CHAPTER 3

Coordinating Research on Neglected Parasitic Diseases in Southeast Asia Through Networking

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Abstract

The new dialogue between stakeholders, that is, scientists, research administrators and donors as well as the populations victimised by endemic infections, is initiating a virtuous circle leading to lower disease-burdens, improved public health and the mitigation of poverty. There is now general agreement that control activities need research collaboration to advance, while surveillance plays

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an increasingly important role in sustaining long-term relief. On the part of the Regional Network on Asian Schistosomiasis and Other Helminth Zoonoses (RNAS$^+$), this has led to a new vision not only focused on general strengthening of research capabilities but also on furthering efforts to close the gap between research and control and bridge different branches of science. From its original, exclusive focus on schistosomiasis, RNAS$^+$ has expanded to include food-borne and soil-transmitted helminth infections as well. Its current repository of data on the distribution, prevalence and severity of these diseases is increasingly utilised by decision makers charged with epidemiological control in the endemic countries. Thanks to a more rapid translation of research results into control applications and the dissemination of data and new technology through networking, the overall situation is improving. Working as a virtual organisation of researchers and control officers in the endemic countries of Southeast Asia, RNAS$^+$ is playing an important role in this conversion. Its responsibilities are divided along disease lines into five main areas, but no serious, endemic disease is considered to be outside the network's sphere of interest. This chapter recounts some of the more important RNAS$^+$ accomplishments, pinpoints potential directions for future operations and highlights areas where research is most needed.

3.1. ROLE OF NETWORKS IN PUBLIC HEALTH

Mechanisms for information-sharing play an increasingly important role with regards to the prompt accessing of information that is useful for the improvement of local technical standards. Networking can be defined as a process framework for empowering stakeholders not only to share and apply new knowledge but also to identify and prioritise problems systematically and to participate in the development of appropriate solutions. Geographical information systems (GIS) and satellite-based remote sensing (RS) are particularly interesting in this connection as these techniques generate databases that can be used for the distribution of continuously updated risk maps covering endemic areas for the various endemic diseases under study. When connected with national and regional databases, huge amounts of data can instantly be accessed, even in remote places, contributing to the perception of diseases in the wider social context. Stensgaard et al. (2009) discuss interactive map services based on satellite imagery as user-friendly tools that can make a difference with respect to presentation of the risk for different diseases in different places. Although public health-associated networks can act as clearing houses for this type of data, they are first and foremost interactive grids for the rapid dissemination of research news and progress of national control programmes, and for becoming acquainted with key technologies and evidence-based policies.

3.2. HISTORY AND OVERARCHING GOALS OF RNAS^{+}

The idea of establishing a regional network of scientists and control officers was initiated by the UNICEF/UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases (TDR) at the international workshop on ''Research, Surveillance and Control of Schistosomiasis japonica'', held in 1996 in Nanjing, People's Republic of China (P.R. China). The Regional Network on Asian Schistosomiasis (RNAS) started as a bid to coral stakeholders for research on schistosomiasis japonica in the region. A plan was presented at a later meeting in Wuxi, P.R. China, which attracted the interest of the 70+ researchers and representatives of control authorities. A status report (McGarvey et al., 1999) on schistosomiasis japonica produced after this meeting marked the informal beginning of the network based on intersectoral, interregional and international collaboration for work on schistosomiasis japonica. Further discussions at another TDR-supported project meeting entitled 'Establishment of a Regional Network for Research, Surveillance and Control of Asian Schistosomiasis', in 2000 in Tagaytay City, the Philippines, led to the formal establishment of RNAS (Zhou et al., 2002). The network consisted originally of a relatively small group of scientists, mainly from P.R. China and the Philippines, exclusively focused on oriental schistosomiasis. At this early stage, when activities were still exclusively focused on schistosomiasis, some important research priorities were identified which are still being pursued:

- improve sensitivity of stool examination and/or substitute it with serology;
- determine the contribution of animal reservoir hosts to transmission to humans;
- estimate production losses due to animal schistosomiasis and determine the effect of changing agricultural practices; and
- estimate the effect of climatic changes on transmission.

However, the interest in the network continued to grow and more diseases and member countries were added along the way (Zhou et al., 2004, 2008a,b). A strong reason underpinning the decision to formally establish RNAS was the need for a closer relation between research and control activities in the struggle against the endemic diseases in the region. RNAS has contributed to the strengthening of the dialogue between control programme managers and academic researchers and this task can now be regarded as essentially accomplished, as has been schematically illustrated in Fig. 3.1. Applied research continues to play a

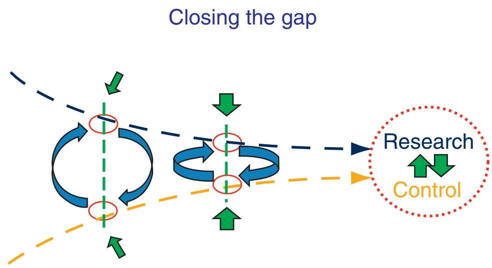

FIGURE 3.1 Closing the gap between research and control.

big role, but projects are always collaborative efforts initiated to solve specific problems in the control of one or more of the endemic diseases.

