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Miscellaneous

Conquering schistosomiasis in China: the long march

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Abstract

The last half-century of schistosomiasis control activities in China have brought down the overall prevalence of human infection with *Schistosoma japonicum* to less than 10% of the level initially documented in the mid 1950s. Importantly, this reduction is not only, or even mainly, due to the advent of praziquantel in the 1970s and its subsequent dramatic fall in price. Instead, it is the result of a sustained, multifaceted national strategy, adapted to different eco-epidemiological settings, which has been versatile enough to permit subtle adjustments over time as the nature of the challenge changed. Consequently, prevalence has been falling relatively smoothly over the whole period rather than suddenly dropping when mass chemotherapy became feasible. Thus, early recognition of the huge public health and economic significance of the disease, and the corresponding political will to do something about it, underpinned this success. In addition, intersectoral collaboration and community participation played important roles in forming a sustained commitment to a working control strategy based on local resources. The unfolding story is presented from the early years' strong focus on snail control, by means of environmental management, to the last period of praziquantel-based morbidity control carried out under the 10-year World Bank Loan Project (WBLP). An important legacy of the WBLP is the understanding that a research component would sustain control measures and enable future progress. We are now witnessing the payoffs of this forward thinking in the form of a new promising class of drugs, improved diagnostics, and budding vaccine development in addition to novel ways of disease risk prediction and transmission control using satellite-based remote sensing. Different aspects of social and economic approaches are also covered and the importance of health promotion and education is emphasized. Issuing from the review is a set of recommendations, which might further consolidate current control activities, with the ultimate aim to eliminate schistosomiasis from the Chinese mainland.

Keywords: Schistosomiasis; *Schistosoma japonicum*; *Oncomelania hupensis*; China; Morbidity; Transmission; Control; Chemotherapy; Praziquantel; Artemisinins; Diagnostics; Epidemiology; Vaccines; Geographic information systems; Socio-economic research; Health promotion and education

1. Introduction

Achievements in schistosomiasis control in China have reduced by more than 90% the peak estimates of human prevalence in the mid 1950s, which varies between 10.5 and 11.8 million (Mao and Shao, 1982; Chen and Feng, 1999). The reasons include early recognition of the huge public health and economic significance of the disease, sustained commitment to a working control strategy based on local resources and, not least, political will (Maegraith, 1958; Mao and Shao, 1982; Chitsulo et al., 2000; Engels et al., 2002; Utzinger et al., 2003a). However, the success depends also on effective delivery, intersectoral collaboration – especially between the health and agriculture, water conservancy, forestry

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and education sectors – community participation, and a strong emphasis on environmental management for control of the intermediate host snail, i.e. *Oncomelania hupensis* (Maegraith, 1958; Mao and Shao, 1982; Chen and Feng, 1999). In addition, interventions were usually implemented in an integrated fashion and readily adapted to local eco-epidemiological settings (Mao and Shao, 1982; Chen, 2002). In the early 1990s, further impetus was added through the launch of the 10-year World Bank Loan Project (WBLP) that particularly emphasized praziquantel-based morbidity control (Yuan et al., 2000a; Chen et al., 2005).

There is now optimism in informed Chinese public health circles that continued commitment will ultimately lead to the elimination of schistosomiasis. However, this will depend crucially on rigorous implementation of integrated control measures in areas where *Schistosoma japonicum* remains endemic, and the adaption of effective surveillance systems where transmission of the disease has been interrupted. In Japan, elimination of this infection in the human host was reached through emphasis on transmission control by different environmental management interventions (i.e. land reclamation to enhance agricultural production and cementing ditches used for rice irrigation), as well as social and economic development (Tanaka and Tsuji, 1997; Bergquist et al., 2005). Since the late 1970s, China's economy is developing as fast as that of Japan in the 1950s, not only facilitating integrated control of schistosomiasis (Chen et al., 2005), but also improving sanitation and modifying the environment, which are key factors for the observed general decline of mortality.

There are, however, dark clouds on the horizon. Epidemiological data obtained from a national parasitological cluster sample survey and detailed surveillance from 2000 to 2003 in the seven provinces where *S. japonicum* remains endemic, suggest that schistosomiasis is re-emerging (Zhao et al., 2005; Zhou et al., 2005c). The interplay of several factors may explain these observations. First, unusually severe floods along the Yangtze River in 1998 have contributed to a renewed spread of *O. hupensis* (Zhou et al., 2002c). Second, an anti-flood policy has been developed, which calls for the return of reclaimed land to the Dongting Lake and other buffer lakes, plus the relocation of farmers into newly established towns, which has led to altered transmission dynamics of *S. japonicum* (Chen, 2002; Jiang et al., 2002; Zhou et al., 2002b). So far, this policy has resulted in the return and infestation by snails of over 6000 km^2 of land, which had previously been cleared (Chen, 2002). Third, social and economic reforms commencing in the late 1970s changed the way support was provided. While control activities were previously funded by county, province and central level, support now is granted by local government (Jiang et al., 2002). Fourth, when the WBLP for schistosomiasis control in China ceased in 2001, the achievements made in research were seldom consolidated and integrated into everyday control activities (Yuan et al., 2000a). Fifth and finally, a recent study carried out in 10 local anti-schistosomiasis control stations in the Hunan province concluded that there has been a shift in emphasis from prevention to clinical services, partially driven by market and health sector reforms (Bian et al., 2004).

Due to the role of the amphibious intermediate host snail in the distribution of schistosomiasis japonica, the control programme finds itself in conflict with water resources developments required by the transformation of society as a whole, a situation exacerberated by man-made climate change. It is quite probable that the Three Gorges dam and the South-to-North water transfer project will create new habitats for *O. hupensis* while population movements from non-endemic to endemic areas have already caused new infections (Xu et al., 2000; Yang et al., 2005a). Alarmingly, China's average January temperature has increased by almost 1 °C over the past 30 years (Yang et al., 2005b). This tendency could be an expression of the global warming scenario, blamed for significant temperature increases over the past decades, particularly in the northern hemisphere and during the winter months (Easterling et al., 1997; IPCC, 2001). Since disease transmission dynamics is sensitive to the temperatures at the boundaries of endemic areas (Sutherst, 2004) and the distribution of *O. hupensis* is effectively limited by the temperature of the coldest month of the year (Zhou et al., 2002d; Yang et al., 2005b), even a slight elevation of the mean temperature could contribute to spreading *O. hupensis* further north.

This special issue of *Acta Tropica*, devoted to the control of schistosomiasis in China, is an attempt to provide information stemming from a full half-century of integrated disease control based on insights from clinical, economic, epidemiological, malacological and public health research. The overriding aim is to make this information, often only available in the Chinese literature, readily accessible to the broader scientific community. As depicted in Fig. 1, the issues discussed cover a wide array of topics, not only including the development of new ideas regarding tools for control, but also options for delivery of chemotherapy and the role of domestic animals in disease transmission. Discussed as well are the implementation of sound surveillance systems based

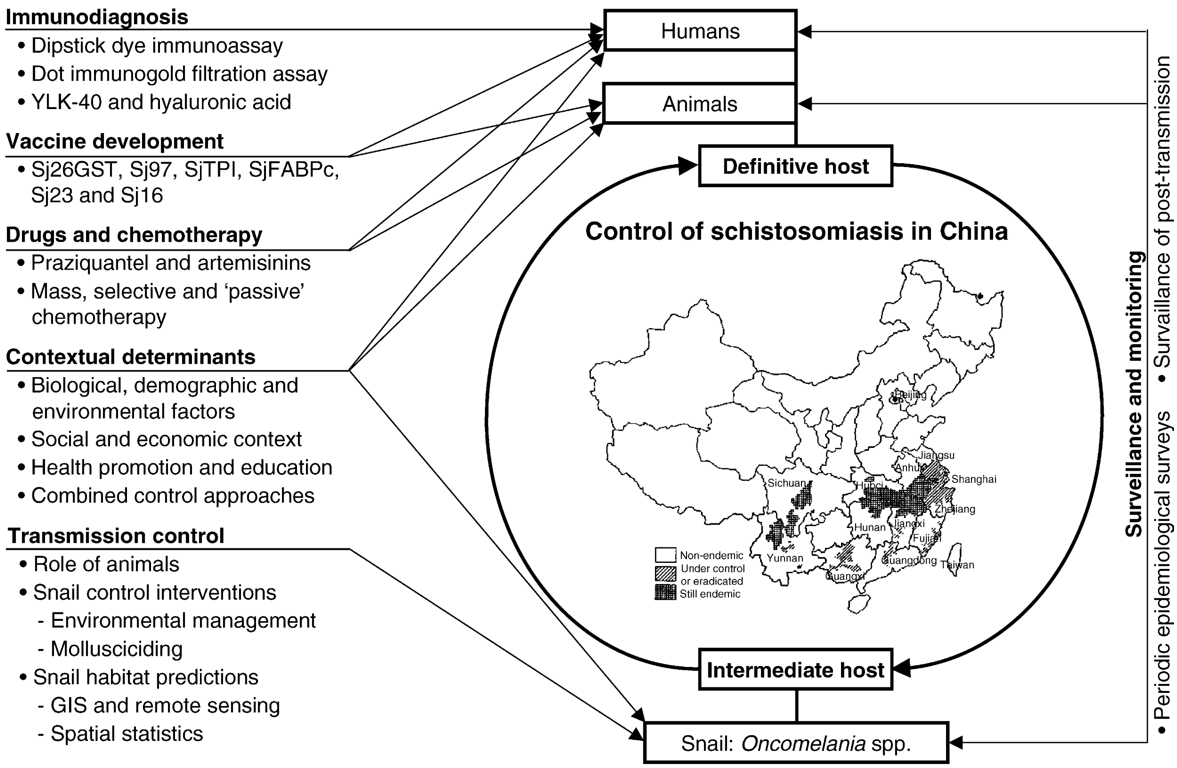

Fig. 1. Topics covered in this special issue of *Acta Tropica* with an emphasis on how they impact the life cycle of *S. japonicum* (source of map depicting the endemic areas and progress made since the mid 1950s: Chen and Feng (1999)).

on geographic information systems (GIS), remote sensing and spatial statistical approaches for *O. hupensis* habitat predictions. This special issue brings together 25 contributions, all of which have been developed by Chinese scientists, public health specialists, Ministry of Health personnel and provincial staff of the local anti-schistosomiasis control stations. Some of the authors have devoted their entire academic careers to enhance our understanding of the epidemiology of schistosomiasis japonica, and have facilitated the development of important new tools and strategies to control and ultimately eliminate the disease, paying tribute to the late Mao Zedong's famous poem entitled "Farewell, God of Plague".

2. Recognizing the problem and responding to it

2.1. Once upon a time

The presence of schistosomiasis japonica in China has been documented for more than two millennia and most probably was known as a specific disease in historic times. Two old corpses, one buried in Changsha county, Hunan province and the other in Jianglin county, Hubei province, were exhumed in the 1970s and scientists successfully recovered *S. japonicum* eggs from the liver tissue (Mao and Shao, 1982; Chen and Feng, 1999). However, it was not until 1905 that the first parasitologically confirmed case of schistosomiasis japonica was described (Logan, 1905). Over the next 35 years, schistosomiasis was confirmed in a total of 12 provinces (Zhou et al., 2005c).

The wide distribution of schistosomiasis japonica in China was acknowledged in an early review of its epidemiology, defining important disease foci along the Yangtze River basin, the lake regions, and mountainous areas in the provinces of Sichuan and Yunnan with endemic areas at altitudes above 2000 m (Mao, 1948). This report showed that the disease was restricted to areas where the mean annual precipitation ranges between 1000 and 1600 mm, winter temperatures rarely drop below the freezing point, and the soils are rich in organic content. The wide spectrum of definitive hosts other than humans – i.e. 43 mammalian species, with buffaloes, cattle, goats, sheep, rats, dogs and cats playing particularly important roles (Chen and Mott,

1988) – and the amphibious nature of *O. hupensis* was stressed. On the basis of limited hospital-based data and fragmentary epidemiological survey reports, it was estimated that in 1947 schistosomiasis japonica was endemic in 138 counties. The rural population at that time in those counties was approximately 25.3 million, which was considered the at-risk population. The estimated number of people infected with *S. japonicum* was 5.3 million (Mao, 1948). However, using different sources and province-specific prevalence data, considerably higher estimates of the number of people infected and at-risk populations were put forward (Stoll, 1947; Wright, 1950). The latter author estimated that 32.8 million Chinese were infected with *S. japonicum* in the late 1940s. Despite these large discrepancies, it was widely acknowledged that schistosomiasis-related morbidity, including mortality, was substantial and that the disease caused social and economic hardship (Mao, 1948; Maegraith, 1958; Mao and Shao, 1982; Chen and Feng, 1999; Zhou et al., 2005c). These early studies had also revealed that infection was primarily governed by occupational risk factors of rice-field farmers, fishermen and boatmen, all identified as high-risk groups (Mao, 1948).

2.2. *Launch of the national control programme*

Recognizing the enormous public health and economic significance of schistosomiasis japonica, disease control became an important focus in the wake of the founding of the People's Republic of China in 1949. The Chinese Communist Party and its Central Committee was strongly committed to halt the suffering of their working population. As a first step, health education campaigns were launched in the mid 1950s. People living in the southern part of China were invited to report the presence of the "devil snail" (i.e. *O. hupensis*) and the number of patients in their villages, recording in particular the number of children with "big bellies". Next, special teams were sent to the identified villages and broad-based malacological and parasitological surveys were carried out. The presence of *O. hupensis* and patients suffering from schistosomiasis japonica were confirmed in 345 counties located in 12 provinces, including the autonomous region of Guangxi and the municipality of Shanghai (Mao and Shao, 1982). Table 1 summarises historical data with regard to the number of people infected (cumulative figures from the mid 1950s to the early 1980s) and the snail-infested area (Mao, 1990).

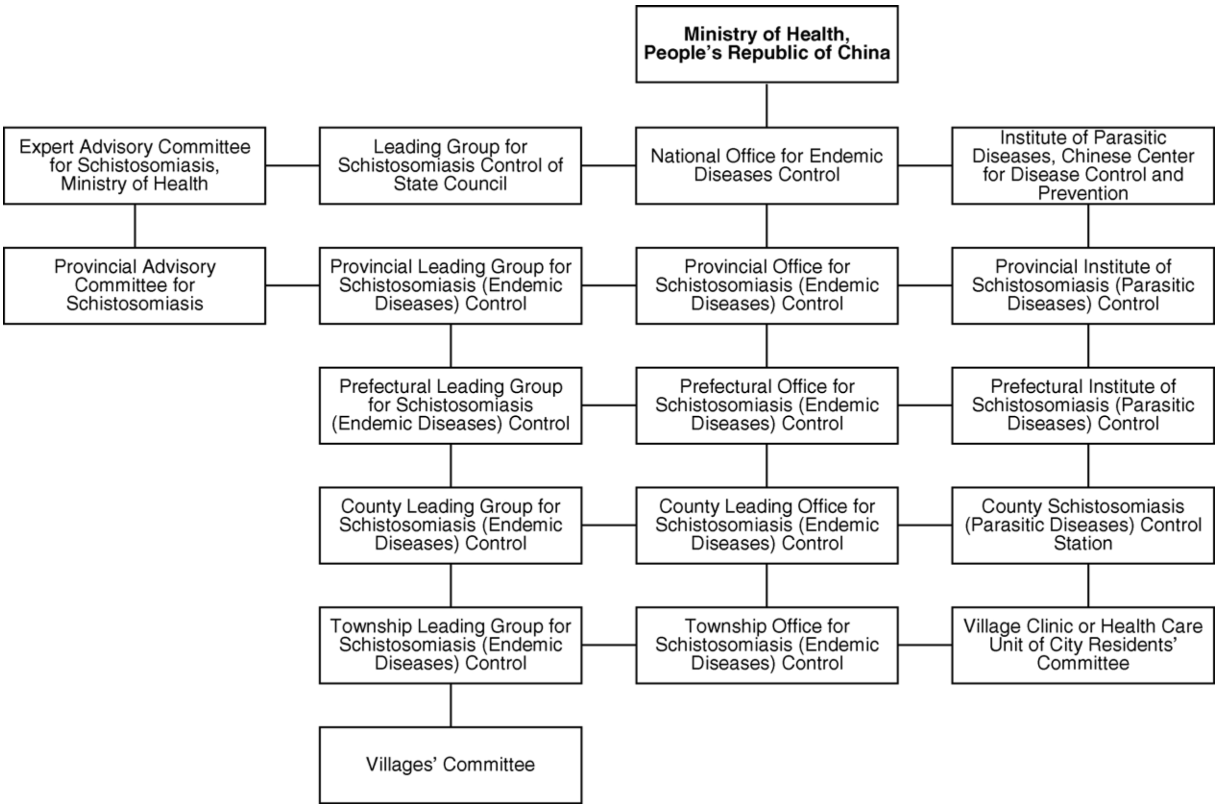

Fig. 2. Organizational structure of schistosomiasis control at different levels in China.

