-response of endemic situation, and monitoring & evaluation of the programme. The NIPD-CTDR has mastered the transmission status of schistosomiasis, mapped the snail distribution, and explored strategies and measures suitable for different types of endemic areas in China. With a good understanding of the life cycle of *Schistosoma japonicum* and transmission patterns of the disease, advanced research carried out in the NIPD-CTDR based on genomics and modern technology has made it possible to explore highly efficient and soft therapeutic drugs and molluscicides, making it possible to develop new diagnostic tools and produce vaccine candidates. In the field, epidemiological studies, updated strategies and targeted intervention measures developed by scientists from the NIPD-CTDR have contributed significantly to the national schistosomiasis control programme. This all adds up to a strong foundation for eliminating schistosomiasis in China in the near future, and recommendations have been put forward how to reach this goal.



## 1. Introduction

Schistosomiasis japonica caused by *Schistosoma japonicum* is endemic in the People's Republic of China (P.R. China) and has had a long history. In 1972, *S. japonicum* eggs found in the liver and intestinal tissues of a female

corpse unearthed from No. 1 Han Tomb in Mawangdui, Changsha, Hunan province, which proved that schistosomiasis has been prevalent in P.R. China for more than 2100 years ([Hunan Medical College, 1980](#)). Human beings and more than 40 kinds of mammals serve as definitive host, and the *Oncomelania* snail is the only intermediate host. Various infection sources and recurrent infection have made the prevention and control of schistosomiasis difficult. In the early 1950s, just before the national schistosomiasis control programme was started. It was estimated that over 10 million people and 1 million cattle were infected. Schistosomiasis was therefore one of the major infectious diseases in P.R. China, imposing a huge burden on human and veterinary health. After the founding of the P.R. China in 1949, the Chinese government has started to pay attention to controlling the disease. The Central Committee of Schistosomiasis Control was established in 1955 and a national campaign against schistosomiasis was launched ([Lv et al., 2019](#)).

During the past seven decades, researchers from the National Institute of Parasitic Disease, affiliated to the Chinese Center for Disease Control and Prevention (China CDC) and the Chinese Center for Tropical Diseases Research (NIPD-CTDR) have devoted themselves to the national schistosomiasis control programme and relevant research activities. These activities included the provision of technical support and the development and implementation of new control strategies in P.R. China. These activities include research and production of advanced tools and technologies for schistosomiasis control. We review here the contribution of the NIPD-CTDR to the national schistosomiasis control and elimination programme and put forward recommendations for eliminating schistosomiasis in the near future.



## **2. The endemic status of schistosomiasis in P.R. China**

According to a nation-wide investigation in the mid-1950s, schistosomiasis was prevalent in 400 counties of 12 provinces, autonomous regions and municipalities in P.R. China, namely Jiangsu, Zhejiang, Anhui, Jiangxi, Fujian, Shanghai, Hunan, Hubei, Guangdong, Guangxi, Yunnan and Sichuan in the south of the Yangtze River Basin. The endemic area of schistosomiasis in P.R. China stretched as far north as Baoying County in Jiangsu Province (latitude 33°15') , and as far south as Yulin County in Guangxi Zhuang Autonomous Region (latitude 22°5'), as far east as Nanhui County in Shanghai Municipality (longitude 121°51'), and as far west as

Yunlong County in Yunnan Province (longitude 99°50′). The lowest altitude of the endemic area was 0m (Shanghai) and the highest altitude was about 3000m above the sea level (Yunnan Province). In the 1950s, about 11.6 million people and 1.2 million cattle were infected by *S. japonicum* in P.R. China, while 100 million people were at risk. The land area infested with *Oncomelania* spp. snails had a surface of 14.5 billion m<sup>2</sup> (Zhou et al., 2004). Before the founding of the People's Republic of China in 1949, the prevention and treatment on schistosomiasis was inadequate due to poverty, war, and lack of effective technical tools that had led to very high prevalence, incidence and mortality. According to surveys at that time, the infection rates with schistosomiasis in some villages was over 70%.

In order to carry out large-scale treatment and prevention, a national committee for schistosomiasis control was set up to organize the treatment of patients in known endemic areas, and organize schistosomiasis control groups in a short period of time (Wang et al., 1989). In 1950, the East-China Branch of the National Institute of Health—the earliest precursor of the NIPD-CTDR was established in Nanjing (Wang, 2011). This institute was later named as Institute of Parasitic Diseases (IPD) affiliated to the Chinese Academy of Medicine, before it moved from Nanjing to Shanghai in 1957, and became a national centre for technical support to the national schistosomiasis control programme and carry out research on various innovative tools and strategies.

In 1953, after reading the report on the endemic situation of schistosomiasis in Southern China, Chairman Mao Zedong, pointed out that “the harm of schistosomiasis is very serious, and we must focus on prevention and control of schistosomiasis” (Zhou et al., 2007c). In 1955, Chairman Mao Zedong issued a great call to “eliminate schistosomiasis” after visiting the epidemic areas and listening to professional opinions widely. As proposed by Chairman Mao Zedong's, the Central Committee of the Communist Party of P.R. China quickly established a central committee of schistosomiasis control (commonly known as nine-member leading group for the control of schistosomiasis) (Lv et al., 2019). Meanwhile, the local leading groups for schistosomiasis control composited of major leaders in charge of the party and government were set up. Professional organizations and teams for control of Schistosomiasis were subsequently established at all levels. This initiated the national schistosomiasis control programme in P.R. China.

The seven decades' efforts by the national schistosomiasis control programme have resulted in outstanding achievements. Among the 12 provinces initially endemic of schistosomiasis japonica, 5 provinces, namely Shanghai, Zhejiang, Fujian, Guangdong and Guangxi, continued to consolidate status

of elimination of schistosomiasis. Sichuan Province achieved transmission interrupt and six other provinces namely Yunnan, Jiangsu, Hubei, Anhui, Jiangxi and Hunan maintained the status of transmission control by the end of 2018. Out of the all endemic counties, city, district with 58.44% (263/450), 27.56% (124/450) and 14% (63/450) achieving the criteria of elimination, transmission interruption and transmission control, respectively (Fig. 1). The endemic situation of schistosomiasis in P.R. China has been reduced to the lowest level in history. In 2018, only eight people and two cattle were still testing positive. Seventy years of schistosomiasis control have reached these remarkable achievements thanks to technically support by professionals and the leadership of the party and the government in cooperation with various departments. At present, the national schistosomiasis control programme in P.R. China is gradually entering the process of elimination.

The national control programme has moved the schistosomiasis situation in stages from being widely endemic, to endemic control, morbidity control, transmission control, transmission interruption to finally being on the way towards elimination. The NIPD-CTDR, as a national scientific research institution, has played an important role on the improvement of control technology and has promoted the transition from control to elimination of schistosomiasis in P.R. China.

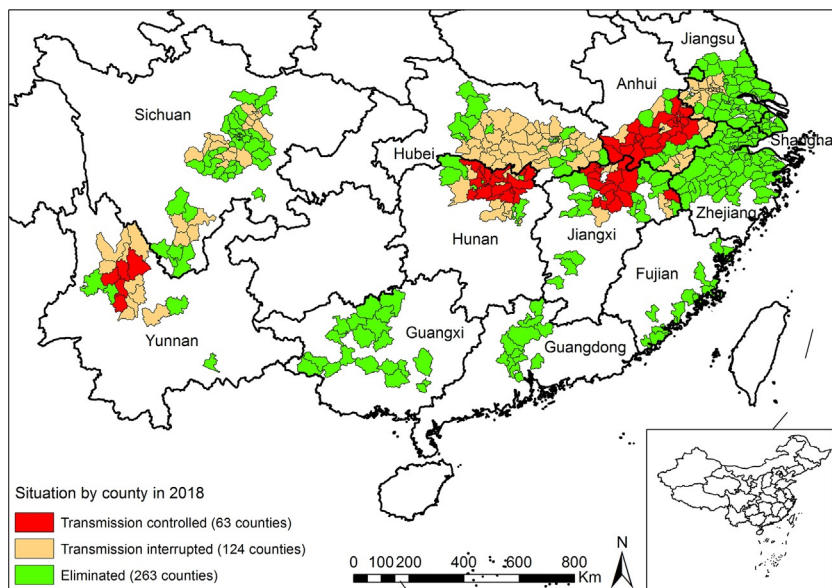


Fig. 1 The epidemiology situation of schistosomiasis by county in P.R. China in 2018.



### **3. Transmission patterns and evolution of the control strategy on schistosomiasis**

#### **3.1 Epidemiological patterns**

Through field investigations and in-depth studies, the NIPD-CTDR classified the endemic areas of schistosomiasis in P.R. China into three different categories according to the ecological features of snails habitats, namely plains & water network regions, marshland & lake regions, and hilly & mountainous regions. The NIPD-CTDR conducted a wide variety of pilot studies in different regions of P.R. China, such as Guichi County in Anhui Province in the 1950s, 1960s and 1980s; Changshu County in Jiangsu Province in the 1960s; Poyang, Yugan, Xingzi, Pengze counties in Jiangxi Province in the 1970s and 1980s; and Weishan County in Yunnan Province in the 1980s and 1990s. Based on those research results, it put forward that interventions and control strategies be adapted to local settings. In the 1980s, with the achievement of schistosomiasis control, most of the endemic areas in the plains & water network regions have reached the so-called “eradication standard” formulated at that time, while the control programme in marshlands & lakes regions, and hilly & mountainous regions faced more difficulties. The NIPD-CTDR continued to conduct pilot studies on epidemiology and control strategies in these two areas at that time.

##### **3.1.1 Plains & water network regions**

Changshu County in Jiangsu Province is a typical area with water network where schistosomiasis was once highly prevalent. From 1961 to 1966, the NIPD-CTDR cooperated with the local institutes to carry out clinical research on treating large numbers of patients with acute, chronic and advanced schistosomiasis. In-depth research on the pathogenesis and treatment methods of advanced schistosomiasis were conducted and scientific achievements were made. Since 1965, in view of the task to eliminate schistosomiasis in Changshu County, pilot control studies on schistosomiasis control were carried out in two communes, Mocheng and Zhitang. In the former, a wide variety of measures had adopted, including treating positive patients, eliminating snails, managing excrement, protecting citizens and promoting health education. In addition, the NIPD-CTDR also formulated proposals and suggested constructing water conservancy and improving environment to eliminate *Oncomelania hupensis*. To implement these control measures efficiently, a large number of local health workers

were trained well and attended the project. The NIPD-CTDR invested substantial human and material resources in the general survey, general treatment and control as well as research for eliminating snails. A hundred technical and administrative staff from the NIPD-CTDR participated in this work. This practice involved an ordered system involving soil burial and chemical extermination to eliminate the snails according to local conditions. After long and arduous efforts, the whole Changshu County reached the standard of schistosomiasis elimination in the 1980s. In Zhitang commune, on the other hand, the work mainly focussed on investigation and analysis of acute schistosomiasis infection and the implementation of personal self-protection. The results provided a reference for the prevention of acute schistosomiasis infection in areas where *Oncomelania hupensis* had not been eradicated.

### **3.1.2 Marshlands & lakes regions**

Guichi County in Anhui Province is adjacent to the East Lake and the South Lake where snails are widely present in large areas (more than 50,000 acre). After a rigorous survey on topography of the snail habitats and analysing with hydrological data, several snail control methods have been proposed which have tailored to local settings, such as changing the water course from lake-type to river-type, building dikes on boundary between the Yangtze River and the lakes to stop river water flowing back, transforming the East Lake and the South Lakes to fertile farmlands, etc. After the implement of these measures, both lakes witnessed an earthshaking change, with large scales of agricultural production bases sprouting out. Such kind of changes not only help to control schistosomiasis through eliminating *Oncomelania* snails, but also increased agricultural output with more than 500 million tons of grain produced annually.

The NIPD-CTDR continued to investigate and analyse the relationship between snail distributions and infested lake water in other areas, such as Shima Lake in Huaining County, Anhui Province, Danyang Lake and the Jiangxin marshlands in Dangtu County, Anhui Province, as well as Bali Lake in Jiujiang City, Jiangxi Province. Combining with these results, the NIPD-CTDR put forward that efforts should focus on eliminating the snails near residential areas and boat mooring sites, as well as other measures to establish safe zones. This concept and measures have been adopted by many endemic areas in the following years.

In the 1980s, when praziquantel had been discovered as a highly safe medicine for schistosomiasis, the NIPD-CTDR established a research pilot

at Tuniu Village in Xinzi County of Jiangxi Province along the banks of Poyang Lake. The coverage of human and cattle treatment with praziquantel was expanded in epidemic area to thoroughly eliminate the source of infection, and proposed intervention measures were subjected to long-term monitoring. One year later, the effectiveness of schistosomiasis control had significantly improved. However, since the infection sources and infected snails still existed, it was difficult to prevent the re-infection in human and animals, and the achievements were this difficult to sustain.

