CHAPTER FOUR

From country control programmes to translational research

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Abstract

From the time it was conceptualized in 1998 to the present, RNAS^{+} has largely concentrated on research that will generate results to facilitate control, prevention and elimination of its target diseases. Diagnostics has remained an active field of research in order to develop tools that are appropriate for each stage from the first efforts until attempts to block transmission. For example, with regard to schistosomiasis, chemotherapy has excellent impact on morbidity, while better diagnostics and vaccine research have been promoted to complement the other components of the control programme. The need for surveillance in areas where the prevalence has been brought down to very low levels necessitated development of spatio-temporal tools and ecological models based on geographical information systems (GIS) to produce risk and distribution maps for monitoring and evaluation of programme success. New knowledge and experiences in management of the diseases contribute to the formulation of new schemes in management and treatment. Ways of drawing attention to the disease, such as determining disability weights for use in computation of burden of disease, updating epidemiological profile and unravelling new aspects of the disease provide bases for modifying the operation of control programmes as we move forward. Programme evaluation based on reports of actual implementation of activities brought to the fore problems related to the distribution of chemotherapy as well as social, cultural and behavioural aspects of endemic communities. Importantly, this highlighted the necessity of adapting control activities to specific situations of the endemic areas. New models evolving from reviews of this kind and success stories, such us the elimination of lymphatic filariasis (LF) in PR China and Cambodia are presented.

1. Introduction

Research concentrating on various aspects of the target diseases that will facilitate their control and prevention has always been the focus of the Regional Network on Asian Schistosomiasis and other Helminthic Zoonoses (RNAS^{+}). Annual meetings of the network showcase research findings and advances of member institutions and countries that are expected to address obstacles in control and clarify issues to better implement control programs. As control targets are reached and the disease situation improves considerably, new and more relevant fields emerge such as enhancement of diagnostics, development of surveillance tools and more comprehensive database systems and integration of other disciplines and sectors in the programmes. This chapter presents advances in these fields that are foreseen to untangle current snags in the control, prevention and eventual elimination of RNAS^{+} target diseases.

2. Significant developments

2.1 Diagnostics

In the early years of RNAS^{+}, Zhu et al. (2002) developed a rapid, simple immunodiagnostic assay for schistosomiasis using soluble egg antigen of *S. japonicum* conjugated with a blue colloidal dye and used to determine antibodies in sera of schistosomiasis patients. Results of field trials show the dipstick dye immunoassay (DDIA) to have high sensitivity and high specificity in detecting schistosomiasis aside from the advantages of being rapid, simple and cheap and without need for special equipment. It was deemed more useful compared to other immunoassays in screening target populations to identify cases for selective chemotherapy. This tool was successfully used in Lao PDR and Cambodia for detection of schistosomiasis mekongi.

Zhang et al. (2016) reviewed the development and use of parasitological, immunodiagnostic and molecular techniques in the diagnosis of schistosomiasis concluding that the main techniques that performed well in the past are not as efficient at present use because of the progress and success in control that have brought prevalence and intensity to levels close to elimination in many areas, in particular in PR China. A flexible approach is recommended to be used in the choice of the most appropriate diagnostic technique relevant for each control stage and area as well as varying the methodology based on the prevailing needs of sensitivity and specificity (Bergquist et al., 2009). Diagnostic tools should be an integral part of the national control programme and should include collaboration among research laboratories, epidemiologists and control programme managers.

Li et al. (2018) presented the evaluation of the performance of four immunodiagnostic kits for detecting clonorchiasis in China in order to address the limitations of other less sensitive techniques. Compliance with respect to submission of stool samples is also low, not to mention the reluctance of health personnel to handle stools. Molecular techniques such as PCR and LAMP may be highly sensitive; however, their cost and high risk with regard to contamination may prevent them from field use. Immunological diagnosis has become the technique of choice especially for its high sensitivity and specificity in low-intensity infections. Results of the evaluation show a relatively high performance of three diagnostic kits in detecting IgG, while the kit for detecting IgM did not perform as well as the former.

The kits that detect IgG show high sensitivity for heavier intensities of infection but is not completely reliable in area characterized by low-intensity of infection, hence the need to improve sensitivity and specificity.

Diagnostic techniques such as examination of stool, urine and biopsy material for the presence of schistosome eggs, detection of antibodies or antigens in patient body fluids and molecular techniques to detect DNA are all limited by their inability to show the severity of end organ pathology and resulting complications due to the lesions. Prolonged and extensive use of antischistosomal drugs such as praziquantel cause changes in the clinical manifestations of the disease. Olveda et al. (2014c) showed advantages in using ultrasonography to assess morbidity in schistosomiasis. The group presented several advantages of ultrasonography over other imaging techniques, such as *computer tomography* (CT) and magnetic resonance imaging (MRI). Ultrasound provides real-time images without acquisition or processing delay; it is not only portable and can be brought to the point of care (POC), but is also cheaper and does not use harmful ionizing radiation. Doppler ultrasound is more advanced providing additional prognostic information aside from the routine grey-scale ultrasound imagery. MRI however can be used in getting into sites that ultrasound may not be able to visualize.