Table 1
Progress made in the control of schistosomiasis japonica in China between the mid 1950s and 2003

Situation in the mid 1950s					Situation in 2003							
Province	Endemic counties	Number of cases[a]		Snail-infested areas (ha)	Endemic counties where transmission is				Number of cases			Snail-infested areas (ha)
		Total	Advanced		Interrupted	Controlled	On-going	Re-emerging	Total	Advanced	Acute	
Anhui	44	846,329	30,091	125,198	14	13	14	10	60,647	5640	256	29,000
Fujian	16	67,777	2012	2724	16	–	–	–	0			
Guangdong	12	78,197	3407	9696	12	–	–	–	0			
Guangxi	19	76,854	1379	2612	19	–	–	–	0			
Hubei	44	2,125,096	73,619	424,273	23	10	25	9	295,383	4257	247	81,000
Hunan	37	923,405	29,110	354,307	6	1	27	2	205,461	5408	234	175,000
Jiangsu	45	2,465,341	89,947	139,335	49	7	15	1	25,438	2781	116	8000
Jiangxi	35	537,337	27,493	236,796	19	9	11	1	131,253	3659	126	78,000
Shanghai	9	759,287	20,451	16,648	9	–	–	–	0		2[b]	
Sichuan	62	1,134,493	9922	25,105	27	20	15	8	76,888	1509	58	7000
Yunnan	17	286,545	1355	21,257	12	3	3	7	46,750		73	2000
Zhejiang	54	2,035,137	68,162	64,230	54	–	–	–	1,189	1,187	2[b]	
Total	351	11,335,798	357,038	1,421,287	150	63	110	38	843,011	24,441	1114	380,000

[a] Cumulative numbers from the mid 1950s to 1981 (source: Mao (1990)).
[b] Imported cases from other *S. japonicum*-endemic provinces.

Mao and Shao (1982) report that the estimated number of people infected with *S. japonicum* was 10.5 million, while Chen and Feng (1999) mention 11.8 million. Whatever estimate is closest to the true figure will never be known for sure but one can safely say that prevalence rates in affected provinces were very high. Once this became clear to the authorities, research and operational structures were set-up at different administrative levels to implement concerted control activities (Maegraith, 1958; Chen, 1989). The overall structure is depicted in Fig. 2. At the national level, the 'Expert Advisory Committee for Schistosomiasis', the 'Leading Group for Schistosomiasis Control of State Council' and the 'National Office for Endemic Diseases Control' were put in place. At the provincial level, the 'Provincial Advisory Committee for Schistosomiasis', the 'Provincial Leading Group for Schistosomiasis (Endemic Diseases) Control' and the 'Provincial Office for Schistosomiasis (Endemic Diseases) Control' were created. At the prefecture, county and township levels, special leading groups, offices and institutes were established to carry out the day-to-day control measures according to the higher-level plans of action. The history and evolution of the Institute for Parasitic Diseases, Chinese Center for Disease Control and Prevention is detailed in another contribution published in this special issue of *Acta Tropica* (Zhou et al., 2005a).

2.3. A broad-based attack on the intermediate host snail

The early control strategy included free diagnosis plus treatment, a wide array of snail control measures adapted to the main eco-epidemiological situations, improved access to water supply, better sanitation and health education to foster personal hygiene (Maegraith, 1958; Mao and Shao, 1982; Chen and Feng, 1999; Lin et al., 2005). In rivers of the plains and in the smaller streams of hilly regions, breeding places of *O. hupensis* are found mainly along banks of water bodies confined to an area located approximately 1 m above and below the water level. Burying the snails under a thick layer of soil proved highly efficacious. When molluscicides were applied before burying, the effect was further accelerated (Mao and Shao, 1982). Another simple and effective means for exterminating intermediate host snails consisted of filling old irrigation ditches with the freshly dug-out soil of new ones. Lowering the water level of canals and tributaries of important rivers facilitated the shovelling off of the surface soil containing the snails. In marshland and lake regions, where the habitats accounted for over 80% of the total area, different environmental management interventions were implemented, for example, modification of breeding habitats through construction of dykes and fish ponds.

In summary, although a large number of infected people received treatment from the mid 1950s through the mid 1980s, the emphasis of China's national schistosomiasis control programme was fully focused on transmission control in line with the global control strategy at the time (WHO, 1985). As a result, besides curing a large number of patients, the snail-infested areas were reduced by more than two-thirds (Mao and Shao, 1982). Towards the end of the 1980s, the disease had been eliminated in four previously *S. japonicum*-endemic provinces, namely Guangdong (1985), Shanghai (1985), Fujian (1987) and Guangxi (1989) (Zhou et al., 2005c). However, although transmission was under control in numerous counties and the national criteria for transmission interruption had been reached in some areas, it was still endemic in eight other provinces. By the end of the snail control era, on the basis of the first national sampling survey carried out in 1989 by means of a stratified randomised sampling of 1% of the population living in endemic areas, the estimated number of people infected with *S. japonicum* had been reduced to an estimated 1.52–1.64 million (Zhen, 1993; Chen and Feng, 1999).

2.4. Shift from transmission control to morbidity control

Following the advent of praziquantel, a conceptual shift occurred in the global strategy of schistosomiasis control changing from transmission to morbidity control (WHO, 1985, 1993). Discovered in the 1970s, praziquantel is a safe, orally active, broad-spectrum and highly efficacious antischistosomal drug (Gönnert and Andrews, 1977; Groll, 1984). The specific contributions from Chinese scientists to enhance our understanding of the antischistosomal properties of praziquantel have been reviewed for this special issue by Xiao (2005) and are briefly summarized in Section 5. In a companion piece (Chen, 2005), also published in this issue, the successful application of praziquantel for clinical treatment and community-based morbidity control of schistosomiasis japonica is reviewed.

2.5. The World Bank Loan Project (WBLP) for schistosomiasis control

Additional impetus for schistosomiasis control in China was gained in the 1990s when the World Bank committed US$ 71 million in the form of a loan to China and the Government of the People's Republic of China provided a complementary US$ 82 million as counterpart funds for control activities (Yuan et al., 2000a). The WBLP for schistosomiasis control was launched in 1992 and its goal was to enhance morbidity control through large-scale administration of praziquantel to both humans and bovines. Chemotherapy was complemented by health education and snail control by means of environmental management and limited mollusciciding as key strategies to sustain transmission control. The specific objectives were to reduce the prevalence of *S. japonicum* infection in both humans and bovines by at least 40%, and to lower the snail infection rate and the density of infected snails by 50% (Chen et al., 2005). An important feature of the WBLP was the standardised implementation and monitoring of control measures and careful documentation of the achievements made over time, including economic evaluations.

Significant progress was made during the 10-year WBLP. Data obtained from the national evaluation carried out in 1995 revealed that transmission interruption was achieved in the province of Zhejiang (Zhou et al., 2005c). Moreover, the human infection rate, as assessed by egg-positive faecal examinations, decreased from 10.2% in 1989 to 4.9% six years later (a reduction of 52.1%). Over the same period, the average bovine infection rate decreased from 13.3% to 9.1%, which translates to a reduction of 31.8%. In 1995, approximately 865,000 people were estimated to be infected with *S. japonicum* (MOH, 1998). Five years later, this number had further decreased to just below 700,000. In 2001, at the end of the WBLP, transmission had been interrupted or controlled in many counties of the seven provinces where *S. japonicum* remained endemic. A final evaluation was carried out in 2002. Comparison of outcome measures with the designated baseline in 1989 revealed that most of the specific project objectives had been met; i.e. the prevalence in humans had been reduced by 55% and halved in the bovines, while the density of infected *O. hupensis* had been reduced by three-quarters. However, the diminishing trend of snail infections stalled and rates kept fluctuating at a low level rather than disappearing completely (Chen et al., 2005). In conclusion, although schistosomiasis is partly under control in Anhui and Jiangsu and the mountainous regions of Sichuan

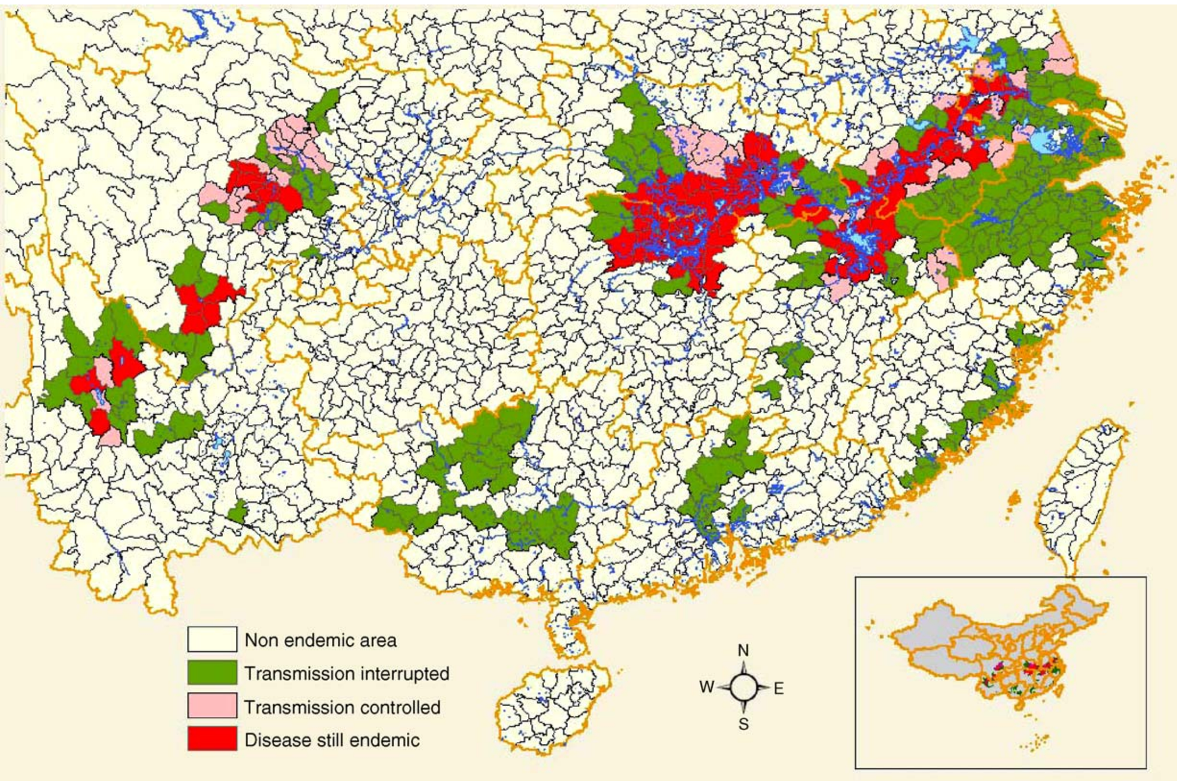

Fig. 3. Map of southern China showing the progress made in the control of schistosomiasis to date at the county level (green colour: transmission interrupted; pink colour: transmission under control; red colour: transmission still ongoing in 2004).

and Yunnan, the frequency and transmission dynamics are still considerable in the lake regions (Hunan, Hubei and Jiangxi) constituting a challenge for the control programme.

2.6. The current situation

Since the end of the WBLP, the number of people infected with *S. japonicum* gradually increased to approximately 850,000 in 2003. In parallel, the number of acute cases had also increased and the snail-infested areas expanded. These trends have been consistently picked-up by the various surveillance systems put in place (summarised in Section 8). Fig. 3 shows the counties where schistosomiasis japonica was still endemic in 2004 (red colour). While the disease was once endemic in 12 provinces and possibly in as many as 433 counties, transmission interruption has been achieved in five provinces and 260 counties (green colour). Furthermore, transmission is under control in 63 counties (pink colour). Table 1 summarises the key achievements made over the same period, with emphasis on active snail habitats and the numbers of people and bovines infected.

In light of these worrying trends, which suggest that schistosomiasis japonica is re-emerging, it is encouraging to note that in 2004 China re-defined its top priorities in communicable disease control, placing schistosomiasis control alongside the fight against HIV/AIDS and tuberculosis (Engels et al., 2005; Zhou et al., 2005). With regard to schistosomiasis, the endemic classifications and the national guidelines for control have been adopted and new ambitious goals have been defined for the next two 5-year periods. In the plain and mountainous regions, transmission is aimed to be under control by 2008, and interrupted by 2015 (Engels et al., 2005; Zhou et al., 2005). In the lake regions, the plan is to achieve control of both infection and transmission by 2008 and 2015, respectively (Engels et al., 2005; Zhou et al., 2005).

2.7. The burden of schistosomiasis japonica

The extent of the schistosomiasis problem in China has been reduced dramatically over the past 50 years which brings us to the question of how one defines and ranks the burden of disease from a global, national and local point of view. In the mid 1990s, an index termed ‘disability adjusted life year’ (DALY) was introduced (Murray, 1994; Murray and Lopez, 1996) which intended to gauge the gap between the current health status and an ideal situation where everyone lives into old age free of disease and disability. However, the DALY score does not fully account for all morbid sequelae such as anaemia, growth retardation and impaired cognitive development. Taking this into account, a WHO expert committee conjured that the ‘true’ burden of schistosomiasis might be as high as 4.5 million DALYs (WHO, 2002), almost three times higher than other official estimates (WHO, 2004). This difference underlines the difficulty in calculating the impact of schistosomiasis. Possible explanations are that: (i) most parasitic infections are chronic and asymptomatic; (ii) some symptoms and signs are non-specific; and (iii) parasitological diagnosis is not sufficiently sensitive to reveal all infections (de Vlas and Gryseels, 1992; Yu et al., 1998; Utzinger et al., 2001a). Indeed, a recent systematic review and meta-analysis of available literature on the subject argues that the burden of schistosomiasis is considerably higher than realized, which not only supports the estimate put forth by the WHO expert committee, but suggests that the ‘true’ burden can be still higher (King et al., 2005; Savioli et al., 2005).

It is envisaged that after revision of DALYs lost due to schistosomiasis japonica, this burden measure could become an essential measure in future schistosomiasis control assessments in China (Li et al., 2005b). This is of relevance as economic considerations have become an important feature of the national schistosomiasis control programme in order to further improving control strategies (Zhou et al., 2005b). The introduction of DALYs in China’s national schistosomiasis control programme is therefore of high priority and warrants thorough investigation.

2.8. Operational research and further integration

Although the national control programme is on a good footing, there is always a need for new ideas and innovative methods to consolidate advances made. International collaboration is a mutually beneficial activity facilitating progress in general and encouraging the training of the next generation of researchers and control staff in particular. The ‘Regional Network for Asian Schistosomiasis’ (RNAS), established in the late 1990 (Leonardo and Bergquist, 2002; Zhou et al., 2002a), has been very useful in this respect and also provides an excellent platform for teaching, and exchange of expertise and experiences.

The suppression of the schistosomiasis problem opens the opportunity to integrate its control with that of other parasitic diseases such as food-borne trematodiasis, soil-transmitted helminthiasis and other parasitic zoonoses (e.g. cysticercosis and echinococcosis).

Particularly, the emerging problem of food-borne trematodiasis, most notable clonorchiasis in China (Keiser and Utzinger, 2005; Lun et al., 2005), is a prominent candidate as assessment and control are accomplished by the same or similar epidemiological surveys and public health interventions.

2.9. Post-transmission schistosomiasis

The suffering caused by schistosomiasis is not over when the disease has been eliminated. For example, there are still a large number of people in Japan suffering from the chronic sequelae of schistosomiasis, although they were cured decades ago. The need for future care for patients with chronic lesions due to previous schistosome infection does not figure prominently in our review, but it has been mentioned by one research group in this special issue of *Acta Tropica* (Wu et al., 2005a). This report mentions that the number of advanced cases in Zhejiang province amounts to 60% of all cases. Table 1 shows that there were more than 24,000 cases of advanced schistosomiasis in China in 2003, which will require care and attention long after the last case of active schistosomiasis has been cured. The whole concept of post-transmission schistosomiasis is a looming problem that is seldom discussed (Giboda and Bergquist, 1999, 2000). However, it will have to be addressed as it will be part of the general public health scenario in China for perhaps as long as another 50–60 years.

3. Progress in vaccine development

3.1. Why a vaccine against schistosomiasis?

Convincing arguments support the likelihood that useful vaccines against schistosome infection can be developed (Taylor, 1994; McManus, 2000; Lebens et al., 2004; Bergquist et al., 2005). These arguments are now compelling thanks to strong and rapid progress in developments such as proteomics (Ashton et al., 2001; Curwen et al., 2004; Wilson et al., 2004; Cheng et al., 2005) and, particularly, the exploration of the schistosome genome databases which is currently expanding at a rapid pace led by researchers in Brazil (Verjovski-Almeida et al., 2003, 2004) and in China (Hu et al., 2003; McManus et al., 2004).

Although a schistosomiasis vaccine would not be 100% effective it is well worth, even necessary, to continue this line of research. The inclusion of a partially effective vaccine into the current praziquantel-based morbidity control strategy against schistosomiasis would add versatility in approach, enhance drug treatment effect and revitalize national plans of action (McManus, 2000; Bergquist et al., 2005). In the case of *S. japonicum*, with bovines and other domestic animals acting as reservoir hosts and substantially contributing to disease transmission (Li et al., 2000; Wang et al., 2005), not only treatment of bovines, but immunization efforts as well would benefit humans, as predicted by mathematical modelling (Williams et al., 2002). However, whether these predictions will hold when implemented in the field remains to be seen.