### 3.1.2.1 Combination of sluice construction and snail control in the Poyang Lake

From 1970 to 1972, many professionals engaged in research on schistosomiasis control in Poyang and Yugan counties of Jiangxi Province. Based on observations in the field, the NIPD-CTDR's scientists believed that control and elimination of snails is essential to control schistosomiasis in marshland and lakes region (He, 2005). Because *Oncomelania* is an amphibious snail the concept of "snail-drowning" has proved successful to eliminate snail in other endemic areas. To that end, the technical staff from the NIPD-CTDR put forward the proposal to the local government to build sluices at the intersection of the Poyang Lake that can store water and maintain water level to eliminate snails. These measures could also be integrated with other comprehensive development engineering projects and better utilization of other resources. With the support and cooperation with leading departments of the local government, the NIPD-CTDR's professionals visited relevant departments, communes and farms in more than 10 counties and cities around Poyang Lake, held more than 60 seminar sessions and listened to opinions. They collected data on industry, agriculture, water conservancy, hydrology, aquatic products, meteorology, land and water transportation, geology and schistosomiasis control weighing up the advantages and disadvantages of eliminating snails by building sluices to store water. The opinion of the NIPD-CTDR staff was that the way of building sluices in Poyang Lake would change the lifecycle patterns of *Oncomelania* snails that spent "winter on land and summer in water" on the grass beaches of the lake. This would solve the dilemma of having to choose between water conservation and snail elimination, after building sluice to control the water level, the lake resources could be developed. With the active support of the relevant departments in Jiangxi provincial government, the NIPD-CTDR's professionals completed the proposal on "building sluice connection in the Poyang Lake to save water and eliminate snails in combination with better utilization



of resources and thus contribute to the comprehensive development of the area”. After investigation for more than 2 years, the proposal was submitted to the Leading Group on Schistosomiasis Control in the State Council, Jiangxi Provincial Committee for Schistosomiasis Control.

#### **3.1.2.2 Test for snail control by aircraft spraying**

In 1970, given the difficulties in snail elimination due to the snail specific ecological patterns, such as the wide range of snail distribution, short season for snail living in the marshland above the water, the Jiangxi Provincial Government decided to carry out the filled trial on snail control by spraying pentachlorophenol sodium, a molluscicide, by airplane. The NIPD-CTDR professionals were invited to participate in this field trial, and has successively carried out airplane spraying of molluscicide to kill the snails of 40,000 acre in the marshland. The results showed that under appropriate conditions, i.e. high temperature, appropriate water level, long immersion time, and flat grass beaches, etc., good results could be obtained to control snail populations. The effectiveness of eliminating snails was better in the Spring than that the autumn (Guo et al., 2002). In the 1970s, in spite of the adverse effects on the environment, it was considered that large-scale airplane spraying to kill snails had the advantages of saving manpower and time, particularly in areas far away from settlement and where it is difficult to eliminate the snails by manpower.

#### **3.1.3 Hilly & mountainous regions**

More than 50% of the schistosomiasis endemic counties (cities) in P.R. China are located in the hilly & mountainous regions. According to the natural geographical environment and the epidemic characteristics of schistosomiasis, these areas can be divided into three subtypes: hilly areas, canyon and flatland. Guichi County in Anhui Province is one of the highly prevalent counties of schistosomiasis in P.R. China, where most of endemic areas are belong to the marshlands & hill. In the hilly area of Guichi County, professionals chose two pilot villages (Pailou and Douxi) to conduct a study combining praziquantel treatment with comprehensive snail elimination in Pailou Village or snail elimination in hot spots in Douxi village. Two years later, schistosomiasis transmission had initially been interrupted in both villages. However, in Douxi, several new cases of infection and positive snails appeared in the next year, spinning the situation out of control. Therefore, it was believed that the spread of schistosomiasis could be

controlled by mass dug distribution (MDA) in combination with the overall elimination of snails in those hill-endemic areas that have become independent epidemic units.

As a key scientific and technological research project during the seventh five-year plan period (1986–1990), pilot studies were carried out in Weishan County, Yunnan Province and Xichang City, Sichuan Province. The ecology, biological, natural and social factors affecting schistosomiasis, prevalence in mountainous areas were investigated by using epidemiological methods and satellite images systematically and comprehensively (Cao et al., 2004; Zheng, 2000; Zheng et al., 2000). Based on the data collected, different intervention measures were implemented to provide evidence for improving the control strategy of schistosomiasis in mountainous areas. The Weishan County pilot represented the canyon area, which is the long-term and systematic observation area of the NIPD-CTDR. The Xichang City pilot was in flatlands, which was the key observation area of Sichuan Provincial Institute of Parasitic Diseases Prevention and Control. According to a systematic analysis with the probability accumulation method, six main factors were found to affect schistosomiasis prevalence in the mountainous areas, namely temperature, rainfall, the number of infection sources, the number of positive snail points, water source for agriculture production and the use of ditch water, which served as important reference for formulating intervention measures.

Three measures adopted in three different pilot areas of Weishan County, namely, synchronous chemotherapy for humans and animals with elimination of snails in infected spots/areas (group A), synchronous chemotherapy for human and animal (group B), and routine control (group C). Two years later, the positive rate in faecal tests of residents in A and B groups decreased by 80% and 55%, respectively, while there was no significant change in C group. This indicated that the two intervention programmes have certain effects on controlling local schistosomiasis prevalence even under continued transmission.

Based on research carried out during the seventh five-year plan, the eighth five-year plan focussed on controlling and interrupting the transmission of schistosomiasis in the mountainous areas. The study took 4 years. According to the epidemic factors, such as social, economic, behavioural and psychological factors, a series of prevention and control measures were formulated, emphasizing chemotherapy and health education, supplemented by key environmental control measures. Pilot studies were carried out in Zhonghe Village of Weishan County, Yunnan Province

and Chuanxing Village of Xichang City, Sichuan Province, and satisfactory results were achieved (Qin et al., 2012). This study shed light on the characteristics of faecal pollution, snail distribution and ecological characteristics of positive snail in the mountainous area. According to the peak of schistosomiasis infection, the life history of schistosomiasis and the pharmacodynamics of praziquantel treatment in the mountainous area, scientists from the NIPD-CTDR proposed the optimal time of chemotherapy would be 1 month after the peak of infection with the number of peak were equal to the number of treatment. According to the obvious family aggregation of local schistosomiasis, MDA carried out in families, which clarified the distribution rule of infected *O. lupensis* and helped to establish a simple and effective evaluation method for hazardous environmental improvement in hazardous areas. In addition, the method of comprehensive molluscicidal replaced by the method of niclosamide buried in soil, with less environmental impact. Systematic investigation of residents' attitudes towards schistosomiasis control and health education contributed to make health education more targeted, and triggered the establishment of a comprehensive evaluation systems for schistosomiasis prevention and control.

According to the results of epidemiological investigation, six different control strategies were carried out, mainly including human and animal chemotherapy, crucial environment control by eliminating snail, and health education. After 3–4 years of prevention and control, satisfactory results have been obtained. In Weishan County pilot, the infection rate of residents in one observation group decreased from 24.9% before the intervention to 0.2%, and that of livestock decreased from 4.6% to 0%. No positive snails found and there were no new infections in humans, animals or sentinel rat in water. All these improvements initially interrupted the transmission of schistosomiasis. In the other two groups, the infection rate of human and animal dropped to less than 3%, with no new infection detected in human and animal. The natural infection rate and density of snails declined to very low levels, which has controlled the spread of schistosomiasis. Similar results were obtained in the Xichang City pilot. Specific interruption of transmission was obtained in one strategy group, and transmission control in the other two groups. These results clearly showed that after 3–4 years of control, each strategy group in Weishan and Xichang pilots had successfully interrupted the transmission of schistosomiasis, and two strategy groups controlled the transmission of schistosomiasis. They therefore have guided the formulation of prevention and control plans or their improvement in mountainous areas.

### 3.1.4 The influence of Three Gorges Dam on schistosomiasis transmission

Many reports have suggested that the construction of water conservancy projects can change the ecological environment so as to intensify or spread the epidemic of schistosomiasis (Guo and Zheng, 1999; Hunter et al., 1982; Wang and Zheng, 2003).

The Three Gorges Water Conservancy Project is a large-scale comprehensive project to develop and harness the Yangtze River, whose functions mainly involving flood control, power generation, shipping, sand drainage and environmental protection. There has been no history of schistosomiasis in the area before or after the construction of The Three Gorges Dam (TGD). Yet, with the social and economic development and ecological environment changes, many researches have focussed on whether schistosomiasis infection sources and *Oncomelania* can imported into the reservoir area where was no schistosomiasis in history after the construction of TGD. In order to understand the risk factors of schistosomiasis transmission in the TGD area and put forward the corresponding control measures, the NIPD-CTDR researchers participated in the design and implementation of the research to understand the impact of the TGD on the epidemic of schistosomiasis (Zheng et al., 2003).

In the 1990s, based on hydrology, sediment and other materials provided by the Yangtze River Water Resources Commission and prediction results of water and sediment changes after the dam built, the NIPD-CTDR's scientists conducted a series of field surveys and analysed the possible impact of ecological environment changes on schistosomiasis transmission. Also, the scientists took the principles and methods of epidemiology, ecology and social medicine were taken into consideration and investigated the infection situation in human and animals, as well as the social and economic behaviour factors in the TGD reservoir area and the middle and lower reaches of the Yangtze River. The growth and development of *O. hupensis* were investigated through simulating the conditions of similar reservoirs. Systematic analysis was conducted to predict the relationship between TGD and schistosomiasis transmission. The results showed that the natural conditions in the TGD area were suitable for snails' breeding and schistosomiasis transmission. After the TGD was built, the water flow in the reservoir area slows down and silt deposition will form many beaches. In the area from 145 to 175 m high, the beaches are below the flood outsourcing line and at the intersection of each tributary river all have the necessary conditions

for snail breeding (Zheng et al., 2002). In addition, irrigation ditches in settlements may were also suitable for snails breeding.

An analogy survey showed that the vegetation, soil and physical and chemical properties in the reservoir area were like those of meadow of lakes in the endemic area. The results showed that the riff-shell snails from Hubei and Sichuan could grow, develop and reproduce under simulated conditions. Epidemiological investigation also confirmed that the snail and the source of infection might be imported into the reservoir area. Therefore, the reservoir area has become a potential schistosomiasis endemic area, and the monitoring and intervention measures should be strengthened to prevent the spread of schistosomiasis from endemic areas to the reservoir area. Jiangnan Plain, the head of the TGD was one of the most serious endemic area. After the construction of the TGD, the water level of the Yangtze River increased at the turn of spring and summer, which may lead to the increase of underground-water level in some areas of Jiangnan Plain and possibly enlarge the snail area and change the planting schedule. To prevent the spread of snail, the production pattern should be changed, water modification and rotation should be promoted, to control the spread of snail and reduce the infection of humans and animals.

The influence of the TGD on Dongting Lake is mainly due to the decrease in sediment entering the lake, and the gradual development of grass and reed areas, conducive to the breeding of snail (Dai et al., 2019a). In autumn, the water recession happened earlier, which may increase the infection risk of human and animals due to an increased frequency with water contact. The construction of TGD has a relatively small impact on the area of Poyang Lake and below. The result from Jiangsu province's survey suggested that early spring flooding is not conducive to the growth and development of *O. hupensis*. At the same time, the scour and siltation of the Yangtze River section were changed. In some areas, erosion is not conducive to snails' breeding, which can reduce the distribution area. In other areas situation may increase snails habitats.

Over the past century, floods have occurred in the middle and lower sections of the Yangtze River. After the construction of the dam, the flood will be effectively controlled, which will not only protect people's lives and property, but also reduce the spread of *Oncomelania* snails and the occurrence of human and animal infection by schistosomes. The construction of TGD was a large-scale project. The ecological changes after its completion will be a gradual process. At present, the relationship between TGD and

schistosomiasis can only be analysed based on prediction. Some results need to be further investigation and verification. According to the results obtained, TGD has both disadvantages and advantages to the spread of schistosomiasis. Therefore, it is urgent to explore effective and feasible countermeasures to prevent the spread of schistosomiasis to minimize the negative effects.

### 3.2 Strategy evolution

In the early days after the founding of P.R. China, there was a tragic scene described in the poem “because of the harm of schistosomiasis, many people died, leaving only empty villages, cold and desolate” (Wang, 2006). The Communist Party Central Committee and the State Council have always attached great importance to the prevention and control of schistosomiasis. In 1955, the Central People’s Government of the Communist Party established a leading group for schistosomiasis control. In 1956, the central government issued a call for “Do eliminate schistosomiasis”, setting off a vigorous mass campaign for the prevention and control of schistosomiasis. In 1984, Comrade Deng Xiaoping gave instructions for the “prevention and control of endemic diseases for the benefit of the people”. In 1989, Comrade Jiang Zemin pointed out in his letter to the conference of schistosomiasis control in five provinces of lake area that “the control and elimination of schistosomiasis is the binding duty of all levels of the governments in the epidemic area”. This upsurged schistosomiasis prevention and control work in the early 1990s (Zhou et al., 2010).

With the efforts of several generations, the strategy of schistosomiasis control in P.R. China has also undergone a transformation process from “snail eradication oriented” to “human and animal chemotherapy oriented” to “infection source control oriented” comprehensive control strategy. Finally, the prevention and control of schistosomiasis in P.R. China has made remarkable achievements (Zhang, 2009). During this process, many scientists of NIPD-CTDR contributed their intelligence and involvement in the formulation and integration of new strategy into national control programmes.

#### 3.2.1 *The first stage, from the mid-1950s to the early 1980s*

A comprehensive prevention and control strategy based on the elimination of *Oncomelania*, the combination of human and animal diagnosis and treatment, and the rescue of critical patients.