At its 5th annual meeting in 2005 in Bali, Indonesia, RNAS could look back on an impressive number of accomplishments and it was clear that the network had started to make an impact on problems related to schistosomiasis. The addition of cysticercosis/taeniasis, clonorchiasis, opisthorchiasis and fascioliasis and the change of the name to the 'RNAS^{+}' were agreed formally. Today, more than 90% of all research institutions and control authorities in the nine member countries working on the RNAS^{+} target diseases are represented in the network, which has become a force in multidisciplinary research and multisectoral collaboration among professionals, scientists and public health experts. The endemic diseases in Southeast Asia have been neglected, but there is now real hope that the situation is about to change, thanks to growing awareness of public health issues and also the economic impact of the diseases targeted for research and control by the network.

RNAS^{+} has passed through three stages of development during the last 10 years. In the establishment stage, from 1999 to 2001, regular scientific meetings were instituted and information-sharing and collaboration between the Chinese and Filipino scientists expanded noticeably. Between 2002 and 2006, in the second or strengthening stage, communications were further strengthened by the creation of the network's Internet homepage enabling continuous exchange on the diagnosis, surveillance and control of *Schistosoma japonicum*. Research and training benefited by efforts to survey the areas endemic for schistosomiasis in a standardised way. Research grants were awarded by TDR for three projects, that is, the application of immunodiagnostic kits, the standardisation of the ultrasonography protocol and the development of survey tools for animal schistosomiasis. These grants encouraged the expansion of the network—which was undertaken by the branches in Cambodia and Indonesia—to jointly study human and animal schistosomiasis prevalence in all four countries where oriental schistosomiasis (caused by *S. japonicum* or *S. mekongi*) is endemic. 'Ecology and transmission of schistosomiasis in Philippines (STEP)' is a good example of a well-managed project leading to another by another funding agency. In this case, the findings produced by the TDR projects resulted in 'add-on' funding from the National Institutes of Health (NIH), Bethesda, MD, USA. Similar funding has been awarded by NIH to research groups in P.R. China as well (Bergquist and Tanner, 2010).

The third stage, which can be called the expanding stage, started in 2005. In an example of technology-enhancing activities, data produced at a training course on GIS applications—offered during the RNAS$^+$ meeting—provided awareness of the utility of implementing GIS capability in each member country and created linkages with the Gnosis network (www.gnosisGIS.org). Alerted by this, several other funding agencies and research institutes took an interest in RNAS$^+$, providing input, collaboration and/or financial support. Examples include the Danish Centre for Experimental Parasitology (DCEP), Copenhagen, Denmark; the Danish International Development Agency (DANIDA), Copenhagen, Denmark; the Swedish International Development Cooperation Agency (SIDA), Stockholm, Sweden; the Wellcome Trust, London, UK; the Queensland Institute of Medical Research (QIMR), Brisbane, Australia; and the Swiss Tropical Institute (STI), Basel, Switzerland, as well as the WHO HQ and the WHO Western Pacific Regional Office (WPRO).

From only 20 participants and two member countries at the 2000 annual meeting, the network attracted increasing numbers of participants from universities, research institutes, control programmes, international organisations and industry, reaching 100 participants and nine member countries in 2008 (Fig. 3.2). The high number attending the 2007 annual meeting in Lijiang, P.R. China was due to the unusually high number of Chinese students who could find the financial means to participate when the meeting was held in their own country that year. Taking this into account, it seems that the core number of participants already reached a plateau of around 100 participants 3 years ago. On the other hand, if the RNAS$^+$ budget permitted the subsidising of students to allow them to attend its meetings (which is highly desirable), the regular number of attendees would probably be at least 50% higher.

Further strengthening of the RNAS$^+$ organisation in response to increased expectations from its members and partners led to the establishment of physical headquarters at the Research Institute of Tropical Medicine (RITM), Muntinlupa, the Philippines, where non-profit organisation legal status was obtained. Since 31 July 2007, RNAS$^+$ has been registered with the Securities and Exchange Commission (SEC), with its functions defined in by-laws and articles of incorporation approved by the SEC in the Philippines.

