CHAPTER SIX

From inspiration to translation: Closing the gap between research and control of helminth zoonoses in Southeast Asia

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Contents

1. Introduction 112
2. Research activities and raison d'être 114
3. International research funding 117
4. What is still missing? 118
5. Lessons learnt and the way forward 119
References 121

Abstract

Poverty magnifies limitations resulting from traditional biases and environmental risks in endemic areas. Any approach towards disease control needs to recognise that socially embedded vulnerabilities can be as powerful as externally imposed infections. Important for RNAS was networking across borders, not just on schistosomiasis but on the whole spectrum of endemic helminthiases, and this bore fruit in the form of the expansion of RNAS into the 'Regional Network on Asian Schistosomiasis and other Helminth Zoonoses (RNAS$^+$)', which focuses on technical standardization, supporting the growth of research capacity and the further development of networking. Administration is lean and largely virtual with the focus on connecting members via the Internet, providing databases and administrative back-up. The strategy emphasizes ways and means to alleviate the spectre of disease and poverty from the endemic areas through boosting research on target diseases and supporting collaboration between basic and operational research on the one hand and control/elimination activities on the other. RNAS$^+$ also benefits from continuing input from outside research institutions in areas outside Southeast Asia. This paper is aiming to identify the priority actions to close the gap between researcher and policy makers.

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1. Introduction

Helminth infections constitute a considerable public health burden covering such diverse diseases as dracunculiasis echinococcosis, food-borne trematodes (FBTs), lymphatic filariasis (LF), onchocerciasis, soil-transmitted helminths (SHTs), schistosomiasis as well as *Strongyloides* and *Taenia* infections including cysticercosis. Trematodes and nematodes tend to be the most investigated parasitic worms, while work on cestodes is trailing. Thanks to the growing awareness of public health issues, Ministries of Health are gauging the economic impact of these diseases and considering political and financial commitments directed against the neglected tropical diseases (NTDs). Poverty magnifies limitations of any approach towards disease control and, like all tropical, poverty-stricken areas, Southeast Asia's panorama of parasitic diseases, have a tendency to emerge/re-emerge when control activities are not sustained. Only access to up-to-date data and support systems capable of locating high-risk areas can block the vicious circle of endemic presence of NTDs and poor people unable to work and provide for themselves and their families due to disease.

Thanks to the Internet and television, the world of today is fully aware of public health needs in low- and middle-income countries in the tropical part of the world. Governments, non-government organizations (NGOs) and donor foundations are all trying to improve the situation. For example, the World Health Organization (WHO) has developed a 'roadmap' for the elimination or strongly reducing the prevalence of the major endemic diseases within the current decade (WHO, 2012), a proposal endorsed by the World Health Assembly (WHA) resulting in the largest public health initiative in history. In London, UK, the same year, senior government officials in the industrial world together with their counterparts in the endemic countries, research institutions, universities, major donor organization and leading pharmaceutical industry corporations issued the *London Declaration* on the Neglected Tropical Diseases (https://unitingtocombatntds.org/london-declaration-neglected-tropical-diseases/). This joint commitment issued aims to: eradicate or prevent transmission of dracunculiasis (Guinea worm disease); eliminate LF, leprosy, African trypanosomiasis (sleeping sickness) and trachoma; and control American trypanosomiasis (Chagas), river blindness (onchocerciasis), schistosomiasis, STHs and visceral leishmaniasis. Inspired by these initiatives, universal health coverage has become a central component of the United Nations' 17 Sustainable Development

Goals (SDGs) for the period 2015–2030 (United Nations, 2015), which aims to bring today's 'medical toolbox' to bear on the NTDs and lift the burden of disease from all in countries currently lacking full access to health services.