At this stage, the focus of prevention and control schistosomiasis is to eliminate *Oncomelania* and treat patients actively according to local

conditions. As *Oncomelania* is the only intermediate host of *S. japonicum*, the life cycle of schistosomes will be blocked and the transmission will stop once the snails are eliminated. At that time, there were no good methods to control pathogens and avoid contact with epidemic water, and no safe, cheap and effective drugs to treat schistosomiasis cases. To reduce the harm of schistosomiasis, mobilization of the masses and resources were good news to control the snails at that time. In general, it can be concluded that large scope and large-scale molluscicidal projects focussed on water conservancy and farmland infrastructure construction, as well as large-scale drug molluscicidal projects, large-scale investigation and treatment of patients and infected livestock, were supplemented by water and faeces management, individual protection, publicity and education, etc. At this stage, great achievements have been made in the prevention and control of schistosomiasis in P.R. China. The area of the epidemic area has been greatly reduced, and the disease condition has been significantly reduced. In places with a relatively developed economy and high population density, where snail breeding area was relatively limited, such as in Guangdong, Shanghai, Guangxi, Fujian and Zhejiang etc., snail control and chemotherapy were taken as the main measures, combined with other control measures, to eliminate schistosomiasis and effectively block the spread of schistosomiasis. However, snail eradication not only costs a lot of money, but also needs long-term and repeated prevention and control. In addition, mollusciciding will cause environmental pollution. It is very difficult to interrupt the transmission of schistosomiasis by taking the above measures before the environment has been completely transformed in seven epidemic areas and provinces of Hunan, Hubei, Jiangsu, Jiangxi, Anhui, Sichuan and Yunnan, where snails are widely distributed, the breeding environment is complex and the water level is also difficult to control (Zhang, 2009). By the end of 1984, more than 11 million patients had been treated and more than 11 billion m<sup>2</sup> of snails had been eradicated. Seventy six of the 370 endemic counties (cities) in P.R. China had reached the “standard of schistosomiasis elimination”, 193 of them had reached the threshold of “basic elimination of schistosomiasis”, and 4 provinces (cities) in the East, Shanghai, Fujian and Guangxi, mainly mountainous or water network type, had eliminated Schistosomiasis (Zhou et al., 2010).

### **3.2.2 The second stage, from the 1980s to the beginning of the 21st century**

In the mid-1980s, with the advent of praziquantel, an effective, cheap and safe anti-schistosome drug, the World Health Organization (WHO)

recommended the implementation of a strategy of “morbidity control”. The prevention and control strategy focusses on chemotherapy on human beings and a change in their behaviours. It was believed that the transmission of schistosomiasis does not caused by oncomelanade snails, but by human behaviour of contacting with infected water containing cercariae. Therefore, only focussing on human and human behaviour, can we prevent water pollution and reduce the contact frequency between human and contaminated water, to achieve the purpose of preventing and reducing infection (Zhou et al., 2010). For this reason, WHO suggested that schistosomiasis control should be focussed on health education and the role of human behaviour, in addition to chemotherapy. The prevention and control of schistosomiasis can be divided into three stages and implemented gradually: (a) to reduce the number of severe cases, especially acute and advanced patients with obvious symptoms; (b) to reduce the infection rate and infection intensity; (c) to control and interrupt the transmission. In 1980–1985, the research on control strategy was mainly focus on the chemotherapy supplemented by eliminating *Oncomelania* in susceptible areas, to realize the goal of morbidity control. Thus, researchers from the NIPD-CTDR coordinated and conducted numerous pilot studies, based on four pillars: (i) to eliminate the source of infection, and at the same time to eliminate snails in the susceptible areas; (ii) to eliminate snails in a large area, and eliminate the source of infection simultaneously; (iii) to expand the coverage of chemotherapy to eliminate the source of infection; (iiii) to eradicate infectious sources in mountainous areas and conduct molluscicidal trials in key areas (Guo, 2006; Zhou et al., 2010).

The NIPD-CTDR researchers have studied the epidemic features and patterns of schistosomiasis in the mountainous area, and put forward that health education and environmental snail and cercariae control should be placed in a very important position while carrying out the expanded chemotherapy for human and livestock in this area (Zheng et al., 1996, 2001). Our country also began to adjust the strategy of schistosomiasis control to morbidity control strategy with “taking simultaneous chemotherapy of human and animal as the main intervention, eliminating snails in susceptible areas and conducting health education as the supplementary methods”. This strategy was strongly supported by the World Bank Loan Project (WBLP) for schistosomiasis control in China between 1992 and 2001, with a total investment of 890 million RMB yuan (approximately US\$152 million), of which 416 million RMB yuan (US\$71 million) was a loan provided by the World Bank and 474 million RMB yuan (US\$ 81 million) came from counterpart



funds provided by the Chinese government at all levels (Xianyi et al., 2005). The overall goal of the WBLP project was to reduce and control the prevalence of schistosomiasis and to block the transmission in some areas. Through the implementation of the project, the infection in human and animals was effectively controlled (Zhou et al., 2010). The number of people infected with schistosomes decreased from 1.638 million in 1989 to 928 thousand in 1995. By the end of 2002, the infection rate of humans and livestock in P.R. China had decreased by 55% and 50%, respectively, the density of infected snails in the national epidemic area declined by 75% compared with that before the implementation of the project in 1992, and Zhejiang province had reached the “standard of schistosomiasis elimination” in 1995 (Zhou et al., 2010). In order to understand the cost-effectiveness of the World Bank Loan Project, a retrospective economic evaluation was done in 2001. Six representative counties, i.e., Huarong in Hunan province, Qianjiang in Hubei province, Yugan in Jiangxi province, Tongling in Anhui province, Xichang in Sichuan province and Dali in Yunnan province, were selected for the study. The total financial input in these counties from 1992 to 2000 was RMB Yuan 90.334 million with the World Bank loan accounting for 40.9%. Control efforts resulted in reduction of human prevalence rates in the six counties from 0.7%–9.0% in 1992 to 0.1%–2.7% in 2000. The net benefit-cost ratio was 6.20, which means that this project gained US\$ 6.20 for every dollar spent. The correlation coefficients of the net benefit-cost ratio to the human and bovine infection rates at the beginning of the project were 0.55 and 0.66, respectively. It is conceivable that further progress in schistosomiasis control is an important feature for sustained growth of the local economy, particularly in areas where control of the disease has been most challenging (Zhou et al., 2005c). However, although chemotherapy based disease control measures can quickly control the epidemic situation of schistosomiasis, it is difficult to control reinfection and consolidate the control effect in the lake region (Zhou et al., 2004, 2012). By the end of 2003, schistosomiasis rebounded in 17 of 150 counties (cities, districts) which had reached transmission interruption. Among the 63 counties (cities, districts) in the stage of transmission control, 21 counties (cities, districts) showed a significant increase in snail or infections in humans or livestock (Guo, 2006).

### **3.2.3 The third stage, from 2004 to present**

At the beginning of the 21st century, the number of people infected with schistosomes was on the rise. For example, in some areas where had reached

the standards of transmission control or transmission interruption had the acute infection and infected snails, indicating schistosomiasis transmission reestablished in those areas; new epidemic areas were occurred in some non-endemic areas; and the disease was spreaded from rural areas to cities. There are several reasons for this kind of resurgence as follows: (i) the environment changes or continues to deteriorate, and the floods occurred more frequent. In addition, affected by the national policy of returning farmland to Lake after serious flooding in 1989, the distribution of *Oncomelania* snail was expanding in wider scale (Lin et al., 2002). (ii) the existing molluscicides have a certain degree of pollutive impacts on the environment, so that more and more marshland could not apply the molluscicides any more due to its side effect on toxicity. (iii) with the development of a socialist market economy and animal husbandry in P.R. China, livestock trade had been frequent, and the role of the animal host in the whole process of schistosomiasis transmission had become more prominent, with increased opportunities for exposure of people and animals (Wu et al., 2007). (iv) by the beginning of the 21st century, the national schistosomiasis control programme had lasted for quite a long time, and the compliance and coverage of chemotherapy have decreased year by year (Guo, 2006).

In order to strengthen the national schistosomiasis control programme to protect the health of the people and promote the economic and social development in the endemic areas, the State Council established a leading group for schistosomiasis control again in 2004. A series of important documents, such as “The Notice of the State Council on Further Strengthening the Schistosomiasis Control Programme”, “The National Medium- and Long-Term Strategic Plan for Schistosomiasis Control Programme (2004–2015)” and “The Planning Framework of the Key Project on Integrated Control on Schistosomiasis (2004–2008)”, were issued by ministries in various sectors, including National Commission of Planning, Ministry of Finance, Ministry of Agriculture, Ministry of Water Conservation, Ministry of Forestry, Ministry of Health, etc. The national conferences on schistosomiasis control were held and facilitated the coordination and collaboration of multi-sectoral ministries on the national schistosomiasis control programme (Wu et al., 2007; Zhang, 2009). The National Med- and Long-Term Strategic Plan for Schistosomiasis Control Programme in P.R. China (2004–2015) put forward the following goals: (1) by the end of 2008, all the epidemic counties (cities and districts) reach the threshold of infection control, and no or only a very few outbreaks occur, (2) by the end of 2015, all endemic counties (cities and districts) reach the transmission control, and all counties (cities and districts) that have reached

transmission control more than 10 years interrupted the transmission of schistosomiasis while other historical epidemic areas and areas with potential transmission risks (such as the Three Gorges Reservoir Area) consolidate and expand prevention and control achievements (Guo, 2006; Zhou et al., 2004).

An integrated control strategy focussing on the control of infectious sources had been formulated for the national programme in 2006 after pilots studies, and became the new control strategy in P.R. China. The strategy was based on the transmission chain of schistosomiasis, the eggs of adults are the most critical link, so how to prevent the eggs from polluting the environment is the most important step to reach the transmission blocking standard of schistosomiasis. The key control measures for the new strategy are as follows: (i) to “replace cattle with machines”, that is, to vigorously develop modern agriculture, apply modern industrial civilization to agriculture, gradually eliminate the backward agricultural production mode dominated by cattle, and reduce the number of infectious sources of livestock. (ii) the government to strengthen the infrastructure construction of schistosomiasis endemic areas, for example, to build a new harmless sanitary toilet to directly kill the eggs in the faeces and prevent the faeces from polluting the environment. (iii) continue to strengthen advertising and education, popularize the knowledge of disease detection and treatment, snail detection and egg killing among people and livestock in epidemic areas, and raise the awareness of the people in disease prevention and treatment (Wang, 2006; Wang et al., 2009c).

In 2005, the leading group of the national schistosomiasis control programme of the State Council set up five counties to verify the effectiveness of the new strategy and the feasibility of its popularization and application. The five counties were Anxiang county of Hunan province, Hanchuan county of Hubei province, Puge county of Sichuan province, Jinxian county of Jiangxi province and Guichi District of Anhui province. According to the actual situation of each county and local control programme, with the purpose of controlling the source of infection, new strategies had been adopted along with the routine activities. In 3 years, all the pilots have achieved good results, and the effects have been continuously consolidated, which shows that the new strategies have significant effects in epidemic areas and can be popularized and applied nationwide (Chen et al., 2011). It was the fundamental way out for the prevention and control of schistosomiasis in the lakes and marsh areas in P.R. China, and improve living standards. Scientific and technological progress and long-term compliance are two important cornerstones for significant achievements of schistosomiasis control. Next, the work of schistosomiasis control in P.R. China should focus on scientific research, rely on the

comprehensive control strategy of infectious source control, continue to strengthen the publicity and education of the masses in the epidemic area, so that all the epidemic areas of schistosomiasis can reach the standard of transmission interruption as soon as possible, and truly deliver Take the “God of plague” to realize the sustainable development of the economy in the epidemic area (Guo, 2006; Li et al., 2012; Utzinger et al., 2005; Wang et al., 2009b,c).

In summary, the NIPD-CTDR has actively carried out research on the epidemic environment and characteristics of schistosomiasis in P.R. China in order to determine scientific control strategies in the different type of endemic regions. Through 70 years of continuous exploration, the NIPD-CTDR has established control strategies corresponding at different control stages, and gradually defined control strategies and measures for different environmental settings. In addition, it was verified and popularized through the piloting studies, which provided the epidemiological theoretical reference for decision making in the national schistosomiasis control programme in P.R. China. Particularly in 2005–2015, several pilot studies involved young staff from the NIPD-CTDR which fostered the capacity building for young generation of the institute, and set milestones for the scaling up of the new strategy and promotion of the national schistosomiasis control programme to reach the transmission control criteria with prevalence less than 1% in the whole country.



## **4. Diagnostics and vaccine development**

### **4.1 Development and application of diagnostics**

Diagnosis provides the necessary information and scientific evidence for schistosomiasis control programme in P.R. China. Over the past 70 years, Chinese scholars, especially NIPD-CTDR researchers, have been working on the development, evaluation and quality control of the diagnostic techniques for schistosomiasis. During this period, the parasitological methods have been improved, and a variety of immunoassay techniques have been developed and are commercially available. Meanwhile, many innovative ideas have been derived. These tools have played an important role in the prevention and control of schistosomiasis, which has effectively promoted the process of schistosomiasis elimination in P.R. China (Zhang et al., 2016a). The main contribution of NIPD-CTDR in the field of schistosomiasis diagnosis is elaborated below.

#### 4.1.1 Parasitological diagnosis

Detection of *Schistosoma* eggs in faeces or tissue biopsies is the direct way to confirm the infection of schistosome and some parasitological tests have been most widely used for the diagnosis of schistosomiasis in the endemic areas. In spite of reduced sensitivity especially for low infection intensity, Kato-Katz thick smear (Katz et al., 1972) and the miracidium-hatching test (Qiu and Xue, 1990) remain the gold standard for the diagnosis of schistosomiasis. Over the years, the NIPD-CTDR has made a number of improvements in the method of faecal examination, including nylon silk egg hatching test and improved Kato-katz thick smear combined with faecal hatching, which has contributed to the improvement of the detection rate of schistosomiasis.