3.2. S. japonicum vaccine candidates

Vaccine development has been focused on *S. mansoni* antigens purely because its life cycle happens to be established in the majority of schistosomiasis research laboratories. Consequently, *S. japonicum* vaccine development trails that of *S. mansoni*, but the difference is shrinking. The great majority of antigens currently under study are those first reported for *S. mansoni* (Shi et al., 2001; Gan et al., 2004; Liu et al., 2004; McManus and Bartley, 2004; Zhu et al., 2004; Kumagai et al., 2005), but an increasing body of specific *S. japonicum* antigens is appearing, e.g. the 67 kD surface membrane antigen Sj67 (Solomon et al., 2004) and a 13.7 kDa protein (Bian et al., 2001; Hu et al., 2005b). The latter antigen seems to correspond to an immunomodulatory protein present in secretions from *S. mansoni* schistosomula (Bickle and Oldridge, 1999), but the molecular weight is different. The review on *S. japonicum* vaccine candidates in this issue (Wu et al., 2005c) discusses a large number of antigens in different stages of development. The fact that this schistosome species – in contrast to *S. mansoni* and *S. haematobium* – is a zoonosis permits a number of excellent animal models (Chen et al., 2000; Johansen et al., 2000), which are not available in other experimental systems.

Clinical trials with the currently most promising candidates, alone and in combination with chemotherapy, are needed in order to find out to which degree partially effective vaccines could mitigate or markedly delay recurrent pathology. The question of whether or not current vaccine candidates are capable of contributing to the amelioration of rebound morbidity after chemotherapy remains to be answered (Bergquist et al., 2005). As costing is becoming increasingly important, this has sparked an interest in scenario modelling to find the best possible way to tackle the problem (Williams et al., 2002). If a model indicates, as recent research suggests, that the bovine population is indeed more important for transmission to humans than is the human-to-human transmission in China, animal vaccination would be the obvious first step on the road to a human vaccine (McManus, 2000).

3.3. Human correlate studies

The testing for antibodies and cytokine correlates of apparent resistance and apparent susceptibility in relation to specific antigens in human populations is a key approach to establishing reliability and usefulness of vaccine candidates (Bergquist et al., 2002). Further work on the role of cytokine responses in immune modulation, regulation of granulomatous responses and fibrosis (Oliveira et al., 2000; Booth et al., 2004) and the fact that treatment of *S. mansoni* infection increases helminth-specific type 2 cytokine responses and HIV-1 loads in co-infected adults (Brown et al., 2005) do not represent directly vaccine-associated observations, but indicate that cytokine studies are needed for vaccine development. More pointed emphasis on data regarding protective human immune responses and susceptibility to infection is needed and this is now taking place also in China (Wu et al., 2005c).

3.4. Bottlenecks in development

The current problem in vaccine development seems to be that of scale-up and industrial production. The scaling-up of a laboratory product relies on many points in the development pathway, e.g. process development, candidate optimization and formulation. Industrial development of large-scale production is considerably more expensive than laboratory research, but it should be remembered that the capabilities and national regulatory frameworks have improved significantly in several schistosome-endemic countries in recent years. There is also a vested interest of the endemic countries in producing the products they need. For example, the Research Institute of Tropical Medicine (RITM) in the Philippines has acquired a modular turn-key production facility capable of GMP-grade production of a BCG vaccine and is further interested in producing plasma-derived products and there are plans to add a research module for the scaling-up of experimental vaccines. The UNICEF/UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases (TDR) is a strong proponent of this idea and has successfully negotiated partnerships for drug development regarding its target diseases, both in industrialized and developing countries (Ridley, 2003; Bergquist, 2004). China has a clear interest and capability in developing a vaccine against schistosomiasis and is rapidly acquiring a strong economic and industrial capability that could facilitate vaccine production. In order not to be delayed by the problems discussed above, the authorities should already now start to think about industrial vaccine production.

4. Need for better diagnostics

4.1. Diagnostic challenges arising from successful schistosomiasis control programmes

The standard methods for the detection and quantification of egg burdens are the Kato–Katz thick smear stool examination for the intestinal form of the infection (Katz et al., 1972), and urine filtration for urinary schistosomiasis (Plouvier et al., 1975; Mott, 1983). The hatching test improves test sensitivity for intestinal schistosomiasis somewhat and has been widely used in China for several decades (Qiu and Xue, 1990), but it is doubtful if the added time and cost required justify its wider use.

The shift from ubiquitous high egg counts to low-grade intensities of infection presents a problem for the microsopic approach. Given the dilution factor of human excreta and the fact that about half of all parasite eggs never leave the host, the number of eggs found in faeces or urine by currently used diagnostic approaches corresponds to about the same number of worm pairs (Gryseels and de Vlas, 1996). During the last decade, a new classification has been adopted in China which sets 100 eggs per gram of faeces (epg) as the lower limit for a heavy infection; 40–99 epg denote a moderate infection, while 40 epg is the upper limit for a light infection. However, this new classification strains the reliability of microscopy which can miss patients with less than 100 epg altogether if not subjected to multiple stool examinations. It must therefore be concluded that the generally lower infection levels and insensitivity of currently applied diagnostic techniques conspire to produce increasingly inaccurate estimates of disease impact. This threatens the successful drive towards full control of schistosomiasis, an issue of particular relevance in China where the potential risk of false negative results is rapidly becoming important due to the success of its schistosomiasis control programme (Wu, 2002).

4.2. Immunodiagnostic approaches

Currently, the most urgent need is a sensitive and specific assay for monitoring re-infection in areas targeted for elimination and to assess efficacy of chemotherapeutic interventions. Practically useful diagnostic assays should not only have a high sensitivity and specificity, but they should also be inexpensive and reliable.

Serology lends itself to standardisation and can easily be adopted for large-scale screening operations. Testing for serum antibodies is highly sensitive, but titres abate only slowly limiting their usefulness. In addition, it has been argued that the approach is not quantitative and that it cannot differentiate between current and cured infections. Regarding the first argument, recent research suggest that at the population level, antibodies correlate well with egg counts, probably because individual day-to-day and sample-to-sample variations in faecal egg counts average out. In any event, testing for serum antibodies is an excellent means for surveying areas from where the infection has been eliminated. The study of immune responses in young people living in a previously *S. mansoni*-endemic area in Puerto Rico provides a good example (Hillyer et al., 1999). Chinese survey teams have tentatively included a serological approach based on the assumption that it suffices in areas with modest transmission and low expected prevalence. Although this is correct, areas recently brought under control require assessment of cure and incidence of infection or re-infection.

Serology is, however, a wider entity than just antibody testing and can be adapted, by use of specific monoclonal antibodies, for the detection of circulating antigens such as the anodic (CAA) and the cathodic (CCA) schistosome antigens. Both these antigens rapidly reach stable, measurable levels in the infected host (van Lieshout et al., 2000). The great advantage is that they disappear from the host with the parasite, which permits the approach to be used for assessment of cure. In addition, at least one circulating antigen (i.e. CCA) can also be detected in the urine and has been commercialized (van Dam et al., 2004). This has a bearing on the problem of steadily diminishing compliance with regard to stool examination and provision of blood samples. However, the problem with this approach is that it is not much more sensitive than the classical stool examination. In spite of intensive investigations during the past two decades of the use of circulating antigens for the diagnosis of *S. japonicum* infection in China, it has never been implemented on a large scale in the field.

4.3. Comparison of different diagnostic approaches

In contrast to quantifying worm burdens in experimental animals, the diagnosis of human schistosomiasis must always be an indirect approach relying on egg excretion, determination of circulating antigens, specific antibodies, etc. It is, therefore crucial that what is actually measured is accurate. Three parameters decide the assay quality, namely: (i) sensitivity; (ii) specificity; and (iii) reproducibility. When it comes to the actual implementation of a test in the field, the true prevalence decides the predictive value, which is also influenced by the number of people sampled among the target population. In addition, attention must also be paid to the following factors:

- species-specificity;
- purity, and hence requirements of test reagents;
- storage capacity (conditions to be specified);
- suitability for quality-controlled industrial production;
- intellectual property rights;
- availability; and
- cost.

The Kato–Katz technique remains the test of choice for faecal examination. Sensitivity is enhanced by microscopic examination of multiple faecal samples (Yu et al., 1998; Utzinger et al., 2001a), but remains a limiting factor when the intensity of infection is low. A considerably more sensitive approach has been proposed, i.e. the polymerase chain reaction (PCR) which found a prevalence of infection of 38.1% in one faecal sample, while three faecal samples examined by the Kato–Katz method only detected 30.9% (Pontes et al., 2003).

The case for antibody detection is well argued in a recent review article (Doenhoff et al., 2004), which holds that egg antigens have a strong potential both for clinical and epidemiological purposes. Antibody-detection is definitively needed in areas characterised by low levels of transmission and low prevalence, i.e. in countries with successful control programmes such as China. On the other hand, it seems that direct techniques have a role in areas of presumed high prevalence where the lower sensitivity is of less interest than showing whether or not an individual is currently infected. Integration of serology into national control programmes requires collaboration between research laboratories, health service laboratories and epidemiologists, and assays should be defined in terms of sensitivity, specificity, predictive values and reproducibility using sera from clinically well-characterised subjects. Implementation of serological testing with standardised testing systems would permit comparisons between different geographical areas providing a sound basis for decisions regarding national policies.

4.4. Immunodiagnostic tests developed and used in China

From the simple immunodiffusion tests developed half a century ago to the various elaborate immunoassays the step is not far. Many of these are adaptations of already existing assays for other microbiological agents, but several dedicated tests for schistosomiasis were developed early on (for a review see Li (1991)). Prominent examples are the circumoval precipitin test (COPT) (Oliver-Gonzalez et al., 1954) and the cercarial hullen reaction (CHR) developed by Vogel and Minning (1949). Before long, a large number of tests were in use and it was obvious that there was a need for quality control and standardisation (Mott and Dixon, 1982; Yuan et al., 2000a). Much work was spent on this issue and some progress was noted, but there are still many assays which have not been subjected to rigorous quality control. In addition, many new test systems appear which also are implemented without prior quality control. WHO/TDR has recently established a committee which is working on a scheme for quality control of immunoassays in the field of schistosomiasis. A chain of certified testing facilities, able to compare any assay against a battery of standard sera from well-investigated infected and non-infected individuals, is planned. The idea is appealing, but it will take some time before it can be used globally. In the meantime, one has to work with what is available locally for quality control.

Zhu (2005) provides an overview of immunodiagnosis and reviews new serologic diagnostic developments in China. It is stressed that the level of sensitivity of microscopy is eroded by generally low infection intensities and significant day-to-day fluctuations of faecal egg excretion. This claim is supported by findings in China (Yu et al., 1998) as well as in other schistosome-endemic settings (Engels et al., 1996; van Lieshout et al., 2000; Utzinger et al., 2001a), which is an important subject showing that sensitivity itself is not the only issue. The immunoassays reviewed are the main assays that have been, and continue to be, used in China today and the author feels that success of schistosomiasis control activities in China has contributed to an increased understanding of the need for better and more sensitive screening methods. The observation that compliance rates decline after repeated rounds of chemotherapy, mentioned above and also discussed elsewhere in this special issue (Guo et al., 2005a), makes it increasingly problematic to achieve good coverage for the long-term. It is interesting that immunodiagnostic techniques gained early acceptance by control programme managers in China and have already been integrated into the national schistosomiasis control programme (Zhao et al., 1993; Xiao et al., 2005).

A number of immunodiagnostics tests, all based on antibody-detection, have relatively recently been developed in China, e.g. the one-step enzyme immunoassay (EIA) (Wang et al., 1999), the colloidal dye immunofiltration assay (CDIFA) (Xiao et al., 2003, 2005), a dipstick dye immunoassay (DDIA) (Zhu et al., 2002; Zhu, 2005), and the dot immunogold filtration assay (DIGFA) (Wen et al., 2005). Both CDIFA and DDIA use a similar approach and have both been published in the peer-reviewed literature outside China, but seem to have been developed independently as none make reference to the other. They were both developed for a specific purpose, i.e. for use in the field to screen the populations being targeted for elimination of schistosomiasis. Furthermore, the tests have been evaluated in the laboratory as well as in the field and have showed high sensitivity. Specificity may still be a problem as they are based on non-purified schistosome egg antigens (SEA), but this can – and should – be remedied. In addition, in an unusual move, the DDIA has also been evaluated outside mainland China. This was done in order to determine whether *S. japonicum* antigens are sufficiently cross-reactive to make the assay applicable for the diagnosis of schistosomiasis mekongi as well. High sensitivity (97–98%) was recorded in a study using SEA in Cambodia and Laos (Zhu et al., 2005). Although this investigation is limited to two study sites and it does not include large numbers of subjects, the outcome supports its usefulness in also areas endemic for *S. mekongi*. It should, however, be said that the test in its current form suffers from cross-reactions with *Opisthorchis* spp. and *Paragonimus* spp., a problem that could be solved if SEA were substituted with more specific antigens. Recently, the DDIA kit has been evaluated for *S. mansoni* infections in Egypt and the outcome is said to be as good as that reported for *S. mekongi* (Zhu, 2005).

Another rapid test, DIGFA, also described in this section, shows a sensitivity that is as good as that of other commonly used immunodiagnostic tests. Parallel serum tests using DIGFA and various other assays in more than 1000 residents living in *S. japonicum*-endemic areas showed a high rate of agreement between the various sets of results (Wen et al., 2005). Although the assay does not show any cross-reaction with antibodies to clonorchiasis, patients infected with *Paragonimus* spp. reacted positively. The shortcoming is a comparatively higher cost that prevents this test to be used in the field on a large scale.

In a different approach focusing on the specific risk for the liver due to *S. japonicum* infection, Zheng et al. (2005) note that hepatic fibrosis is the most common cause of death in advanced schistosomiasis japonica. It has already been speculated that there might be circulating markers that could be used to predict the risk for fibrosis in schistosomiasis patients (Cai et al., 1996), and

Zheng's research group showed the strong correlation between the serum level of a human cartilage glycoprotein (YKL) with hepatic fibrosis (Zheng et al., 2005). Moreover, the authors find that serum level of YKL also correlates with the degree of fibrosis. These observations are novel and show that immunoassays can be useful not only for diagnosing the infection, but also for predicting its clinical development.

The field of diagnostics has flourished since technology had advanced to a point permitting the use of monoclonal antibodies. The first trials comparing different assays were carried out in China in the 1980s (Mott et al., 1987) and we now have a multitude of new tests that need to be compared, both in the laboratory and in the field. Zhu (2005) mentions many assays in his review and there are surely more which have never been published, but are still used in different areas. It is obvious that 'head-to-head' testing is needed, not necessarily to find the very best one, but to establish levels of quality which must be fulfilled. Such a testing scheme should be initiated in China and we should also hope that the WHO/TDR committee on diagnostic quality control mentioned above includes *S. japonicum* assays in its objectives.

5. Antischistosomal drugs and chemotherapy

5.1. Early drug discovery and development

Starting in the early 1950s, and lasting for about three decades, progress was made with regard to antimony compounds, non-antimonials (of which amoscanate and niridazole are the best known) and various effective principles stemming from traditional Chinese herbs. However, due to adverse toxicological findings and lack of sufficient therapeutic efficacy, none of these compounds lent themselves to further development. This body of antischistosomal drug discovery and development, alongside comprehensive reviews pertaining to praziquantel and the artemisinins, highlighting China's contributions, is covered in this special issue (Xiao, 2005).

5.2. Praziquantel

The synthesis of praziquantel by Bayer and Merck in Germany and the discovery of its antischistosomal properties in the 1970s (Gönnert and Andrews, 1977; Seubert et al., 1977), followed by rapid and convincing documentation of the drug's broad spectrum of activity, excellent safety profile and high therapeutic efficacy, amounted to a breakthrough for the control of schistosomiasis (Andrews et al., 1983; Groll, 1984). The advent of praziquantel not only greatly facilitated treatment of patients infected with schistosomes, but also provided the means for the shift in the global control strategy from transmission containment to morbidity control, which occurred in the mid 1980s (WHO, 1985). The key, however, was not only praziquantel's superiority, but also its dramatic reduction in price over the past years, i.e. the average cost for treating an adult is now below US$ 0.30 in most parts of the world where schistosomiasis remains endemic.

The contributions by Chinese scientists to further our understanding of the outstanding antischistosomal drug praziquantel with a focus on *S. japonicum* are reviewed by Xiao (2005). In brief, praziquantel was first synthesized in China in 1978. The three main pharmacological effects the drug exhibits on *S. japonicum* consist of: (i) stimulation of worm motor activity; (ii) induction of Ca^{2+}-dependent spasmodic contraction of the worm musculature; and (iii) tegumental disruption. These observations are2 in agreement with the experience with other schistosome species (Cioli et al., 1995). Exposure of *S. japonicum* worms to praziquantel alters their metabolism, characterized by marked reductions in glycogen content. Further in vitro studies suggested that the efficacy of praziquantel is antibody-dependent. Subsequent in vivo studies established a positive relationship between the antibody level in the host and the duration of infection (Xiao et al., 1987). These observations confirm an earlier report of stage-specific susceptibility of *S. mansoni* to praziquantel (Sabah et al., 1986).