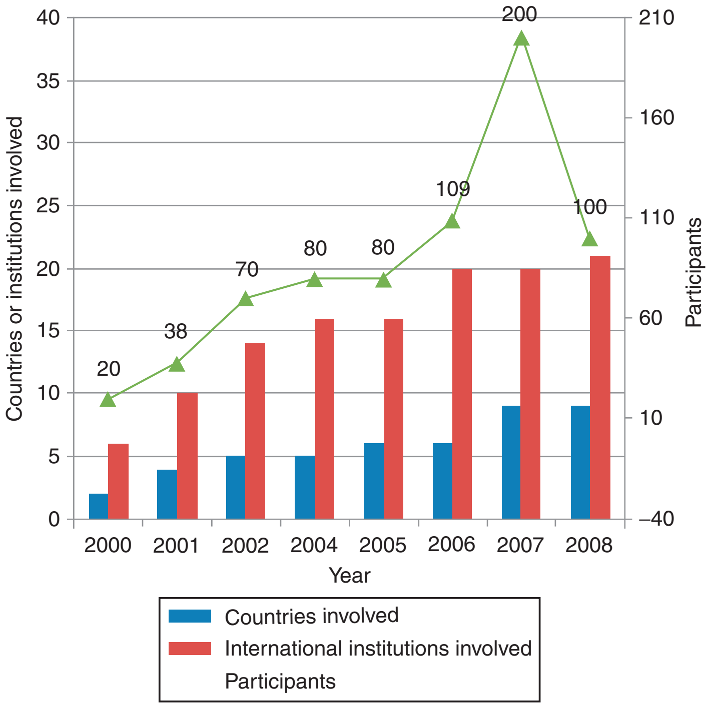

FIGURE 3.2 The number of participants, countries and international institutions involved in the RNAS^{+} annual meetings 2000–2008.

3.2.1. Organisational structure

Design and technical standardisation are important issues aiming at fostering research capacity, and fostering the development of the RNAS^{+} networking capacity and access to information databases. Figure 3.3 depicts a virtual organisation where the administrative body provides the platform connecting the RNAS^{+} members via the Internet; providing databases and administrative back-up. This design reflects the strategy to boost research on the target diseases by placing a strong emphasis on the ways and means to alleviate the spectre of the disease and poverty, as well as on the creation of interconnected, disease-specific groups capable of operating as 'nodes' on the RNAS^{+} website (http://www.rnas.org.cn). Although no serious, endemic disease is left outside the RNAS^{+} charter, the main disease 'nodes' are cysticercosis (CYS), food-borne trematode infections (FTI), schistosomiasis (SCH) and other helminth zoonoses (OHZ). Apart from these four main areas, there is also a crosscutting 'node' called trans-disease activities (TDA) that is concerned with the maintenance of databases, connectivity and other technical questions. The general work is concentrated on:

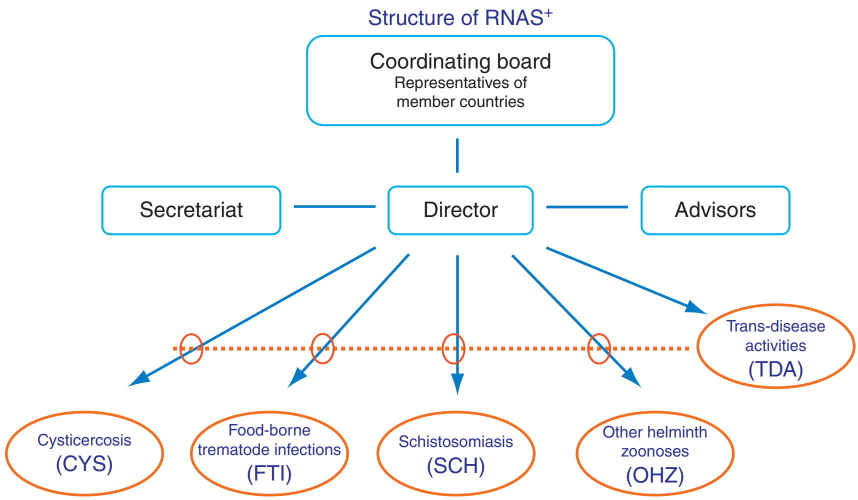

FIGURE 3.3 The RNAS+ organisational chart.

- implementation of operational and control-associated research;
- retrieval of data of particular interest and identification of areas where RNAS+ fills a need;
- identification of knowledge gaps and promotion of innovative synthesis of findings relevant to infectious diseases control in settings characterised by poverty; and
- acquainting researchers with the advantages of working via the RNAS+ website as a knowledge management platform, encouraging active participation in the joint effort to continuously update information on the diseases of poverty.

The specific research priorities are to:

- support research on the impact of social determinants and economic issues on the epidemiology of helminth zoonotic infections in Southeast Asia;
- document, develop and apply health metrics in practice;
- promote GIS/RS techniques for the study of the impact of climate change on the RNAS+ target diseases and other applications;
- improve and standardise diagnostic capabilities, including development of new products and techniques; and
- encourage the study of genetics and the immune responses against parasites to better understand the pathology caused and ultimately to apply the new knowledge to the development of new drugs and vaccines.

RNAS$^+$ aims to improve the research environment through the standardisation of technologies, procedures and protocols used in the prevention and control of endemic diseases and, in particular, to facilitate the dissemination of reliable and up-to-date information about helminth zoonotic infections. The vision is to become the recognised platform for evidence-based information and intersectoral communication bridging the gap between research scientists and control authorities for the prevention of neglected tropical diseases (NTDs) in Southeast Asia. Science is not easily regulated which contributes to increasing inequality at different levels. This is no different in the field of parasitic diseases, but the best way forward seems to be the establishment of a business model with 'accountables'. In contributing to reducing the burden and impact of NTDs in vulnerable populations, the immediate mission is to steer research progress onto specific targets and to harness new findings into easily accessible repositories with the aim to foster communication between scientists and control authorities. RNAS$^+$ also aims to be the primary centre in the region for specific research such as the assessment of health metrics, surveillance, diagnostics, GIS/RS, etc., introducing global standards and developing state-of-the-art technologies.