##### 4.1.1.1 Hatching test

The main method for the diagnosis of schistosomiasis by faecal examination was the combination of faecal sedimentation and miracidium-hatching test (sedimentation-hatching) in P.R. China before 1970. However, the infection intensity of patients was greatly reduced due to the strengthened control, and hence it was still difficult to detect infections with 3 times sedimentation-hatching. Therefore, NIPD-CTDR developed the nylon-bag-collection method. Compared to the conventional method of sedimentation-hatching, the method is able to reduce the loss of eggs, simplify the operation steps, improve the work efficiency, reduce the labour intensity, save the water consumption, and increase the detection rate. This diagnostic method is very popular among field workers and has been widely used in the endemic areas for investigation of schistosomiasis infection and assessment of the treatment efficacy. Currently, this method has been further improved and used as the way for evaluating the infection rate of schistosomiasis in human beings in areas where aiming for transmission interruption and elimination.

##### 4.1.1.2 Improved Kato-Katz method combined with faecal hatching evaluation

In 2005, the NIPD-CTDR researchers evaluated the effect of modified Kato-Katz method on large-scale on-site screening of Schistosomiasis (Zhu et al., 2005). They found that modified Kato-Katz method alone has a high rate of misdiagnosis. The detection rate further significantly increased when in combination with hatching techniques. This research provided a useful reference for setting diagnosis criteria and application

strategy of schistosomiasis. The diagnostic strategy of combing Kato-Katz thick smear method and miracidia hatching technique applied to sero-positive human was firstly integrated into the national surveillance project in 2011, and then widely implemented in the national schistosomiasis elimination programme since 2018.

#### **4.1.2 Immunological diagnosis**

Since the 1950s, NIPD-CTDR has contributed to the development and implementation of new immunological diagnostics for schistosomiasis. The antigen used is involved in various stages of the life cycle of schistosomes. The methods used include intradermal test (ID), Cercarien-Hullen-Reaktion (CHR), circumoval precipitin test (COPT), latex agglutination test (LAT), indirect hemagglutination assay (IHA), enzyme-linked immunoelectron transfer blot assay (EITB), enzyme-linked immunosorbent assay (ELISA), rapid diagnostic tests (RDT) and so on (Wu, 2002, 2005; Yan et al., 2006; Zhu, 2005).

##### **4.1.2.1 The intradermal test**

Gan (Kan, 1936) first introduced the intradermal test in the diagnosis of schistosomiasis in P.R. China. In the early 1950s, we used cold soak liquid of adult worm frozen dry powder as the antigen for ID, however, the yield of adult antigens obtained from infected rabbits is limited. In order to meet the needs of control work, NIPD-CTDR replaced adult antigens with egg antigens collected from infected rabbit liver, which achieved similar effects, and made mass production available (Li and Yan, 1956). In addition, NIPD-CTDR also develops antigens derived from adult metabolites of *S. japonicum*, that is, metabolic antigens, and presented high sensitivity and specificity (Mao et al., 1956).

From 1956 to 1957, according to the national investigation requirements, NIPD-CTDR produced 58 million copies of antigens for intradermal testing, which played an active role in determining the epidemic area, infection status and prevalence of schistosomiasis in P.R. China. In the 1980s, due to the simplicity and sensitivity of this method, but the antibody persisting a long time in the infected people after treatment, NIPD-CTDR only used this method for comprehensive investigation, and screening those population without history of treatment (Mao and Shao, 1982). Later, it was soon replaced by other tests due to its lower specificity.

#### 4.1.2.2 Cercarien-Hullen-Reaktion

The cercarien-hullen-reaktion established in 1951 has high sensitivity to schistosomiasis patients and early diagnostic value. However, the need for fresh cercariae as an antigenic material limited its practical applications. NIPD-CTDR researchers explored the use of freeze-dried cercariae to replace fresh cercariae. Through animal experiments and field observations, freeze-dried cercariae achieved the same sensitivity as fresh cercariae but lower false positive rate. The freeze-dried cercariae can be stored at room temperature or in the refrigerator ( $4^{\circ}\text{C} \sim 6^{\circ}\text{C}$ ) for 4 to 5 weeks; it was more suitable for field application.

#### 4.1.2.3 The circumoval precipitin test

Because of the high sensitivity and appropriate specificity of the circumoval precipitation test, it was regarded as one of the effective serological diagnostic methods for schistosomiasis. However, it is not easy to preserve fresh eggs. To this end, the scientific researchers have studied the method of replacing the fresh eggs with freeze-dried eggs, but because the eggshell is easily broken and affecting the reaction effect. Then, the NIPD-CTDR researchers treated the fresh eggs with formaldehyde and then frozen them with decompression. This method overcomes the phenomenon that the eggshell is easily broken. After field tests, the efficiency of dry egg antigen detection on schistosome infection was no less than that of fresh egg antigen (Qiu, 1975; Yan, 1976). The use of freeze-dried technology has made the COPT the most widely used immunodiagnostic method for schistosomiasis in the 1960s and 1980s (Chen, 1980; Li, 1976), but because of the high labour intensity of COPT operation, which limits its large-scale applications on site, this method currently was no longer used in endemic areas.

There was no report on immunological diagnosis of *S. mansoni* infection using *S. japonicum* antigens before the 1970s. From 1974 to 1975, NIPD-CTDR first used three immunological methods including ID, CHR and COPT for the diagnosis of foreigners returning from Guinea where is the endemic area of schistosomiasis mansoni. A faecal test and immunological examination were performed, and the positive rate of faecal test was 54.0%. The positive rate of CHR and COPT in the faecal test positive group was 97.0% and 94.0%, respectively, while the positive rate in the ID was only 42.9%, suggesting that the COPT and CHR using antigens from *S. japonicum* can also diagnose the infection of *S. mansoni* (Yu et al., 1979).

#### 4.1.2.4 Latex agglutination test

In the 1960s and 1970s, experimental studies on the detection of antibodies against *Schistosoma* by latex agglutination test was carried out at home and abroad, but the physical method of sensitizing latex has poor stability and low sensitivity. Since the 1980s, research teams from the NIPD-CTDR have collaborated with the Shanghai Medical Laboratory and the US CDC to apply the chemical cross-linking method to prepare schistosome antigen according to the principle and method of latex pregnancy test. This method characterized with good stability, simple and fast operation without special instruments, and ease-of-use for field application. Animal experiments, clinical case tests and field applications have shown that the method achieves similar efficacy with indirect hemagglutination assay, enzyme-linked immunosorbent assay and circumoval precipitation test, in terms of stability, specificity and sensitivity. This method has been applied within a certain range of field (Yan et al., 1985, 1986, 1987).

#### 4.1.2.5 Enzyme-linked immunoelectron transfer blot assay

Enzyme-linked immunoelectrotransfer blot assay (EITB), also known as Western blot, is a new diagnostic technique developed in the late 1970s and early 1980s. Qiu et al. from NIPD-CTDR first established an enzyme-linked immunoelectron transfer blotting technique for serum antibody analysis in patients with schistosomiasis in 1988 (Qiu et al., 2000). Results showed that the sera from acute, chronic and advanced schistosomiasis patients recognize different adult antigen strips. The specific antibodies decreased or disappeared rapidly after treatment with praziquantel in acute infection. This method is helpful to distinguish between chronic and acute schistosomiasis, and has certain reference value for the evaluation of the efficacy of schistosomiasis after treatment (Yan et al., 1988).

#### 4.1.2.6 Enzyme-linked immunosorbent assay

In the late 1970s, Enzyme linked immunosorbent assay (ELISA) was used for the detection of schistosomiasis in Japan. After that, the NIPD-CTDR scholars developed various improved techniques based on classical ELISA. Yan et al. from the NIPD-CTDR first applied the enzyme-linked immunosorbent assay for the detection of schistosomiasis mansoni with good sensitivity and specificity (Yan, 1979; Yu et al., 1979). Because the ELISA method recommended by the World Health Organization Tropical Diseases Programme requires 6h of reaction time, the reagents need to be refrigerated and stored, and the results need to be read by the instrument, so there are certain restrictions on the field application.



For this reason, Yan et al. from the NIPD-CTDR developed a rapid-ELISA method in the 1990s for the detection of antibodies against *Schistosoma* with a sensitivity of 94% and a specificity of 96%, which is identical to the performance recommended by the World Health Organization. Fast-ELISA only takes 30–40 min. The antigen plate and reagent can be stored at room temperature for more than 4 weeks, and can be used separately for the detection of sporadic samples. The results can be visually observed, which is very suitable for field application (Yan et al., 1996). However, because antibody-based detection is difficult to distinguish between active and past infections, this method cannot be used for efficacy evaluation.

The detection of schistosomes' circulating antigen can reflect the host active infection, the load of the worm and evaluate the effect of drug treatment. With the advent of hybridoma technology, NIPD-CTDR has conducted in-depth research on the detection of schistosoma antigens. In the late 1980s and early 1990s, Yan et al. from NIPD-CTDR collaborated with the researchers from the University of Leiden in the Netherlands. They discovered high-efficiency monoclonal antibody 3D8A against *Schistosoma* intestinal-associated cathodic antigens and monoclonal antibody SM21-3 against *Schistosoma* egg antigen through preparation and screening of more than 30 monoclonal antibodies (Yan and Deelder, 1988; Yan et al., 1990b). In this way, monoclonal antibody-based sandwich ELISA and Dot-ELISA were developed to detect the corresponding circulating antigen in the serum of patients with Schistosomiasis (Yan et al., 1990a,c, 1992a,b), and the sensitivity was 90.6% and 83.2% for acute and chronic schistosomiasis patients, respectively. The cross-reaction with other worm is very low. In 1990, Xue et al. improved the Dot-ELISA method, and the NC film with the antigen was fixed in a PVC plate for testing. The improved operation was simple and convenient, and it was more suitable for field application (Xue et al., 1990). In 2000, Qiu et al. (2000) reported the detection of circulating antigen in the schistosomiasis patients' sera based on polyclonal and monoclonal antibody sandwich ELISA, compared the detection effect of dot ELISA with polyclonal-monoclonal antibody sandwich ELISA. The results of field test showed that both methods performed high sensitivity and specificity, and had a certain cure efficacy evaluation value. Dot-ELISA is more sensitive, simple, low-cost, with less blood and do not need special equipment. It can be visually observed and is suitable for field applications.

#### 4.1.2.7 Rapid diagnostic kits

Rapid diagnostic kits based on immunofiltration or immunochromatography principles with dyes or colloid gold as markers have been

developed and applied in field because of its rapid, sensitive and simple advantages. The rapid diagnostic tests commonly used in P.R. China including the dot immunogold filtration assay (DIGFA) where the probe is anti-human IgG labelled with colloidal gold, the dipstick dye immunoassay (DDIA) where it consists of the antigen labelled with a blue colloidal dye and the latex immuno-chromatographic assay (DLIA). The results of the test are revealed by anti-human IgG tagged with red latex particles (Zhu, 2005).

Hu et al. from the NIPD-CTDR has constructed a cDNA library of different stages of schistosomes since 2000 through the research of *S. japonicum* functional genomics (Hu et al., 2003, 2004), and obtained effective recombinant antigen by cDNA library immunoscreening (Lu et al., 2012). Then, they developed a dynamic flow method based on gold standard immunochromatography strip for anti-*S. japonicum* IgG based on the recombinant antigen. The laboratory evaluation showed the assay performed high sensitivity and specificity, and the operation was simple and stable. Currently, this assay has got patent and now transferred to a company to apply certificates from NFDA, considering its potential value for large-scale screening of schistosomiasis in field settings in future.

### **4.1.3 Assessment of diagnostic assays and quality control**

#### **4.1.3.1 Assessment of diagnostic assays**

Assessment of the efficacy, reliability and operational characteristics of diagnostic assays in use are important to ensure the diagnostic accuracy. Being a national institute, NIPD –CTDR has conducted many studies to evaluate the immunodiagnosis assays to provide scientific information for national control programme.

In 1995, the National Center for Schistosomiasis Immunodiagnosis and Testing, funded by the World Bank loan-financed Schistosomiasis Control Project Joint Scientific Research Management Committee, was established. The centre is based on the National Institute of Parasitic Diseases of the Chinese Academy of Preventive Medicine (the former name of the NIPD-CTDR). One of the tasks is to monitor and evaluate the existing diagnostic reagents for schistosomiasis in P.R. China, in order to maintain the quality supervision of existing diagnostic reagents, and select several test systems recommended for on-site use. In 1995 and 1996, the Centre evaluated 12 circulating antigen kits and other nine antibody detection reagents collected by the various units (Xu et al., 2005). These evaluations demonstrated that the CAg kits evaluated were inappropriate for use by the schistosomiasis control programme at that time, especially in endemic areas

characterized by low-level infections. On the contrary, most antibody-based detection kits had specificities over 90% and sensitivities higher than 80% in chronic infection. The results of these evaluations suggest that the detection of antibodies should consider the value of their efficacy assessment, and further researches are needed on component antigens, short-range antibodies and their quantitative detection (Feng et al., 1998; Guan and Shi, 1996).

At the beginning of the 21st century, Xu et al. from the NIPD-CTDR conducted a study on the detection of *S. japonicum* antibodies by colloidal gold immuno-infiltration (DIGFA) and on-site evaluation. The results of laboratory and on-site evaluation showed that the colloidal gold diafiltration method and F-ELISA method were sensitive. There was no significant difference between the sensitivity and the specificity ( $P > 0.05$ ), and the two methods had high consistency (Xu et al., 2006). Subsequently, the NIPD-CTDR combined with the provincial schistosomiasis control system to evaluate the performance of the colloidal dye test strip method (DDIA) in the low-endemic area (Xu et al., 2011a). The results showed high sensitivity, but the specificity is only 53.08%, because these two methods are simple, fast and sensitive, they are suitable for the screening of schistosomiasis patients.