A review done by Olveda et al. (2014a) show that eggs cause bowel lesions ranging from colitis to polyp formation. In the liver, granuloma formation and subsequent fibrosis involve immune responses initially mediated by Th1 and later by Th2 lymphocytes. As a result of severe fibrosis, there may be portal hypertension-related complications causing significant morbidity and eventually death. Liver biopsy and imaging techniques such as ultrasonography, CT and MRI can assess hepatosplenic disease for proper management. There are also new serum markers that are most promising for the evaluation of schistosome-induced hepatic fibrosis, namely, hyaluronic acid, collagen type III, YKL-40 and laminin. Because of the strong correlation between the expression profile of miRNAs and the disease status/progression, circulating host miRNAs can be possibly used biomarkers for schistosomiasis diagnosis. Fabre et al. (2011) suggest that the Tissue Inhibitor of Metalloproteinase-1 (TIMP-1) is a promising biomarker for assessing risk of hepatic fibrosis in schistosomiasis and, potentially, other infectious and non-infectious causes of liver disease. With the use of a multiplex assay that quantifies predictors and effect modifiers of fibrosis (FibroPlex), these authors (2011) show that individuals with detectable tissue inhibitor of TIMP-1 have a 3.5-fold greater risk of fibrosis 1 year after praziquantel treatment. Since TIMP-1 inhibits most

enzymes responsible for collagen degradation, the results indicate that schistosome-associated hepatic fibrosis could arise from excessive inhibition of collagen remodelling.

2.2 Vaccine research

The potential of vaccine development continues to be explored especially with mathematical models showing the effective contribution of a vaccine when added to the conventional components of the control programme. Shi et al. (2002) developed two experimental DNA vaccines that have been proved to be capable of inducing protection in water buffalos that are naturally exposed to schistosome infection in the field. In the field trial of the vaccines in cattle, worm and egg counts conducted at the end of the experiment showed partial resistance in each vaccine group. It is envisioned that these vaccines would be combined with selective population chemotherapy of both human and bovine populations. The group evaluation vaccines recommended more trials to determine whether protection can be improved with vaccination of multiple DNA plasmids compared to single administration of individual DNA vaccines.

Jiz et al. (2008) developed a pilot scale expression and purification scheme for recombinant full-length *S. japonicum* paramyosin, while Wu et al. (2017) in a follow-up study conducted three vaccine trials to assess the efficacy of recombinant full-length paramyosin (rSj 97) in protecting water buffalos from infection. Lower worm burdens were recorded for buffalos immunized with the recombinant molecule indicating that rSj97 is a safe and promising molecule for use as vaccine against schistosomiasis japonica in water buffalos.

2.3 Drug development

Pakharukova et al. (2015) conducted the first functional study of the flatworm cytochrome P450 (CYP) enzyme in *Opisthorchis felineus*, which causes biliary tract diseases in Russia, Kazakhstan and central Europe. This enzyme belongs to a group of proteins that are specifically involved in the synthesis of physiologically active compounds, in drug metabolism, and in biotransformation of xenobiotics. Although only one CYP450 enzyme was identified in *O. felineus*, this could be a promising drug target but a better understanding the physiology of this liver fluke is needed before a drug can be developed.

Jiang et al. (2017) developed an *in situ* slow-release formulation of praziquantel by subcutaneous injection, which should be capable of resisting new *Echinococcus* infections for at least 6 months.

Jia et al. (2019) reported a new compound Luo-Wei from the plant extracts against the intermediate host snails in China and Egypt, and evaluate its environmental safety to non-target organisms. It was demonstrated that this drug was active against *O. hupensis*, *B. alexandrina* and *B. truncatus* under laboratory and field conditions, and it may be a candidate molluscicide of plant origin.

3. Database for surveillance in the elimination phase

The relevance and success of control programmes depend on the initial data used in developing the various strategies to be implemented. As targets are achieved and prevalence goes down, surveillance becomes a necessity in following up and treating the remaining infected humans and reservoirs and monitoring intermediate hosts and environmental conditions that perpetuate infections.

Distribution of opisthorchiasis viverrini includes Thailand, Lao PDR and Cambodia where the disease is considered a major public health problem. To ascertain the extent and distribution of opisthorchiasis in Cambodia, Miyamoto et al. (2014) conducted surveys that found four Cambodian provinces to be endemic to the disease. The group proposed a more widespread nationwide survey to complement the partial results obtained. Furthermore, they recommended that field surveys be carefully planned to address the complex environmental factors that could influence distribution of *O. viverrini* infections in endemic areas.

Sithithaworn et al. (2012) assessed the present situation and control of liver fluke infections such as *O. viverrini* and *Clonorchis sinensis* in the Mekong Basin countries. Most recent data on prevalence and distribution were obtained from presentations during the "96 Years of Opisthorchiasis. International Congress of Liver Flukes" held in Khon Kaen, Thailand on March 7–8, 2011.They found that in spite of treatment and control programmes enforced for decades, the two liver flukes remain in high prevalence in all countries of the Lower Mekong Basin with the situation aggravated by the frighteningly high levels of the circulating cathodic antigen (CCA). It was noted that in each endemic country there is higher transmission in the lowlands resulting in higher prevalence compared with that in the highlands. The high transmission in the lowlands has been correlated with wetlands, flooding patterns and more human movement and settlements.

