

## Helminthiases in the People's Republic of China: Status and prospects



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### ABSTRACT

Helminth infections, many of them listed as neglected tropical diseases by the World Health Organization, remain a public health issue in many parts of the world. The People's Republic of China (P.R. China) stands out due to impressive progress in the control and local elimination of helminth infections. An important contextual factor is P.R. China's sustained social and economic development that allowed implementation of health-related poverty alleviation, improving water, sanitation and hygiene, enhancing information, education and communication, coupled with major engineering and infrastructure development and intersectoral collaboration. Nonetheless, food-borne trematodiasis, soil-transmitted helminthiases, echinococcosis, cysticercosis/taeniasis and schistosomiasis still exert a considerable burden in P.R. China, even though the numbers of infected people have decreased substantially since the new millennium. This special issue of *Acta Tropica* provides a comprehensive update of the current knowledge of the main helminth infections in P.R. China, summarises progress in research and discusses future prospects for gaining and sustaining control towards the final goal of breaking transmission and hence, eliminating helminthiases. It consists of 34 articles with a wide coverage that can be grouped into six domains: (i) epidemiological assessment and disease burden estimates; (ii) diagnostics and antigen characterisation; (iii) drug and vaccine development; (iv) host-parasite interactions and snail genetics; (v) surveillance and public health response; and (vi) capacity building and international cooperation. The control and elimination of helminthiases not only furthers the health and wellbeing of the Chinese people, but also provides innovative approaches, tools and strategies, which can be adopted and applied in other countries and regions of the world where helminthiases still prevail.

### 1. Introduction

This special issue of *Acta Tropica* pertaining to the status and prospects of helminthiases in the People's Republic of China (P.R. China) was initiated to shed new light on which helminth infections pose the greatest threat and what is being done domestically to improve the situation. In spite of available drugs and vaccines for some helminth infections, continuation of deeply rooted lifestyles and behaviours contribute to the emergence, re-emergence and spread of infections, while the lack of sufficiently sensitive diagnostics makes it difficult to produce reliable estimates of the distribution and burden of the endemic helminth diseases when infection intensity falls (Bergquist et al., 2009; Utzinger et al., 2015).

The cross-disciplinary perspective applied here brings together disease-specific research, innovative approaches and information on prevalence rates as it highlights research priorities and suggests ways to take them forward. Early recognition of the role of poverty in sustaining the panorama of endemic diseases has led to a deeper understanding of health-related poverty alleviation (King, 2010; Wang and Zhou, 2020). Meanwhile, political will, intersectoral collaboration and community participation will underpin the sustained commitment needed to achieve a working control strategy in P.R. China and elsewhere (Hotez, 2019; Nakagawa et al., 2015; Wang et al., 2008). The unfolding story of conquering the endemic helminthiases started with the elimination of lymphatic filariasis (Fang and Zhang, 2019), and other

helminths are now being dealt with in a consorted manner (Fig. 1). As a consequence, we are witnessing the payoffs of this forward thinking in the form of novel ways of disease risk profiling, transmission control and different aspects of social and economic approaches, emphasising the importance of health promotion and education. The set of recommendations issuing from this special issue will no doubt further consolidate current control activities with the ultimate aim to eliminate all the main endemic helminthiases from P.R. China.

The purpose of this special issue was to investigate and update the current situation of the major helminthiases in P.R. China, including geographical distribution, epidemiological characteristics and risk factors. This is supported by the work of Chinese scientists in diverse areas of study, covering epidemiological assessment and disease burden estimates, progress in surveillance and public health responses, diagnostics, treatment, host-parasite interaction capacity building and international cooperation. The overarching theme concerns how laboratory and applied research are working hand-in-hand to produce and utilize control tools that contribute to the gaining and sustaining of control and eventually elimination of helminth infections in P.R. China.

### 2. General profile

Basic research facilitates discovery that leads to a deeper understanding of biology and disease mechanisms that, in turn, spurs innovation for development of novel tools for disease control and

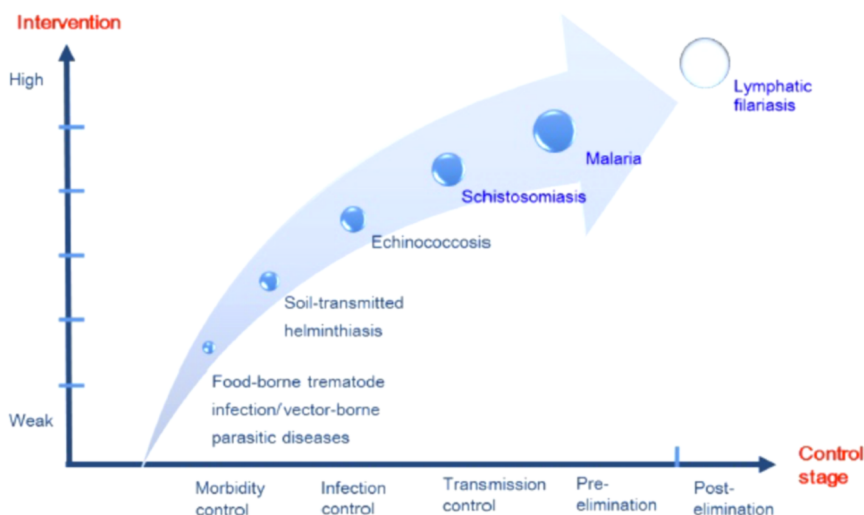


Fig. 1. Progress in intervention and control of helminthiases and malaria in the People's Republic of China (Chen et al., 2020a).

elimination. Applied research promotes the validation and application of improved tools, including diagnosis, drugs and vaccines. Together, these activities contribute to the advancement of control and elimination strategies, which play a key role in the decrease of helminth infections and interruption of disease transmission in P.R. China that we are increasingly witnessing (Qian et al., 2019a).