Less than 7 years later, it is already clear that the situation has improved in a general way, making a more detailed view worthwhile. The treetops need to know what is going on at the grassroots level and this is where networking comes in. Stimulation of multi-disciplinary approaches for the control of endemic, helminth diseases in Southeast Asia by long-term input from the UNICEF/UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases (TDR) through the creation of the 'Regional Network on Asian Schistosomiasis (RNAS)' in the year 2000 was pivotal. This was not only a first attempt to improve interchange between national research institutes and research groups in the region, but also a way to promote collaboration between individual researchers and their counterparts working for national control programmes of various kinds. RNAS worked closely with the WHO Western Pacific Regional Office (WPRO) and benefitted also from ongoing parallel projects funded by the Rockefeller Foundation, the United States' (U.S.) National Institutes of Health (NIH) and the World Bank, while expanding its support base with dedicated grants from the Canadian International Development Research Centre (IDRC). Basic and operational research took off followed by investigation of new control strategies. Important for the activities encouraged by these initiatives was networking across borders, not just on schistosomiasis but on the whole spectrum of endemic helminthiases, and this bore fruit in the form of the expansion of RNAS into the 'Regional Network on Asian Schistosomiasis and other Helminth Zoonoses (RNAS$^+$)'.

Activities started with a collaboration on schistosomiasis japonica between scientists in the People's Republic of China (PR China) and the Philippines, but as soon as the new network had been formed, it rapidly added Cambodia, Indonesia, the Lao People's Democratic Republic (Lao PDR) and Japan that were not much later joined by the Republic of Korea, Vietnam and Thailand and finally Myanmar. Meanwhile, clonorchiasis, cysticercosis, fascioliasis, opisthorchiasis, paragonimiasis and schistosomiasis mekongi were added to the roster. The network vision is to become the recognized platform for evidence-based information and communication bridging the gap between research scientists and control authorities for the prevention of NTDs in Southeast Asia. To that end, RNAS$^+$ focuses on technical standardization, supporting the growth of research capacity and the development of networking. Administration is lean and largely virtual with the focus on connecting members via the Internet, providing databases and administrative back-up. The strategy emphasizes ways and means to alleviate the spectre of disease and poverty from the endemic areas through boosting research on its target diseases and supporting collaboration between basic and operational research on the one hand and control/elimination activities on the other. RNAS$^+$ also benefits from continuing input from outside research institutions in Australia, Denmark, Switzerland, the United Kingdom and United States.

2. Research activities and raison d'être

RNAS$^+$ has provided critical research with regard to several parasitic diseases common in the Southeast Asian region. Network members are involved in various fields disseminating information to the whole group as it is gained. Traditional epidemiological approaches are utilized as well as advanced, spatial statistics linked to the use of geographical information systems (GIS) and satellite-generated data (remote sensing). The basic line of investigations, such as operational research and implementation of evidence-based policies along with dedicated work on key technologies, such as advanced diagnostics, modelling and development of vaccines and new drugs continue to be key research objectives. Most of the tools needed for the different research activities are regularly taught at 1–2 day RNAS$^+$ training courses following the annual meetings and the new skills later applied in field and laboratory in collaboration with experienced scientists. Sometimes, separate, longer training activities have been held outside the region. For example, with respect to schistosomiasis in animals, a workshop on diagnostic tests was held in September 2003 at the Danish Bilharziasis Laboratory (DBL) in Copenhagen, Denmark. It had a wider participation than just from Southeast Asia but was attended by 16 participants connected with RNAS$^+$ from countries including Cambodia, PR China, Indonesia, Lao PDR and the Philippines. The purpose of the workshop was to demonstrate, compare and reach consensus about diagnostic tests to be used for surveys, control and surveillance on animal schistosomiasis in Asia (Olveda et al., 2010; Zhou et al., 2008).

The success achieved is based on an overall aim to strengthen collaboration between scientists and the authorities responsible for disease control in the endemic countries. The RNAS$^+$ framework, website, databases, publications and its annual meetings have helped building local technical standards and instituting mechanisms for information-sharing with emphasis on platform design and technical standardization fostering strengthened research capacity (Bergquist and Whittaker, 2012). $RNAS^+$'s administrative body is largely virtual connecting members via the Internet, providing background information (databases when available) and general back-up. The underlying philosophy is that the overall goal should benefit from the creation of interconnected disease-specific groups capable of operating as nodes accessible at the $RNAS^+$ website (http://www.rnas.org.cn). Brief introductions to commonly used approaches, such as GIS, modelling and diagnostics follow below.