Qian and Zhou (2017) reported that scarce and deficient data coupled with the complex and chronic nature of cancers make it difficult to obtain a correct valuation of how many cases of cholangiocarcinoma can be associated with liver flukes. Research should be intensified to obtain correct data which could be used to raise awareness of the impact of liver flukes in east Asia and hence advance control and prevention strategies.

Angiostrongyliasis caused by the nematode *Angiostrongylus cantonensis* is a food borne-parasitic zoonosis transmitted by consumption of molluscs infected with the third stage larvae of the parasite. Hu et al. (2018) investigated the infection status and spatial distribution of the rodent and mollusc host in three villages from Nanao Island in Guangdong Province, PR China which could be used as basis in developing appropriate strategy for prevention and control of the disease. Results showed positive spatial correlation in the distribution of the mollusc host *Pomacea canaliculata* and rats. It was concluded that there is a risk of angiostrongyliasis in the island and therefore both mollusc and rodent hosts should be intensely monitored.

Li et al. (2007) concluded that three approaches that were adopted to accurately describe the epidemiology of schistosomiasis in PR China were national sampling survey, active sentinel surveillance and passive routine report. Results from these methods showed an increase in schistosomiasis which was attributed to a better reporting system rather than real increase in incidence. The integrated control strategy in 2004 brought down the prevalence of schistosomiasis considerably spurring PR China to aim for elimination by 2025.

PR China is known for its high endemicity for echinococcosis that has been given high priority especially in western endemic areas where considerable control activities are being implemented. Recognizing the importance of using dependable data to control the disease, China conducted the largest epidemiological survey from 2012 to 2016 covering all nine endemic provinces. Results revealed the presence of cystic echinococcosis in 368 counties, 115 of which were also co-endemic for alveolar echinococcosis. The necessity for a global database for echinococcosis has been similarly recognized to intensify the fight against this disease. In the late 2017, a network was established in Chengdu, PR China to build capacity for the research and development necessary to reach the control targets for echinococcosis.

Taenia solium has also been selected for strong control activities due to its role in the development of cysticercosis in humans. It is expected that through commitment, coordination and cooperation of all endemic countries and the international community, this infection would be brought under

control by 2030. Called the Belt and Road Network for the Elimination and Control of echinococcosis and cysticercosis (B&R-NEC), experts from 13 countries signed the Chengdu Declaration and the network was opened to all countries willing to join the fight against the disease (Qian and Zhou, 2018).

Fasciola hepatica and *F. gigantica* are common parasites among ruminants all over the world causing death among this livestock. Chen et al. (2013) reported an outbreak of human fascioliasis in Yunnan Province caused by consumption of the herb (*Houttuynia cordata*) which local people consume frequently in the summer (June to September). This has been recognized as a new source of infection for fascioliasis in PR China. The group expect that this new information can be integrated into the One Health approach to lessen transmission and virulence of both human and animal fascioliasis. Important intervention measures that should be sustained include health education and cessation of use of animal faeces as fertilizers.

In PR China, two of the most important natural hosts for *S. japonicum* are 'yellow cattle' and water buffalo with the former observed to be more compatible for development of the parasite. Yang et al. (2012a,b) determined the immunological basis for this higher susceptibility of yellow cattle and the more serious pathology that is observed with the infection. This information will certainly be critical in designing vaccines in addition to understanding the mechanism of self-cure in water buffalos that can further advance schistosome vaccine research and application.

Habib et al. (2018) using both morphological and molecular evidences reported that the *Biomphalaria* populations from Guangdong are *B. straminea*, the intermediate host of *S. mansoni* in Brazil. These snails could have been introduced via passive dispersal or through several introduction routes from this country. In the light of increasing reports of active *S. mansoni* infections among workers returning from Africa, increased surveillance for all entry ports and inspection of exotic species are recommended to decrease probability of further introduction of such type of species and emergence of new diseases in PR China.

The study of Yang et al. (2013b) showed the usefulness of spatio-temporal analysis in evaluating the risk for schistosomiasis. Results of mouse bioassay from 2009 to 2011 analysed by directional distributional analysis and scan statistics were used to illustrate the spatio-temporal risk pattern. The spatial distribution was focused along the Yangtze River and the directional distributions for the percentage of infected mice and average worm burdens resemble those observed for positive sentinel sites. The group

concluded that this approach would be valuable for surveillance and response especially as progress is achieved in moving from morbidity control to transmission control.