This special issue of *Acta Tropica* consists of 34 articles, the majority of which focuses on zoonotic helminthiases, mainly schistosomiasis and food-borne trematodiasis (FBTs), as summarised in Table 1. The provenance of the papers is divided between national and provincial centres, research institutions, universities and hospitals. As shown in Table 2, most articles stem from provincial centres for disease control and prevention (CDC) and institutes of parasitic diseases, particularly the National Institute of Parasitic Diseases (NIPD) based in Shanghai.

Summing up all the authors on the 34 articles revealed a total number of 310. Of note, there were 241 unique authors, while 37

Table 2

Affiliations of the 34 papers published in this special issue of *Acta Tropica* pertaining to helminthiases in the People's Republic of China, based on address details of the corresponding authors.

| Administrative level  | Number of papers |
|-----------------------|------------------|
| China CDC-level       | 1                |
| Provincial CDC        | 4                |
| National IPD          | 15               |
| Provincial IPD        | 2                |
| University            | 5                |
| Hospital              | 3                |
| Independent institute | 4                |
| Total                 | 34               |

CDC, Center for Disease Control and Prevention; IPD, Institute of Parasitic Diseases.

Table 1

Diversity and classification of the 34 articles published in this special issue of *Acta Tropica* pertaining to helminthiases in the People's Republic of China.

| Route of transmission | Disease                     | Number of articles |
|-----------------------|-----------------------------|--------------------|
| Zoonotic              | Total                       | 14                 |
|                       | Schistosomiasis             | 11                 |
|                       | (including: Snail genetics) | (2)                |
|                       | Echinococcosis              | 3                  |
| Soil-transmitted      | Total*                      | 3                  |
| Food-borne            | Total                       | 12                 |
|                       | Clonorchiasis               | 5                  |
|                       | Paragonimiasis              | 2                  |
|                       | Fascioliasis                | 2                  |
|                       | Cysticercosis/taeniasis     | 1                  |
|                       | Trichinellosis              | 1                  |
| Other                 | Hepatic capillariasis**     | 1                  |
| Other                 | Cross-cutting***            | 4                  |

\* Includes infection with *Ascaris lumbricoides*, *Trichuris trichiura* and two species of hookworm (*Ancylostoma duodenale* and *Necator americanus*); infection most commonly due to contaminated water but can also occur through consumption of raw food.

\*\* Infection with *Capillaria hepatica*; infection most commonly due to faecal contaminated food, water or soil.

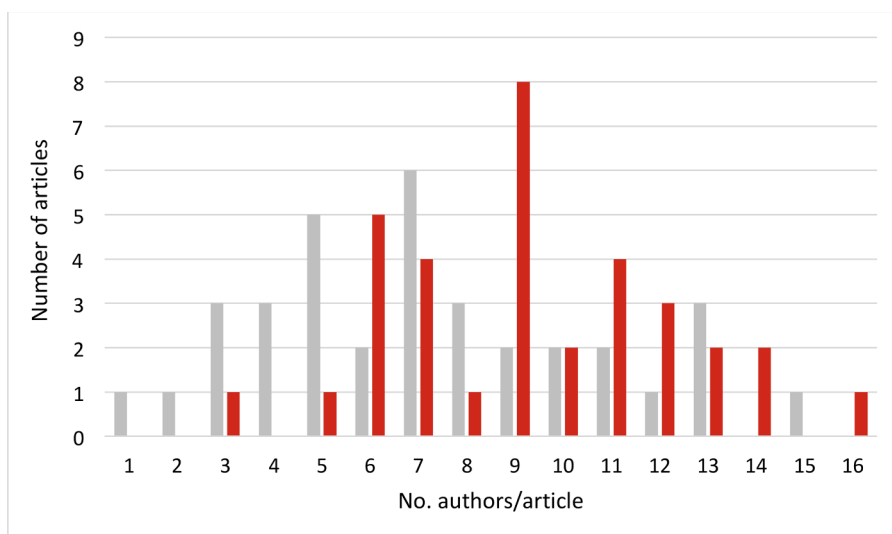
\*\*\* Four articles on drug development, on surveillance and control, on capacity building and international cooperation pertain various helminths.

authors contributed to two articles or more, one author to as many as 14 articles. The median number of authors per article is 9 with a range from 3 to 16 (Fig. 2). Compared to a special issues of *Acta Tropica* pertaining to helminthiases in Asia, published in 2015 (Uttinger et al., 2015), the median number of authors per article is somewhat higher (9 vs. 7). Our meta-data therefore suggest that there is considerable collaboration, at least in terms of multiple authorships. However, this observation must be juxtaposed with the provenance of the 34 articles in terms of country affiliations of the authors (Fig. 3). In brief, each of the 34 articles is given the same weight. For example, if an article is written by only three authors, each contributes a third to the overall weight of this specific article, while 10 co-authors on a single paper contribute one-tenth each. For authors who are affiliated with two different countries, each country is accounted half. Taking this weighing into account, P.R. China was the predominant country (94.5%), followed by Mongolia (1.3%), the US (1.3%) and the UK (0.8%).