Experiences made in China to date with praziquantel with regard to large-scale morbidity control, and when used for case treatment, are reviewed by Chen (2005). The first clinical trials of tolerance to praziquantel and its therapeutic efficacy against *S. japonicum*, carried out in Japan (Ishizaki et al., 1979), in the Philippines (Santos et al., 1979) and in China (Yang et al., 1981), date back to the late 1970s. Praziquantel's excellent safety profile was confirmed and extended findings of its high therapeutic efficacy against the two other major species infective to man, i.e. *S. haematobium* (Davis et al., 1979) and *S. mansoni* (Katz et al., 1979). On the basis of detailed dose-finding studies, the recommended treatment for praziquantel is a single oral dose of 40–50 mg/kg. In hospital settings, a dose of 60 mg/kg, divided into 3 or 6 split-doses, administered over 1–2 days, is also used. Praziquantel is highly efficacious in patients with acute and chronic schistosomiasis japonica and in subjects with extensive hepatosplenic involvement. A total dose of up to 120 mg/kg administered over 4–6 days is used in patients with acute schistosomiasis japonica. Adverse effects observed following praziquantel administration include gastrointestinal disturbance, headache, dizziness, insomnia, fatigue, myalgia, transient skin eruption and pruritus. However, they are usually mild and disappear within 24 hours.

Since the mid 1980s, and further promoted through the WBLP, large-scale use of praziquantel has become the backbone of China's national schistosomiasis control programme. The drug is also widely and effectively used in the treatment of bovines to lessen their contribution to disease transmission. To date, over 50 million doses of praziquantel have been administered to people infected with *S. japonicum* or to those at high risk of contracting the disease due to their occupation (e.g. fishermen and other people engaged in water-related occupations) or local residency (e.g. living in close proximity to snail-infested areas). There is only one other country in the world where praziquantel has been employed as widely, namely Egypt (Fenwick et al., 2003). Fortunately, thus far, there are no indications of tolerance and/or resistance development in *S. japonicum* worms to praziquantel (Shi et al., 2004; Song et al., 2004).

5.3. The artemisinins

The success of praziquantel has effectively removed the little incentive there was to invest in research and development of alternative antischistosomal drugs (Cioli, 1998). The artemisinins constitute the one notable exception and their development as antischistomals is serendipitous rather than the result of targeted research.

Xiao (2005) reviews this compelling 25-year Chinese story and complements and expands previous reviews on the subject (Xiao et al., 2000, 2002; Utzinger et al., 2001c,d; Utzinger and Keiser, 2004). In brief, the first report documenting artemisinin's activity against *S. japonicum* in animal models was published in 1980 (Chen et al., 1980). This observation was confirmed for artemether and artesunate in 1982 and 1983, respectively (Le et al., 1982, 1983). There are at least four important features of the artemisinins worth highlighting. First, approximately 10 years before the discovery of their antischistosomal properties, Chinese scientists documented their antimalarial properties (Klayman, 1985; Li and Wu, 2003) which has made them key drugs for treatment and control of malaria, often in combination with other antimalarials (Woodrow et al., 2005). Second, it was found that the antischistosomal effect is not general, but particularly directed against immature worms, i.e. schistosomula (Xiao and Catto, 1989; Xiao et al., 1995). Third, administration of artemether to different host animals infected with juvenile *S. japonicum* results in extensive disruption of the tegument and subtegumental structures (Xiao et al., 2000; Utzinger et al., 2001d). Fourth, in vitro studies suggest that artemether interacts with haemin, an observation that might be of relevance to elucidate its mechanism of action against schistosomes (Xiao et al., 2001).

Since the artemisinins had already been widely and effectively used in the treatment of malaria, rapid progress could be made to assess the tolerance and efficacy of these compounds for schistosomiasis japonica also. Consequently, a series of randomised controlled trials were carried out in the mid 1990s. The experimental design and techniques were similar to the ones used in the latest trial with artemether to prevent the development of patent *S. japonicum* infections in study subjects in Hunan province, as described in a separate paper in this special issue (Li et al., 2005a). In this trial, more than 750 individuals were enrolled. After an initial oral dose of 50 mg/kg praziquantel, they were randomly assigned oral artemether (6 mg/kg) or placebo. A total of 9–11 doses were administered at 2-week intervals. Compliance for multiple doses of artemether was above 80% and the drug was well tolerated. There were no acute cases of schistosomiasis japonica among artemether recipients, whereas three such cases occurred in the placebo group. Only 3/373 artemether recipients (0.8%) had *S. japonicum* eggs in their stool samples one month after the final dosing compared to 56/361 in placebo recipients (15.0%). The difference is highly statistically significant.

To date, 16 randomised controlled trials have been carried out with artesunate (Wu et al., 1995; Li et al., 1996, 1999; Xu et al., 1999; Lu et al., 2000; Zhang et al., 2000; Tian et al., 2001) and eight with artemether (Xiao et al., 1996a,b; Tian et al., 1997; Wang et al., 1997; Xu et al., 1997; Song et al., 1998; Li et al., 2005a). These trials assessed the safety and efficacy of the artemisinins for prevention of acute schistosomiasis japonica and the development of patent infections with *S. japonicum*. The main outcomes of these trials are summarised by Xiao (2005) and shown here as Forrest plots in Fig. 4a and b. The relative risks of using repeated artesunate or artemether for prevention of patent *S. japonicum* infection was estimated by using version 2.4.5 of the StatsDirect software package (StatsDirect Ltd., Cheshire, UK). Employing random effects models, the pooled relative risk for artesunate is 0.10 (95% confidence interval (CI) = 0.05–0.19) and that for artemether is 0.14 (95% CI = 0.08–0.27). In other words, repeated orally administered doses of artesunate and artemether reduce the risk of establishing patent infec-

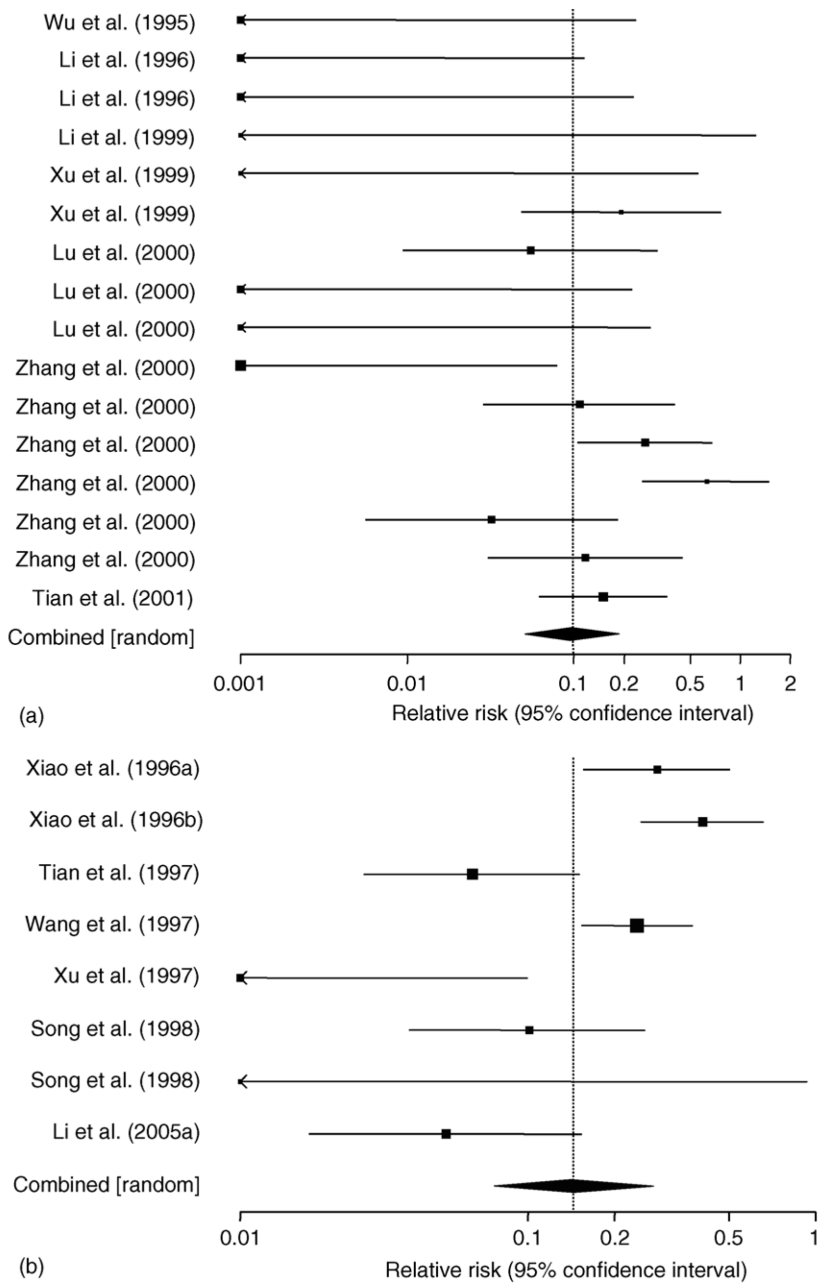

Fig. 4. Random effects meta-analysis of repeated oral artesunate (a) or artemether (b) for prevention of patent *S. japonicum* infection.

tions with *S. japonicum* by 90% (95% CI = 81–95%) and 86% (95% CI = 73–92%), respectively.

The significance of developing both artemether and artesunate for use against schistosomiasis has been stressed (Yuan et al., 2000a). Interestingly, it stimulated research outside of China, and hence the initial laboratory investigations and clinical trials were extended from *S. japonicum* to *S. mansoni* (De Clercq et al., 2000; Utzinger et al., 2000) and *S. haematobium* (Borrmann et al., 2001; De Clercq et al., 2002; N'Goran et al., 2003; Inyang-Etoh et al., 2004). A recent in vivo study also documents activity of artesunate against *S. mekongi* (Jiraungkoorskul et al., 2005).

A base of evidence has been generated showing that the artemisinins have a broad spectrum of activity against the major human schistosome species and can play a seminal role in the control of schistosomiasis, particularly for prevention of patent infection and hence morbidity development in special high-risk groups (e.g. flood relief workers). In this connection, it is important to note that 130,000 relief workers had received repeated oral artesunate during the 1998 floods of the Yangtze River, and another 15,000 people were given oral artemether. The drugs were highly successful in preventing acute schistosomiasis japonica and the development of patent *S. japonicum* infections (Xiao, 2005). Furthermore, combination chemotherapy with an artemisinin derivative and the current drug of choice against schistosomiasis (i.e. praziquantel) showed promising results against *S. japonicum* in experimentally infected animals (Utzinger et al., 2001b) and against the other schistosome species both in vivo and in the first clinical trials (for a review see Utzinger et al. (2003b)). It has been speculated that a praziquantel–artemisinin combination could be useful for disease elimination in areas where the number of infected people is very low (Utzinger et al., 2001d, 2003b). It would be of interest to test this hypothesis in circumscribed sites with limited populations.

5.4. Innovations in drug delivery

As discussed before, and reviewed by Chen (2005), praziquantel-based chemotherapy became widely used indeed. It follows that many communities have been repeatedly subjected to mass chemotherapy and some people have been treated with praziquantel up to 20 times (Wu et al., 2005a). One of the consequences of this strategy is that compliance rates drop. Guo et al. (2005a) designed a 2-year study comparing routine mass chemotherapy with ‘passive chemotherapy’ plus health education. The term ‘passive chemotherapy’ means that medical teams treat individuals who request treatment based on symptoms or after a recent history of water contact. With regard to treatment coverage among *S. japonicum*-infected people, ‘passive chemotherapy’ reached a level of 96.2–97.1%. The few egg-positive individuals missed by ‘passive chemotherapy’ had only very light infections (<10 epg). The cost of ‘passive chemotherapy’ plus strengthening of health education turned out to be half that of mass chemotherapy. Since ‘passive chemotherapy’ lends itself for integration into the primary health care system, it was felt that it offers an attractive strategy for schistosomiasis control, particularly during the maintenance and consolidation phase.

6. Contextual determinants

It is increasingly acknowledged that the frequency and transmission dynamics of infectious diseases are governed by a wide array of factors, including behavioural, climatic, demographic, economic, environmental, institutional, social and technical factors (Ezzati et al., 2005). Interestingly, recent attempts to predict the impacts of global warming on the distribution and incidence of malaria have sparked discussions on how to incorporate social and economic determinants, alongside those evolving from biological, demographic and environmental variables (Casman and Dowlatabadi, 2002). Also with regard to schistosomiasis, models employed thus far for prediction of climate change were primarily driven by biological and environmental factors (Martens et al., 1995, 1997; Yang et al., 2005b). Consequently, there is a need to take into account the social and economic variables in addition to the other contextual determinants, so that model sensitivity can be further improved.

6.1. Biological, demographic and environmental factors

Recent reviews have focused on the life cycle of *S. japonicum* as a useful means for identifying key variables (Ross et al., 2001, 2002). It comprises two features that are distinctively different to the other forms of schistosomiasis, i.e.: (i) the amphibious nature of the intermediate host and (ii) the fact that not only humans, but also a large number of domestic (and wild) animals can act as definitive hosts, and hence serve as important reservoirs. As discussed elsewhere, bovines are of particular relevance for the transmission to humans (Williams et al., 2002; Wang et al., 2005). The challenge these biological factors pose for snail control is discussed in a separate paper also published in this special issue (Yuan et al., 2005b). However, non-biological determinants can be as important as the biological ones in shaping the prevalence and incidence of infectious diseases, such as schistosomiasis. The relative contributions of these factors and their interactions have been investigated in numerous studies briefly discussed below.

With regard to environmental factors, these have been reviewed quite comprehensively for vector-borne diseases, including schistosomiasis (Brooker and Michael, 2000; Hay et al., 2000; Malone, 2005). The advent of GIS and remote sensing techniques provide important advances to our understanding of key environmental factors. Studies that applied GIS and remote sensing approaches in the epidemiology and control of schistosomiasis japonica in China are reviewed in a separate chapter of this special issue (Yang et al., 2005c).

Demographic factors include age, sex, level of education and ethnicity, and their associations with the risk of a schistosome infection have been investigated in different settings across Africa, Asia and South America (for two selected publications see Huang and Manderson (1992); Kloos et al. (1998)). In more recent years, several anthropological investigations employed a gender perspective for research and control of infectious diseases, including schistosomiasis. It was argued that such a gender perspective enhances the understanding of a disease, which in turn aids adaptation of control interventions and evaluation of control programmes (Vlassoff and Manderson, 1998). In this special issue of *Acta Tropica*, the literature is reviewed with regard to socio-demographic variables with an emphasis on schistosomiasis japonica in China. Gender has been taken into account and it is stressed that it is often tightly connected with age (Huang and Manderson, 2005).

6.2. Social and economic context

In addition to the biological, demographic and environmental factors articulated above, understanding the social and economic context in which they are embedded helps to appreciate the epidemiology of schistosomiasis japonica.

In their review, Huang and Manderson (2005) summarize a large body of mainly Chinese literature that will undoubtedly improve knowledge on the social and economic context of schistosomiasis japonica, which in turn may render current control interventions more effective. They cover the policy environment (e.g. agricultural production systems), economic factors (e.g. occupation, wealth and income), domestic environment (access to clean water, improved sanitation and proximity of human habitation to *O. hupensis*-infested areas), and social factors coupled with demographic variables mentioned above. There are two important features emanating from their review. First, the change in the political and economic landscape from a collective system to family-based production led to a clustering of *S. japonicum* infection in certain families. These changes were also accompanied with health sector reforms, which, in the case of schistosomiasis, resulted in a shift of emphasis from prevention to clinical services (Bian et al., 2004). It is conceivable that this shift will increase inequities in access to essential health care, such as treatment for an infection with *S. japonicum*. Second, the sustained growth of China's economy, initiated in the late 1970s, led to a significant rural-to-urban migration, which influences the patterns of *S. japonicum* transmission. Increased population mobility, which is not exclusively directed into towns and cities, bears the risk of spreading the parasite to areas where the transmission of the disease has been brought under control. This calls for a rigorous surveillance system so that imported cases of schistosomiasis can be identified promptly and contained, as discussed elsewhere (Wu et al., 2005b; Zhao et al., 2005).

It has been emphasised before that simultaneous implementation of different control interventions is a key factor explaining the success of China's national schistosomiasis control programme, and that there is an empirical basis for this claim (Macdonald, 1965). The feasibility and cost-effectiveness of such an integrated disease control approach is analysed in the context of local economic conditions and existing technical variables (Lin et al., 2005).

6.3. Health promotion and education

Health education as a strategy for schistosomiasis control dates back to the 1930s, but it was not until the 1970s that it was considered in the larger social and economic context (Kloos, 1995). This view is challenged by an early report on schistosomiasis in China, where the author notes "Working through radio, village communal news-sheets, talks, cinemas, and village committees (also containing a member of the Communist Party), the propaganda is persistent and all-pervading and is clearly getting results. . ." (Maegraith, 1958). It appears that health education continued to be an integral part of China's national schistosomiasis control programme ever since and that modernization added development and validation of new tools to this approach. For example, a previous report (Yuan et al., 2000b), and two papers published in this issue, describe the use of cartoons and video tapes alongside other educational materials (Hu et al., 2005a; Yuan et al., 2005a). Two aspects are worth highlighting. First, health education is the root for changing human behaviour, i.e. avoiding or reducing the frequency of exposure to *O. hupensis*-infested areas. Second, health education is also important for enhancing compliance with respect to other control intervention, i.e. drug treatment with praziquantel. The latter point is of considerable relevance, as the heavy emphasis on large-scale chemotherapy resulted in declines of compliance to annual blanket treatments (Guo et al., 2005a).