The feasibility of stopping transmission of STH from a global view was considered by Brooker and colleagues and they included China as one of the most feasible groups that can achieve this. The far-reaching economic development and intense helminth control programs of China have greatly impacted control efforts and resulted in the tremendous reduction in soil-transmitted helminth in PR China as shown by the considerable decline in the number of infected people from 536 million in 1988–1992 to 129 million in 2001–2004 and the decreasing trend has since been sustained. Qian et al. (2015) proposed that prevalence and intensity levels reflected at the provincial level could be used as assessment map by policy makers to evaluate progress of interruption of transmission and prioritize provinces for more intensified control measures. General prevalence surveys should be followed by setting up of surveillance spots that will regularly provide real time data to determine progress in transmission interruption in order to adjust the interventions accordingly. The success of transmission interruption in China will not only benefit local people but could create a large impact on worldwide efforts to control STH.

Zhou et al. (2009) reported on the proceedings of the 1st International Symposium on Geospatial Health presentations showed proofs of the wide and extensive use of spatially-explicit analyses and other geospatial approaches across Southeast Asia. Applications of these approaches on parasitic infections with considerable impact in the region such as soil-transmitted, food-borne and water-borne helminthic infections, lymphatic filariasis (LF), leishmaniasis and malaria were shown. Advances in GIS and satellite-generated remote-sensing techniques together with spatial statistics have been utilized to show the impact of climate change and ecological transformations.

Examples of these include time series analyses, advanced modelling and Bayesian geostatistics in addition to random-effect models and transmission dynamics can improve knowledge about epidemiology of schistosomiasis and control. Geospatial tools are expected to provide warnings especially in areas further north where schistosomiasis is expected to advance as a consequence of climate change. The spread of disease as a consequence of large-scale water resources development and management projects such as the Three Gorges Dam completed in 2009 and the South-North Water Transfer Project under construction currently can be effectively monitored through these advanced geo-spatial tools (Yang et al., 2013a).

The symposium showed current initiatives that prove that remotely-sensed environmental data and advanced mathematical modelling in a spatially-explicit framework can be used to monitor demographic, eco-epidemiological and socio-economic changes and from these develop early warning systems to mitigate possible detrimental consequences of climate change or other massive and drastic ecological changes. Applications are not only limited to human public health but extended to veterinary medicine.

Schistosomiasis is still endemic in 7 out of the 12 original endemic provinces in PR China. The control of the snail intermediate host *Oncomelania hupensis* is crucial in the elimination of the disease. However, schistosomiasis endemic areas in hilly and mountainous areas in China are much more complicated and difficult to access making efficient and accurate snail surveys extremely hard to conduct compared to the endemic areas located in plains/swamp and lake regions.

Zhu et al. (2015) proposed an ecological niche model integrated with NDVI, LST, elevation, slope and distance from every village to its nearest stream that has satisfactorily predicted the snail habitats in the mountainous region. The model was validated in two counties with the same ecological conditions in Yunnan Province, PR China producing a predictive value of 76.67% and 83.3% for the two villages. It was concluded that the potential of this model for use in snail surveillance in mountainous regions is high.

In the light of the near elimination status of schistosomiasis in PR China, there is a growing need for a rapid and sensitive technique for monitoring the distribution of infected *O. hupensis* in the remaining endemic areas in the seven endemic provinces. Tong et al. (2015) used LAMP assay targeting 28 SrDNA for the quick and accurate detection of *Schistosoma japonicum* DNA in infected and prepatent infected snails. For the first time, infected snails from field sites of low endemicity areas were successfully monitored by LAMP assay using pooled samples which essentially provides an alternative but a more efficient way of screening of increasing large numbers of samples collected from endemic areas especially those with low endemicity requiring larger number of samples to be collected. The risk map that can be generated from the LAMP results has huge potential in being used as an innovative tool to direct surveillance and response strategies in risk areas that can eventually lead to elimination of the disease in such low endemicity areas (Tong et al., 2015).

4. New guides for clinicians

The study of Olveda et al. (2017) showed that treatment with praziquantel produced a short-term impact on prevalence and intensity of

infection but little impact on morbidity that has already set in. The grade of liver fibrosis was found to be associated with higher tissue inhibitor of TIMP-1 and hyaluronic acid serum levels and enhanced liver fibrosis (ELF) cut-off score of 8. These figures therefore can be used by physicians in identifying individuals who are more predisposed to serious morbidity. Programme managers can therefore be guided in allocating their resources to areas where they are needed. In addition, the ELF test could be made available and affordable in the field for use by clinicians to evaluate patients with heavy intensities of infection (>400epg) and or those with manifestations of advanced disease (e.g. MCL > 3) to detect their risk of developing severe liver fibrosis.

Olveda et al. (2014b) presented the results of a successful clinical management of a 12-year-old boy in the advanced stage of schistosomiasis from the province of Northern Samar, the Philippines. Massive bleeding due to ruptured oesophageal varices and pancytopenia due to hypersplenism are the major complications of portal hypertension in schistosomiasis with massive bleeding causing majority of the deaths from the disease. The group proposed that for bleeding oesophageal or gastric varices, the best immediate procedure is endoscopy-guided injection sclerotherapy or band ligation of the bleeding varices. The group recognized the limitation in facilities and expertise in developing countries and recommended vasoactive drugs to lower the splanchnic vascular pressure as a temporary solution. As was done in the reported patient, splenectomy is recommended as an appropriate and possibly life-saving procedure for patients with considerably large spleens with pancytopenia caused by hypersplenism but with no history of bleeding from oesophageal or gastric varices and without ascites.