Table 3 shows the contribution of the 34 articles, grouped into six domains, stratified by 10 helminthiases. Fig. 4 shows a cloud tag of the 178 keywords put forth in the collection of 34 articles. Of note, P.R. China and the three most widely covered helminthiases (i.e. schistosomiasis, soil-transmitted helminthiases and food-borne trematodiasis (FBTs)) stand out.

### 3. Target helminths: a landscape of different distributions

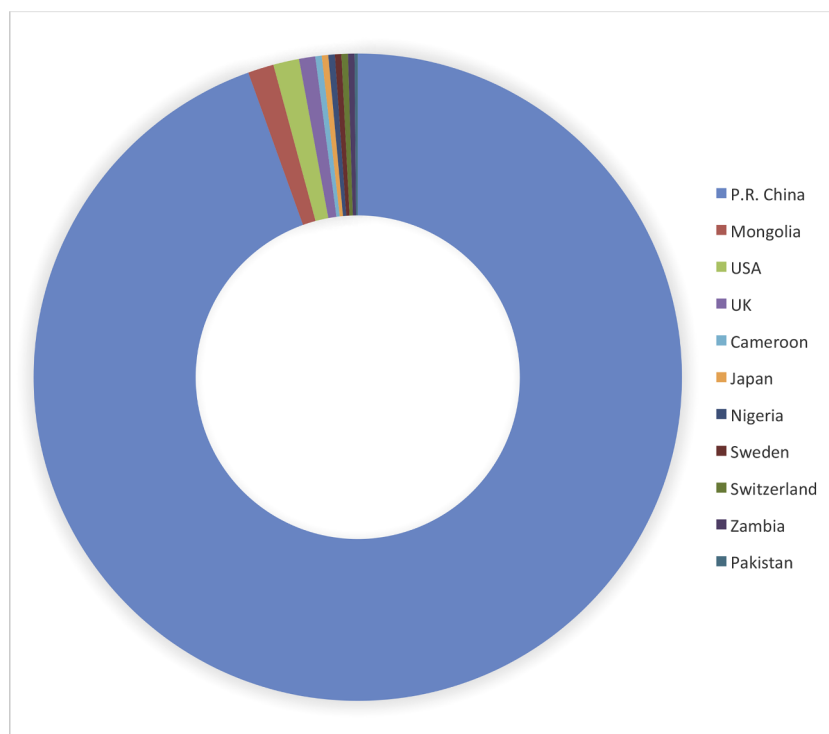
From a historical point of view, the disease caused by the blood fluke *Schistosoma japonicum* ranks as the most important helminth



**Fig. 2.** Histogram showing the number of authors per article in a collection of 34 articles in a special issue of *Acta Tropica* pertaining to helminthiases in the People's Republic of China (red bars). For comparison, the number of authors in 35 articles in a previous special issue focussing on research and control of helminthiases in Asia is also given (grey bars; Utzinger et al., 2015).

infection in P.R. China (Chen et al., 2018; Li et al., 2017; Utzinger et al., 2005). High morbidity countered national development and the government continues giving control of schistosomiasis a high priority since the 1950s when an estimated 11–12 million people were affected (Utzinger et al., 2005). The main control strategy over time changed from snail control to chemotherapy – of both humans and livestock – when praziquantel became available in the 1980s. Since 2004, integrated control is being implemented, combining chemotherapy, snail control, water, sanitation and hygiene (WASH) as well as information, education and communication (IEC) (Xu et al., 2016). Considerable progress has been made over the past 70 years; the number of infection officially reported in 2018 has been as low as 29,000 cases in the whole country (Zhang et al., 2019d). Hence, the work towards achievement of schistosomiasis elimination in P.R. China by 2030 is a convincing exercise (Sun et al., 2017).

Of note, P.R. China has the largest burden of alveolar echinococcosis worldwide to deal with and the country is also endemic for cystic echinococcosis. The former type of the disease is caused by *Echinococcus multilocularis* (Wang, 2016; Wang et al., 2012), and the latter by *E. granulosus* (Qian et al., 2017). The latest national survey estimates that approximately 170,000 individuals are infected (Qian and Zhou, 2018a). Echinococcosis is prevalent in the mountainous, western provinces, where the various domestic animals play the role of intermediate hosts, with humans often but accidentally infected. In recent years, echinococcosis obtained growing attention from the government, which has led to integrated measures being implemented in the endemic areas. Local populations are screened and those found positive treated with benzimidazoles (albendazole or mebendazole), or subjected to surgical interventions, while dogs are either killed or also treated with benzimidazoles as they are the main definitive hosts



**Fig. 3.** Provenance of the 34 articles, stratified by authors' country affiliations, of the current special issue of *Acta Tropica* pertaining to helminthiases in the People's Republic of China.