The strength of GIS in the area of vector-borne diseases lies in the environmental vector requirements that limit these infections to highly specific ecological niches (Malone et al., 2016), and hidden relationships and patterns may be revealed by using location as the key index (Rinaldi et al., 2011). GIS generally uses data downloaded from satellites collecting environmental data on a continuous basis (Malone et al., 2019). This type of remote sensing can be utilized for the development of predictive models showing the association between environmental conditions and parasite prevalence. In addition, Google Earth and its web-based pendant Google Maps are conducive to combination of results from literature and field findings (Stensgaard et al., 2009; Twardzik et al., 2018). The concept of time geography, long ago advanced by Hägerstrand (1970), has now produced the space-time cube (STC), where the base represents a 2-D geographical map with the vertical axis treated as time instead of altitude. The revived interest in Hägerstrand's innovative idea eventually led to an ESRI application (https://support.esri.com/en/technical-article/000017460) where the visualized fusion of space and time facilitate understanding of the spread of diseases.

Mathematical modelling can help predicting the potential impact of a specific control intervention (Williams et al., 2019) and represents a way to understand reality by simplification. Although all models are by definition wrong, some capture essential features of reality more closely than others, which means that the data are better fitting. Depending on the question studied, a model should only be as complex as needed, an approach referred to as the principle of parsimony or Occam's razor after the British mediaeval thinker. However, the ecological dynamics of infections have a wide range of interconnected spatial scales, some are directly transmitted within a single species, whereas others circulate among multiple hosts. Even if this creates a situation where the mathematics become complex, modelling still offer valuable tools to understand the epidemiological patterns needed for deciding which strategy to implement (Heesterbeek et al., 2015).

RNAS$^+$ has a strong interest in diagnostic approaches for all its target diseases, but most work has been carried out on schistosomiasis. The daily variations in host egg excretion is particularly pronounced in *Schistosoma japonicum* infections (Yu et al., 1998) and can therefore result in falsely negative tests in areas characterized by low-intensity infection. The solution lies in modifying the methodology according to the diagnostic need (Bergquist et al., 2009), which means that a shift to a more sensitive and specific test is needed when the priority moves from traditional individual diagnosis and monitoring to surveillance and response in a well-controlled landscape. Today, disease and infection are diagnosed through the expression of biomarkers (http://www.biomarkersconsortium.org/). However, this concept varies from the vague, e.g. increased body temperature, to the specific, such as the demonstration of a schistosome egg. Both are biological markers, but NTD epidemiology deals with more narrow subsets, such as what is discovered by microscopy, immunological techniques, genomics or technologies that visualize pathology, e.g., ultrasonography.

The thick stool smear technique, originally described by Kato and Miura (1954) and later standardized by the introduction of a 41.7 mg template by Katz et al. (1972), is a standardized approach to helminth egg detection, but the miracidium hatching test for schistosomiasis diagnosis is widely used in PR China (Qiu and Xue, 1990). The sensitivity of the hatching technique is slightly better than the Kato-Katz technique, probably due to large volumes of faeces, but a combination of stool examination and hatching produces even better results (Zhu et al., 2014). The development of the dipstick dye immunoassay (DDIA) kit for schistosomiasis japonicum diagnosis (Zhu et al., 2002) and its subsequent successful application for community diagnosis of schistosomiasis mekongi in Cambodia and Lao PDR (Zhu et al., 2005) on the one hand, and the standardization of ultrasound findings in Asian schistosomiasis (Li et al., 2004) on the other, were promoted by RNAS$^+$ using funds from TDR.

There has also been progress involving highly sensitive diagnostic techniques, e.g., by using the loop-mediated isothermal amplification (LAMP) for surveying snails for schistosome infection (Qin et al., 2018) and application of the up-converting phosphor lateral flow (UCP-LF) technology for detection of *S. japonicum* and *S. mekongi* infection through the presence of circulating antigens (van Dam et al., 2015) as well as various variants of the polymerase chain reaction (PCR) (Cai et al., 2019; Weerakoon et al., 2018).

Vaccine development in Southeast Asia is quite different from the mainstream as it targets the reservoir hosts, such cattle and water buffaloes, which are the main culprits in sustaining the *S. japonicum* life cycle. For this reason, vaccination is a valid means to reduce the excretion of egg from domestic animals. A DNA-based vaccine (SjCTPI) has shown encouraging efficacy against *S. japonicum* in Chinese water buffaloes (Williams et al., 2019). This trial confirms that human praziquantel treatment is an effective intervention at the population level, while mollusciciding has an indirect ~50% efficacy in reducing human infection rates. A transmission blocking vaccine targeting bovines, such as the SjTPI for the prevention of *S. japonicum* with the required protective efficacy, would be invaluable in tandem with these and other preventive measures.