The internal connections and facilities within the overall structure of the RNAS$^+$ are described in Fig. 3.4. The platform represents the

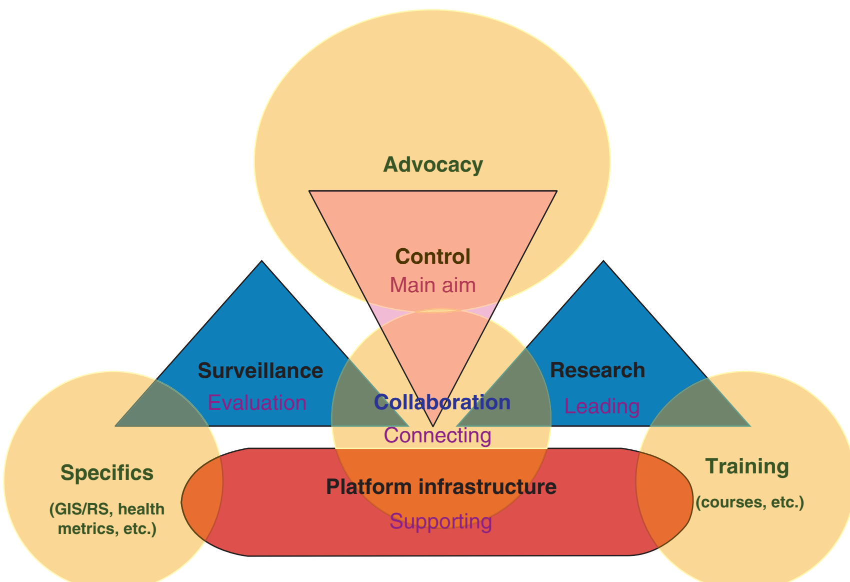

FIGURE 3.4 Schematic description of the internal functions and connections in RNAS$^+$.

supporting scaffolding of this virtual reality where collaboration is the connecting centrepiece. Research and surveillance, symbolised by the blue triangular shapes, are the bedrock activities that closely join with the main aim, that is, the progress of control activities. Advocacy, training and the short courses are peripheral to the central activities but the network could not work without them.

3.2.2. Achievements

The overall aim of RNAS+ is to strengthen collaboration between researchers and control authorities in the endemic countries and the network has provided critical input in this respect for several parasitic diseases as highlighted in the following sections.

3.2.2.1. Diagnostics

Several problems plaguing control programmes are due to the insensitivity and variability of commonly used diagnostic assays as has been reported at several RNAS+ meetings. For example, the Kato-Katz stool examination (Katz et al., 1972), generally used for the diagnosis of schistosomiasis, has become increasingly unreliable due to the lower parasite loads in controlled areas (Lin et al., 2008). In addition, the declining compliance rates commonly observed after repeated rounds of stool examinations and treatment (Guo et al., 2005a) have become a problem in the national control programmes, both in P.R. China and the Philippines. To overcome the aforementioned problems through the network, a diagnostic technique, developed at the Danish Bilharziasis Laboratory (DBL), used for the diagnosis of animal trematode infections, was shown to work well when tried in a survey (Anh et al., 2008). With respect to immunodiagnostic approaches, the DDIA kit for schistosomiasis, developed at the Jiangsu Institute of Parasitic Diseases (Zhu et al., 2002), was successfully transferred from P.R. China to Cambodia and Lao People's Democrabic Republic (Lao PDR) for the diagnosis of *S. mekongi* (Zhu et al., 2005).

3.2.2.2. Vaccine research

Owing to the role of domestic animals in the transmission of schistosomiasis japonica, vaccine research in P.R. China and the Philippines has focused on the possibility of transmission-blocking vaccines for livestock (Zhu et al., 2004, 2006). An experimental advantage with respect to *S. japonicum* vaccine research is the possibility to use full-size animal models thereby escaping the limitations of the mouse model (Johansen et al. 2000; Zhu et al., 2004). Based on the idea that reduced water buffalo infections would reduce transmission to humans, field trials of two *S. japonicum* antigens (Sj28-TPI, Sj23) are ongoing in P.R. China, (Da'dara et al., 2008; Dai et al., 2009). Results published so far show a greater than 50% protection of many animals, which could be further boosted by an integrated approach using praziquantel also.

In the Philippines, both RITM and the College of Public Health, University of the Philippines have had vaccine research groups for many years. More recently, RITM has analysed human immune responses to a panel of *S. japonicum* recombinant antigens in an effort to find out which antigens are the most promising (Acosta et al., 2002).