Table 3

Diversity between research foci. While apart from cysticercosis and fascioliasis, all helminthiases are addressed in the eight articles of the chapter on diagnostics and antigen characterisation, only selected helminthiasis could be addressed in the other chapters.

| Disease         | Study reference   |  |                              |   |   |   |
|-----------------|---|--|------------------------------|---|---|---|
|                 | Epidemiological assessment and disease burden estimates | Diagnostics and antigen characterisation | Drug and vaccine development | Host-parasite interactions and snail genetics | Surveillance and public health response | Capacity building and international cooperation |
| Capillariasis   | –   | 1  | –                            | 1   | –                                       | –   |
| Clonorchiasis   | –   | 1  | –                            | 1   | 3                                       | 1   |
| Cysticercosis   | –   | –  | 1                            | 1   | –                                       | –   |
| Echinococcosis  | 1   | 1  | –                            | –   | –                                       | 2   |
| Fascioliasis    | 2   | –  | –                            | –   | –                                       | –   |
| Paragonimiasis  | –   | 2  | –                            | –   | –                                       | –   |
| Schistosomiasis | 2   | 3  | 2                            | 2   | –                                       | 2   |
| STH             | –   | 1  | 1                            | –   | 4                                       | 1   |
| Taeniasis       | –   | 1  | 1                            | 1   | –                                       | –   |
| Trichinellosis  | –   | –  | 1                            | –   | –                                       | –   |

STH, Soil-transmitted helminthiasis.

contaminating the environment with parasite eggs (Qian et al., 2019a). Integrated measures are implemented in the endemic areas, but much work remains before control can be established

The STHs are roundworms, mainly *Ascaris lumbricoides* and *Trichuris trichiura* and, in tropical areas, the two hookworm species, *Ancylostoma duodenale* and *Necator americanus*, are also prevalent. The prevalence of STHs in P.R. China was very high (estimates suggest well above 50%) as late as 30 years ago (Xu et al., 1995). Periodic deworming with albendazole or mebendazole is effective for morbidity control. Along with

improved provision of clean water and sanitation plus IEC, the prevalence of the STHs were strongly reduced. These infections are only common – currently affecting about 30 million people – in the southwestern parts of P.R. China (Qian et al., 2019a).

*Clonorchis sinensis*, *Opisthorchis* spp., *Fasciola* spp. and *Paragonimus* spp. are trematode flatworms acquired through ingestion of raw or undercooked food contaminated with the larval stages of the parasite (Keiser and Utzinger, 2009; Qian et al., 2016). They are grouped as FBTs caused by consumption of dishes containing raw fish, crustaceans



**Fig. 4.** Cloud tag based on the 178 keywords put forward in the collection of 34 articles of the current special issue of *Acta Tropica*.

and water plants that are perpetuated by entrenched traditional cultural practices. These infections are zoonotic and affect primarily domestic or wild animals, but they can also be transmitted to humans. Clonorchiasis is the most prevalent FBT in P.R. China with an estimated 13 million people infected, which globally represents 85% of all cases (Qian et al., 2012, 2013a,b). The 2015 national survey estimated that 6 million people were infected (Zhou, 2018). However, other groups reported that the number of infections with *C. sinensis* might still be as high as 14 million (Lai et al., 2017). Overall, however, the endemicity of *Paragonimus* spp. infections should be decreasing, but outbreaks are still frequently reported (Lan and Song-Ping, 2018). Fascioliasis is highly prevalent in animals, such as sheep, but human infections are also frequently reported and sometimes outbreaks cause significant burdens in local areas where people like to eat raw water plants (Chen et al., 2013).

Historically, taeniasis and cysticercosis were highly endemic in P.R. China (Qian et al., 2019a). Concerted control activities were then adopted, including chemotherapy for taeniasis, waste management of human and animal faeces, pork inspection, and treatment and disposal of infected pigs (Ma et al., 1992). These measures contributed to a significant decrease nationally, especially in the northern part of P.R. China. Local endemic areas are now majorly concentrated in the western part of the country, where traditional husbandry, poor sanitation and consumption of raw pork are common (Zang et al., 2019a,b). Ingestion of raw pork also causes the nematode infection trichinellosis, which is occasionally reported in the western part of P.R. China (Cui et al., 2011; Liu and Boireau, 2002).

Hepatic capillariasis can occasionally also infect this way, but transmission to humans occurs most commonly by drinking contaminated water.

### 3.1. Epidemiological assessment and disease burden estimates

With respect to schistosomiasis, Zhang et al. (2019b) analysed the epidemiological trend in P.R. China between 2002 and 2017, describing the situation following directly after the completion of a 10-year World Bank loan project (WBLP) for schistosomiasis control (Chen et al., 2005; Utzinger et al., 2005). The WBLP emphasised an approach on chemotherapy. Meanwhile, Xue et al. (2019) applied high-resolution, remote sensing and developed a model based on environmental conditions, such as the normalized difference vegetation index (NDVI), soil moisture and distance from the intermediate host snails to water sources, to predict the potential risk areas of schistosomiasis. Comparing these modelling results with manual snail surveys demonstrated that this approach predicted the potential risk areas well, and hence, could be used in the national schistosomiasis control programme.

Regarding echinococcosis, Wang et al. (2019b) analysed the burden in terms of disability-adjusted life years (DALYs) in Tibetan communities. A total of 126,159 DALYs were estimated based on data from 151 Tibetan counties, out of which 105,829 DALYs were attributed to the alveolar type and 20,330 to the cystic one. The survey suggests that the echinococcosis burden in the central region of Qinghai-Tibet plateau is higher than that of other regions, and that more control and health services for that reason should be provided locally.