7. Transmission control

The advent of praziquantel in the 1970s and, particularly, its steep price reduction in the 1990s changed the strategic and operational possibilities for schistosomiasis control profoundly (WHO, 1993, 2002). The philosophy of control shifted as the focus moved from limiting the distribution of the intermediate host snail to reducing the pathology caused in the human host, i.e. control of morbidity took precedence over that of transmission of the infection. This transition stemmed from a recommendation by a WHO expert committee on schistosomiasis that met in Geneva in 1984 (WHO, 1985). Although this recommendation led to the abandoning of snail control in most endemic countries, the outcome of the new *modus operandi* was positive and the expert committee was vindicated as the burden of disease strongly receded in those parts of the world where the new strategy was implemented (WHO, 1993, 2002). However, although the importance of schistosomiasis diminished, the burden of infection, i.e. the general prevalence, remained an obstacle to elimination of the disease as a public health threat.

7.1. Keep controlling the snails

The great difference between schistosomiasis control in China and corresponding activities in the rest of the world is that the change of approach was only instituted slowly, keeping the spectrum of proven control tools intact. Consequently, in contrast to other endemic countries, snail control – although reduced in scope – remained an integral part of the control programme. This claim is usefully illustrated by the recent evaluation of the WBLP on schistosomiasis control in China (Chen et al., 2005). Progress made to date is to a great part due to successful snail control and in here lays the root to the continuing progress, which has not only reduced the intensity of disease, but also succeeded in interrupting transmission in large parts of the country. For example, by 1995, this had been achieved in five provinces, markedly reducing the endemic areas and reducing the snail habitats by three-quarters (Zhou et al., 2005c). Snail control is a fixture of the control programme and the need for further research in this area is agreed. Examples include work towards superior molluscicides, emphasizing the development of both chemical and plant molluscicides, and environmental management. Incorporation of new technologies such as GIS and remote sensing, often coupled with innovative spatial statistical approaches, are increasingly used for identification of snail habitats, as reviewed by Yang et al. (2005a).

Transmission is far from a simple variable. In reviewing the literature, Yuan et al. (2005b) conclude that implementation of integrated snail control is an important measure that gives leverage to further accelerate the control process, which in turn leads to improved schistosomiasis control. Another study published in this special issue attempts to assess the relative contribution by humans and a range of domestic animals in various settings (Wang et al., 2005). The results suggest that transmission varies significantly within Chinese farm districts as well as between host species with water buffaloes accounting for nearly 90% of the transmission in some settings. This result is not entirely surprising, as others have stressed the importance of domestic animals in the transmission dynamics of *S. japonicum* (Mao and Shao, 1982; Li et al., 2000; Williams et al., 2002), but the influence on control outcomes might be stronger than appreciated so far. Indeed, a very useful picture of the transmission situation might emerge if specific transmission index determinations of the different possible contributors were introduced. However, it is doubtful if the addition of transmission variables such as egg hatchability and faecal deposition habits would be cost-effective.

7.2. Mapping and prediction of snail habitats

Traditionally, snail densities and rates of infection are calculated after snails have been painstakingly collected on site. However, there is now ample evidence that it is feasible to predict the snail distribution with the aid of remotely sensed environmental data (Zhou et al., 2001; Brooker, 2002; Malone, 2005; Yang et al., 2005c). An innovative study presented in this issue (Zhang et al., 2005) applied spatial analysis based on satellite imagery data to predict the distribution of *O. hupensis*. Although final proof of the presence of infected snails requires microscopy, this research group was able not only to confirm that snail densities in the marshlands relate to vegetation, wetness and land surface temperature, but also demonstrated that a combination of the stepwise regression model of snail density and the kriged prediction of the regression residual is required to arrive at a useful determinant coefficient. Using the same basic satellite data slightly differently, Guo et al. (2005b) developed a useful model to predict snail habitats in the form of centroids with buffer zones of various sizes around them. The model holds promise for identifying high-risk areas with regard to infection and has revealed a gradient of high-to-low prevalence with increasing distance from the centroids. This approach could play a role for schistosome-affected regions that lack accurate surveillance capabilities.

An important aspect of both studies mentioned above is that Landsat satellite images were subjected to a tasseled cap transformation for spectral feature extraction, in addition to more commonly used surrogate environmental measures, such as the normalized difference vegetation index. With regard to the tasseled cap transformation, Guo et al. (2005b) only used the wetness feature, while Zhang et al. (2005) also derived brightness and greenness. Another aspect worth mentioning is that these two studies enhance the current understanding of the spatial distribution of *O. hupensis*, and hence *S. japonicum* transmission, on the meso-scale. In their literature review, Yang et al. (2005c) summarize all studies on the epidemiology and control of schistosomiasis japonica in China based on GIS and satellite data and present an attempt to stratify them by scale, ranging from the micro- (village, county) to the macro-scale (national level).

8. Surveillance

8.1. Rationale for surveillance

Progress in controlling a disease is of little value if achievements made cannot be sustained, and this requires reliable and sound surveillance. The schistosomiasis control programme in China has been recognized as one of the most successful control programmes against this disease in the world, not the least because of rigorous surveillance (Zhou et al., 2005c). However, even spectacularly good results can easily slip back, as happened with the crusade against malaria during the 'Global Malaria Eradication Campaign' in the 1950s resulting in the re-emergence of the disease in its old endemic areas in many parts of Asia and elsewhere. Interestingly, a different story unfolded in China. Here, implementation of malaria control over the past several decades was highly successful. Factors explaining the success include strong political will and sustained government commitment, integration of vector control with a rigorous early diagnosis and treatment approach with special emphasis on surveillance (Yip, 1998; Carter and Mendis, 2002).

8.2. Surveillance of schistosomiasis in China

The Ministry of Health remains highly committed to consolidate achievements made with the ultimate goal of eliminating this scourge (Engels et al., 2005). An important feature of the national control programme is rigorous surveillance, mainly in settings that have reached the criteria of transmission interruption or transmission control. Here, the emphasis is on careful monitoring of active infections among local residents and domestic animals and infestations of intermediate host snails (Wu et al., 2005b). Some surveillance teams work only locally or are province-based, but quite a few surveillance projects have been nation-wide. For example, the latest surveillance results obtained from 20 sentinel sites located in the seven provinces where *S. japonicum* remains endemic are presented in this special issue of *Acta Tropica* (Zhao et al., 2005).

Good surveillance is not a static approach, but evolves steadily thanks to feedback mechanisms linked to research activities. This subject is usefully illustrated in two papers of this special issue (Li et al., 2005b; Wu et al., 2005b). The former takes a general view analysing the situation with regard to economic consideration and efficiency of epidemiological survey methods, whereas the latter focuses on snail control and human diagnosis as the key components in the five previously *S. japonicum*-endemic provinces. With a sound surveillance system in place, consolidation of achievements made is easy and decisions can be straightforward. However, the steady increase of mobile populations is a problem. Immunodiagnostic screening with positive results followed-up by stool examination (Wu et al., 2005a; Zhu, 2005) has confirmed infection in a small, but increasing number of people (Liu et al., 1991; Tao and Li, 1999). Although active infections are generally imported, it is noted that they can also be due to residual habitats of infected *O. hupensis* found in areas where the transmission of *S. japonicum* has been officially interrupted (Wu et al., 2005b). These observations show that, although chemotherapy is generally successful, it is not completely effective with regard to containing so called 'endemic hot spots' leading to the conclusion that an integrated approach is preferable (Jiang et al., 1996). Historically, the broad-based attack on the snail has been the key to success in China as summarized in Section 2. It is therefore worrying that the extent of snail habitats has been on the rise in quite a few places (Gao et al., 1998; Tao and Li, 1999; Chen et al., 2003). To prevent further extension of habitats, snail surveillance would need to be carried out regularly not only in the endemic areas, but also in non-endemic areas.

Li et al. (2005b) note that periodic epidemiological surveys enable the dynamic trends of schistosomiasis epidemics to be closely pursued and strategies adjusted when needed. The authors further feel that an analysis of cost-effectiveness is necessary to identify the most financially feasible yet effective control options and stress the imperative need for periodic surveys using samples that are true representations of the population investigated (Li et al., 2005b). Changes in the sample data over a period of time are detected by longitudinal surveys using non-probability sampling, but data are required to be collected over long periods, i.e. years or even decades (Li et al., 2000, 2002).

The third national epidemiological sampling survey on schistosomiasis, carried out in 2004, made use of tech-

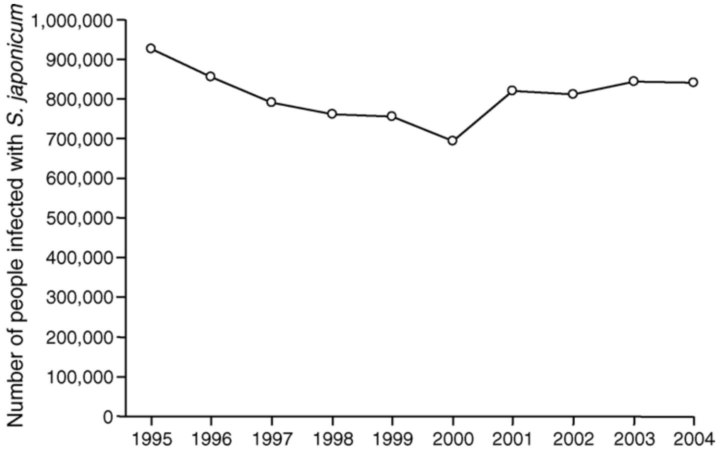

Fig. 5. Estimated number of people infected with *S. japonicum* in China between 1995 and 2004.

nical improvements, for example sampling of subjects for schistosome-induced fibrosis using ultrasonography, and sampling of snails in a selection of sentinel sites in each of the seven provinces where *S. japonicum* remains endemic. The results of this survey are not yet fully available, but there seems to be little real progress since the previous survey in 1995. Fig. 5 illustrates this claim; the estimated number of people infected showed no real decline over the past nine years. One might have expected a strong decline in view of the large-scale chemotherapy campaigns which continued through 2001 within the framework of the WBLP. This issue requires detailed analysis as a weakening ability of the current control strategy to further improve the situation would have a profound impact on the future approach.

The drop in compliance among residents, extensively treated and re-treated with praziquantel, led to a need to reassess the prevailing approach. Justified by the change from a planned to a market-oriented economy in China, an economic evaluation of the strategies used was carried out with the aim to facilitate allocation of scarce resources in a cost-effective manner (Gold et al., 1996; Drummond et al., 1997). The need to foster this thinking in China's schistosomiasis research and control community was emphasized strongly by the 'Joint Research Management Committee' which steered research activities during the operation of the WBLP (Yuan et al., 2000a). It was, for example, demonstrated that selective chemotherapy significantly reduced the prevalence and infection intensity at a lower cost than large-scale administration (Tang et al., 2001) and that costs for treating *S. japonicum*-infected people could be halved by means of 'passive chemotherapy' together with health education, compared to mass chemotherapy (Guo et al., 2005a). Another example shows that selective chemotherapy is more cost-effective and that questionnaire-based water contact surveys would be the optimal method for chemotherapy selection (Wang et al., 2000).

In the late 1990s, a questionnaire was developed specifically for schoolchildren and it was demonstrated that its efficiency to identify *S. japonicum*-infected children depended critically on the questions selected (Zhou et al., 1998). Recently, the questionnaire approach was further developed for identification of high-risk individuals in areas that are prone to flooding events (Tan et al., 2004). In the present issue, the area of economic evaluation and its effect on schistosomiasis control is reviewed (Li et al., 2005b). The authors set forth that it is imperative to develop mathematical transmission models incorporating different intervention measures to facilitate the analysis of indicators, underscoring some of their earlier work (Williams et al., 2002).

The remaining endemic areas in China are not as easily accessible as those which have now been cleared of schistosomiasis. The situation is further complicated by fluctuating water-ways. The construction of the Three Gorges dam across the Yangtze River demonstrates how difficult it can be to predict the outcome with regard to schistosomiasis, which is indeed necessary to mitigate possible impacts in the future. For example, although the fluctuation of water levels downstream will be less dramatic in the future, some feel that the construction is likely to increase schistosomiasis transmission (Xu et al., 2000). In addition, the forced move of over a million people from the now flooded Three Gorges upstream area to new homes, many of which are located in schistosome-endemic areas is precarious as these people have previously not experienced schistosomiasis, and hence are likely to be more vulnerable to the infection. The establishment and operation of rigorous surveillance systems will play a seminal role in such areas that have undergone major ecological transformations.

9. Conclusions and recommendations

The 50-year long struggle to control schistosomiasis in China is a great public health success story often referred to. This overview of progress made to date is an attempt to summarize and integrate the wealth of information provided in the 25 contributions presented here. It builds on and expands previous reviews on this subject (Maegraith, 1958; Mao and Shao, 1982; Chen, 1989; Yuan, 1995; Ross et al., 1997, 2001; Chen and Feng, 1999). The synthesis of this large body of data, derived from various aspects of targeted research and the experiences gained through implementation and sustaining integrated schistosomiasis control approaches, have led to a set of conclusions and recommendations, which are offered here for consideration and critical review. Our hope is that they will provide inspiration for the final moves towards the ultimate goal of eliminating the “God of Plague”.

The last two decades of emphasis on morbidity control has served China – and the world – well but snail control is the key to the ultimate elimination of schistosomiasis. An important lesson learned from the current examination is that the various methods applied for the containment of the snail intermediate host, primarily based on environmental management but in concert with a wide array of other control measures including the influence of social and economic development, have shown long-term effectiveness. Snail control has never been abandoned in China as in other parts of the world.

The growth of the economy as a whole governs all aspects of life. Therefore, evaluations need to go beyond schistosomiasis-specific outcome measures to include appraisal of overall improvement in health, general well-being and equity. Major ecological transformations such as the development of the country’s water resources for drinking, intensification of agriculture and generation of electricity constitute examples of necessary activities that could impact schistosomiasis control negatively and therefore need to be addressed in long-term research programmes in order to develop and implement sound mitigation strategies in a timely and effective manner. Climate change, that seems to have become an undeniable phenomenon, can only be arrested by global coordinated efforts, but its effects must be included in any serious discussion of future epidemiological developments. Another looming problem is the concept of post-transmission schistosomiasis, which will require medical care and attention long after transmission has been interrupted.

The tools of the trade extracted from the current analyses, with some pointed emphasis on how to further strengthen them, are briefly summarized below.

9.1. Diagnosis

There is a need for standardized tests, which are sufficiently sensitive to gauge and ascertain the achievements of the national schistosomiasis control programme with high accuracy. These ultimate, superior tools are still eluding us, but this fact should not deter from a critical review of the large number of assays for antibody detection in current use. To be useful, the selection criteria for such a review should go beyond high sensitivity and specificity issues and also consider species-specificity, purity, shelf life, suitability for quality-controlled industrial production, intellectual property rights, availability and cost.

9.2. Drugs and chemotherapy

Although praziquantel-based chemotherapy is the current cornersone of the national control programme, there is a need to assess the safety, efficacy and cost-effectiveness of alternative treatment schedules and delivery mechanisms. There is no doubt that the artemisinins have a place in the prophylactic and therapeutic arsenal as they have been shown to successfully prevent acute schistosomiasis japonica and to prevent the development of patent *S. japonicum* infections, stimulating corresponding research on other major schistosome species. However, further applied research on the use of artemisins alone and in combination with praziquantel is needed. In addition, the search for novel, orally active antischistosomal drugs with a broad spectrum of activity against the juvenile and adult stages of the parasite must be pursued.

9.3. Vaccine development

China has taken the joint lead with Brazil in mining the schistosome genome for superior vaccine candidates. Although these products will not appear overnight, partially effective vaccine candidates for veterinary use are already available. Progress with this generation of vaccines is now more a question of industrial production and commercialization. The inclusion in the control strategy of a vaccine approach targeting domestic animals would – in our opinion – reinforce the effect of chemotherapy and enhance the possibilities of disease elimination.

9.4. Surveillance and risk mapping

Future progress in controlling schistosomiasis depends crucially on monitoring systems that are able to accurately gauge the present situation, particularly at non-sampled locations. Surveillance systems need to respond operationally to ecological and epidemiological challenges in a timely and cost-effective manner. The targeting of interventions would benefit from support of state-of-the-art GIS and remote sensing technologies, alongside innovative spatial statistical analysis, such as Bayesian-based approaches.

9.5. Health education

The role of health promotion and education is of particular relevance for control since it induces the behavioural changes not only needed to reduce contact with infested water but also for enhancing compliance with respect to diagnosis, treatment and other control interventions. Due consideration of social, economic and other contextual variables maximises this positive effect.

9.6. Operational research

Testing of new ideas and novel approaches are needed as the control programme must adapt to changing situations. International collaboration facilitates this with the RNAS providing a suitable platform for the exchange of expertise for schistosomiasis control.

9.7. Scope for integrated control

As assessment and control of schistosomiasis depend on the same or similar epidemiological methods as those applied against soil-transmitted helminthiasis and the emerging problem of food-borne trematodiasis, control of these parasites could be integrated into one control programme. The migration of the current 'one disease approach' towards an increasingly horizontal programme is worth contemplating since the integration of other helminthiases and parasitic zoonoses as well is likely to be cost-effective.