In 2005, the NIPD-CTDR organized a comprehensive evaluation of nine reagents from eight institutions used for national schistosomiasis surveillance. The sensitivities and specificities of some kits have reached the field application standards, and a kit with better comprehensive evaluation indicators was recommended as a screening tool in the national surveillance sites. (Xu et al., 2007).

In 2008, funded by TDR/WHO, the NIPD-CTDR carried out a two-step evaluation for existing immunodiagnostic reagents for schistosomiasis diagnostic. In laboratory evaluation stage, 10 kinds of immunodiagnostic reagent widely used in the field, such as ELISA, IHA, DDIA, DIGFA, etc., were assessed using archived serum samples. The results show that the sensitivity and specificity of most reagents reached more than 90%. The field evaluation for five excellent diagnostic reagents selected through laboratory evaluation proved that these antibody-based assays were acceptable as tools for community survey, targeting chemotherapy, monitoring and elimination verification (Xu et al., 2011b; Zhou et al., 2011).

Before 2008, the State Food and Drug Administration (SFDA) in P.R. China used many assays for schistosomiasis diagnosis without having passed certification. However, the evaluations carried out previously provided data for the manufacturer to apply for licence from NFDA. Until now, at least 9 kits have been commercial available in P.R. China market,

which indicates that the quality of the assays is improving under the NIPD-CTDR's monitoring and management.

It should finally mentioned that in 2015, the NIPD-CTDR and Leiden University jointly conducted a small-scale field trial for the evaluation of UCP-LF to detect CCA of *S. japonicum* in urine samples in low endemic areas in P.R. China (van Dam et al., 2015). The assay exhibited a much higher sensitivity than that of the Kato-Katz technique and detected a significant number of egg-negative cases.

#### 4.1.3.2 Quality control

In order to strengthening the capacity of control stations/agencies for schistosomiasis diagnostics, since 2009, the NIPD-CTDR organized a diagnostic network platform aiming at establishing a systematically perfect system with disease control institutions at all levels. This platform run through a set of reference or sentinel laboratories for external quality control activities, and also holds training courses to ensure the quality of schistosomiasis prevention and control work in the country (Qin et al., 2013). So far, a national diagnostic centre established in the NIPD-CTDR, it is responsible for assay assessments; external control and improvement of diagnostic quality control scheme; planning and organizing training activities, providing technical support for subordinate laboratories, exploration of the feasibility of molecular biology technology for schistosomiasis monitoring. The isothermal amplification technique developed by the NIPD-CTDR based on this platform has been used in the rapid assessment of the transmission risk of schistosomiasis in the country (Qin et al., 2018). The establishment and improvement of the schistosomiasis diagnosis network system is of great significance to improve the ability of monitoring and early warning of schistosomiasis in P.R. China and to promote the elimination process of schistosomiasis.

## 4.2 Vaccines development

Vaccines are an important means of controlling infectious diseases. In the 20th century, schistosomiasis vaccines were envisaged to prevent from infection with *S. japonicum*. In view of the repeated infections, the possibility of drug-resistant strains of long-term use of praziquantel, and the existence of a large number of mammalian host, schistosomiasis vaccine development could reduce infection rate, worm and eggs burden by inhibiting the invasion, development and reproduction of schistosoma is considered important approach in the control of schistosomiasis. It is expected that vaccine prevention as a long-term control measure to solve the problem of

schistosomiasis. It is of great significance for controlling and blocking the transmission of schistosomiasis and finally eliminating schistosomiasis. The development of schistosomiasis vaccine has gone through the process of exploration from dead vaccine, weak live vaccine, subunit vaccine to genetic engineering vaccine. However, due to the complexity of schistosomes, there is still no effective schistosomiasis vaccine entering the clinic or apply for on-site prevention from infection. Since the 1990s, NIPD-CTDR has carried out a large number of vaccine candidate antigen screening, development, laboratory evaluation and field trials. The main contributions are as follows:

#### **4.2.1 Vaccine candidate antigens**

From the biological point of view and the actual situation of vaccine research, the development of *S. japonicum* vaccine is more difficult than *S. mansoni*. Since the 1990s, with the support of the National “863” Programme, the Prime Minister’s Fund and international cooperation projects, NIPD-CTDR has made great progress in screening, gene cloning, expression and immune protection of schistosomiasis vaccine candidate antigens. NIPD-CTDR researchers firstly carried out the research in collaboration with domestic and abroad experts, on glutathione-S-transferase of the *S. japonicum*, detoxification enzyme-related antigen (Liu et al., 1993; Liu et al., 1997), the triose phosphate isomerase involved in the glycolysis of *S. japonicum*, the hypoxanthine, the natural antigens such as ribose transferase, thioredoxin, more than 90% muscle-related muscle structural proteins, paramyosin and tropomyosin, and the full sequence of the coding genes and recombinant antigens. In addition, other candidate vaccine recombinant antigens, such as myosin, fatty acid binding protein, Mr. 10,000 dynein light chain antigen, Mr. 38,000 muscle-associated protein antigen, glyceraldehyde triphosphate dehydrogenase, Serine protein inhibitors, heat shock proteins, cathepsin B, myosin-like protein, and T, B cell epitope protein antigens of *S. mansoni* Mr. 20,000 were studied (Cao et al., 2005; Chen et al., 2006; Hu et al., 2010; Li et al., 2005; Qi and Liu, 1996; Tong et al., 2007; Yan et al., 2005).

#### **4.2.2 Multivalent vaccines**

*S. japonicum* worm is a compound cell parasite with complex life history and multiple developmental stages. Antigens can be expressed as species-specific or phase-specific. Different antigen molecules have different antigenic determinants, and the types and mechanisms of host immune responses

are incomplete same. The use of multivalent vaccines prepared with different antigens or different epitopes to synergistically induce different immune insecticidal mechanisms may kill schistosomes at multiple developmental stages, possibly overcoming the problem of low levels of immune protection induced by single antigen molecules. In particular, schistosomiasis vaccines can be designed for multiple stages of schistosomes life cycle. The NIPD-CTDR researchers obtained a batch of multivalent vaccine recombinants, and the protective level of multivalent vaccines was significantly improved. In addition, the Sj26GST gene was successfully expressed in combination with the *Escherichia coli* (ETEC) cilia antigen gene (encoding the pili-antigen K99 gene that causes acute diarrhoea in livestock), which can prevent not only diarrhoea in young animals caused by ETEC but also schistosomiasis and has a broad application prospect.

#### **4.2.3 Immunization test on cattle**

Infected livestock is an important source of infection, and it is importance of development of vaccine against schistosomiasis japonica in animals. During the “Tenth Five-Year Plan” period (2001–2005), the multivalent genetic engineering vaccine candidates (multivalent protein vaccine and multivalent DNA vaccine) against *S. japonicum* were developed in the laboratory of the NIPD-CTDR. Based on the preclinical experimental research on the safety, effectiveness and production process of the vaccine, the effectiveness of multivalent vaccine on the on-site immunization of buffalo to interrupt the transmission was observed (He et al., 2002a,b, 2003). Liu et al. vaccinated the recombinant 26 kDa GST (reSjc26GST) in mice and pigs, with a 22.3% reduction in worm numbers, and 50% reduction in faecal egg output and eggs deposited in host tissues. In addition to the anti-fecundity effect, reSjc26GST reduced by nearly 40% the egg-hatching capacity of *S. japonicum* eggs into viable miracidia (Liu et al., 1995). Therefore, the NIPD-CTDR’s researchers applied the reSj26GST to 96 Bos buffalo as experimental group vs 90 buffalo without vaccine as control group in the field to observe its impacts on the endemicity of schistosomiasis. As a result, 20 months after immunization, the infection rate of *S. japonicum* in vaccinated buffalo was 60.4% lower than that before immunization (infection rate reduced from 13.54% to 5.36%), and 67.9% lower than that of the unimmunized bovine control group. After the buffalo was immunized with the reSj26GST antigen, it had a significant egg-reducing effect within the first 3 months of infection, and then the ovulation volume gradually decreased to negative, which was helpful to reduce the spread of schistosomiasis (He et al., 2002a,b).

In summary, during last 7 decades, experts on immunodiagnosis from NIPD-CTDR have carried out long-term research and development of schistosomiasis parasitological and immunological detection technologies suitable for on-site application in P.R. China, continuously improving detection specificity and sensitivity, and optimizing various detection technologies for pathogens and immunity. They have provided accurate diagnostic techniques for on-site diagnosis of schistosomiasis in P.R. China.



## **5. Research and development of drugs and molluscicides**

### **5.1 Drug development for human treatment**

Drug treatment has always been one of the main means of schistosomiasis control measures. Since 1980, the NIPD-CTDR has carried out extensive and in-depth research on clinical pharmacology studies on praziquantel, artemether and artesunate and screening of other anti-schistosomiasis drugs. A fruitful progress obtained initially contributed greatly to the successful implementation of schistosomiasis control in P.R. China.

#### **5.1.1 Praziquantel**

The advent of praziquantel in the 1970s has had a profound impact on the global prevention and control of schistosomiasis (Balén et al., 2007; Davis and Wegner, 1979; Sleight et al., 1998; Tallo et al., 2008; Taylor, 2008). Praziquantel is currently the only effective drug for five *Schistosoma* spp. infections in humans. However, for more than 40 years, the global schistosomiasis prevention and treatment has long relied on the application of praziquantel. People have worried about whether repeated use of praziquantel would induce resistance against schistosomes (Viana et al., 2017; William et al., 2001). Due to the lack of new effective drug replacement drugs, it is necessary to understand the mechanism of action of praziquantel against schistosomiasis. In the past 40 years, scientists and technicians represented by Prof. Xiao Shuhua from the NIPD-CTDR have conducted systematic and in-depth research on praziquantel against Schistosomiasis.

**5.1.1.1 Effect of praziquantel on the nervous system activity of schistosomes**  
Xiao Shuhua et al. explored the mechanism of action of praziquantel-exciting schistosomiasis by using neural media related to worm activity and its blockers. It found that praziquantel neither increased the endogenous 5-HT of the worm nor enhanced its exogenous 5-HT intake, either in vivo

or in vitro. Thus, praziquantel-induced anti-schistosomiasis does not act through 5-HT, but possibly a 5-HT-like or a 5-HT receptor agonist (Xiao et al., 1984). Xiao et al. found in the initial experiment that the action model of praziquantel against schistosomiasis depends on the presence of  $\text{Ca}^{2+}$  that was restricted by  $\text{Mg}^{2+}$  (Xiao et al., 1980). Therefore, under the action of a high concentration of praziquantel, it is difficult to explain the accumulation of  $\text{Ca}^{2+}$  in the worm for a short time (Xiao et al., 1987). Praziquantel causes muscle contracture and cortical damage of schistosomiasis depending on the presence of  $\text{Ca}^{2+}$ , but there is no consensus on how praziquantel acts through  $\text{Ca}^{2+}$ .

#### 5.1.1.2 Effect of praziquantel on the metabolism of schistosomes

For the effect of praziquantel on the metabolism of schistosomes after treated by praziquantel, the study showed that praziquantel not only inhibits the glucose uptake and glycogen synthesis of the worm, but also promotes the glycogenolysis of the worm (Xiao et al., 1985a). Further observation of histochemical methods found that glycogen, alkaline phosphatase and ribonucleic acid was significantly reduced or disappeared, acid phosphatase and basic protein were significantly increased, while deoxyribonucleic acid, tryptophan, histidine, tyrosine Acid, etc. didn't change significantly (Xiao et al., 1985b).

#### 5.1.1.3 Effect of praziquantel on the ultrastructure of different stages of schistosomes

Praziquantel has a strong killing effect on adult worms and cercariae of *S. japonicum*. Two hours after treated by praziquantel at a concentration of 1  $\mu\text{g}/\text{mL}$ , the glycocalyx in the outer surface of tegument decreased markedly or even disappeared and the matrix of tegument became sparse and indistinct with a decrease in membranous vesicles. Meanwhile, the muscle layer beneath the tegument exhibited swelling or lysis, and the mitochondria distributed in the muscle and parenchymal cells showed swelling and degeneration. After 4 h, an extensive lysis of cercariae tissues which resulted in the formation of numerous vacuoles with varying sizes could be seen. No apparent alteration in the ultrastructure of cercariae exposed to praziquantel in normal saline was observed. The ultrastructural changes of schistosomula within mouse skin in worm tegument, muscle and parenchymal tissues were similar to those mentioned above 0.5–24 h after intragastric praziquantel 600 mg/kg to mice infected with cercariae for 3 h (Xiao et al., 1988).