Ai et al. (2019) summarised the epidemiology of fascioliasis by reviewing four comprehensive databases, which revealed only 306 cases (both *F. hepatica* and *F. gigantica*), covering 19 provinces for a period of almost 100 years (1921–2018), most of which in the southern part of P.R. China. The risk factors were found to be related to habitually ingesting uncooked vegetables, and hence, IEC was suggested as a suitable control approach. The authors also recommended strengthening the diagnostic potential as well as storage of medicines. Gao et al. (2020) carried out a survey pertaining to *F. hepatica* in yaks and sheep in the Qinghai-Tibet plateau. High serological prevalence of fascioliasis was demonstrated, namely 44% (1,452 positive among 3,276 surveyed) in yaks and 37% (405/1,092) in sheep. It is

conjectured that control activities should be implemented due to the risk of transmission to humans.

### 3.2. Diagnostics and antigen characterisation

To capture the applicability of diagnostic tests developed for *S. japonicum* infections for *S. haematobium*, Zhang et al. (2019c) examined 148 schoolchildren from Zambia, comparing microscopic diagnosis and two serological tests, the dipstick dye immunoassay (DDIA) and the indirect haemagglutination assay (IHA). Children were microscopically examined for infection with *Schistosoma* and STHs. Overall, 61% children tested positive for *S. haematobium*, while 31% and 36% were infected with hookworm and *A. lumbricoides*, respectively. The sensitivity of DDIA and IHA were 60% and 74%, respectively, with specificity at very similar levels. It was also demonstrated that STH co-infections decreased the specificity by DDIA but had no impact on that found by IHA. This study indicates that IHA holds promise as an alternative diagnostic tool for identifying *S. haematobium*, but needs further improvement before it can be employed more widely.

Specific IgG and IgE levels against the *S. japonicum* soluble worm antigen protein (SWAP) were evaluated by Zhao et al. (2019) in a sample of 837 residents from an endemic area in Hubei province of P.R. China. The authors found that infected individuals had higher levels of SWAP-specific IgG, IgG<sub>4</sub> and IgE, and lower IgE/IgG<sub>4</sub> ratio than uninfected individuals, while both infected and uninfected subjects had a high prevalence of IgG seropositivity. SWAP-specific IgG could thus be used as a biomarker for identifying those previously exposed to *S. japonicum*, while the SWAP-specific IgE/IgG<sub>4</sub> could be used as biomarker for *S. japonicum* infection in endemic areas with low prevalence and intensity.

The diagnostic performance of extracellular vesicle proteins from *S. japonicum* for schistosomiasis epitope prediction was investigated by Chen et al. (2020b) who used DNASTAR software to evaluate the diagnostic potential of selected peptides based on enzyme-linked immunosorbent assay (ELISA). The sera showed detectable antibody levels against two of the antigens in mice, rabbits and humans infected with *S. japonicum*. Further analysis demonstrated that DNASTAR software is useful for finding potential biomarkers for developing new diagnostic tools for schistosomiasis.

Xunhui et al. (2019) developed a loop-mediated isothermal amplification (LAMP) assay, coupled with a lateral flow dipstick (LFD) for the rapid detection of *P. westermani*. No cross-reaction was observed with other parasitic pathogens, including *Trichinella spiralis*, *Anisakis simplex*, *S. japonicum* and *Gnathostoma spinigerum*. Although LAMP-LFD could not distinguish *P. westermani* from *P. skrjabini* and *P. heterotremus*, the assay is a rapid and convenient for specific detection of *Paragonimus* spp. in humans.

An unusual outbreak in Henan province caused by *P. skrjabini* was reported by Chen et al. (2019b). Based on a retrospective survey, this outbreak was finally attributed to an excursion, during which freshwater crabs were caught and consumed after incomplete cooking. Metacercariae of crabs were collected from the infection site identified by morphological and molecular examination. Clinical examination showed high occurrence of eosinophilia and pulmonary manifestations. These cases had previously been misdiagnosed as tuberculosis and treated as such, which indicates the importance of anamnestic data in combination with both laboratory and clinical diagnosis.

Contemplating the risk for clonorchiasis, Qian (2020a) implemented a large comparison screening of people ingesting raw freshwater fish. Overall, 16,230 participants from 16 counties in four major clonorchiasis endemic provinces were included with *C. sinensis* infection ascertained by faecal examination, while data on the practice consuming raw freshwater fish was collected. The researchers found sensitivity and specificity reaching 82% and 80%, respectively, yielding a Youden's index of 0.6. The overall positive and negative likelihood ratios were 4.2 and 0.2, respectively, while the overall positive and negative



predictive values were 34% and 97%, respectively. Thus, this rapid screening approach could be useful as an indicator for selective treatment, and performance could be further improved by adding more parameters.

Shang et al. (2019) analysed *Echinococcus* spp. employing a molecular approach in humans in Sichuan province, P.R. China. Lesions were collected from echinococcosis patients clinically diagnosed as alveolar or cystic echinococcosis, while some were unclassified echinococcosis. Mitochondrial *cox1* gene sequencing showed that *E. granulosus* was the predominant species, followed by *E. multilocularis*. In addition, one case of *E. canadensis* was isolated. In conclusion, the clinical diagnosis often resulting in unclassified cases as well as misdiagnosis in both alveolar and cystic echinococcosis makes molecular diagnosis essential for confirmation of the clinical specimen of human echinococcosis.