3.2.2.3. Drug development

Since it has now been convincingly shown that artemether and artesunate can kill schistosomula, they may be used as preventive drugs against schistosomiasis and also against food-borne trematodes (Xiao, 2005; Xiao et al., 2010). Indeed, impressive reductions in worm-burdens have been obtained with artemisinins and synthetic trioxolanes in rodents infected with either *S. japonicum*, *Clonorchis sinensis*, *Fasciola hepatica* or *Opisthorchis viverrini* (Keiser and Utzinger, 2007). A year after these reductions in worm-burdens were demonstrated, Hou et al. (2008) carried out and published the first randomised, double-blind, placebo-controlled trial evaluating combined artemether/praziquantel chemotherapy for the treatment of acute schistosomiasis japonica. Since these patients should harbour a comparatively high number of young parasite forms, an improved efficacy compared to praziquantel alone was expected. Surprisingly, however, apart from showing a good safety record, the results were negative. This could have various explanations. For example, acute schistosomiasis is a clinical diagnosis which, for obvious reasons, must leave out the determination of the number of schistosomula in the patients. One could speculate that the results might have been different if the drugs had been given earlier in the course of the infection. On the other hand, it would only be possible to test this occasionally. Possibly, a very large study in a very highly prevalent area could have shown a small difference between the different drug regimens. In spite of this difficulty, it would be useful to continue testing the effect of various combinations of various artemisinins together with praziquantel (Xiao et al., 2010).

3.2.2.4. Health metrics

The assessment of the personal impact of a disease is far from straightforward, in particular for chronic diseases with subtle pathologies. Already more than 50 years ago, Pesigan et al. (1958) noted the ravages caused by schistosomiasis and their paper marks the start of a long-lasting controversy about how to gauge the magnitude and duration of infection-related, chronic diseases. Stothard and Gabrielli (2007) argue that much of the morbidity caused by schistosomiasis appears one or two decades after the first incidence of infection in early childhood and that this fact was not sufficiently addressed in the original disability-adjusted life year (DALY) estimate by Murray and Lopez (1996). As pointed out by King et al. (2005) and King (2010a), the real impact of schistosomiasis can be 10 or even 15 times higher than current figures. Several courses have been given under the auspices of RNAS+ on the subject of health metrics and work along these lines has been initiated (Jia et al., 2007; King, 2010b; Li et al., 2005).

3.2.2.5. GIS/RS applications

It is now feasible to predict the distribution of the intermediate schistosomiasis host snail with the aid of remotely sensed environmental data (Guo et al., 2005b; Yang et al., 2005; Zhou et al., 2001). In addition, applied spatial analysis can be used to predict the distribution of the *Oncomelania hupensis* snail at the micro level (Zhang et al., 2005). While Guo et al. (2005b) only used the wetness feature in their approach, Zhang et al. (2005) also derived brightness and greenness. These two studies have enhanced our understanding of *S. japonicum* transmission at high resolution. As the research spectrum broadened, more applications, in particular with respect to climate change, were implemented and methodologies based on GIS/RS have led to a vastly improved knowledge base in the region (Chen et al., 2007; Leonardo et al., 2007; Li et al., 2009; Malone et al., 2010; Wu et al., 2007; Yang et al., 2006; Zhou et al., 2004, 2008c)

3.2.2.6. Control

An interesting report from Cambodia focuses on the cost of running the schistosomiasis control programme presenting an evaluation of its cost-effectiveness and cost-benefit (Croce et al., 2010). The drug cost amounted to about 17% of the implementation cost. The annual costs of keeping an individual free from infection was estimated at US$1, while that of restoring one severely infected adult to complete productivity, was estimated at US$114. It was calculated that the return in increased productivity was US$3.85 for each US$ invested.

The development of the schistosomiasis control programme in the Philippines can be followed in two papers (Leonardo et al., 2002, 2008). For example, instead of active case-finding, random sampling was implemented in a national prevalence survey, carried out between 2005 and 2008 (Leonardo et al., 2008). Although prevalence was found to have generally declined, places with high prevalence and high transmission were discovered in poor areas without proper sewage systems. The survey confirmed that more than 80% of all schistosomiasis in the Philippines is found in Mindanao and Visayas, the two big provinces in the south of the country.

Using diagnostic (stool examination + serology), demographic and environmental data obtained from a large area in P.R. China's Hunan province, Raso et al. (2009) found that demographic factors such as age, sex and occupation and the presence of reservoirs of infection (water buffaloes), rather than environmental factors, drive human transmission of schistosomiasis. The results, highly significant as they issue from a cross-sectional study comprising almost 50,000 participants from 47 villages, are practically useful for epidemiologic surveillance and future planning of interventions.

An advanced study on control strategy, looking towards the elimination of schistosomiasis, has been carried out in lake regions of P.R. China. This control strategy was implemented with an integrated approach which emphasised on elimination of the infectious sources or animal reservoir hosts in order to reduce the faecal contamination to oncomelanid snail intermediate host, since the previous approach of mass chemotherapy could not stop the transmission (Wang et al., 2009a,b). It encouraged us to put a greater effort into the elimination of schistosomiasis through long-term planning, intersectoral government coordination and commitment over a period of decades (King, 2009, 2010a).