In another experiment, the results obtained in the mice infected with *S. japonicum* at different intensities and treated intragastric with single doses of praziquantel at 300 mg/kg at different durations were similar to the results in the rabbits. The correlation between efficacy and specific antibody level was confirmed by calculating the coefficient of correlation which was  $R=0.45-0.98$  ( $P<0.01$ ). The results also indicated that heavy infectious with *S. japonicum* were still more responsive to praziquantel treatment. In addition, the efficacy of praziquantel was closely related to the specific antibody response in the host (Yue et al., 1989). After praziquantel treatment, the sensitivity of the cercariae to the metabolic inhibitor NaF increased, making NaF easy to infiltrate into the worm body, if it will be treated with praziquantel in water. The cercariae were transferred to the drug-free HBSS for 2 h, and the tegument of the most cercariae returned to normal (Xiao et al., 1991b). When the cercariae is cultured in the serum of the isotonic salt balance solution after praziquantel is removed, the worm body not only can survive but also could develop into schistosomula. Praziquantel has no obvious effect on the worms that developed into schistosomula for 3, 7, 14, and 21 days (Xiao and Catto, 1989). However, a larger dose of praziquantel has a direct killing effect on 21-day larvae (Xiao and Catto, 1989). Praziquantel has a strong killing effect on adult schistosomes (Xiao et al., 1991a). The changes in the surface of schistosomes after praziquantel treatment are not completely consistent, even if the same worm can be mixed with normal tegument and damaged tegument. Body damage caused by damaging the sucker between the mouth is happened later and lighter (Xiao et al., 1992; Xiao et al., 1995). The tegument of schistosomes is rapidly damaged by the action of praziquantel, and the surface antigens of the worm are exposed to the microenvironment of the host which making the worm susceptible attacked by the host immune system. The white blood cells of the host can quickly attach to the damaged surface of the worm, indicating that the specific antibody is involved in action together with praziquantel (Xiao et al., 1997; Zhai et al., 2002). Based on the all research results, the action process of praziquantel includes two aspects, including the direct action of the drug on the worm as well as the immune effect of the host on the worm. The above two aspects are indispensable, but only taking effect when the worm body has been damaged through the action of praziquantel, then the immune effects of the host can play a role in action, thus showing that the direct action of praziquantel on the worms is particularly important in its action process (Xiao et al., 2002b).

#### 5.1.1.4 Comparison of the effects of different structures of praziquantel on schistosomes

Praziquantel is a racemic mixture of levo-praziquantel (L-praziquantel) and dextro-praziquantel (D-praziquantel). Xiao et al. determined the effects of racemic praziquantel, including L-praziquantel and D-praziquantel, on *S. japonicum* in different developmental stages, and found that in L-praziquantel is an active ingredient against *S. japonicum*. Scanning electron microscopic observation on the damage of *S. japonicum* tegument by L-praziquantel and D-praziquantel showed that the actions of the two optical enantiomers of praziquantel were different in quantity but not in quality. The effect of L-praziquantel on worm was better than that in D-praziquantel (Xiao and Shen, 1994).

### 5.1.2 Artemether

Artemether is a new type of anti-malarial sialoin derivative. Since its discovery in the last century, it has demonstrated artemether is effective against *S. japonicum* (Huang et al., 1999; Xiao et al., 2002a). Scientists from NIPD-CTDR have carried out systematic research on the mechanism and treatment trials in the endemic area.

#### 5.1.2.1 Mechanism of action

Artemether has a wide-ranging effect on the glucose metabolism of *S. japonicum* (Huang et al., 1999; Xiao et al., 1987). Hexokinase, phosphoglucose isomerase, phosphofructokinase, glyceraldehyde phosphate dehydrogenase, phosphoglycerate light kinase, acetone involved in glycolysis various enzyme activities such as acid kinase and lactate dehydrogenase were inhibited in various degrees, resulting in a significant decrease in the amount of lactic acid produced. Researches also indicated that artemether has a glycogenolytic action that inhibits schistosome and inhibits its glycolysis (Xiao et al., 1987, 2002a). Subsequent mouse experiments suggest that phosphofructokinase (PFK) may be one of the target enzymes of artemether on the enzymatic pathway of schistosomes (Xiao et al., 2002a). In vitro, the schistosomes were cultured in medium containing artemether and hemin for 24h, or infected mice were treated with artemether 300mg/kg for 6–24h in vivo. Results showed that in vitro, 50  $\mu\text{mol/L}$  of artemether and hemin caused a significant decrease in the total antioxidant capacity of female worms. In vivo, artemether acts on *S. japonicum* for 6h, and the total antioxidant capacity of female worms decreased significant.

Artemether has no effect on the total antioxidant capacity of males in vivo and in vitro (Xiao et al., 2003).

Xiao et al. also found that artemether had significant effects on the ultrastructure of 7 d's and 35 d's adults of *S. japonicum*, which was characterized by fuzzy, loose, dissolved and vacuolar formation in the cortical matrix (Xiao et al., 1988). The outer membrane of cortical cytoplasmic processes was blurred, fused, increased electron density and rupture, as well as degeneration of sensory structures. Muscle bundles, syncytial cells, and intestinal epithelial cells under the cortex can be found to have extensive swelling, dissolution, and vacuolation. Female yolk cells also showed changes in nuclear vacuoles, reduced rough endoplasmic reticulum, and yolk globule lysis. At 14–28 days after treatment, the ultrastructural changes of some surviving worms have been restored, but some worms still show damage. Artemether treatment of schistosomes-infected mice, infected rabbits, dogs, and cattle showed that it has the effect of treating early infection of schistosomes (Xiao and Catto, 1989; Xiao et al., 1987, 1995, 1997, 2002a,b, 2003, 2011).

#### 5.1.2.2 Field trials

In order to evaluate the effect of artemether-preventing schistosomes infection, Xiao et al. first conduct a field study in August–October 1994 in Minglang Village, a schistosomiasis endemic area in the south bank of Dongting Lake located in Hunan Province (Xianyi et al., 2005). Preliminary results showed that oral artemether preventive treatment could significantly reduce the infection rate and intensity, and might prevent the occurrence of acute schistosomiasis. Subsequently, the research team further conducted therapeutic trials in Guichi City, Anhui province (Liu et al., 1997), and in Hanshou county, Hunan Province in 1996 (Tian et al., 1997), and in the severely endemic areas of the Poyang Lake, Jiangxi province (Chen et al., 2006). It indicated that artemether had a good preventive effect on the population of severe schistosomiasis in lake areas, and thus provided a new measure for prevention and control of schistosomiasis in lake region. Furthermore, Xiao et al. further selected Dali County and other mountainous counties to observe the effect of oral artemether to prevent the infection of schistosomes (Xiao et al., 1996). Studies proved that oral artemether had a good preventive effect on schistosomiasis in mountainous endemic areas and could prevent acute schistosomiasis (Wang et al., 1997). Huang et al. (1999) observed that artemether also has a good effect on preventing schistosomiasis in people who were working on boats.

### 5.1.3 Other new anti-schistosomiasis drugs

Artemisinin-based artemether and artesunate are anti-malarial drugs but show effect against *S. mansoni* and *S. japonicum*. Xue et al. compared the effects of seven other antimalarial drugs against *S. japonicum* in vivo and in vitro, and found that quinine and hemin can significantly enhance the anti-schistosome effect in vitro, while pyronaridine in combination with hemin shows antagonism (Xue et al., 2013). Mefloquine has a strong direct insecticidal effect in vitro, and animal experiments have further observed that mefloquine has an inhibitory effect on the formation of granuloma caused by *S. japonicum* eggs (Tao et al., 2015; Xue et al., 2013, 2014). Xiao et al. observed that the synthetic snail adamantane odour oxide (OZ78) has extensive damage to the cortical and subcortical tissues of *S. japonicum* adult worms, including cortical cells, parenchymal tissues, intestinal epithelial cells and yolk cells (Xiao et al., 2018).

## 5.2 Molluscicides development

*Oncomelania* snail is the only intermediate host of *S. japonicum*. Eliminating snails is one of the important measures to control and block the transmission of schistosomiasis (Zhou, 2005). Therefore, snail control is an important component in the national schistosomiasis control programme in P.R. China.

### 5.2.1 Bromoacetamide

In 1980, the NIPD-CTDR first screened and found a new molluscicide, namely bromoacetamide (Zhu et al., 1984). Zhu et al. did experimental studies showed that bromoacetamide has an effective role in killing snails with low toxicity, easily dissolved in water and ease for application in the field (Yin et al., 1986; Zhu and Yin, 1986). The field trials have shown that at the concentration 0.5 ppm of bromoacetamide, the compound had good molluscicidal effect with the means of immersion at 1 ppm, spraying at 1 g/m<sup>2</sup>, and immersion with shoving the canal banks at 1 g/m (Zhu and Yin, 1986). No toxicity effects to fish were observed when the concentration of bromoacetamide used in the field at 6 ppm that was 6 times higher than that used for mollusciciding. Spraying the chemical with molluscicidal dosage could damage to plants, but no toxicity to rice at 10 ppm (Zhu and Yin, 1986). In order to clarify the action mechanism of bromoacetamide, observation was conducted to explore the effects at different concentrations of bromoacetamide on different stages of *Oncomelania* snail. After bromoacetamide treatment, the fecundity of female snails was significantly reduced, and the mature snail ovary was obviously atrophied. When snail

was immersioned with 3H-labelled bromoacetamide, it is observed that bromoacetamide could enter into the snail eggs, with its radioactive content became higher when increased drug concentration (Zhang and Gao, 1992). Experimental results provided an evidence to select appropriate period of season and appropriate concentration of the molluscicide to control snails on site (Zhu et al., 1998). Application of bromoacetamide at the double concentrations of the conventional mollusciciding dose of bromoacetamide sprayed to the fishponds, the clams that were suspended in the ponds were well survived (Yin et al., 1994). Therefore, the drug can be used to kill snails in fish-raising water body (Zhu et al., 1995). The acute oral toxicity of bromoacetamide to mammals is moderately toxic, acute dermal toxicity is low toxicity. The chemical is also no sensitization to the skin, no mutagenic, teratogenic and carcinogenic effects, but irritate to the skin and eye mucosa (Hu et al., 1996). Bromoacetamide is highly degradable in soil and water. Residues in the environment are easily degradable and short-residue pesticides. The use of bromoacetamide to kill snails will not cause residual harm to the environment. Bromoacetamide was included in the World Health Organization's pesticide evaluation plan in 1986 and listed as a scientific and technological research top project in the national R&D programme (1980–1990) (Bao et al., 2011; Zhu et al., 1998).

### 5.2.2 Niclosamide

Niclosamide is the only chemical molluscicide that WHO has retained and recommended since 1972. It is low in toxicity to mammals but poor in water solubility and highly toxic to fish (Li and Wang, 2017; Souza, 1995; Yang et al., 2010). Zhang et al. used niclosamide paste in water body where *Oncomelania* snails habitated, and found that it not only kill some snails but also reduced the infection rate of the snails. Zhu et al. (Zhu et al., 2001) from NIPD-CTDR tested the value of niclosamide combination with local insecticide (shachongding, [dimethylamine] trithacyclohexane hydrochloride) in 1997–1999. When combined use of niclosamide at 0.2 mg/L and shachongding at 0.1 mg/L, the LC<sub>90</sub> for *Oncomelania* snail was 0.198 mg/L, which was slightly better than the molluscicidal effect of niclosamide alone, in addition, this combined practice with two molluscicides can inhibit 92.7% of snail climbing, so as to improve the molluscicidal effect and reduce the cost of mollusciciding. It is a potential alternative to the molluscicides, such as sodium pentachlorophenol and niclosamide, but the mechanism of inhibition of snail climbing by shachongding remains further study. In recent years, niclosamide ethanolamine salt wettable powder has

been gradually promoted and applied in P.R. China, which has improved the molluscicidal effect, but the toxicity of niclosamide ethanolamine salt to fish is difficult to overcome, which restricts its field application (Yang et al., 2010).

### 5.2.3 Development of novel chemical molluscicides

#### 5.2.3.1 Pyrrolidine

Duan et al. synthesized a series of compounds and studied on the chemical mechanism of niclosamide (Duan et al., 2014). It was found that the molluscicidal activity of salicylic acid compound 31, namely pyrrolidine, with its chemical structure as 4-chloro-2-(morpholine-4-carbonyl)phenyl-4'-methoxybenzoate ( $C_{19}H_{18}ClNO_5$ ,  $Mr=375.79$ ), is better than other molluscicides. Bioassays experiments showed its  $IC_{50}=0.15\text{ g/m}^2$ , lower than that of niclosamide ( $IC_{50}=0.25\text{ g/m}^2$ ), and its ( $IC_{50}=10\text{ g/m}^2$ ) toxicity to zebrafish is only 1/40 times lower than that of niclosamide ( $IC_{50}=0.25\text{ g/m}^2$ ), the compound was proved to be less toxic to mammals as the acute toxicity test of mice  $LD_{50}>5000\text{ mg/kg}$  (Wang et al., 2015). This pyrrolidine, a 5-chlorosalicylic acid derivative incorporating morpholine moiety, is conveniently synthesized through two steps and crystallized. Duan et al. further developed pyrrolidine into a formulation of 25% pirosose sulphate wettable powder, and tested the molluscicidal effect in schistosomiasis endemic area in the lake and the mountain region, respectively. The field results showed that the molluscicidal effect of pyrrolidine by using immersion and spraying methods at the concentration of  $1.0\text{ mg/L}$  and  $2.0\text{ g/m}^2$  respectively, is comparable to that of niclosamide ethanolamine salt wettable powder, and it is low-toxic to fish as no dead fish found in the field trail (Luo et al., 2018). Pyrrolidine has several advantages such as simplicity to prepare, high solubility and good dispersibility, and easily mixing with water evenly on site. Further multi-site expansion trials should be conducted to formulate field application technical specifications, and it is expected to develop into a new high efficient, low toxic, inexpensive molluscicides (Luo et al., 2019).