Sripa et al. (2017) reviewed most recent results that deal with the role played by liver-fluke associated *Helicobacter pylori* in hepatobiliary disease and malignancy. The group proposed that the presence of both *O. viverrini* and *H. pylori* is at the core of liver fluke infection associated with cholangiocarcinoma. Recent literature point to liver fluke being a reservoir of *Helicobacter* spp. and explains the role of liver fluke associated *H. pylori* in hepatobiliary disease and malignancy.

Gouveia et al. (2017) report results that show that *O. felineus* should be included in the Group 1 list of biological carcinogens just like its related flukes *O. viverrini* and *C. sinensis*. Biochemical and histopathological changes resulting from *O. felineus* infection in the rodent model led to formation of precancerous lesions contributing to malignancy.

Coutinho et al. (2005) concludes that, in children, adolescents, and young adults infected with *S. japonicum*, hepatic fibrosis is associated with impaired nutritional status. Early recognition and treatment of this type of morbidity can be critical because of the strong evidence linking malnutrition with the detrimental effects on morbidity, mortality, cognitive development, reproduction, and the capacity for physical activity. The group further show that even low-grade hepatic fibrosis is associated with significantly worse nutritional status. These researchers hypothesized that it could lead to malnutrition and anaemia through a systemic increase in the levels of proinflammatory cytokines, specifically IL-1 and IL-6, and possibly TNF-α.

Wieringa et al. (2016) conducted a national micronutrient survey in children and women that was linked to the Cambodian Demographic Health Survey 2014 (CDHS-2014) to determine the prevalence of micronutrient deficiency, haemoglobin disorders and intestinal parasite infection. Results of the survey were meant to provide data on causes of anaemia which is a condition highly prevalent among Cambodian women and children with over 50% under 5-year old suffering from the condition. The survey revealed that the very high prevalence of anaemia in Cambodian women and children cannot be attributed solely to micronutrient deficiencies and haemoglobin disorders. Therefore, micronutrient interventions to reduce anaemia prevalence would possibly have limited impact in the Cambodian setting. Iron deficiency prevalence was found to be low in children above 2 years of age and in women. Wieringa et al. (2016) recommended that the focus of the present interventions to decrease the high prevalence of anaemia in children and women should be expanded and should involve provision of zinc and folic acid for women of reproductive age, as well as effective anti-hookworm measures.

5. High burdens of target diseases generate interest in control

Clonorchiasis is a recognized public health problem in PR China. However, Qian et al. (2013b) noted that researches are not enough to generate needed information of the disease. The group suggested that the serious threat of clonorchiasis to public health in PR China can be demonstrated by comparing this disease with hepatitis B in terms of epidemiology, clinical symptoms and carcinogenicity, disability and changing trends. It is expected that the intensity of control efforts put forth by PR China will impact considerably on the global agenda for control and elimination of this disease.

More researches are therefore awaited from Chinese researchers which hopefully will snowball and expand to include international cooperation.

Paragonimiasis, caused by the lung fluke *Paragonimus* spp., is a food-borne trematodiasis (FBT) and one of the 20 NTDs on the WHO list. The suffering caused by this disease is however not that well understood. In addition, quantification by the disability weight of the DALYs is largely variable in various global burden of disease (GBD) estimates. The top two contributors to disability weight are lung outcomes and headache. Feng et al. (2018) conclude from the systematic analysis that they did that further modification should be done to calculate the disease burden of paragonimiasis. This is important for public health prioritization of paragonimiasis in research, monitoring and control.

Torgerson et al. (2015) reported on the initial estimations of 10 helminth diseases and toxoplasmosis that may be associated with contaminated food which could provide deeper understanding of the big effect of food-borne diseases regionally and globally. It was revealed that the disease burden attributed to most food-borne parasites is very focal and leads to substantial morbidity and mortality among vulnerable population groups.

In spite of the impact of clonorchiasis in Southeast Asia and its classification as a biologic carcinogen, it remains unlisted among the Global Burden of Disease (GBD) and disability weight is still lacking. Disability weight refers to the average degree of loss of life value due to a certain chronic condition and ranges between 0 for complete health and 1 for death. It is a very important parameter for estimating the morbidity part of any disease burden in terms of DALYs. Qian et al. (2011) reported the results of their study which was the first attempt to calculate the disability due to clonorchiasis which refers to average loss of life caused by some conditions and crucial for computing for disease burden as expressed as DALYs. The group showed that the overall disability was higher in male compared to female and that there is positive correlation between disability and infection intensity and gallstone got the major attributable proportion. Results may spur further studies that can produce results that can be used for the final estimation of disease burden which in turn can be provide sufficient basis for promoting health awareness and implementation of intervention.