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References

Andrews, P., Thomas, H., Pohlke, R., Seubert, J., 1983. Praziquantel. Med. Res. Rev. 3, 147–200.

Ashton, P.D., Curwen, R.S., Wilson, R.A., 2001. Linking proteome and genome: how to identify parasite proteins. Trends Parasitol. 17, 198–202.

Bergquist, N.R., 2004. Improving public health through collaboration in research. In: Mita, R., Satoh, K. (Eds.), International Collaboration in Community Health. Elsevier, pp. 7–16.

Bergquist, N.R., Leonardo, L.R., Mitchell, G.F., 2005. Vaccine-linked chemotherapy: can schistosomiasis control benefit from an integrated approach? Trends Parasitol. 21, 112–117.

Bergquist, R., Al-Sherbiny, M., Barakat, R., Olds, R., 2002. Blueprint for schistosomiasis vaccine development. Acta Trop. 82, 183–192.

Bian, G.W., Yu, X.B., Wu, Z.D., Xu, J., Shan, Z.X., Ma, C.L., Shao, X., 2001. Prokaryotic expression of Sj16 gene of *Schistosoma japonicum* Chinese strain. Chin. J. Schisto. Cont. 13, 333–336.

Bian, Y., Sun, Q., Zhao, Z.Y., Blas, E., 2004. Market reform: a challenge to public health—the case of schistosomiasis control in China. Int. J. Health Plann. Manage. 19 (Suppl. 1), S79–S94.

Bickle, Q.D., Oldridge, J., 1999. Characterization of a stage-specific Mr16000 schistosomular surface glycoprotein antigen of *Schistosoma mansoni*. Mol. Biochem. Parasitol. 100, 85–94.

Booth, M., Mwatha, J.K., Joseph, S., Jones, F.M., Kadzo, H., Ireri, E., Kazibwe, F., Kemijumbi, J., Kariuki, C., Kimani, G., Ouma, J.H., Kabatereine, N.B., Vennervald, B.J., Dunne, D.W., 2004. Periportal fibrosis in human *Schistosoma mansoni* infection is associated with low IL-10, low IFN-γ, high TNF-α, or low RANTES, depending on age and gender. J. Immunol. 172, 1295–1303.

Borrmann, S., Szlezák, N., Faucher, J.-F., Matsiegui, P.-B., Neubauer, R., Binder, R.K., Lell, B., Kremsner, P.G., 2001. Artesunate and praziquantel for the treatment of *Schistosoma haematobium* infections: a double-blind, randomized, placebo-controlled study. J. Infect. Dis. 184, 1363–1366.

Brooker, S., 2002. Schistosomes, snails and satellites. Acta Trop. 82, 207–214.

Brooker, S., Michael, E., 2000. The potential of geographical information systems and remote sensing in the epidemiology and control of human helminth infections. Adv. Parasitol. 47, 245–288.

Brown, M., Mawa, P.A., Joseph, S., Bukusuba, J., Watera, C., Whitworth, J.A.G., Dunne, D.W., Elliott, A.M., 2005. Treatment of *Schistosoma mansoni* infection increases helminth-specific type 2 cytokine responses and HIV-1 loads in coinfected Ugandan adults. J. Infect. Dis. 191, 1648–1657.

Cai, W.M., Sun, Y.L., Zhang, L.H., Liu, R.H., Yu, Y.X., Yang, H.Q., Zho, Z.L., 1996. Assay and clinical signification of 12 parameters of serum in patients with hepatic fibrosis of schistosomiasis. Chin. J. Zoon. 12, 13–15.

Carter, R., Mendis, K.N., 2002. Evolutionary and historical aspects of the burden of malaria. Clin. Microbiol. Rev. 15, 564–594.

Casman, E.A., Dowlatabadi, H., 2002. The Contextual Determinants of Malaria. Resources for the Future, Washington, DC.

Chen, D.J., Fu, L.F., Shao, P.P., Wu, F.Z., Fan, C.Z., Shu, H., Ren, C.X., Sheng, X.L., 1980. Experimental studies on antischistosomal activity of qinghaosu. Zhong Hui Yi Xue Zha Zhi 60, 422–425.

Chen, H.G., Nara, T., Zeng, X.J., Satoh, M., Wu, G.C., Jiang, W.S., Yi, F.Y., Kojima, S., Zhang, S.J., Hirayama, K., 2000. Vaccination of domestic pig with recombinant paramyosin against *Schistosoma japonicum* in China. Vaccine 18, 2142–2146.

Chen, M.G., 1989. Schistosomiasis control program in the People's Republic of China: a review. Southeast Asian J. Trop. Med. Public Health 20, 511–517.

Chen, M.G., 2005. Use of praziquantel for clinical treatment and morbidity control of schistosomiasis japonica in China: a review of 30 years' experience. Acta Trop. 96, 168–176.

Chen, M.G., Feng, Z., 1999. Schistosomiasis control in China. Parasitol. Int. 48, 11–19.

Chen, M.G., Mott, K.E., 1988. Progress in assessment of morbidity due to *Schistosoma japonicum* infections: a review of recent literature. Trop. Dis. Bull. 85, R1–R45.

Chen, X.Y., 2002. The challenges and strategies in schistosomiasis control program in China. Acta Trop. 82, 279–282.

Chen, X.Y., Wang, L.Y., Cai, J.M., Zhou, X.N., Zheng, J., Guo, J.G., Wu, X.H., Engels, D., Chen, M.G., 2005. Schistosomiasis control in China: the impact of a 10-year World Bank Loan Project (1992–2001). Bull. World Health Organ. 83, 43–48.

Chen, X.Y., Wu, X.H., Wang, L.Y., Dang, H., Wang, Q., Zheng, J., Guo, J.G., Jiang, Q.W., Zhao, G.M., Zhou, X.N., 2002. Schistosomiasis situation in the People's Republic of China in 2002. Chin. J. Schisto. Contr. 15, 241–243.

Cheng, G.F., Lin, J.J., Feng, X.G., Fu, Z.Q., Jin, Y.M., Yuan, C.X., Zhou, Y.C., Cai, Y.M., 2005. Proteomic analysis of differentially expressed proteins between the male and female worm of *Schistosoma japonicum* after pairing. Proteomics 5, 511–521.

Chitsulo, L., Engels, D., Montresor, A., Savioli, L., 2000. The global status of schistosomiasis and its control. Acta Trop. 77, 41–51.

Cioli, D., 1998. Chemotherapy of schistosomiasis: an update. Parasitol. Today 14, 418–422.

Cioli, D., Pica-Mattoccia, L., Archer, S., 1995. Antischistosomal drugs: past, present . . . and future? Pharmacol. Ther. 68, 35–85.

Curwen, R.S., Ashton, P.D., Johnston, D.A., Wilson, R.A., 2004. The *Schistosoma mansoni* soluble proteome: a comparison across four life-cycle stages. Mol. Biochem. Parasitol. 138, 57–66.

Davis, A., Biles, J.E., Ulrich, A.M., 1979. Initial experiences with praziquantel in the treatment of human infections due to *Schistosoma haematobium*. Bull. World Health Organ. 57, 773–779.

De Clercq, D., Vercruysse, J., Kongs, A., Verlé, P., Dompnier, J.P., Faye, P.C., 2002. Efficacy of artesunate and praziquantel in *Schistosoma haematobium* infected schoolchildren. Acta Trop. 82, 61–66.

De Clercq, D., Vercruysse, J., Verlé, P., Niasse, F., Kongs, A., Diop, M., 2000. Efficacy of artesunate against *Schistosoma mansoni* infections in Richard Toll, Senegal. Trans. R. Soc. Trop. Med. Hyg. 94, 90–91.

de Vlas, S.J., Gryseels, B., 1992. Underestimation of *Schistosoma mansoni* prevalences. Parasitol. Today 8, 274–277.

Doenhoff, M.J., Chiodini, P.L., Hamilton, J.V., 2004. Specific and sensitive diagnosis of schistosome infection: can it be done with antibodies? Trends Parasitol. 20, 35–39.

Drummond, M.F., O'Brien, B., Stoddart, G.L., Torrance, G.W., 1997. Methods for the Economic Evaluation of Health Care Programmes. Oxford University Press, New York.

Easterling, D.R., Horton, B., Jones, P.D., Peterson, T.C., Karl, T.R., Parker, D.E., Salinger, M.J., Razuvayev, V., Plummer, N., Jamason, P., Folland, C.K., 1997. Maximum and minimum temperature trends for the globe. Science 277, 364–367.

Engels, D., Chitsulo, L., Montresor, A., Savioli, L., 2002. The global epidemiological situation of schistosomiasis and new approaches to control and research. Acta Trop. 82, 139–146.

Engels, D., Sinzinkayo, E., Gryseels, B., 1996. Day-to-day egg count fluctuation in *Schistosoma mansoni* infection and its operational implications. Am. J. Trop. Med. Hyg. 54, 319–324.

Engels, D., Wang, L.Y., Palmer, K.L., 2005. Control of schistosomiasis in China. Acta Trop. 96, 67–68.

Ezzati, M., Utzinger, J., Cairncross, S., Cohen, A.J., Singer, B.H., 2005. Environmental risks in the developing world: exposure indicators for evaluating interventions, programmes, and policies. J. Epidemiol. Community Health 59, 15–22.

Fenwick, A., Savioli, L., Engels, D., Bergquist, N.R., Todd, M.H., 2003. Drugs for the control of parasitic diseases: current status and development in schistosomiasis. Trends Parasitol. 19, 509–515.

Gan, Y., Shi, Y.E., Bu, L.Y., Zhu, X.H., Ning, C.X., Zhu, H.G., 2004. Immune responses against *Schistosoma japonicum* after vaccinating mice with a multivalent DNA vaccine encoding integrated membrane protein Sj23 and cytokine interleukin-12. Chin. Med. J. 117, 1842–1846.

Gao, Z.Q., Jiang, X.J., Cai, Z.R., Wang, L.X., Zheng, Z.G., Huang, D.S., 1998. Surveillance report on schistosomiasis ten years after reaching the criteria for elimination in Shanghai Municipality. Chin. J. Schisto. Contr. 10, 159–161.

Giboda, M., Bergquist, N.R., 1999. Post-transmission schistosomiasis. Parasitol. Today 15, 307–308.

Giboda, M., Bergquist, N.R., 2000. Post-transmission schistosomiasis: a new agenda. Acta Trop. 77, 3–7.

Gold, M.R., Siegel, J.E., Russel, L.B., Weinstein, M.C., 1996. Cost-Effectiveness in Health and Medicine. Oxford University Press, New York.

Gönnert, R., Andrews, P., 1977. Praziquantel, a new broad-spectrum antischistosomal agent. Z. Parasitenkd. 52, 129–150.

Groll, E., 1984. Praziquantel. Adv. Pharmacol. Chemother. 20, 219–238.

Gryseels, B., de Vlas, S.J., 1996. Worm burdens in schistosome infections. Parasitol. Today 12, 115–119.

Guo, J.G., Cao, C.L., Hu, G.H., Lin, H., Li, D., Zhu, R., Xu, J., 2005a. The role of 'passive chemotherapy' plus health education for schistosomiasis control in China during maintenance and consolidation phase. Acta Trop. 96, 177–183.

Guo, J.G., Vounatsou, P., Cao, C.L., Utzinger, J., Zhu, H.Q., Anderegg, D., Zhu, R., He, Z.Y., Li, D., Hu, F., Chen, M.G., Tanner, M., 2005b. A geographic information and remote sensing based model for prediction of *Oncomelania hupensis* habitats in the Poyang Lake area, China. Acta Trop. 96, 213–222.

Hay, S.I., Omumbo, J.A., Craig, M.H., Snow, R.W., 2000. Earth observation, geographic information systems and *Plasmodium falciparum* malaria in sub-Saharan Africa. Adv. Parasitol. 47, 173–215.

Hillyer, G.V., Tsang, V.C., Vivas-Gonzalez, B.E., Noh, J., Ahn, L.H., Vorndam, V., 1999. Age-specific decrease in seroprevalence of schistosomiasis in Puerto Rico. Am. J. Trop. Med. Hyg. 60, 313–318.

Hu, G.H., Hu, J., Song, K.Y., Lin, D.D., Zhang, J., Cao, C.L., Xu, J., Li, D., Jiang, W.S., 2005a. The role of health education and health promotion in the control of schistosomiasis: experiences from a 12-year intervention study in Poyang Lake area. Acta Trop. 96, 232–241.

Hu, S.M., Wang, H., Ruan, Z.Y., Yu, X.B., Wu, Z.D., 2005b. Construction and identification of recombinant baculovirus with *Schistosoma japonicum* Sj16 gene. J. Trop. Med. 5, 8–11.

Hu, W., Yan, Q., Shen, D.K., Liu, F., Zhu, Z.D., Song, H.D., Xu, X.R., Wang, Z.J., Rong, Y.P., Zeng, L.C., Wu, J., Zhang, X., Wang, J.J., Xu, X.N., Wang, S.Y., Fu, G., Zhang, X.L., Wang, Z.Q., Brindley, P.J., McManus, D.P., Xue, C.L., Feng, Z., Chen, Z., Han, Z.G., 2003. Evolutionary and biomedical implications of a *Schistosoma japonicum* complementary DNA resource. Nat. Genet. 35, 139–147.

Huang, Y.X., Manderson, L., 1992. Schistosomiasis and the social patterning of infection. Acta Trop. 51, 175–194.

Huang, Y.X., Manderson, L., 2005. The social and economic determinants of schistosomiasis japonica. Acta Trop. 96, 223–231.

Inyang-Etoh, P.C., Ejezie, G.C., Useh, M.F., Inyang-Etoh, E.C., 2004. Efficacy of artesunate in the treatment of urinary schistosomiasis, in an endemic community in Nigeria. Ann. Trop. Med. Parasitol. 98, 491–499.

IPCC, 2001. Climate Change 2001: The Scientific Basis (Intergovernmental Panel on Climate Change). Cambridge University Press, Cambridge, UK.

Ishizaki, T., Kamo, E., Boehme, K., 1979. Double-blind studies of tolerance to praziquantel in Japanese patients with *Schistosoma japonicum* infections. Bull. World Health Organ. 57, 787–791.

Jiang, Q.W., Wang, L.Y., Guo, J.G., Chen, M.G., Zhou, X.N., Engels, D., 2002. Morbidity control of schistosomiasis in China. Acta Trop. 82, 115–125.

Jiang, Q.W., Zhang, S.J., Yuan, H.C., Liu, Z., Zhao, G.M., Brinkmann, U., 1996. The effect of a combined approach to schistosomiasis control on the transmission of *Schistosoma japonicum* in Xingzi of Poyang Lake area, China. Southeast Asian J. Trop. Med. Public Health 27, 535–541.

Jiraungkoorskul, W., Sahaphong, S., Sobhon, P., Riengrojpitak, S., Kangwanrangsan, N., 2005. Effects of praziquantel and artesunate on the tegument of adult *Schistosoma mekongi* harboured in mice. Parasitol. Int. 54, 177–183.

Johansen, M.V., Bøgh, H.Ø., Nansen, P., Christensen, N.Ø., 2000. *Schistosoma japonicum* infection in the pig as a model for human schistosomiasis japonica. Acta Trop. 76, 85–99.

Katz, N., Chaves, A., Pellegrino, J., 1972. A simple device for quantitative stool thick-smear technique in schistosomiasis mansoni. Rev. Inst. Med. Trop. Sao Paulo 14, 397–400.

Katz, N., Rocha, R.S., Chaves, A., 1979. Preliminary trials with praziquantel in human infections due to *Schistosoma mansoni*. Bull. World Health Organ. 57, 781–785.

Keiser, J., Utzinger, J., 2005. Emerging foodborne trematodiasis. Emerg. Infect. Dis. 11, 1507–1514.

King, C.H., Dickman, K., Tisch, D.J., 2005. Reassessment of the cost of chronic helmintic infection: a meta-analysis of disability-related outcomes in endemic schistosomiasis. Lancet 365, 1561–1569.

Klayman, D.L., 1985. Qinghaosu (artemisinin): an antimalarial drug from China. Science 228, 1049–1055.

Kloos, H., 1995. Human behavior, health education and schistosomiasis control: a review. Soc. Sci. Med. 40, 1497–1511.

Kloos, H., Gazzinelli, A., Van Zuyle, P., 1998. Microgeographical patterns of schistosomiasis and water contact behavior; examples from Africa and Brazil. Mem. Inst. Oswaldo Cruz 93 (Suppl. 1), 37–50.

Kumagai, T., Maruyama, H., Hato, M., Ohmae, H., Osada, Y., Kanazawa, T., Ohta, N., 2005. *Schistosoma japonicum*: localization of calpain in the penetration glands and secretions of cercariae. Exp. Parasitol. 109, 53–57.

Le, W.J., You, J.Q., Mei, J.Y., 1983. Chemotherapeutic effect of artesunate in experimental schistosomiasis. Acta Pharmaceut. Sin. 18, 619–621.

Le, W.J., You, J.Q., Yang, Y.Q., Mei, J.Y., Guo, H.F., Zang, C.W., 1982. Studies on the efficacy of artemether in experimental schistosomiasis. Acta Pharmaceut. Sin. 17, 187–193.