Although hepatic capillariasis is not often seen in clinical settings, Wang et al. (2019a) reported a series of 16 cases between 2011 and 2017. They found eosinophilia (100%) and leukocytosis (94%) together with elevated hepatic enzymes and proteins related to liver fibrosis in most cases, often in combination of sustained temperature elevation (56%), respiratory disorder (38%), abdominal pain (38%) and diarrhoea (25%). Although liver biopsy is confirmatory, diagnosis in rural areas is not easy.

### 3.3. Drug and vaccine development

Zhang et al. (2019a) reviewed the history of anthelmintic drug development in P.R. China from the 1950s until recent years. The work covers optimization of production techniques, improvements in drug formulation, application in clinical settings and mechanism of action studies. The relatively recent development and follow-up of clinical trials of tribendimidine showing an effect against 18 different parasite species carried out by NIPD was especially emphasised. For instance, tribendimidine is superior to the benzimidazoles against *N. americanus* (Steinmann et al., 2008; Xiao et al., 2005, 2013). High efficacy has also been demonstrated for praziquantel and tribendimidine against *C. sinensis* based on two clinical trials carried out in P.R. China (Qian et al., 2013b; Xu et al., 2014). Another line of research with roots in traditional medicine has shown anthelmintic activity in pumpkin seeds and betel nuts used for treatment of taeniasis.

Sanguinarine, a toxic polycyclic ammonium ion extracted from the bloodroot *Sanguinaria canadensis* and some other plants, kills animal cells through its action on the  $\text{Na}^+/\text{K}^+$ -ATPase transmembrane protein (Pitts and Meyerson, 1981). Its anthelmintic activity against the enteral and parenteral phases of trichinellosis in laboratory mice was investigated by Huang et al. (2020). It was demonstrated that sanguinarine had a lethal effect on muscle larvae, adults and new-borne larvae *in vitro*. The worm burden was significantly reduced during the pre-adult, migrating stages and larval encystation, strengthening the support for further development as a potential drug against trichinellosis.

Embarking on vaccine development, Tang et al. (2019) investigated regulatory T cells with respect to the efficacy of a glyceraldehyde-3-phosphate dehydrogenase (GAPDH) as a vaccine against *S. japonicum* in BALB/c female mice. The authors found that the protective effect of this vaccine could be improved by decreasing the number of regulatory T cells and enhancing both  $\text{Th}_1$ - and  $\text{Th}_2$ -type immune responses. This research group further explored the impact of glutathione S-transferase (GST) on young developmental stages of *S. japonicum*. The study revealed that mRNA levels of GST were higher in schistosomula and eggs, and that the egg reduction rate and abnormal egg ratio were significantly higher in the GST-silenced group than in the negative control group (Tang et al., 2019). Thus, GST has convincing potential as a potential vaccine due to its strong effect on *S. japonicum* egg formation.

### 3.4. Host-parasite interactions and snail genetics

The molecular characterisation of exosome-like vesicles in *Taenia*

*asiatica* is discussed by Liang (2020). The author collected exosome-like vesicles from the excretory/secretory products of *T. asiatica*, from which 455 different proteins were identified by proteomics analysis, of which several were found to be enzymes, e.g. GAPDH that is implicated in the metabolic process (Tang et al., 2019), in addition to fructose-1, 6-bisphosphate aldolase, cytosolic malate dehydrogenase and enolase. It was further demonstrated that experimentally labelled, exosome-like vesicles could be internalized by a colorectal cancer cells *in vitro*, which provides new insights into the interaction between tapeworms and hosts.

Gao et al. (2019) studied the effects of programmed cell death protein 10 (PCDP10) on the female reproductive system in *S. japonicum*. The results show that the number of cortical granules around oocytes decreased, while the number of immature oocyte cells increased, which demonstrates that PCDP10 plays an important role in the female reproductive system. PCDP10 has also an effect on eggshell formation, which provides a basis for further analysis of its role in schistosome egg formation and embryo development.

To understand the regulatory molecular mechanisms of schistosome growth and development in relation to the host immune system, Liu et al. (2019) analysed the metabolic profiles in sera between the immunodeficient mice and immunocompetent mice before, and after *S. japonicum* infection. Different serum metabolic profiles and uniquely perturbed serum metabolites with enriched pathways were demonstrated, which provide clues to the underlying molecular events of host metabolic changes on the growth and development of *S. japonicum* worms. These findings provide promising candidates for exploitation of drugs or vaccines against schistosome and schistosomiasis.

Li (2020) studied the potential mechanism of toll-like receptor 4 (TLR4) in the regulation of the activation by *C. sinensis* excretory/secretory products (ESPs) of hepatic stellate cells (HSCs) that eventually cause liver fibrosis. The findings indicate the activation of the hepatic stellate cells due to ESPs from *C. sinensis* by a cross-talk of TLR4 and the transforming growth factor- $\beta$ /Smads signaling pathway. This information might lead to a potential treatment strategy to interrupt the process of liver fibrosis caused by *C. sinensis* infection.