With the recognition of *O. viverrini* as a carcinogenic parasite and the major risk factor for CCA, both government and public sectors have provided more attention to liver fluke surveillance and control. In north-eastern Thailand, for example, academic researchers and public health workers have bonded together for more intense and comprehensive investigations not

only of the prevalence of infection but importantly treatment and surgical therapy of CCA. All these concerted efforts are expected to alleviate the situation of the poor suffering from this fatal disease and more successful prevention and control resulting in improved quality of life and increased productivity leading to socioeconomic advances.

Nowadays, the importance of echinococcosis has been demonstrated in China. Many surveys showed the high endemic areas, especially in western areas.

6. Review of control programmes

Chen et al. (2018) presented the 60-year history of schistosomiasis control and prevention in China that reaped considerable success in bringing down levels of the disease to near elimination levels in many endemic areas. Chairman Mao Zedong himself led the intensive campaign calling for elimination of schistosomiasis recognizing the magnitude of the problem in 12 provinces along the Yangtze River. Yujiang County responded immediately and using a multipronged approach composed of snail control through environmental modification, repeated screening and molluscicide treatment for 2 years eventually declared elimination of the disease.

Strong political leadership and support at the highest level of the government have always marked the programme in all three stages of implementation marked by mass campaigns and vertical control focusing on snail eradication in the first stage followed by praziquantel-based morbidity control in the second stage and accelerated implementation of an integrated strategy concentrating on all sources of transmission together with continued snail control, agricultural mechanization construction of lavatories with continuous supply of water and treatment and health education in the third and final stage. Out of the previously 12 endemic provinces, five have eliminated schistosomiasis; one has achieved transmission control and six have reached status of transmission interruption. PR China also helps other endemic countries as shown by the China-Zanzibar-WHO project which also adopted the strategy of high-level government communication and technical cooperation. The importance of socio-economic development in schistosomiasis elimination is seriously recognized and addressed through the current Belt and Road initiative project that is intended to uplift local economies together with global health development.

Xu et al. (2015) reviewed the progress of control programs for major helminthiases in PR China such as schistosomiasis, STH, clonorchiasis and echinococcosis each in a different control stage that requires specific

approach. It was concluded that the significant economic development in PR China coupled with the improved consciousness on the burden of parasitic diseases brought about greater attention to control of parasitic diseases. Scientific control policies and control approaches consider different eco-epidemiological settings in their implementation which are expected to eventually succeed in achieving targets for control.

Sustainable financial resources and political commitments can further sustain progress and assure attainment of goals for control, prevention and eventually elimination. Integration of preventive chemotherapy of the different helminthiases requiring broad spectrum anthelminth drugs, such as praziquantel, mebendazole and albendazole is highly possible since endemic areas for these diseases overlap and they are co-endemic with each other. Finally, gains from these efforts can further be magnified to achieve the long term goal of interruption of transmission by improvement of hygiene, housing and sanitation conditions. Provision of safe water supply and latrines for adequate disposal of excreta and solid waste and environmental modification to improve sanitation can decrease contamination of the environment with helminth eggs and reduce transmission of helminthiases.

Progress can be further accelerated through stronger collaboration among different departments like Water Conservancy, Agriculture, Husbandry, and Education. In spite of progress in control, there are still obstacles that have to be overcome to control morbidity and eliminate helminthiases. In 2012, a gap analysis on helminth control was conducted by the diseases reference group on helminth infections (DRG4), a group established in 2009 by the Special Programme for Research and Training in Tropical Diseases (TDR). A research and development agenda for helminthiases control was also promoted covering seven topics such as interventions, diagnostics, basic biology, mathematical modelling, social, and environmental determinants and capacity building. The need for sustainable and additional funding to support more advanced studies is continuously reiterated as well as translation of potential scientific advancements into improved or novel interventions.

Olveda et al. (2014d) concluded that in the Philippines, MDA alone will not be able to control incidence, prevalence and morbidity due to schistosomiasis. The zoonotic nature of the disease where livestock like water buffalos and cattle contribute considerably to the transmission can confound control efforts that are based mainly on MDA. The success of Japan in eliminating schistosomiasis in the 1990s and of China in purging the disease in 5 out of 12 endemic provinces is founded on integrated

strategies of snail control, mass chemotherapy of the endemic population, health education, provision of sanitary facilities, environmental modification and improved agricultural methods. Such success may not be expected easily from the Philippines because of the year-round transmission of the disease in the Philippines compared to just 5 months in China in addition to the limited budget allocated for schistosomiasis control. The group proposed that should bovine vaccine be successful in the pilot study that they are conducting, this could be incorporated to an integrated approach composed of human mass chemotherapy, targeted molluscicides and bovine (water buffalo and cattle) treatment.

The cornerstone of the national control programme for schistosomiasis in the Philippines is annual MDA with 40 mg/kg of praziquantel in endemic areas with prevalence of 10% or more. Ross et al. (2015) however concluded that MDA is not enough to control the prevalence and intensity of infection or morbidity of the disease. MDA is marked by increasing problems of inadequate drug coverage, low cure rates, poor drug compliance, absence of baseline information before starting MDA, and insufficient monitoring and evaluation from the time started all of which should be addressed in control programs based on MDA. Multisectoral and intersectorial strategies to complement MDA are clearly needed for more effective control and prevention of the disease.