#### 5.2.3.2 Meta-Li

Meta-Li is a low-toxicity and environmental friendly pesticide produced by Swiss Longsha (Hong Kong) Co., Ltd. Meta-Li is mainly composed of tetraacetaldehyde, which is characterized by rapid degradation and no residue in the environment after administration. Scientists from NIPD-CTDR conducted laboratory and field tests using domestic bioassay method, In on-site spraying tests of Meta-Li, it was showed that the

mortality of snails was over 90% at a concentration of 2 g/m<sup>2</sup> 7 days post spraying. The amine 1 g/m<sup>2</sup> is equivalent and has a significant inhibition of the snail climbing (Zhu et al., 2006). On this basis, the mechanism of mollusciciding was investigated by observing the changes of enzyme activity of snail tissue treated with Meta-Li (40% tetraacetaldehyde). The results show that inhibiting the energy supply of snails which eventually caused the death of snails may be the molluscicidal mechanisms of Meta-Li, so that the relatively long process of energy depletion is one of the reasons for the slower molluscicidal effect after application of Meta-Li (Zhu et al., 2007). Subsequent studies have obtained the safe concentration of Meta-Li on zebrafish, carp fry, *Eriocheir sinensis*, *Macrobrachium nipponense*, *Hyriopsis cumingii*, and river carp, with their LD50 are >10 mg/L in all of them. Based on the requirements for pesticide using in freshwater aquaculture species in P.R. China that needs all low-grade toxicity (LC50 > 10 mg/L), it was indicated that Meta-Li is a safe molluscicide for aquatic organisms when it is used mollusciciding. Due to its low-toxicity and friendly use in environment, it is warranted to conduct further studies on being a molluscicidal candidate (Zhu et al., 2010).

#### 5.2.4 Plant molluscicides

Chemical molluscicides limit their use due to environmental pollution and toxicity to non-target organisms. The use of phytochemical ingredients to kill snails and organic synthesis of new biomolecular molluscicides is currently encouraged with focus on plant molluscicides (Li et al., 2016). *Eucalyptus* tree is a native to Australia and also known as white diesel. Chen et al. tested the molluscicidal effect of the *Eucalyptus* leaves and found that the mortality rates of *Oncomelania hupensis* snails reached 80% with the volatile oil extracted from five species of *Eucalyptus* leaves immersed at the concentrations of 100 mg/L for 48 h, and the mortality rates were both 93.3% with the volatile oil from *Corymbia citriodora* and *Eucalyptus urophylla* leaves. The mortality rate was up to 95% with the chloroform extract, and the mortality rate reached 60% at the concentrations of 10 mg/L for 48 h (Chen et al., 2012). They also found the active components against snails are mainly found in extracts with petroleum ether and chloroform solutions, and the molluscicidal effect of chloroform extracts is better than other organic solvent extracts. The correlation of the main components in 12 extracts of *Eucalyptus camaldulensis* from different month of a year and their molluscicidal activities was performed by the grey relative correlation analysis model with an assistance of the software GTMS 3.0. Results showed that all the dichloromethane extracts of eucalyptus leaves showed excellent

molluscicidal activities, the highest LC<sub>50</sub> was 0.257 mg/L and 0.242 mg/L for the samples in June and July, and the lowest LC<sub>50</sub> was 6.802 mg/L and 5.406 mg/L in December and January, respectively. The structures of 16 main chemical components were demonstrated by gas chromatography-electron impact-mass spectrometry (GC-MS) and NIST Mass Spectral Library, most of which were monoterpenes and sesquiterpenoids. The most of main ingredients in the dichloromethane extracts of *E. camaldulensis* leaves show good correlations with the molluscicidal activity' which suggests that the molluscicidal effects are synergistically made by the multiple components together (Yin et al., 2014). According to WHO's standards for screening plant molluscicides, the five eucalyptus leaves extracts collected from Guangdong province contained higher molluscicidal components. Wang et al. from the NIPD-CTDR also have found that tea seed was effective reagent against *Oncomelania* snails through damaging the gonads and liver of snails (Song et al., 1992; Wang and Song, 1990).

In order to provide safe and effective control methods for control of the intermediate snail host of *Schistosoma japonicum*, the NIPD-CTDR actively carried out the research on the development of molluscicides, in order to provide safe molluscicides for interrupting the transmission of schistosomiasis in P.R. China. Because of the long-term existence of snails in the complex environment in the lakes and mountainous regions in P.R. China, mollusciciding has the characteristics of quick effect, low cost compared to other approaches, but its environmental pollution has been concerned. Over the years, several generations of the NIPD-CTDR researchers have done a lot of pioneering research on application of molluscicides development, which has made a significant contribution to the national schistosomiasis control programme in P.R. China.



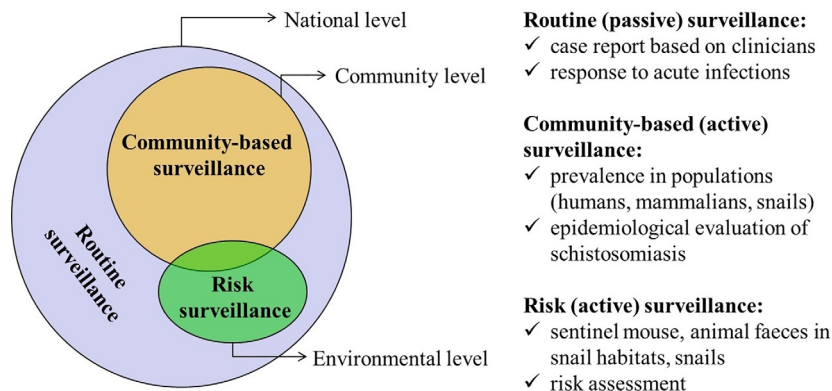
## 6. Monitoring and evaluation

The NIPD-CTDR takes a leading role in monitoring and evaluation for the national schistosomiasis control programme. The institute conducted four times of the national sampling surveys and established a surveillance system to support the control programme (Fig. 2).

### 6.1 National sampling surveys

Four national sampling surveys on schistosomiasis were conducted by NIPD-CTDR in 1989, 1995, 2004 and 2016, respectively (Department of Diseases Control, 2006; Department of Endemic Diseases Control, 1993, 1998).





**Fig. 2** The surveillance system of schistosomiasis in P.R. China.

Successful control of schistosomiasis before 1980 was owing to mass campaign in the era of the planned economic system. However, the reform in rural area at the end of 1970s changed the situation. Schistosomiasis resurged in some areas where the disease transmission had controlled. In order to evaluate the national status of schistosomiasis in time which provide the reference to the decision making in the national control programme, the first national survey was initiated by Ministry of Health in 1989. The estimated prevalence in humans was 10.2% and the inferred infections of human was 1,638,103 people. The survey provided very informative results for formulating the “Eighth Five-year Plan of the national schistosomiasis control programme.

The second national survey was carried out in 1995 in order to evaluate the effect of new control strategy since 1992 when the World Bank Load Project on schistosomiasis control started. Before the initiation of the project the control strategy focussed on shrinking the snail infested areas. The massive drug administration with praziquantel replaced the previous strategy with the advent of praziquantel. The overall prevalence was 4.9% and the estimated number of human cases was 865,084. The survey demonstrated that the new strategy was effective at that time.

The third national survey performed in 2004 under the circumstance that the prevalence in some area increased and acute infections re-occurred, after the World Bank Load Project on schistosomiasis control terminated. The Ministry of Health organized the third survey in order to understand the situation and prepare for the long-term action plan. The survey revealed an overall prevalence of 2.5% and the inferred human infections were 726,112. The decline pattern of the prevalence had slowed down from 1995 to 2004, which requiring the new strategy to be adjusted to the

new situation, particularly in the lake region where resurgence happened seriously. This resulted in the effort to develop a new strategy and finally proposed the integrated strategy focussing on control sources of infection (Wang et al., 2009b). Both the results of the third national sampling survey on schistosomiasis prevalence and the new integrated strategy had provided the baseline data and approaches to the national schistosomiasis control programme, which achieved the expected goal to control the transmission with prevalence less than 1% by 2015. The fourth survey, however, focussed on the intermediate host snails due to following reasons: the disease prevalence has been at low level ( $<1\%$ ), potential risk closely related to the distribution of snail habitats remained, and the surveillance system on human infections has fully established since 2004.

The fourth survey had produced a snail distribution map for the first time, showing that appropriately 400 thousand of snail habitats in the whole country, including all historical and existing habitats. The results will be informative to assess the emergence and re-emergence of *O. hupensis* and thus to prepare the further control plan.

## 6.2 Routine control programme

The tasks for the NIPD-CTDR in routine control programme on schistosomiasis varied in different stages. In the mid-1950s when the national control programme commenced, the institute was in charge of collecting annual data pertaining infections and treatments of humans, cattle and snails as well as the elimination process at county level. After 1985, the institute also took the responsibility to draft the annual report on schistosomiasis prevalence in China every year, based on the national schistosomiasis database established. Such database is of importance to provide the basic information for control policy making of the national schistosomiasis control programme.

For a long time before 2011, the data on schistosomiasis prevalence was submitted to the NIPD-CTDR by provincial department of schistosomiasis control in paper or later in electronic sheets manually. The NIPD-CTDR constructed a Reporting System for Parasitic Disease Prevention and Control to improve the timeliness and accuracy of data, and realized the network report of the data (Zhang et al., 2016b). The information system was officially launched in 2011, which mainly included data on schistosomiasis control and schistosomiasis surveillance work. The reporting system covered the users from different levels, from provincial and municipality users to counties (or districts) and townships users. Level-by-level management

mode was adopted to manage the data systems and users. The system is divided into four modules according to its functions: data collection, statistical analysis, data management and system management. Data on schistosomiasis epidemic situation and control works could be collected, and can be used for the evaluation of the national control programmes at different levels through these four modules.

### 6.3 Schistosomiasis surveillance system

The revised Chinese Law of Prevention and Treatment of Infectious Diseases (version 2004) up-graded schistosomiasis from C catalogue to B catalogue in the national notifiable infectious disease list of China. Accordingly, schistosomiasis cases based on the national criteria of schistosomiasis diagnosis must be reported within 24 h after diagnosis. In order to push forward the internet-based health information system and strengthen management on infectious diseases, China CDC has launched the the National Notifiable Disease Reporting System (NNDRS) since 2004 (Dai et al., 2019b; Li et al., 2010). In contrast to the data collected from the departments of schistosomiasis control as described in the part of 6.2 of this Chapter, the human cases are normally reported by clinician through the NNDRS. The NNDRS is currently mainly used for response to submit the information of acute infections and parasitologically diagnosed cases. The message on case reporting is automatically sent to mobile phone of users once information of an acute case was submitted into this system. NIPD-CTDR staff is responsible to clarifying the cases and accomplish the annual report based on the information downloading from the NNDRS.

Community-based sentinel surveillance is one key part of national schistosomiasis surveillance system. The community-based sentinel surveillance for a purpose of epidemiological observation commenced since early 1990s. There were only 13 communities in the sentinel surveillance system in the beginning of setting up those communities as the national sentinel surveillance sites in early 1990s. The First Shanghai Medicine University (now the Medicine School of Fudan University) was responsible for running the sentinel surveillance system (Zhou et al., 2005b). After the China CDC was set up, and the central government transfer payment system for the disease control programme was initiated, the NIPD-CTDR took the responsibility to manage the community-based sentinel surveillance since 2005. The sentinel surveillance sites increased to 80 communities in 2005, and extended to the potential endemic areas for the sentinel surveillance since 2013.

Therefore, a meeting on surveillance of potential endemic areas of schistosomiasis was held in 2013, with the outcome documents of Surveillance Plan from 2013 to 2018 in Potential Endemic Areas of Schistosomiasis and its implementation protocols was formulated also. At the same time, the quality control and evaluation programme for schistosomiasis sentinel surveillance was issued. With the significant reduction of schistosomiasis prevalence, all 450 endemic counties in P.R. China are involved in the sentinel surveillance system by selecting one community in each county as the sentinel sites since 2014. In the sentinel community each county, the active surveillance was conducted based on the standard protocol, including infections in human, domestic animals and snails. The NIPD-CTDR prepared the guideline and control the quality for the community-based sentinel surveillance.

Risk assessment was initiated in the face of declining infection rate and density and normally conducted in the highly potential transmission environment along the lakes or rivers. In contrast to the community-based sentinel surveillance, the risk assessment focussed on identifying the potential contamination of *S. japonicum* cercariae in water body by sentinel mice, looking for the infective animal faeces in snail habitats, and screening the infected snails by molecular technology, such as LAMP. The NIPD-CTDR collected the data under the help of local departments of schistosomiasis control and conducted the risk assessment annually.

## 6.4 Early warning and modelling

In order to eliminate schistosomiasis, it is crucial to improve the sensitivity of schistosomiasis surveillance and early warning and to improve the effectiveness of on-site intervention measures in low-prevalence areas. In order to meet the important needs in initiation of the national elimination programme of schistosomiasis, establishment of the surveillance and response system with highly sensitivity and real-time monitoring in the lower prevalence of the disease is necessary. The NIPD-CTDR focussed on three parts, i.e., development of key detecting technologies, upgrading of surveillance technologies, and development of innovative technologies on forecasting transmission risks of schistosomiasis. In addition, those technologies in the surveillance and response system to mitigate the transmission risks of schistosomiasis were applied in the field. Three major innovative achievements were gained as follows: (i) An assessment system on

sero-diagnostics for schistosoma infections were established and quality control systems for diagnosis with networking laboratories were formed (Xu et al., 2011a). An innovative estimation methodology for human infection rate with *S. japonicum* was developed based on the Bayesian model (Wang et al., 2006, 2008), and the optimized strategy for diagnosis and treatment evaluation were developed for the different control stages in national schistosomiasis elimination programme; (ii) A series of surveillance indicators relevant to biological, natural and social factors that affecting the schistosomiasis transmission were developed and optimized (Cao et al., 2013a,b). The spatiotemporal distribution scenarios and transmission patterns of schistosomiasis were explored, and the transmission threshold of transmission under various snail densities were found, which have provided the technical support the formulation of the national schistosomiasis control and elimination programme; (iii) The forecast models along with various indicators relevant to the prediction and analysis of schistosomiasis transmission patterns were developed based on different impact factors and indicators in various endemic areas of schistosomiasis, and networking platform for surveillance and response in highly risk areas of schistosomiasis transmission were established in order to support the quick response activities in mitigation of the outbreaks and special status in schistosomiasis control programme (Wang et al., 2008; Xu et al., 2013).