Qiu et al. (2019) explored population genetics of the schistosomiasis intermediate host snail *Oncomelania hupensis* in different habitats. Nine microsatellite loci were used to analyse the population genetics. Snails were collected from three habitats, namely a new habitat, a habitat where snails had been eliminated after which they had re-emerged, and a persistent habitat where snails occurred continuously. The smallest effective population size was inferred in the re-emerged snail habitat, but the largest was in the new habitat rather than in the habitat with snail persistence. No bottleneck effects were detected in new or re-emerged habitats. Snails from the three sites were clearly separated and the gene flow between sites was estimated to be low. The findings presented might help predicting the future transmission of schistosomiasis. Another study focused on the intestinal microbiome profiles of *O. hupensis* in different ecological areas (Hao et al. (2020)). DNA was extracted from the intestines of collected *O. hupensis* snails and bacterial communities detected by pyrosequencing. A total of 3799 operational taxonomic units belonging to 507 genera, 265 families, 140 orders, 74 classes and 29 phyla were obtained. It was demonstrated that, at the phylum level, *Proteobacteria*, *Firmicutes* and *Actinobacteria* were the dominant bacterial taxa, and *Bacillus* and *Lactococcus* the most common genera. These findings have improved the understanding on the biology of snails.

### 3.5. Surveillance and public health response

Community-based integrated interventions for STHs and clonorchiasis were piloted in the period 2006–2009. Eight counties were included for STHs interventions and another two for clonorchiasis. Integrated measures included drug administration, IEC, and improvement in provision of clean water and sanitation. The strategy revealed a

significant decrease in both infections in all 10 counties. The overall prevalence of STHs and clonorchiasis decreased by 78% and 83%, respectively, supporting the application of integrated community-based intervention in the control of helminthiasis.

The study by Tian et al. (2019) reviewed the epidemiology and control on STHs in Sichuan province, situated in the south-western part of P.R. China. Different control measures had already been implemented with good results, including health education, preventive chemotherapy and improved water supply. However, in the hilly and mountainous areas of the province, the generally lower level of social development, insufficient resources, lack of staff and inadequate health education challenged progress.

Zeng et al. (2019) reported the changing STHs trends in Jiangxi province based on three national surveys, which showed a decrease of prevalence from 78% in 1989 to 29% in 2002 and 6% in 2014. Simultaneously, the type of STHs composition changed with hookworm becoming the predominant species. The decrease was argued to be due to preventive chemotherapy, health education, better water, improved sanitary facilities and environmental management.

Meanwhile, Zhu (2020a) analysed the development of the national STHs surveillance approach in 2016. An improvement was observed in 301 counties across 30 provinces where over 300,000 people were subjected to stool examination. The prevalence had been reduced to 2.4% (7,366/305,081) and, in accordance with Zeng et al. (2019), hookworm infection, particularly *N. americanus*, was higher than infections with *A. lumbricoides* and *T. trichiura*. It was also shown that the highest prevalence rates were found in the south-western provinces, in females, in the elderly and in illiterate or semi-literate groups.

Zhu et al. (2020b) analysed the epidemiology of clonorchiasis in 2016 based on the national surveillance system. A total of 305,081 individuals were subjected to faecal examination, out of which 6,226 were detected harbouring *C. sinensis* eggs, yielding a crude prevalence of 2%. Close to 90% of the cases were concentrated in four high endemic provinces in the south-eastern and north-eastern parts of P.R. China. The prevalence in males was higher than in females, and the peak prevalence was observed among middle-aged people. This article demonstrates the importance of the establishment of national surveillance for clonorchiasis. Deng et al. (2019) noted that several provincial level surveys in Guangdong province in the south-eastern part of P.R. China had demonstrated the increasing trend of clonorchiasis between 1988 and 2010. However, the prevalence turned downwards after the adoption of massive or selective chemotherapy, as shown in the 2015 survey.

### 3.6. Capacity building and international cooperation

Chen et al. (2020a) reviewed the work carried out by NIPD over the past 70 years, which focussed on the epidemiology and control of parasitic diseases. The review also highlighted the recent expansion of NIPD into global health and discussed future prospects. Taken together, NIPD contributed decisively to deepen the understanding of the epidemiology, control and elimination of parasitic diseases. For instance, the expertise and hands-on of NIPD staff contributed to the elimination of lymphatic filariasis, which was verified in P.R. China in 2007 (Fang and Zhang, 2019; Sudomo et al., 2010). NIPD, together with the provincial CDCs, was instrumental in reducing schistosomiasis to such low levels that transmission control is the declared objective in those seven provinces where the disease remains endemic. An important contemporary focus on NIPD's work pertains to the lowering of the endemicity of echinococcosis, FBTs and STHs. The transition from a national institute focussing on parasitic diseases to a player in the global health arena would not have been possible without a strong emphasis on a spectrum stretching from innovative basic research to applied and operational research. Importantly, NIPD also contributed to information dissemination by the establishment of technical platforms and capacity building. The strengthened engagement in global health is

characterised by a more active international cooperation, participation in transnational partnerships and being part of global consortia.

In an assessment of the quality of teaching and training covering the period 2012–2016, Ruan et al. (2019) introduced theoretical tests and technical skill examination. The former involved specific knowledge on the morphology, life cycle, epidemiology and control of different parasitic diseases, while the latter focused on diagnostic capacity, including the preparation of Kato-Katz thick smears and detection and quantification of helminth eggs under a microscope.