Collaboration among the community, educational, public health and government sectors is needed to successfully control the disease. The most possible reason for the failure of the control programs could be the paucity of culturally sensitive and proper and clear information about "raw attitudes" in eating behaviour of the people in the Lower Mekong Basin (Ziegler et al., 2013).

7. Components needed for successful control programmes

O. viverrini is one of three very important species of liver flukes that are highly pathogenic to humans and are transmitted by consumption of poorly cooked or raw infected fish. Opisthorchiasis viverrini is an important public health problem in Southeast Asia particularly in Thailand where the prevalence remains high in the north-eastern provinces in spite of the long history of control. Sripa et al. (2015) reported on a new control strategy that he and his group developed called the Lawa model which was introduced in the Lawa Lake area in Khon Kaen province where the liver fluke is highly endemic.

Based on the EcoHealth/One Health Approach, the components of the novel programme included anthelminth treatment, novel intensive health education methods both in the communities and in schools, ecosystem monitoring and active community participation. The new programme resulted in the decrease in infection rate in the 10 villages located around the lake by one-third of the average of 50% from the baseline survey. Infection in the cyprinoid intermediate fish host also went down to 1% compared to the very high 70% baseline prevalence. The Lawa model is presently recognized not only nationally but also internationally as an effective control programme and is being extended to other parts of Thailand and neighbouring Mekong countries. Prior to the development of the Lawa model, community-based surveillance and intervention against FBTs were lacking, particularly with regard to opisthorchiasis.

The current Lawa model is an ecosystem approach to health and is described as transdisciplinary, participatory and considers gender and equity and ecological principals in the development of intervention measures. Variables that are responsible for transmission are identified so that an integrated intervention programme can be developed that has a high degree of sustainability. The Lawa model implemented in villages around the Lawa Lake uses the EcoHealth approach and has been successful in bringing down the prevalence of opisthorchiasis dramatically. A similar strategy called Pilot EcoHealth for human liver fluke was intended for implementation in endemic areas of Lao PDR, Cambodia, Vietnam and southern China.

The success of an intervention programme for schistosomiasis depends on consideration of the socio-ecological context. The eco-social factors influencing existence of perpetuation of schistosomiasis are not that well understood especially at the household or village levels. The study of Yang et al. (2014) showed that the important factors identified in 26 villages of Eryuan county, Yunnan Province, People's Republic of China that are associated with schistosomiasis are absence of a sanitary stall house for livestock and presence of living and infected intermediate host snails in close proximity. The group concluded that an approach involving spatially explicit Bayesian multilevel analysis can help understand more deeply the eco-social determinants that influence schistosomiasis transmission at a small geographical scale.

In PR China, schistosomiasis remains in five provinces of lake and marshland regions and in two provinces mainly composed of mountainous regions. Previous studies have shown that perception both at the individual and community levels, attitudes towards schistosomiasis, and hygiene

behaviours are critical factors that influence control and prevention of schistosomiasis. The study of Liu et al. (2014) assessed the knowledge of, attitudes towards, and practices (KAP) relating to schistosomiasis in two subtypes of a mountainous region in Eryuan County, Yunnan Province, PR China. While the overall knowledge rate of schistosomiasis was found to be high in Eryan County, the group recommended that in the light of varying risk factors, control strategies should be crafted in such a way that the different subtypes of endemic areas, namely, plateau basins and plateau canyons for this mountainous region will be carefully considered. For example, consideration should be made of the higher number of risk factors in plateau canyon regions such as frequently grazing cattle, digging vegetables and cutting grass in the field, as well as raising cattle by free grazing compared with the plateau basin regions.

Qian et al. (2013a) proposed the adoption of different intervention measures in different populations because of the varying knowledge, behaviour and infection intensity among population groups. For adults, especially adult males, priority should be given to chemotherapy. Health education particularly focusing on children can eventually yield good results in the long term control of the disease. Restaurants should also be included in the intervention program.

Hung et al. (2015), in a cross-sectional study conducted in Gia Minh and Gia Thinh communes of Gia Vien District, Ninh Binh province found that these communes remain endemic for FBT even if people are aware of the risks of eating raw fish. The group recommended that for a strategy for controlling helminth diseases to succeed, there should be intensified efforts to educate people on the harm due to FBT and the importance of stopping the habit of consumption of raw fish.

Yang et al. (2013b) reviewed emerging and re-emerging diseases that are presently endemic in China such as schistosomiasis, dengue, avian influenza, angiostrongyliasis and soil-transmitted helminthiasis which are concluded to be attributed to environmental and agricultural change. The review reiterated that environmental changes, agricultural practices and social status significantly influence the existing vicious cycle between poverty and infectious diseases. In order to determine the multiple risk factors associated with global changes the following four-pronged approach was recommended by the group composed of the following: identifying metrics, defining risk factors quantitatively and qualitatively, establishment of risk-factor models, and designing policies and programmes for specific disease for decision makers. Assessment plays a critical role in development of intervention strategies that are suited to the local settings and needs to minimize the impact of global change.