Therefore, the impact factors related to biological, natural and social determinants in the low transmission areas in the national schistosomiasis elimination programme have been systematically investigated, with the defined key factors relevant to the transmission of schistosomiasis. Surveillance indicating system and innovative technologies for forecast models and predicted response has developed, which provided the technical support to the national schistosomiasis elimination programme. The efficiency and suitability of those developed technologies in surveillance, forecast, and rapid response in the field trials has been verified, after the NIPD-CTDR has provided the tools and updated information to the prevention of schistosomiasis infections in advance, and formulated the goals for the next stage of the national schistosomiasis elimination programme (Lei and Zhou, 2015; Zhang et al., 2016b).

With the more progress on the national schistosomiasis elimination programme which launched in 2014, the prevalence of schistosomiasis in P.R. China is at a very low level. For the purpose of effectively monitor the prevalence of schistosomiasis, the NIPD-CTDR took the leadership in carrying

out schistosomiasis surveillance in P.R. China. Based on the National Infectious Disease Surveillance Network System, a direct network reporting system for schistosomiasis at the national level has been established, which fills in the scope of the national schistosomiasis elimination programme. The advanced surveillance techniques have applied in the monitoring transmission risk factors and implementing of the rapidly assessment of the epidemic risk of schistosomiasis. Accurate prediction and early warning of the transmission trend of schistosomiasis have provided a scientific reference for timely response to the potential schistosomiasis epidemics (Cao et al., 2013a; Xu et al., 2012; Zhou et al., 2007b).



## **7. Technical guidelines and expertise support to the control programme**

Great achievements have been made in the national schistosomiasis control programme in P.R. China, due to profiting from the strong leadership of the government and the formulation and implementation of various government decisions, programmes and plans (Chen and Feng, 1999; Department of Disease Control and Prevention, 2008; Lei and Zhou, 2015; Zhou et al., 2005d, 2007a, 2018). Administrative decision-making is a process of analysis and synthesis from experience to reality and then to the future. It needs sufficient, credible, professional and creative information and suggestions (Pautz, 2011). From this view, the NIPD-CTDR played the role of professional think-tank in the national control programme. As a “thought laboratory” of decision-making organization, the NIPD-CTDR not only provides decision-making consultation for the government, but also provides human resources and intellectual support for field control activities (Kui et al., 2017a,b; Zhang, 2017). The NIPD-CTDR has been committed to comprehensive research of schistosomiasis control, with solid theoretical rationale and high scientific research capability (Tang, 2005). Meanwhile, experts and professionals of NIPD-CTDR have been stationed in the serious endemic areas for a long time, to carry out operational research on multiple pilots in various epidemic types of endemic areas in P.R. China. With familiar with the social and economic development as well as local customs and practices of most endemic areas of schistosomiasis in P.R. China, those scientists from NIPD-CTDR also grasp the real demand and current situation of schistosomiasis control in P.R. China (Cao et al., 2010; Guo and Yu, 2005; Zheng et al., 1996, 2000; Zhou et al., 2008).

## 7.1 Providing technical support as major member agency of the Expert Committee on Schistosomiasis Control

In 1955, the Central Research Committee on Schistosomiasis Control was established in Shanghai (Jia, 1995; Mao, 1960; Zhou et al., 2008), and then NIPD-CTDR fully supports the national comprehensive schistosomiasis survey and pilot programme of control from 1956 to 1957. In May 1987, the Ministry of Health set up the first Consultative Committee of Schistosomiasis Experts (the office located in NIPD-CTDR) (Zheng, 1987), which has been held for the fifth time, the specialists of NIPD-CTDR have served as chairman, committee member and secretary. Since its establishment, the committee has played momentous roles of technical support and policy consultation in coordinating the national key scientific research projects, providing technical guidance and formulating national schistosomiasis control plans, standards, regulations and laws.

## 7.2 Involving in the design and implementation of the national control strategy and work plan

In 2006, the NIPD-CTDR organized experts to assist Legal Affairs Office of the State Council and Ministry of Health in formulating the Regulations on Schistosomiasis Control, which promulgated on April 1, and put into effect on May 1 by The State Council of P.R. China, making schistosomiasis control activities having a law to follow (Anonymous, 2006; Er, 2006; Wang et al., 2009a). NIPD-CTDR has given pertinent opinions or suggestions in the drafting or formulation of national planning in the light of topographical features and current situation of schistosomiasis in P.R. China, especially in core technology steps of goal setting, strategies and measures finalization. The comprehensive strategy to reduce the roles of humans and cattle as sources of *S. japonicum* infection in snails proposed in researches along Poyang Lake has adopted by government as the national strategy for the control of schistosomiasis and rapidly expanded to other endemic provinces (Cao et al., 2014; Wang et al., 2009b). Moreover, the Thirteenth Five-year National Plan has emphasized it for Schistosomiasis Control that this strategy should be adhered to at this stage of national schistosomiasis control (Anonymous, 2017). In 2018, NIPD-CTDR assisted in drafting the part of schistosomiasis control in the Three-year Plan and Action for Endemic Disease Control and Prevention following the important instructions gave by President Xi. The short-term goal of current schistosomiasis control in P.R. China is to effectively control and eliminate the harm of schistosomiasis

and a series of corresponding measures around the goal were put forward (Gao, 2019). Furthermore, experts from NIPD-CTDR attended and provided technical supports in drafting or formulating of several national plans or programmes, such as the Seventh Five-Year Plan for Schistosomiasis Control (1986), the Eighth Five-Year Plan for the Comprehensive Control of Schistosomiasis (1991), the National Medium-and Long-term Strategic Plan for Prevention and Control of Schistosomiasis (2004–2015). NIPD-CTDR took the responsibility to detail the work plan, draft technical guidance, monitor and evaluate the progress of programmes, etc.

### 7.3 Technical support to the response systems

In order to effectively prevent, control and standardize the emergency treatment the outbreak of schistosomiasis, the NIPD-CTDR drafted Emergency Response Trial Plan for Major Outbreak of Schistosomiasis which implemented by the Ministry of Health in 2003. Henceforth, perfected Emergency Plan for Outbreaks of Schistosomiasis for Ministry of Health, complicated of work manual of grass-roots schistosomiasis control personnel for department of Disease Control and provided advice about Trail Plan of Transmission Control and Blocking of Epidemic Relapse for the Schistosomiasis Control Office of the State Council in 2005. With the advancement of schistosomiasis control in P.R. China, the endemic areas of schistosomiasis were facing the demand of achieving standard of disease control. In 2007, NIPD-CTDR participated in the formulation of the Schistosomiasis Prevention and Control Area Achievement Assessment Programme (revised and issued in 2010) for Ministry of Health, and assisted the Schistosomiasis Control Office of the State Council in formulating the Schistosomiasis Control Achievement Assessment Pre-assessment Programme. In 2008, the NIPD-CTDR composed the Handbook for Assessment and Evaluation Achieving Infection Control of Schistosomiasis and then completed of the National schistosomiasis epidemic situation validation programme in 2011. In 2015 and 2018, participated in the compilation of Assessment Draft for the Elimination of Schistosomiasis and Code of Practice for the Elimination of Schistosomiasis. In addition, involved Programme of Joint Control of Schistosomiasis between Ministry of Health, Ministry of Agriculture and Hubei and Hunan province (2009, 2010), Evaluation of Criteria of Transmission Control Scheme in Hubei (2013). Following above files, NIPD-CTDR cooperated with Ministry of Health/NHFPC accomplished transmission control situations evaluation of Jiangsu (2011), Hubei (2013), Hunan, Jiangxi and Anhui (2015), carried out the review of



schistosomiasis elimination in Shanghai, Guangdong, Fujian, Guangxi and Zhejiang in 2016, as well as the field assessment on the standard schistosomiasis interruption in Sichuan (2017) and Hubei province (2018).

#### **7.4 Formulating national criteria related to schistosomiasis control**

The NIPD-CTDR experts were devoted them to drafting and formulating national and health criteria for schistosomiasis control, and revising them with the progress of schistosomiasis control in P.R. China. To improve and standardize the diagnosis work for human schistosomiasis especially for control stations and hospitals staff, the NIPD-CTDR organized famous and skilled experts related schistosomiasis diagnosis and control formulating schistosomiasis diagnosis criteria in 1995 and then revised in 2006. The criteria for the Control and elimination of Schistosomiasis in P.R. China evolution seven editions, experts of the NIPD-CTDR chaired each version's discussion and revision. In fact, the latest three versions were led by the experts of NIPD-CTDR (GB15976-1995, GB15976-2006, GB15976-2015). To provide guidance for snails survey for schistosomiasis control stations or institutes, NIPD-CTDR chaired the draft of the criteria for snail survey and the criteria was issued in 2017. In 2018, the experts of the NIPD-CTDR participated in the preparation of "In-direct Erythrocyte Agglutination Test for Schistosomiasis Antibody Detection in Japan (WS/T630-2018).

#### **7.5 Attending field investigation to provide accurate information for policy makers**

From 2004, the NIPD-CTDR dispatch technicians to participate in the investigation and guidance of the State Council's spring investigation of schistosomiasis prevention every year. To understand the real situation of schistosomiasis endemicity and control activities, the NIPD-CTDR organized the activities on rapid risk assessment of the disease transmission in seven major endemic provinces of the lake and mountainous regions since 2012, and also coordinated the field investigation in secret to master the real situation of the disease transmission since 2016, all of which provided the evidence to monitor the programme at all level through the State Council's spring investigation (Zhou et al., 2018). In addition, the NIPD-CTDR conducted rapid assessments on extreme drought effects on Dongting and Poyang Lake at 2011, and a survey on imported schistosomiasis to assess the potential risks of imported schistosomiasis in 2012 etc.

It is honoured for the NIPD-CTDR to bring the top best experts in the country together making efforts on schistosomiasis control and research,

and provide theoretical and practical evidences for the policy making on schistosomiasis control in P.R. China (Zhou et al., 2011). The NIPD-CTDR not only take the synthesis of thought from the expert consultation and demonstration, also provides suggestions for the Chinese government to formulate control plan to design the objectives, policies, measures, and national control standards for the national schistosomiasis control and elimination programmes (Zhou et al., 2010).



## 8. Conclusion and Perspectives

Schistosomiasis japonica has been prevalent in P.R. China for at least 2000 years. The disease mainly distributes in 12 provinces (autonomous regions and municipalities) along and to the south of the Yangtze River. After 70 years of activities in control and research, the NIPD-CTDR has mastered the epidemic situation of schistosomiasis in P.R. China, the distribution of snails, and explored the strategies and measures suitable for different environmental areas (Chen et al., 2020; Zhen and Bin, 2017). Life cycle and transmission patterns of schistosomiasis have been understood well by Chinese scientists, advanced research based on genomics conducted by the NIPD-CTDR made it possible to explore high-efficiency and low-toxicity therapeutic drugs and molluscicidal drugs, laid foundations for developing new diagnostic tools and vaccine candidates. Lessons and experiences were accumulated through the 70 years' control practices for the NIPD-CTDR to be as the only national institute specific for parasitic diseases in the country (Zhou et al., 2005a). The needs of the control programme in development of strategies, intervention measures, diagnostic techniques, monitoring or early warning have changed with the development of social-economic systems and health systems in the country. These changes require our more efforts on the research to develop new tools used in the control programme (Zhen and Bin, 2017). At the same time, the lessons and experience accumulated need to be distilled for guiding further control activities, through reviewing archived documents, publishing more articles or books, and interviewing the senior scholars who attended the national schistosomiasis control activities in early stage.

The strategic plan for the Healthy China 2030 set the goal to eliminate schistosomiasis in all endemic counties in P.R. China by 2030. To realize this final goal, the NIPD-CTDR sustains the capacity to provide technical support to the control and research activities as follows: Firstly, sensitive and rapid surveillance-response system should strengthen to understand the

endemic tendency of schistosomiasis timely and provide evidence for elimination (Feng et al., 2016). Secondly, regulations and guidelines related to schistosomiasis modify to adapt to current situation and requirements and schistosomiasis has moving to very low infection rate and infection intensity (Zhou et al., 2007c). Thirdly, basic and applied research to meet the requirements of schistosomiasis elimination programme need to continuously perform at advanced level (Zhou et al., 2015), such as advance of sensitive molecular diagnostic tools for environmental risk assessments, establishment minimized surveillance database or indicators for early warning, development of more environmental friendly molluscicides for snail control etc. Fourthly, capacity building for schistosomiasis control and research not only for Chinese but also other countries' professionals need to be strengthened, to keep a workforce involving in schistosomiasis elimination campaign in P.R. China and contribute to the China-African cooperation programme for schistosomiasis control along the "One Belt and One Road Initiative" (Chen et al., 2020).

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