3.2.2.7. Surveillance

Progress evolving from the links between monitoring activities and research has shown that surveillance represents more than just the collection of data. The situation has been reviewed with regard to efficiency of monitoring and the utility in relation to human diagnosis (Li et al., 2005; Wu et al., 2005). The questionnaire approach, developed by Lengeler et al. (2002) in Africa, was transferred and further developed for identification of high-risk individuals in areas prone to flooding (Tan et al., 2004).

The application of Bayesian multiple, logistic regression models helped Steinmann et al. (2007) identify associations between serologic results and environmental parameters in a county in Yunnan, P.R. China. Further use of serology has confirmed that infection in mobile populations, that is, fishermen and their families who move around the great lakes in central P.R. China, represent a so-called 'hot spot' of infection which cannot be easily eliminated (Zhu, 2005).

Naturally, this brief overview of a selection of recent research papers is far from exhaustive but it should suffice to make the point that research activities are numerous and that the projects with RNAS$^+$ connections cover a broad range. It also goes to show that new knowledge is being generated and that projects have benefited the end-users (both at the policy and societal levels), contributed to capacity building (both at the individual and institutional level) and enhanced communication.

3.3. SEARCH FOR EVIDENCE

A large part of network-associated collaboration deals with the gathering of data and the presentation of this information in a reliable and understandable format which is easy to follow. Evidence-based medicine (EBM) and evidence-based practice (EBP) represent a rapidly growing area that includes information on Internet search engines for health care disciplines and ideas for handling the information (McKibbon, 1998). EBN and EBP are tools for knowledge dissemination that can support health care decisions by facilitating the identification of appropriate literature from various sources regarding therapy, diagnosis, etc. This approach, developed and applied to find the most efficacious interventions possible, was originally developed to improve individual patient care but could also be used for advising on control efforts in endemic countries. However, any external guidelines must be integrated with epidemiological expertise in order to decide whether and how it matches the endemic predicament and preferences and thus how it should be implemented. EBM is not restricted to randomised trials and meta-analyses but aspires to find the best external evidence with which to answer specific, clinical questions. Proper cross-sectional studies need to be identified in order to ensure the accuracy of diagnostic tests, while proper follow-up studies of infected subjects assembled at uniform points should be retrieved. With regard to therapy, non-experimental approaches should be avoided since these routinely lead to false-positive conclusions about efficacy. Because randomised trials, especially the systematic review of several such trials, are so much more likely to provide the information needed, it has become the ''gold standard'' for judging whether a treatment does more good than harm. Many different kinds of institutions (universities, donor agencies, non-profit organisations, or business-oriented companies) provide information for the assessment of health needs in the world. They differ in approach and scope as seen at the Lamar Soutter Library website of the University of Massachusetts Medical School (http://library.umassmed.edu/EBM/index.cfm). A few examples of the more well-known organisations involved with EBM and EBP are given as follows:

The Institute of Medicine (IOM) (http://www.iom.edu/) is an independent, not-for-profit organisation working outside of Government for the provision of unbiased and authoritative advice on matters of biomedical science, medicine and health. Established in 1970, the IOM is the health arm of the National Academy of Sciences, which has expanded into what is collectively known as the National Academies, comprising the National Academy of Sciences, the National Academy of Engineering and the National Research Council. The IOM's main mission is to serve as adviser to the United States in order to improve health in that country, but its resources are also open to outside users. It provides unbiased, evidence-based, authoritative information and advice concerning health and science policy to policy-makers, professionals, leaders in every secton of society and the public at large. Many of the studies undertaken begin as specific mandates from the US Congress, while others are requested by federal agencies and independent organisations. The IOM also convenes a series of forums, roundtables and standing committees, as well as other activities, to facilitate discussion, discovery and critical, cross-disciplinary thinking.

The Cochrane Collaboration (http://www.cochrane.org), founded in 1993, is another, not-for-profit, international, independent organisation that produces and disseminates systematic reviews of health care interventions. In particular, it promotes the search for evidence in the form of clinical trials. The Cochrane collaboration provides up-to-date, accurate information about the effects of health care worldwide. Its major product is the Cochrane Database of Systematic Reviews which is published quarterly as part of 'The Cochrane Library' which is accessible online through the Cochrane website. The reviewers are health care professionals who volunteer to work in one of the many 'Cochrane Review Groups', with editorial teams overseeing the preparation and maintenance of the reviews.

The Oxford Centre for Evidence-Based Medicine (http://www.cebm.net) was established in 1995 with the aim to develop, teach and promote evidence-based health care. EBM is the conscientious use of current best evidence in making decisions about the care of individual patients. The practice of EBM means integrating individual clinical expertise with the best available external clinical evidence from systematic research. It is based on clinical evidence and relevant research gleaned from the basic sciences of medicine but especially from patient-centred, clinical research into the accuracy and precision of diagnostic tests, the power of prognostic markers and the efficacy and safety of therapeutic, rehabilitative and preventive regimens.