In PR China, the application of chemical molluscicides remains as one of the most effective measures for schistosomiasis control. Yang et al. (2012a) investigated the cost-effectiveness of molluscicide application in order to so recommend an optimal management approach to control intermediate host snail *O. hupensis* under acceptable thresholds based on the goal of the National Schistosomiasis Control Programme. The study concluded that different stages of the national schistosomiasis control/elimination programme, namely, morbidity control, transmission control and transmission interruption, should utilize different molluscicide treatment strategies to maximize cost-effectiveness. The group recommended the use of molluscicide treatment once a year to transition from morbidity control to transmission control. Further, environmental modification of snail habitats could be done as an ultimate option during the transition stage from transmission control to transmission interruption. During the stage of post-elimination/transmission interruption, re-emerging snail habitats must be eliminated immediately.

Developing countries have been plagued by tropical diseases which have been a principal cause of morbidity and mortality. Over the past 20 years, collective efforts have been successful in improving the situation but poor communities continue to struggle with these diseases. In general the trend has been declining especially brought about by improvement in the responses to basic health problems and improving health delivery system to vulnerable populations. Based on the WHO's NTD roadmap, the London Declaration on Neglected Tropical Diseases (NTDs) created the direction for control and eventual elimination of several tropical diseases by 2020, giving the thrust for local and regional disease elimination programmes.

In response, the 'First Forum on Surveillance-Response System Leading to Tropical Diseases Elimination' was organized in Shanghai in June 2012 for the purpose of identifying and prioritizing strategic research on elimination of tropical diseases. During the meeting, there was an evaluation of current strategies and the NTD roadmap which was followed by discussions to identify and analyse prevailing challenges and opportunities together with inter-sectoral collaboration and approaches for elimination of several infectious, tropical diseases. The first forum also saw the development of a priority research agenda within a 'One Health-One World' frame of global health. The components of the research agenda included (i) the establishment of a platform for resource-sharing and effective surveillance-response systems for Asia Pacific and Africa with an initial focus on elimination of lymphatic filariasis, malaria and schistosomiasis; (ii) development of new strategies, tools

and approaches, such as improved diagnostics and antimalarial therapies; (iii) rigorous validation of surveillance-response systems; and (iv) designing pilot studies to transfer Chinese experiences of successful surveillance-response systems to endemic countries with limited resources.

8. Success stories: Elimination of LF

LF caused by the filarial worms *Wuchereria bancrofti, Brugia malayi* and *B. timori* is a NTD that is a major public health problem in many tropical and subtropical countries. The WHO has targeted the disease for elimination as a public health problem by 2020. The Global Programme to Eliminate LF (GPELF) was established in 2000 based on two very important pillars which are (a) transmission interruption through MDA of antifilarial drugs, and (b) alleviation of suffering in chronic patients through morbidity management and disease prevention (MMDP). Before 2000, LF was endemic in 80 countries where 1.1 billion people are residing in known endemic areas and 120 million people were actually infected. Encouraging advances however such as development of new treatment strategies and introduction of new diagnostic tools in the 1980s and 1990s spurred the WHO to endeavour for global elimination.

Khieu et al. (2018) reported the success of Cambodia in having eliminated LF as a public health problem as validated by WHO in 2016. As one of the first countries in the world to craft and implement an LF elimination program, Cambodia's intense efforts as documented in a dossier submitted to WHO included LF mapping in the country to determine endemic provinces, robust implementation of MDA, regular data collection from sentinel and spot check sites, results from surveys where MDA has been stopped and a summary of post-MDA surveillance activities (TASs 2 and 3). The report also documented how access to chronic LF cases was achieved and how the health system has been training, treating, and monitoring those cases to make sure they get the care they need. In 2015, the Ministry of Health (MoH) of Cambodia put together its final report documenting the elimination of LF as a public health problem and submitted to and validated by the Regional Dossier Review Group of WHO's Western Pacific Regional Office. The following year in June 2016, the WHO headquarters publicly and formally recognized that elimination of LF as a public health problem was achieved in Cambodia.

In PR China, LF was eliminated much earlier in 2006 after decades of sustained efforts focused on multisectoral collaboration involving various

departments of the government, intensified control, prevention and elimination programme for LF and continued and massive cooperation from endemic populations (De-jian et al., 2013).

9. Conclusion

The expanded membership of the RNAS^{+} and the inclusion of other target diseases like other helminthic zoonoses and NTDs endemic in the member countries succeeded in securing attention for majority of parasitic diseases causing public health problems in the Asian region. With prevalence going down and reaching near elimination levels, more sensitive diagnostics are developed and surveillance tools particularly based on spatio-temporal analysis see greater promise in monitoring progress in endemic areas. New disciplines and more sectors are integrated to ensure that all aspects of the disease are considered and addressed. Success in the elimination of LF in Cambodia and China illustrates the magnitude of work involved but also heightens optimism that the goal can be achieved.

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