Studies on drugs against liver flukes and intestinal nematodes have shown the diamidine derivative tribendimidine, developed in the late 1980s by the National Institute of Parasitic Diseases (NIPD), to be a good candidate (Ren et al., 1987). Although the drug is ineffective with regard to *S. japonicum,* a collaboration was entered between NIPD and the Swiss Tropical and Public Health Institute (*Swiss TPH*) to screen it further. The drug was found to have a good effect against various helminths of the FBT group but schistosomes and *F. hepatica* were not affected (Keiser et al., 2007; Panic et al., 2014). The work continued within the RNAS$^+$ framework and tribendimidine is currently in advanced clinical trials against *Opisthorchis viverrini* (Sayasone et al., 2018).

3. International research funding

Core funding from WHO and TDR has helped to keep RNAS$^+$ supporting its annual meetings, but it was already clear from the beginning that it would in the longer term need outside funding from other sources as well. To that end several research proposals were developed. The interest from IDRC in Canada in one of these project resulted in a major grant and RNAS$^+$ was pleased to be awarded, a 3-year (2011–2014) multi-country, multi-institution project on ecological intervention approaches to interfere with transmission schistosomiasis and other zoonotic helminths. The general objective of this project was to develop innovative strategies for the sustainable control of target emerging infectious diseases through socio-ecosystem based interventions. The research was shared between by research institutions in Cambodia, Lao PDR, the Philippines, PR China; Thailand and Vietnam.

The main helminths identified as particular problems in the region were found to be STHs, schistosomiasis and the FBTs, but also cysticercosis, echinococcosis and LF are important in large areas. Three cluster zones corresponding to specific helminth groupings were identified and it was confirmed that livestock has the leading role with regard to transmission. Higher re-infection was observed both in humans and livestock, and the lack of multi-sectoral cooperation was noted. Lessons learnt from this project included the understanding that ecosystems govern helminth transmission overall and to move forward a classification system and identification of the hotspots are needed. Children, women and minorities were found to be the most vulnerable, but the importance of the information education and communication (IEC) component was difficult to measure. The lack of professional teams with trans-disciplinary and ecohealth knowledge was also noted. A follow-up IDRC-supported project involving Cambodia, Lao PDR, PR China and Thailand, dealt with the development of country-specific transformation frameworks to advance the elimination of schistosomiasis and effective control of schistosomiasis and liver fluke infections in the Greater Mekong sub region but final results are not yet available.

In addition, three specific projects were supported by TDR: (1) community diagnosis of schistosomiasis mekongi (Zhu et al., 2002); (2) standardization of ultrasonography in Asian schistosomiasis (Li et al., 2004); and development of survey tools for animal schistosomiasis (Olveda et al., 2010).

4. What is still missing?

Reliable, long-term information on mortality and life expectancy has not been much utilized by RNAS$^+$ members, but should be a good guiding principle when attempting to gauge the impact of the endemic diseases in the region. For purposes such as understanding public health trends, health metrics aims to find a single measure that summarizes the impact of both mortality and morbidity on health, e.g., finding a number between 0 (death) and 1 (optimal health) presents a complex methodological challenge. Available publications on this issue that appear under the measurement rubrics of health-adjusted life years provide helpful information, e.g., health-adjusted life expectancy (HALE), quality-adjusted life years (QALYs), years of healthy life (YHLs) and disability-adjusted life years (DALYs) (Field and Gold, 1998; Neiger et al., 2012; Murray et al., 2012).

There needs to be enhanced laboratory ability in areas with significant NTD prevalence to provide technical and scientific support for the diagnosis, surveillance, monitoring and evaluation of national NTD programmes (WHO, 2012). Diagnostic laboratory networks are informal and not well publicized making it difficult to share expertise and provide supervision and quality assurance as well as standardization. Such work has started in connection with RNAS$^+$ but is still not strong. Indeed, a very recent study commissioned by WHO found that although more than 90% of laboratories investigated had adequate technical skills to function as an NTD reference laboratory, almost all of them lacked systems for external verification (Dean et al., 2018). The WHO Strategic and Technical Advisory Group (STAG) for the NTDs therefore prioritizes strengthening laboratories and the establishment of a laboratory network capable of providing quality assurance. RNAS$^+$ could play an important role here by establishing rules for diagnostic assays and how they should be used and issue guidelines for reference laboratories.