3.4. THE FUTURE

New initiatives addressing NTDs are urgently needed and there is an increasing awareness of the role of polyparasitism (Hotez et al., 2007; Sayasone et al., 2009) and the role of the climate and the environment leading to changing epidemiological patterns (Spear et al., 2004; Yang et al., 2005, 2006; Zhou et al., 2004, 2008c). The rapid growth of key technologies (health metrics, GIS/RS, etc.) and the development of evidence-based policies are seen as important, although the latter is still controversial (Behague et al., 2009). To make progress towards these goals, it is necessary to foster research capacity and to develop networking capacities, as well as to provide easy access to information.

Faced with a situation where the means to control many of the different target diseases are available but the financial means to achieve this fully are lacking, RNAS$^+$ is at an important juncture. Operating with nine member countries in Southeast Asia with the vision of becoming a recognised platform for evidence-based information and intersectoral communication, it has made progress in bridging the gap between research scientists and control authorities. RNAS$^+$ also aims to be the forum for the exchange and dissemination of information about current research news and developments on prevention and control of NTDs in the area, through intersectoral collaboration and networking with scientists and control authorities. They intend to offer:

- expertise in diagnostics, GIS/RS and health metrics; drug/vaccine development; competence in developing training packages and short courses;
- mechanisms for sharing information through its website, databases, publications and meetings;
- the capacity to develop multidisciplinary approaches and multi-country proposals for disease control; and
- links with control programmes in member countries and collaborative activities with international organisations and research institutions.

The geospatial sciences have become a driving force in mapping diseases that are closely linked to the environment, ecology and climate. Current applications include a broad range of NTDs such as schistosomiasis, cysticercosis/taeniasis, echinococosis, hookworm disease, strongyloidiasis and food-borne diseases caused by helminth parasites as diverse as *Angiostrongylus*, *Clonorchis*, *Fasciola*, *Opisthorchis*, *Paragonimus*, *Haplorchis* and *Metorchis* (*Metagonimus*). The promotion of ethical issues, the establishment of guidelines for surveillance, the standardisation of diagnostic approaches and the production of training manuals for use in endemic areas are also priorities. To strengthen the research capacity through the network, a work plan has been drawn up in the form of 'business lines' corresponding to regional research needs:

Implementation research with focus on control strategies (Box 3.1);

Ecology and the environment: studies of the potential impact of climate change, large-scale, water resources development and environmental engineering projects;

Product development: the production of new drugs, vaccines, improved diagnostics and better molluscicides/pesticides;

Database development: the establishment of comprehensive databases containing epidemiological data on all the endemic diseases in the region and their vectors;

BOX 3.1 Regional research needs and priorities—implementation research with focus on control strategies:

(1) Identification of risk factors related to multi-helminth infections in different settings, including co-infections such as helminth/TB infections and helminth/HIV.
(2) Role of animal helminthiasis in different settings improving our understanding of the importance of animal infections for transmission to humans.
(3) Investigation of the factors leading to increased vulnerability for acute schistosomiasis.
(4) Assessment of treatment effectiveness after mass chemotherapy in large and diverse communities.
(5) Methods for the rapid evaluation of the community prevalence of *S. japonicum* infections, for example, by a combination of information from serological testing, stool examination and questionnaires used for research on both humans and livestock.
(6) Standardisation of morbidity assessment by ultrasonography for evaluation of the various disease-burdens.
(7) Investigation of the safety, efficacy, cost and effectiveness of drug treatment schedules and delivery mechanisms to assess the potential for novel chemotherapy strategies, for example, studies of the use of artemisinins, alone and in combination with praziquantel, are an integral part of this programme.
(8) Equity of control efforts—the study of the relationship between endemicity and control efforts in endemic areas should be encouraged to provide evidence for equitable allocation of resources.

Serum and specimen banks: the creation of a serum bank, a gene bank focused on *S. japonicum* and *O. hupensis* and a collection of parasite strains and their intermediate hosts;

Technical development and standardisation: the development and testing of diagnostic kits, GIS/RS implantation including expanded use of Bayesian statistics and modelling;

Surveillance (Box 3.2);

Parasite biology: molecular biology, bioinformatics, genome and proteome research, genetic basis for vector reinfection, genetic and the immunological background for human reinfection;

Vector/intermediate host biology and host/parasite relationship (Box 3.3);

Social determinants and human behaviour (Box 3.4);

Health metrics: to serve as a base for the planning and evaluation of efficacy and cost-effectiveness of control programmes;

BOX 3.2 Regional research needs and priorities—surveillance:

Determination of frequency and approach to monitoring, and criteria for changes therein; establishment of managerial tools and procedures for outbreak surveillance, classification and response to permit a timely and effective response; development and introduction of new tools for efficient surveillance of humans, animals and snail habitats after eradication and transmission interruption; and surveillance after interruption of transmission.