Lebens, M., Sun, J.B., Czerkinsky, C., Holmgren, J., 2004. Current status and future prospects for a vaccine against schistosomiasis. Expert Rev. Vaccines 3, 315–328.

Leonardo, L.R., Bergquist, R., 2002. Regional network on Asian schistosomiasis. Trends Parasitol. 18, 434–436.

Li, H.Y., Liu, Z.D., Hu, L.S., Liu, Y.M., Hu, F., Chen, Y.H., Li, S.W., Wu, L.J., Xu, P.S., Xuan, Y.X., Guo, Y., 1999. Observation on the prevention of schistosomiasis japonica by administration of artesunate long-term. Chin. J. Parasit. Dis. Cont. 12, 214–215.

Li, S.W., Wu, L.J., Liu, Z.D., Hu, L.S., Xu, P.S., Xuan, Y.X., Liu, Y.M., Liu, X., Fan, J.T., 1996. Studies on prophylactic effect of artesunate on schistosomiasis japonica. Chin. Med. J. 109, 848–853.

Li, Y., 1991. Advance of the study on immunodiagnosis of schistosomiasis. In: Li, Y. (Ed.), Immunology and Immunodiagnosis of Parasitic Diseases. Jiangsu Science Technology Publishing House, Nanjing, pp. 210–234.

Li, Y., Wu, Y.L., 2003. An over four millennium story behind qinghaosu (artemisinin)—a fantastic antimalarial drug from a traditional chinese herb. Curr. Med. Chem. 10, 2197–2230.

Li, Y.S., Chen, H.G., He, H.B., Hou, X.Y., Ellis, M., P., M.D., 2005a. A double-blind field trial on the effects of artemether on *Schistosoma japonicum* infection in a highly endemic focus in southern China. Acta Trop. 96, 184–190.

Li, Y.S., Sleigh, A.C., Li, Y., Tanner, M., Dessein, A., Williams, G.M., McManus, D.P., 2002. Five-year impact of repeated praziquantel treatment on subclinical morbidity due to *Schistosoma japonicum* in China. Trans. R. Soc. Trop. Med. Hyg. 96, 438–443.

Li, Y.S., Sleigh, A.C., Ross, A.G.P., Williams, G.M., Tanner, M., McManus, D.P., 2000. Epidemiology of *Schistosoma japonicum* in China: morbidity and strategies for control in the Dongting Lake region. Int. J. Parasitol. 30, 273–281.

Li, Y.S., Zhao, Z.Y., Ellis, M., P., M.D., 2005b. Applications and outcomes of periodic epidemiological surveys for schistosomiasis and related economic evaluation in the People's Republic of China. Acta Trop. 96, 266–275.

Lin, D.D., Hu, G.H., Zhang, S.J., 2005. Optimal combined approaches of field intervention for schistosomiasis control in China. Acta Trop. 96, 242–247.

Liu, J.M., Cai, X.Z., Lin, J.J., Fu, Z.Q., Yang, G.Z., Shi, F.H., Cai, Y.M., Shen, W., Taylor, M.G., Wu, X.F., 2004. Gene cloning, expression and vaccine testing of *Schistosoma japonicum* SjFABP. Parasite Immunol. 26, 351–358.

Liu, X.Y., Li, D.J., Lin, P.C., Lin, J.X., 1991. Analysis on schistosomiasis surveillance for four years in Fujian province. Chin. J. Schisto. Contr. 3, 229–230.

Logan, O.T., 1905. A case of dysentery in Hunan province caused by the trematode *Schistosoma japonicum*. Chin. Med. J. 19, 243–245.

Lu, G.Y., Lin, G.J., Sun, M.X., Cui, J.F., Wu, Q.Z., S, L.J., 2000. Probe on scheme with oral artesunate protecting people from infection of schistosome. Chin. J. Parasit. Dis. Cont. 13, 212–214.

Lun, Z.R., Gasser, R.B., Lai, D.H., Li, A.X., Zhu, X.Q., Yu, X.B., Fang, Y.Y., 2005. Clonorchiasis: a key foodborne zoonosis in China. Lancet Infect. Dis. 5, 31–41.

Macdonald, G., 1965. The dynamics of helminth infections, with special reference to schistosomes. Trans. R. Soc. Trop. Med. Hyg. 59, 489–506.

Maegraith, B., 1958. Schistosomiasis in China. Lancet 271, 208–214.

Malone, J.B., 2005. Biology-based mapping of vector-borne parasites by geographic information systems and remote sensing. Parassitologia 47, 27–50.

Mao, C.P., 1948. A review of the epidemiology of schistosomiasis japonica in China. Am. J. Trop. Med. 28, 659–672.

Mao, S.P., 1990. Epidemiology. In: Mao, S.P. (Ed.), Schistosome Biology and Control of Schistosomiasis. Publishing House for People's Health, Beijing, pp. 619–691.

Mao, S.P., Shao, B.R., 1982. Schistosomiasis control in the People's Republic of China. Am. J. Trop. Med. Hyg. 31, 92–99.

Martens, W.J.M., Jetten, T.H., Focks, D.A., 1997. Sensitivity of malaria, schistosomiasis and dengue to global warming. Clim. Change 35, 145–156.

Martens, W.J.M., Jetten, T.H., Rotmans, J., Niessen, L.W., 1995. Climate change and vector-borne diseases: a global modeling perspective. Glob. Environ. Change 5, 195–209.

McManus, D.P., 2000. A vaccine against Asian schistosomiasis: the story unfolds. Int. J. Parasitol. 30, 265–271.

McManus, D.P., Bartley, P.B., 2004. A vaccine against Asian schistosomiasis. Parasitol. Int. 53, 163–173.

McManus, D.P., Hu, W., Brindley, P.J., Feng, Z., Han, Z.G., 2004. Schistosome transcriptome analysis at the cutting edge. Trends Parasitol. 20, 301–304.

MOH, 1998. Epidemic Status of Schistosomiasis in China: A Nation Wide Sampling Survey in 1995. Nanjing University Press, Nanjing.

Mott, K.E., 1983. A reusable polyamide filter for diagnosis of *S. haematobium* infection by urine filtration. Bull. Soc. Pathol. Exot. Filiales 76, 101–104.

Mott, K.E., Dixon, H., 1982. Collaborative study on antigens for immunodiagnosis of schistosomiasis. Bull. World Health Organ. 60, 729–753.

Mott, K.E., Dixon, H., Carter, C.E., Garcia, E., Ishii, A., Matsuda, H., Mitchell, G., Owhashi, M., Tanaka, H., Tsang, V.C., 1987. Collaborative study on antigens for immunodiagnosis of *Schistosoma japonicum* infection. Bull. World Health Organ. 65, 233–244.

Murray, C.J.L., 1994. Quantifying the burden of disease: the technical basis for disability-adjusted life years. Bull. World Health Organ. 72, 429–445.

Murray, C.J.L., Lopez, A.D., 1996. The Global Burden of Disease: A Comprehensive Assessment of Mortality and Disability from Diseases, Injuries, and Risk Factors in 1990 and Projected to 2020. Harvard School of Public Health, Harvard University, Harvard.

N'Goran, E.K., Utzinger, J., Gnaka, H.N., Yapi, A., N'Guessan, N.A., Kigbafori, S.D., Lengeler, C., Chollet, J., Xiao, S.H., Tanner, M., 2003. Randomized, double-blind, placebo-controlled trial of oral artemether for the prevention of patent *Schistosoma haematobium* infections. Am. J. Trop. Med. Hyg. 68, 24–32.

Oliveira, D.M., Silva-Teixeira, D.N., Gustavson, S., Oliveira, S.M.P., Goes, A.M., 2000. Nitric oxide interaction with IL-10, MIP-1α, MCP-1 and RANTES over the in vitro granuloma formation against different *Schistosoma mansoni* antigenic preparations on human schistosomiasis. Parasitology 120, 391–398.

Oliver-Gonzalez, J., Bauman, P.M., Benenson, A.S., 1954. Intradermal response to egg antigen in humans with active and treated (fuadin) *Schistosoma mansoni* infections. Proc. Soc. Exp. Biol. Med. 87, 186–188.

Plouvier, S., Leroy, J.-C., Colette, J., 1975. A propos d'une technique simple de filtration des urines dans le diagnostic de la bilharziose urinaire en enquête de masse. Med. Trop. 35, 229–230.

Pontes, L.A., Oliveira, M.C., Katz, N., Dias-Neto, E., Rabello, A., 2003. Comparison of a polymerase chain reaction and the Kato–Katz technique for diagnosing infection with *Schistosoma mansoni*. Am. J. Trop. Med. Hyg. 68, 652–656.

Qiu, L.Z., Xue, H.C., 1990. Experimental diagnosis. In: Mao, S.P. (Ed.), Schistosome Biology and Control of Schistosomiasis. Publishing House for People's Health, Beijing, pp. 448–527.

Ridley, R.G., 2003. Product R&D for neglected diseases. Twenty-seven years of WHO/TDR experiences with public-private partnerships. EMBO Rep. 4, S43–S46.

Ross, A.G.P., Bartley, P.M., Sleigh, A.C., Olds, G.R., Li, Y.S., Williams, G.M., McManus, D.P., 2002. Schistosomiasis. N. Engl. J. Med. 346, 1212–1220.

Ross, A.G.P., Li, Y.S., Sleigh, A.C., McManus, D.P., 1997. Schistosomiasis control in the People's Republic of China. Parasitol. Today 13, 152–155.

Ross, A.G.P., Sleigh, A.C., Li, Y.S., Davis, G.M., Williams, G.M., Jiang, Z., Feng, Z., McManus, D.P., 2001. Schistosomiasis in the People's Republic of China: prospects and challenges for the 21st century. Clin. Microbiol. Rev. 14, 270–295.

Sabah, A.A., Fletcher, C., Webbe, G., Doenhoff, M.J., 1986. *Schistosoma mansoni*: chemotherapy of infections of different ages. Exp. Parasitol. 61, 294–303.

Santos, A.T., Blas, B.L., Nosenas, J.S., Portillo, G.P., Ortega, O.M., Hayashi, M., Boehme, K., 1979. Preliminary clinical trials with praziquantel in *Schistosoma japonicum* infections in the Philippines. Bull. World Health Organ. 57, 793–799.

Savioli, L., Engels, D., Endo, H., 2005. Extending the benefits of deworming for development. Lancet 365, 1520–1521.

Seubert, J., Pohlke, R., Loebich, F., 1977. Synthesis and properties of praziquantel, a novel broad spectrum anthelmintic with excellent activity against schistosomes and cestodes. Experientia 33, 1036–1037.

Shi, F.H., Zhang, Y.B., Ye, P., Lin, J.J., Cai, Y.M., Shen, W., Bickle, Q.D., Taylor, M.G., 2001. Laboratory and field evaluation of *Schistosoma japonicum* DNA vaccines in sheep and water buffalo in China. Vaccine 20, 462–467.

Shi, M.Z., Yu, D.B., Wei, W.Y., Zhang, C.S., He, H.B., Yang, G.F., Li, G.P., Ren, M.Y., 2004. Experimental study on susceptibility of praziquantel against *Schistosoma japonicum* in repeated chemotherapy areas in Dongting Lake region. Chin. J. Schisto. Cont. 16, 171–173.

Solomon, J.S., Nixon, C.P., McGarvey, S.T., Acosta, L.P., Manalo, D., Kurtis, J.D., 2004. Expression, purification, and human antibody response to a 67 kDa vaccine candidate for schistosomiasis japonica. Protein Exp. Purif. 36, 226–231.

Song, H.T., Liang, Y.S., Dai, J.R., Li, L.G., Shen, X.H., Tian, Q.A., Ji, Z.S., Yin, F., 2004. Studies on sensitivity of *Schistosoma japonicum* to praziquantel—situation in low endemic areas. Chin. J. Schisto. Cont. 16, 58–59.

Song, Y., Xiao, S.H., Wu, W., Zhang, S., Xie, H.Q., Xu, X.P., Hu, X.Y., Cui, Q., Chen, M.G., Zheng, J., 1998. Preventive effect of artemether on schistosome infection. Chin. Med. J. 111, 123–127.

Stoll, N.R., 1947. This wormy world. J. Parasitol. 33, 1–18.

Sutherst, R.W., 2004. Global change and human vulnerability to vector-borne diseases. Clin. Microbiol. Rev. 17, 136–173.

Tan, H.Z., Yang, M.X., Wu, Z.G., Zhou, J., Liu, A.Z., Li, S.Q., Yang, T.B., Zhou, Y.B., Sun, Z.Q., 2004. Rapid screening method for *Schistosoma japonicum* infection using questionnaires in flood area of the People's Republic of China. Acta Trop. 90, 1–9.

Tanaka, H., Tsuji, M., 1997. From discovery to eradication of schistosomiasis in Japan: 1847–1996. Int. J. Parasitol. 27, 1465–1480.

Tang, D.L., Yu, D.B., Li, Y.Y., Xie, M.S., Wen, H.M., Cai, W.B., He, W.L., 2001. Analysis of cost-effectiveness on two chemotherapy schemes to schistosomiasis in hyperendemic villages of Hunan province. Prac. Prev. Med. 8, 165–168.

Tao, H.Q., Li, S.W., 1999. Consolidation and surveillance situation and suggestion for schistosomiasis control in Zhejiang province. Chin. J. Schisto. Contr. 11, 226–227.

Taylor, M.G., 1994. Schistosomiasis vaccines: farewell to the God of Plague? J Trop. Med. Hyg. 97, 257–268.

Tian, Z.Y., Liu, D.S., Xiao, Z.W., Zhou, Y.C., Qu, G.S., Yao, X.M., Zhang, X.Y., 2001. A cost-effect study of artesunate in the prophylaxis of schistosomiasis in an endemic area. Chin. J. Schisto. Cont. 13, 299–300.

Tian, Z.Y., Xiao, S.H., Xiao, J.W., Zhou, Y.C., Liu, D.H., Zheng, J., Chen, M.G., Qu, G.H., Zhang, X.Y., Yao, X.M., Zhang, X.Z., Zhang, D.L., 1997. Reduction of *Schistosoma japonicum* infection in an endemic area in islet with embankment after prophylaxis with oral artemether throughout the transmission season. Chin. J. Parasitol. Parasitic Dis. 15, 208–211.

Utzinger, J., Bergquist, R., Xiao, S.H., Singer, B.H., Tanner, M., 2003a. Sustainable schistosomiasis control—the way forward. Lancet 362, 1932–1934.

Utzinger, J., Booth, M., N'Goran, E.K., Müller, I., Tanner, M., Lengeler, C., 2001a. Relative contribution of day-to-day and intra-specimen variation in faecal egg counts of *Schistosoma mansoni* before and after treatment with praziquantel. Parasitology 122, 537–544.

Utzinger, J., Chollet, J., You, J.Q., Mei, J.Y., Tanner, M., Xiao, S.H., 2001b. Effect of combined treatment with praziquantel and artemether on *Schistosoma japonicum* and *Schistosoma mansoni* in experimentally infected animals. Acta Trop. 80, 9–18.

Utzinger, J., Keiser, J., 2004. Schistosomiasis and soil-transmitted helminthiasis: common drugs for treatment and control. Expert Opin. Pharmacother. 5, 263–285.

Utzinger, J., Keiser, J., Xiao, S.H., Tanner, M., Singer, B.H., 2003b. Combination chemotherapy of schistosomiasis in laboratory studies and clinical trials. Antimicrob. Agents Chemother. 47, 1487–1495.

Utzinger, J., N'Goran, E.K., N'Dri, A., Lengeler, C., Xiao, S.H., Tanner, M., 2000. Oral artemether for prevention of *Schistosoma mansoni* infection: randomised controlled trial. Lancet 355, 1320–1325.

Utzinger, J., Xiao, S.H., Keiser, J., Chen, M.G., Zheng, J., Tanner, M., 2001c. Current progress in the development and use of artemether for chemoprophylaxis of major human schistosome parasites. Curr. Med. Chem. 8, 1841–1860.

Utzinger, J., Xiao, S.H., N'Goran, E.K., Bergquist, R., Tanner, M., 2001d. The potential of artemether for the control of schistosomiasis. Int. J. Parasitol. 31, 1549–1562.

van Dam, G.J., Wichers, J.H., Falcao Ferreira, T.M., Ghati, D., van Amerongen, A., Deelder, A.M., 2004. Diagnosis of schistosomiasis by reagent strip test for detection of circulating cathodic antigen. J. Clin. Microbiol. 42, 5458–5461.

van Lieshout, L., Polderman, A.M., Deelder, A.M., 2000. Immunodiagnosis of schistosomiasis by determination of the circulating antigens CAA and CCA, in particular in individuals with recent or light infections. Acta Trop. 77, 69–80.

Verjovski-Almeida, S., DeMarco, R., Martins, E.A.L., Guimarães, P.E.M., Ojopi, E.P.B., Paquola, A.C.M., Piazza, J.P., Nishiyama Jr., M.Y., Kitajima, J.P., Adamson, R.E., Ashton, P.D., Bonaldo, M.F., Coulson, P.S., Dillon, G.P., Farias, L.P., Gregorio, S.P., Ho, P.L., Leite, R.A., Malaquias, L.C.C., Marques, R.C.P., Miyasato, P.A., Nascimento, A.L.T.O., Ohlweiler, F.P., Reis, E.M., Ribeiro, M.A., Sá, R.G., Stukart, G.C., Soares, M.B., Gargioni, C., Kawano, T., Rodrigues, V., Madeira, A.M.B.N., Wilson, R.A., Menck, C.F.M., Setubal, J.C., Leite, L.C.C., Dias-Neto, E., 2003. Transcriptome analysis of the acoelomate human parasite *Schistosoma mansoni*. Nat. Genet. 35, 148–157.