Decisions regarding interventions require diagnostics to provide data on prevalence and intensity of helminth diseases. Importantly, diagnostic approaches need also detect signs indicating drug resistance. As referred to in previous chapters in this book, many different assays are applied in the region but, with exception of the Kato-Katz stool examination (Katz et al., 1972) for schistosomiasis stool examination, they are not well standardized (Dean et al., 2018), which would be helpful in comparing data from different areas and countries. Although laboratory services are decisive with respect to choice of intervention mode for control and surveillance, the technical staff in most low-resource settings are insufficiently trained (Nkengasong et al., 2010). Preventive chemotherapy through mass drug administration (MDA) not only relies on laboratory data for estimating initial prevalence, but this approach also requires knowledge of intervention effectiveness and documentation of progress. There has been progress with regard to schistosomiasis and also other NTDs. LF has been eliminated in Cambodia (Khieu et al., 2018) and PR China (De-Jian et al., 2013), while malaria is substantially reduced and close to elimination in China (Yin et al., 2013). Still, an accelerated scale-up of existing activities in this area is critical if the stated NTD Roadmap targets for 2020 are to be reached.

5. Lessons learnt and the way forward

In spite of the impressive success of reducing the number of schistosomiasis cases in PR China with more than 95% since the peak human prevalence in the mid-1950s with between 10.5 and 11.8 million (high-intensity) cases (Chen and Feng, 1999; Mao and Shao, 1982). A strong impetus had been added by the 1992–2001 World Bank Loan Project (WBLP) which particularly emphasized praziquantel-based morbidity control (Chen, 2005; Zhang et al., 2012). Although the progress momentarily stalled in the first years of the new millennium, further improvement ensued when snail control, that had been overshadowed by the strong focus on chemotherapy during the WBLP years, was again promoted (Utzinger et al., 2005). RNAS$^+$ was seen as the vehicle to translate the Chinese progress on schistosomiasis elimination into the Philippines, but it was soon realized that the situation in this country is radically different from that in PR China, partly because transmission is not seasonal as in PR China and partly because of the topography: large plains in PR China in contrast to the many islands that are often hilly and covered with wild, tropical vegetation in the Philippines. In addition, the integrated multidisciplinary campaigns used in PR China could not be duplicated in the Philippines because of limited financial resources (Olveda and Grey, 2019). In a global perspective, this is not so unlike the problem with schistosomiasis mansoni in southern and northern Brazil on the one hand, and the Mediterranean countries and sub-Saharan Africa on the other.

The collaboration between Chinese and Filipino researchers that started the network could not immediately breach these seemingly insurmountable differences between their countries, but discussions paved the way for an understanding that elimination cannot just be a question of praziquantel production and distribution. Apart from chemotherapy, a working control strategy must be based on a sustained political commitment to improve the situation (Chen et al., 2018; Maegraith, 1958), it should also be adapted to local eco-epidemiological settings and strangly hinge on a strong emphasis on snail control (Chen and Feng, 1999). Importantly, the WBLP was different from previous World Bank interventions in that a small part (3%) of the financial support was earmarked for research support (Utzinger et al., 2005). This component would eventually turn out to lead to outcomes that could be directly plugged into the ongoing schistosomiasis control activities. Therefore, when WBPL ended in 2001, its legacy was not only case reduction and morbidity reduction but also the promise of a range of new tools.

The strength of RNAS$^+$ is its role as research incubator, as shown by the continued development of transmission-blocking initiatives, such as artemether for schistosomiasis (Xiao, 2005), a domestic animal vaccine (Williams et al., 2019) and the drug tribendimidine with its broad-spectrum action against parasitic helminths including the FBTs (Panic et al., 2014).

Interestingly, by killing immature schistosomes, artemether has been shown to have a dual action as the immature schistosomula that are killed by the drug release antigens that raise immune responses preventing new infections (Bergquist et al., 2004). It is also interesting that the adult stages of the trematodes *S. mansoni*, *C. sinensis*, *F. hepatica* and *O. viverrini*, all found in the bile ducts or the veins in their definitive hosts, differ so much in their susceptibility to tribendimidine (Keiser et al., 2007) that this drug only holds promise for use against intestinal nematodes and the FBTs (Sayasone et al., 2018).

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