BOX 3.3 Regional research needs and priorities—vector/intermediate host biology and the host/parasite relationship:

(1) Development of simple methods for the detection of infected snails for surveillance and outbreak investigations.
(2) Host parasite interaction—acquaintance with systems biology to facilitate the understanding of the interaction between parasite and vector (intermediate host), including insights into their genetic coevolution.
(3) Intermediate host susceptibility to infection—the genetic basis and immunological mechanisms governing infection susceptibility of *O. hupensis* should be further studied.
(4) Genomic bases for infection resistance—genome and proteome studies should be employed to identify functional genes of *O. hupensis* conferring resistance against *S. japonicum* infection. Development of transmission models.

Modelling: employing environmental, demographic and socioeconomic variables to provide the theoretical basis for transmission estimates and the use of immunological and diagnostic variables for the evaluation of the efficacy of chemotherapy and vaccines.

In the latest annual RNAS$^+$ meeting, held in Vientiane, Lao PDR, in October 2009, the network aligned its activities with those of the WHO/WPRO Strategic Research Plan for NTDs, and formulated its vision and activities in terms of the Research Plan by conceptualising five research projects related to the control of NTDs. The projects were concerned with the following subjects:

BOX 3.4 Regional research needs and priorities—social determinants and human behavior:

(1) Socioeconomic context and impact on control approaches—the impact of the social and economic context should be studied in relation to control programmes with the aim to better respond to local conditions and requirements.
(2) Socioeconomic changes—the impact of socioeconomic factors should be studied, including rapid socioeconomic development, increased mobility and changes in agricultural and fisheries practices.

1. Integrated, multisectoral control of neglected tropical diseases.
2. Development of improved diagnostics, new drugs and trematode vaccines.
3. Impact of community-led total sanitation (CLTS) on helminth infections.
4. Risk-mapping of FTI using rapid epidemiological assessment.
5. Integration of large-scale distributions of praziquantel with control interventions against soil-transmitted helminth infections in an area with multiple helminth infections.

Over the coming years, RNAS^{+} expects to spend most of its time on these projects, the concept and rationale of which can be summarised as follows:

(1) NTDs have common risk factors (socioeconomic, environmental, modes of transmission, etc.) and overlapping endemic areas. Hence, a multisectorial integrated control programme for NTDs would potentially be cost-effective and sustainable at the local level. Single vertical interventions, such as mass drug administration on its own, are challenging to maintain (primarily due to cost, compliance, reinfection rates and rebound morbidity).
(2) Diagnostic techniques need to become more sensitive. This is particularly well illustrated in the case of the national schistosomiasis control efforts in P.R. China, where intensity of infection is now often below the limit of detection by Kato-Katz stool examination, the traditionally used method, as has been unambiguously shown by Lin et al. (2008). New drugs are needed for many more diseases even after the introduction of artemisinin, used for the treatment of malaria as well as for the prevention of schistosomiasis (Xiao et al., 2010). Vaccines will increase in importance throughout the elimination phase for several

of the trematode infections (and also other helminths) when integrated with other control methods such as chemotherapy, targeted mollusciciding, sanitation and health education.

(3) It has been noted that poor sanitation is closely related to high prevalence of helminth infections in humans. The efficiency of preventive chemotherapy is thought to be low in poor sanitation scenarios because of high reinfection rates which rapidly engulf the positive effect. CLTS in conjunction with preventive chemotherapy (which would also affect protozoal and other diarrhoeal diseases) could bring added benefits (including cost savings) into facilitating the design of a control programme.

(4) Food-borne trematode infections and taeniasis/cysticercosis are prevalent in many parts of the region and together they constitute a major health problem in many countries of Southeast Asia. Infections occur in ethnic minorities who traditionally eat raw fish and pork (Sripa et al., 2010; Vandemark et al., 2010). High-risk areas should be targeted first and it is therefore imperative that a variety of rapid assessment tools be developed to cope with this situation.

(5) In Southeast Asia, many areas are endemic for multiple helminth infections, for example, lymphatic filariasis, schistosomiasis, opisthorchiasis, taeniasis/cysticercosis etc. Current interventions are limited to large-scale interventions with mebendazole (for soil-transmitted helminth infections) and albendazole/diethylcarbamazine (DEC) (for lymphatic filariasis) and focal distribution of praziquantel (for schistosomiasis). There is a need to expand the control of these diseases in an integrated manner, by piggybacking on existing control activities, for example, by expanding the target for praziquantel distribution to cover all individuals affected by at least two of the aforementioned infections.

3.5. CONCLUSIONS

RNAS$^+$'s aims are strongly supported as a result of long-term association with control programmes in its member countries and collaborative activities with international research institutions, but the network needs increased funding to grow. Its strengths can be summed up as consisting of experience in control strategies, coupled with available mechanisms for information-sharing and expertise in diagnostics, GIS/RS, health metrics and drug/vaccine development.

The network has provided critical research input with regard to several NTDs in Southeast Asia, and the ideas based on which RNAS$^+$ has been working over the last decade have shown that progress can be made with a relatively small network and limited funding. However, the current, larger vision demands the establishment of a permanent clearing house to support the continuous exchange of ideas and data and make it possible for national researchers and control managers to work together with international scientists on a daily basis.

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