Verjovski-Almeida, S., Leite, L.C.C., Dias-Neto, E., Menck, C.F.M., Wilson, R.A., 2004. Schistosome transcriptome: insights and perspectives for functional genomics. Trends Parasitol. 20, 304–308.

Vlassoff, C., Manderson, L., 1998. Incorporating gender in the anthropology of infectious diseases. Trop. Med. Int. Health 3, 1011–1019.

Vogel, H., Minning, W., 1949. Hüllenbildung bei Bilharzia-Cercarien im Serum Bilharzia-infizierter Tiere und Menschen. Zbl. Bakt. Abt. I Orig. 153, 91–105.

Wang, J.L., Xiao, S.H., Yang, Z., Wang, M.K., Yang, H., Liu, Y.H., Zhou, G.S., Zhen, J., Chen, M.G., 1997. Effect of oral artemether in controlling schistosomiasis in Yunnan mountainous endemic area. Chin. J. Parasitol. Parasitic Dis. 15, 138–142.

Wang, T.P., Johansen, M.V., Zhang, S.Q., Wang, F.F., Wu, W.D., Zhang, G.H., Pan, X.P., Ju, Y., Ørnbjerg, N., 2005. Transmission of Schistosoma japonicum by humans and domestic animals in the Yangtze River valley, Anhui province, China. Acta Trop. 96, 198–204.

Wang, X.Y., Hong, X.L., Yan, J.L., Lu, R.G., Shao, D., Yang, S.G., Zhong, J.H., Li, Z.H., 2000. Study on cost-effectiveness of strategy of examination and therapy with IHA after mass questionnaire in middle-endemic areas of schistosomiasis. Chin. J. Schisto. Cont. 12, 277–279.

Wang, X.Z., Li, S.T., Zhou, Z.X., 1999. A rapid one-step method of EIA for detection of circulating antigen of *Schistosoma japonicum*. Chin. Med. J. 112, 124–128.

Wen, L.Y., Chen, J.H., Ding, J.Z., Zhang, J.F., Lu, S.H., Yu, L.L., Shen, L.Y., Wu, G.L., Zhou, X.N., Zheng, J., 2005. Evaluation on the applied value of the dot immunogold filtration assay (DIGFA) for rapid detection of anti-*Schistosoma japonicum* antibody. Acta Trop. 96, 142–147.

WHO, 1985. The control of schistosomiasis: report of a WHO expert committee. WHO Tech. Rep. Ser. No. 728, World Health Organization, Geneva.

WHO, 1993. The control of schistosomiasis: second report of the WHO expert committee. WHO Tech. Rep. Ser. No. 830, World Health Organization, Geneva.

WHO, 2002. Prevention and control of schistosomiasis and soil-transmitted helminthiasis: report of a WHO expert committee. WHO Tech. Rep. Ser. No. 912, World Health Organization, Geneva.

WHO, 2004. The World Health Report 2004—Changing History. World Health Organization, Geneva.

Williams, G.M., Sleigh, A.C., Li, Y.S., Feng, Z., Davis, G.M., Chen, H., Ross, A.G.P., Bergquist, R., McManus, D.P., 2002. Mathematical modelling of schistosomiasis japonica: comparison of control strategies in the People's Republic of China. Acta Trop. 82, 253–262.

Wilson, R.A., Curwen, R.S., Braschi, S., Hall, S.L., Coulson, P.S., Ashton, P.D., 2004. From genomes to vaccines via the proteome. Mem. Inst. Oswaldo Cruz 99 (Suppl. 1), 45–50.

Woodrow, C.J., Haynes, R.K., Krishna, S., 2005. Artemisinins. Postgrad. Med. J. 81, 71–78.

Wright, W.H., 1950. Bilharziasis as a public-health problem in the Pacific. Bull. World Health Organ. 2, 581–595.

Wu, G.L., 2002. A historical perspective on the immunodiagnosis of schistosomiasis in China. Acta Trop. 82, 193–198.

Wu, L.J., Li, S.W., Xuan, Y.X., Xu, P.S., Liu, Z.D., S, W.L., Zhou, S.Y., Qiu, Y.X., Liu, Y.M., 1995. Field application of artesunate in prophylaxis of schistosomiasis: an observation of 346 cases. Chin. J. Schisto. Cont. 7, 323–327.

Wu, W.L., Wang, J.R., Wen, L.Y., Huang, Y.Y., Xu, X.F., Yu, W.M., 2005a. Surveillance and control of post-transmission schistosomiasis in Jiaxing prefecture, Zhejiang province, China. Acta Trop. 96, 282–287.

Wu, X.H., Chen, M.G., Zheng, J., 2005b. Surveillance of schistosomiasis in five provinces of China which have reached the national criteria for elimination of the disease. Acta Trop. 96, 276–281.

Wu, Z.D., Lü, Z.Y., Yu, X.B., 2005c. Development of a vaccine against *Schistosoma japonicum* in China: a review. Acta Trop. 96, 106–116.

Xiao, S.H., 2005. Development of antischistosomal drugs in China, with particular consideration to praziquantel and the artemisinins. Acta Trop. 96, 153–167.

Xiao, S.H., Booth, M., Tanner, M., 2000. The prophylactic effects of artemether against *Schistosoma japonicum* infections. Parasitol. Today 16, 122–126.

Xiao, S.H., Catto, B.A., 1989. In vitro and in vivo studies of the effect of artemether on *Schistosoma mansoni*. Antimicrob. Agents Chemother. 33, 1557–1562.

Xiao, S.H., Chollet, J., Utzinger, J., Matile, H., Mei, J.Y., Tanner, M., 2001. Artemether administered together with haemin damages schistosomes in vitro. Trans. R. Soc. Trop. Med. Hyg. 95, 67–71.

Xiao, S.H., Shi, Z.G., Zhuo, S.J., Wang, C.Z., Zhang, Z.G., Chu, B., Zhen, J., Chen, M.G., 1996a. Field studies on the preventive effect of oral artemether against schistosomal infection. Chin. Med. J. 109, 272–275.

Xiao, S.H., Tanner, M., N'Goran, E.K., Utzinger, J., Chollet, J., Bergquist, R., Chen, M.G., Zheng, J., 2002. Recent investigations of artemether, a novel agent for the prevention of schistosomiasis japonica, mansoni and haematobia. Acta Trop. 82, 175–181.

Xiao, S.H., Wang, J.L., Wang, C.Z., Chu, B., Yang, H., Liu, Y.H., Zheng, J., Chen, M.G., 1996b. Protection of the residents from schistosome infection using oral artemether in mountainous endemic area. Chin. J. Parasitol. Parasitic Dis. 14, 11–14.

Xiao, S.H., You, J.Q., Yang, Y.Q., Wang, C.Z., 1995. Experimental studies on early treatment of schistosomal infection with artemether. Southeast Asian J. Trop. Med. Public Health 26, 306–318.

Xiao, S.H., Yue, W.J., Yang, Y.Q., You, J.Q., 1987. Susceptibility of *Schistosoma japonicum* to different developmental stages to praziquantel. Chin. Med. J. 100, 759–768.

Xiao, X., Wang, T.P., Tian, Z.G., 2003. Development of a rapid, sensitive, dye immunoassay for schistosomiasis diagnosis: a colloidal dye immunofiltration assay. J. Immunol. Methods 280, 49–57.

Xiao, X., Wang, T.P., Ye, H.Z., Qiang, G.X., Wei, H.M., Tian, Z.G., 2005. Field evaluation of a rapid, visually read colloidal dye immunofiltration assay for *Schistosoma japonicum* for screening in areas of low transmission. Bull. World Health Organ. 83, 526–533.

Xu, M.S., Xiao, S.H., Song, Q., Tao, C.G., Xia, C.G., Wang, H., Chen, M.G., Zheng, J., Bu, C.H., Hu, F.Y., Ou, N., Zhang, X.S., 1997. Observation on the effect of artemether on controlling schistosomiasis japonica in an endemic area of marshland. Chin. J. Parasitol. Parasitic Dis. 15, 212–215.

Xu, M.S., Zhang, S.Q., Li, S.W., Wang, T.P., Chen, J.R., Ou, N., Fang, G.R., Wang, Q.Z., Li, J.T., Zhang, X.S., 1999. Field application of oral artesunate for preventing *Schistosoma japonicum* infection. Chin. J. Parasitol. Parasitic Dis. 17, 241–243.

Xu, X.J., Wei, F.H., Yang, X.X., Dai, Y.H., Yu, G.Y., Chen, L.Y., Su, Z.M., 2000. Possible effects of the Three Gorges dam on the transmission of *Schistosoma japonicum* on the Jiang Han plain, China. Ann. Trop. Med. Parasitol. 94, 333–341.

Yang, G.J., Vounatsou, P., Zhou, X.N., Tanner, M., Utzinger, J., 2005a. A Bayesian-based approach for spatio-temporal modeling of county level prevalence of *Schistosoma japonicum* infection in Jiangsu province, China. Int. J. Parasitol. 35, 155–162.

Yang, G.J., Vounatsou, P., Zhou, X.N., Tanner, M., Utzinger, J., 2005b. A potential impact of climate change and water resource development on the transmission of *Schistosoma japonicum* in China. Parassitologia 47, 127–134.

Yang, G.J., Vounatsou, P., Zhou, X.N., Utzinger, J., Tanner, M., 2005c. A review of geographic information system and remote sensing with applications to the epidemiology and control of schistosomiasis in China. Acta Trop. 96, 117–129.

Yang, Y., Shen, G.R., Mei, Y.S., Zhang, C.H., Ying, L.Z., You, B.Y., Dong, Y.Q., Fu, S., Wu, H.M., Qie, Y.D., Yang, J.S., Sheng, H.L., Gu, M.S., Zhou, H.L., 1981. Study on the new drug praziquantel for schistosomiasis. New Med. 12, 5–9.

Yip, K., 1998. Antimalarial work in China: a historical perspective. Parassitologia 40, 29–38.

Yu, J.M., de Vlas, S.J., Yuan, H.C., Gryseels, B., 1998. Variations in fecal *Schistosoma japonicum* egg counts. Am. J. Trop. Med. Hyg. 59, 370–375.

Yuan, H.C., 1995. Schistosomiasis control in China. Mem. Inst. Oswaldo Cruz 90, 297–301.

Yuan, H.C., Guo, J.G., Bergquist, R., Tanner, M., Chen, X.Y., Wang, H.Z., 2000a. The 1992–1999 World Bank schistosomiasis research initiative in China: outcome and perspectives. Parasitol. Int. 49, 195–207.

Yuan, L.P., Manderson, L., Ren, M.Y., Li, G.P., Yu, D.B., Fang, J.C., 2005a. School-based interventions to enhance knowledge and improve case management of schistosomiasis:a case study from Hunan, China. Acta Trop. 96, 248–254.

Yuan, L.P., Manderson, L., Tempongko, M.S.B., Wei, W.Y., Aiguo, P., 2000b. The impact of educational videotapes on water contact behaviour of primary school students in the Dongting Lakes region. China. Trop. Med. Int. Health 5, 538–544.

Yuan, Y., Xu, X.J., Dong, H.F., Jiang, M.S., Zhu, H.G., 2005b. Transmission control of schistosomiasis japonica: implementation and evaluation of different snail control interventions. Acta Trop. 96, 191–197.

Zhang, S.J., Lin, D.D., Liu, Y.M., Liu, H.Y., Liu, Z.D., Hu, L.S., Ga, Z.L., Xu, M.S., Yi, Z.H., Wu, L.J., Li, S.W., 2000. Clinical trials on preventive effect of artesunate on schistosomiasis japonica. Mod. Diagn. Treat. 11, 68–72.

Zhang, Z.Y., Xue, D.Z., Zhou, X.N., Zhou, Y., Liu, S.J., 2005. Remote sensing and spatial statistical analysis to predict the distribution of *Oncomelania hupensis* in the marshlands of China. Acta Trop. 96, 205–212.

Zhao, G.M., Zhao, Q., Jiang, Q.W., Chen, X.Y., Wang, L.Y., Yuan, H.C., 2005. Surveillance for schistosomiasis japonica in China from 2000 to 2003. Acta Trop. 96, 288–295.

Zhao, W.X., Wu, G.L., Guan, X.H., 1993. Immunodiagnosis of *Schistosoma japonicum* infection in China. Chin. Med. J. 106, 623–627.

Zhen, J., 1993. A brief introduction to a nation-wide sampling survey on schistosomiasis. Chin. Med. J. 106, 569–575.

Zheng, M., Cai, W.M., Zhao, J.K., Zhu, S.M., Liu, R.H., 2005. Determination of serum levels of YKL-40 and hyaluronic acid in patients with hepatic fibrosis due to schistosomiasis japonica and appraisal of their clinical value. Acta Trop. 96, 148–152.

Zhou, H., Ross, A.G.P., Hartel, G.F., Sleigh, A.C., Williams, G.M., McManus, D.P., Luo, X.S., He, Y., Li, Y.S., 1998. Diagnosis of schistosomiasis japonica in Chinese schoolchildren by administration of a questionnaire. Trans. R. Soc. Trop. Med. Hyg. 92, 245–250.

Zhou, X.N., Acosta, L., Willingham, A.L., Leonardo, L.R., Chen, M.G., Aligui, G., Feng, Z., Olveda, R., 2002a. Regional network for research, surveillance and control of Asian schistosomiasis (RNAS). Acta Trop. 82, 305–311.

Zhou, X.N., Jiang, Q.W., Sun, L.P., Wang, T.P., Hong, Q.B., Zhao, G.M., Wen, L.Y., Ying, Z.C., Wu, X.H., Lin, D.D., 2005. Control and surveillance of schistosomiasis in China. Chin. J. Schisto. Contr. 17 161–165.

Zhou, X.N., Chen, J.X., Chen, M.G., Bergquist, R., 2005a. The National Institute of Parasitic Diseases, Chinese Center for Disease Control and Prevention: a new administrative structure for schistosomiasis control. Acta Trop. 96, 296–302.

Zhou, X.N., Chen, M.G., McManus, D., Bergquist, R., 2002b. Schistosomiasis control in the 21st century. Proceedings of the International Symposium on Schistosomiasis, Shanghai, 4–6 July 2001. Acta Trop. 82, 95–114.

Zhou, X.N., Lin, D.D., Yang, H.M., Chen, H.G., Sun, L.P., Yang, G.J., Hong, Q.B., Brown, L., Malone, J.B., 2002c. Use of landsat TM satellite surveillance data to measure the impact of the 1998 flood on snail intermediate host dispersal in the lower Yangtze River Basin. Acta Trop. 82, 199–205.

Zhou, X.N., Malone, J.B., Kristensen, T.K., Bergquist, N.R., 2001. Application of geographic information systems and remote sensing to schistosomiasis control in China. Acta Trop. 79, 97–106.

Zhou, X.N., Wang, L.Y., Chen, M.G., Wang, T.P., Guo, J.G., Wu, X.H., Jiang, Q.W., Zheng, J., Chen, X.Y., 2005b. An economic evaluation of the national schistosomiasis control programme in China from 1992 to 2000. Acta Trop. 96, 255–265.

Zhou, X.N., Wang, L.Y., Chen, M.G., Wu, X.H., Jiang, Q.W., Chen, X.Y., Zheng, J., Utzinger, J., 2005c. The public health significance and control of schistosomiasis in China—then and now. Acta Trop. 96, 97–105.

Zhou, X.N., Yang, G.J., Sun, L.P., Hong, Q.B., Yang, K., Wang, R.B., Hua, Z.H., 2002d. Potential impact of global warming on the transmission of schistosomiasis. Chin. J. Epidemiol. 23, 83–86.

Zhu, Y.C., 2005. Immunodiagnosis and its role in schistosomiasis control in China: a review. Acta Trop. 96, 130–136.

Zhu, Y.C., He, W., Liang, Y.S., Xu, M., Yu, C.X., Hua, W.Q., Chao, G.Q., 2002. Development of a rapid, simple dipstick dye immunoassay for schistosomiasis diagnosis. J. Immunol. Methods 266, 1–5.

Zhu, Y.C., Ren, J.G., Da'dara, A., Harn, D., Xu, M., Si, J., Yu, C.X., Liang, Y.S., Ye, P., Yin, X.R., He, W., Xu, Y.L., Cao, G.Q., Hua, W.Q., 2004. The protective effect of a *Schistosoma japonicum* Chinese strain 23 kDa plasmid DNA vaccine in pigs is enhanced with IL-12. Vaccine 23, 78–83.

Zhu, Y.C., Socheat, D., Bounlu, K., Liang, Y.S., Sinuon, M., Insisiengmay, S., He, W., Xu, M., Shi, W.Z., Bergquist, R., 2005. Application of dipstick dye immunoassay (DDIA) kit for the diagnosis of schistosomiasis mekongi. Acta Trop. 96, 137–141.