Between 2017 and 2019, a cluster-randomised controlled trial in primary schools was accomplished in Guangxi province to implement a comprehensive health education package for children (Qian et al. (2020)). Interventions consisted of distribution of knowledge by bulletin boards, education cartoon and brochures, coupled with drawings and writing essays. This led to a high share of students with knowledge on the route of transmission, early signs and symptoms, complications and carcinogenicity in case of clonorchiasis. Hence, this study showed that a comprehensive health education package effectively enhances children's knowledge on clonorchiasis and promotes behaviour change (e.g. avoidance of ingestion of raw freshwater fish).

Qian et al. (2019c) discussed how to enhance the cooperation on the control of echinococcosis under China's Belt and Road Initiative, specifically between P.R. China and Mongolia. The recent successful control of echinococcosis in the western part of P.R. China provided a base with the collaboration adopting the principle 'Mongolia-led, China-supported and results-sharing' based on a detailed situation analysis through on-site investigation, it was emphasised that a cooperation mechanism should be established and resources integrated and optimised, while technical exchange should be strengthened. The P.R. China-Mongolia cooperation on echinococcosis will benefit both sides and could become a role model for future control activities at the global level.

Abe (2020) analysed the epidemiology, current challenges and priorities for the control of schistosomiasis in Africa. The author suggested that Africa places more emphasis on surveillance, following the experience and lessons learned in P.R. China. Integrated control strategies should be considered, including preventive chemotherapy, snail control, provision of sanitary facilities, health promotion and stronger multi-sectoral collaboration.

## 4. Concluding remarks

Infectious diseases of poverty currently affect 3 billion people worldwide and many of these diseases are due to helminths. Since they affect large populations in low- and middle-income countries and cause a considerable global burden, helminth infections constitute a major share of those listed by the World Health Organization (WHO) as neglected tropical diseases (NTDs) (GBD 2017 DALYs and HALE Collaborators, 2018; WHO 2020). Historically, P.R. China has been endemic for a large number of helminthiasis (Qian et al., 2019a, b), a situation that has greatly improved since 1978, when the country embarked on the current policy of economy stimulation that eventually allowed the implementation of health-related poverty alleviation (Engels and Zhou, 2020; Wang and Zhou, 2020). The rising economy's acquiescence of better living standards, including the promotion of public health was first slow but clearly positive results were already obvious by the millennium shift. This change should be seen in the light of fast translation of research results into control activities and follow-up, which has already resulted in the elimination of lymphatic filariasis in 2007 with malaria perhaps following already this year. Even though lymphatic filariasis has been eliminated (Fang and Zhang, 2019) and the course of schistosomiasis drastically reduced (Sun et al., 2019), considerable efforts remain. In fact, P.R. China still harbours a large burden of helminth infections in the rural areas where many people remain comparatively poor locally encouraging the well-known vicious circle that starts with personal economic difficulties that prevents

disease alleviation when it appears which leads to a further scaling down the quality of life.

The 34 articles in this special issue of *Acta Tropica* cover the various helminthiasis that still cause significant disease burden in some areas of P.R. China. The high priority and long period of unbroken progress of schistosomiasis control (Chen et al., 2018) explains that more papers deal with this infection than any other helminth species (Tables 1 and 3). P.R. China aims to eliminate schistosomiasis by 2030 and considerable resources are therefore still focused on this disease even if the absolute numbers of people infected are now comparatively low (Sun et al., 2019). For example, among the 360 projects on parasitic diseases supported by the Chinese National Natural Science Foundation in the period 2009–2018, 85 were focused on schistosomiasis (Yang et al., 2019).

Echinococcosis in the mountainous West has been shown to be locally an equivalent problem that schistosomiasis used to be in the middle and south-western part of the country (Budke et al., 2004; Wang et al., 2012; Wang et al., 2016). As a consequence, several papers on this subject were collected in this special issue. Diverse FBTs, clonorchiasis in particular, form another priority area for applied research in P.R. China. Thus, as a group, 10 papers were collected on this subject from diverse organisations and institutes, which have actively participated in the research and control of helminthiasis (Qian et al., 2019b). The comprehensive education strategy could effectively enhance the knowledge of the children on clonorchiasis promoting the decrease of raw-freshwater fish-consumption practice and strengthening the decision to abstain in future (Qian et al., 2020b).

NIPD focused on epidemiological assessment, risks and disease burden, surveillance and public health responses, while other organisations (university, hospital and independent institutes) took more interest in basic and applied research, including the development of diagnostics, drugs and vaccines. This is consistent with the roles and responsibilities of different organisations in P.R. China and elsewhere. The establishment of surveillance systems is important in control of helminthiasis, and P.R. China has established large comprehensive surveillance system for diverse infectious diseases (Li et al., 2017; Qian et al., 2018b, 2019a). The results are presented in this collection for schistosomiasis, STHs and FBTs (particularly clonorchiasis), providing useful experience for future work in P.R. China as well as other countries (Chen et al., 2019a). For example, the control and elimination of helminthiasis, schistosomiasis in particular, have benefitted from the experience and progress made in P.R. China (Abe et al., 2020). Owing to the achievements in control, international cooperation is a new area where NIPD now plays a core role to be followed by other national, technical and scientific organisations. As an example, three papers can be highlighted that show participation in the global fight against parasitic diseases, especially schistosomiasis and echinococcosis.

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