CHAPTER 1

Important Helminth Infections in Southeast Asia: Diversity, Potential for Control and Prospects for Elimination

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Contents

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Abstract Besides the 'big three'—HIV/AIDS, malaria and tuberculosis—there are a host of diseases that, by comparison, are truly neglected. These so-called neglected tropical diseases (NTDs), many of which caused by helminths, are intimately linked with poverty and are rampant where housing is poor; access to clean water and adequate sanitation is lacking; hygiene and nutrition is substandard and populations are marginalised and vulnerable. More than a billion people are affected by NTDs, mainly in remote rural and deprived urban settings of the developing world. An overview of papers published in two special thematic volumes of the *Advances in Parasitology* is provided here under the umbrella of current status of research and control of important helminth infections. A total of 25 comprehensive reviews are presented, which summarise the latest available data pertaining to the diagnosis, epidemiology, pathogenesis, prevention, treatment, control and eventual elimination of NTDs in Southeast Asia and neighbourhood countries. The focus of the first volume provides the current regional status of schistosomiasis, lymphatic filariasis, food-borne trematodiases, echinococcosis and cysticercosis/taeniasis, less common parasitic diseases that can cause epidemic outbreaks and helminth infections affecting the central nervous system. The second volume deals with the tools and strategies for control, including diagnostics, drugs, vaccines and cutting-edge basic research (e.g. the '–omics' sciences). Moreover, cross-cutting themes such as multiparasitism, social sciences, capacity strengthening, geospatial health technologies, health metrics and modelling the potential impact of climate change on helminthic diseases are discussed. Hopefully, these two volumes will become useful for researchers and, most importantly, disease control managers for integrated and sustainable control, rigorous monitoring and eventual elimination of NTDs in Southeast Asia and elsewhere.

1.1. INTRODUCTION

Over the past 15 years, the world has witnessed growing awareness, unprecedented local commitment and political will, the formation of numerous public–private partnerships and the forging of strategic alliances which, together, provide the necessary human, financial and technical means to combat the 'big three', that is HIV/AIDS, malaria and tuberculosis. For example, in the latest report from the Global Fund to Fight AIDS, Tuberculosis and Malaria (the Global Fund in short), it is estimated that, since its establishment in 2002 until the end of 2009, a total of 4.9 million lives have been saved through programmes with a financial envelope of US $ 19.2 billion (The Global Fund to Fight AIDS, Tuberculosis and Malaria, 2010). Indeed, the human population is not only larger than ever before but, on average, also healthier (e.g. measured by average life expectancy) and

new ambitious goals have been articulated, for example the eradication of malaria (Anonymous, 2007; Greenwood et al., 2008; Hall and Fauci, 2009). Yet, more work remains to be done, particularly with regard to the prevention, control, local elimination and eventual eradication of the so-called neglected tropical diseases (NTDs). Approximately 16% of the world's population suffers from one or more of these NTDs which, in the words of Dr. Margaret Chan, Director-General of the World Health Organization (WHO), during her 2007 David E. Barmes Global Health Lecture in Bethesda, USA, is ''...ancient debilitating diseases strongly associated with poverty. They thrive in areas where water supply and sanitation are inadequate, vectors proliferate, housing is substandard, nutrition is poor and populations are illiterate. These diseases sap the productivity and curtail the human potential of at least one billion people who are the poorest of the poor'' (Chan, 2007).

Recent estimates suggest that the NTDs are responsible for over half a million deaths every year and a global burden in excess of 50 million disability-adjusted life years (DALYs) lost annually (Hotez et al., 2006). Awareness of the intimate connection between NTDs and poverty has a long history. For example, a century ago, the Rockefeller Sanitary Commission embarked on the elimination of hookworm disease in the southern parts of the United States (Anonymous, 1909), in an effort to boost the country's regional economic, political and cultural developments (Brown, 1976). After decades of neglect, finally, there is growing interest in the control of NTDs on a local, regional and global scale, not only because of economic, social and human developments, but also because of human rights and equity considerations (Brady et al., 2006; Daar et al., 2007; Hotez, 2008; Hotez et al., 2009; King, 2010a; Lammie et al., 2006; Maudlin et al., 2009; Miguel and Kremer, 2004; Morel et al., 2005; Yaïch, 2009). For example, progress towards achieving the millennium development goals (MDGs) crucially depends on advances made in the prevention, control and eventual elimination of the NTDs as public health problems (May, 2007; Molyneux, 2008). Thanks to the growing awareness of the global burden of NTDs being grossly underestimated and mounting advocacy, the prospects for their control are finally changing for the better, although these changes have yet to be fully translated into political will and commitment with adequate human and financial resources and technical means for prevention, control and elimination (Fenwick, 2006; Hotez et al., 2006, 2007; Lammie et al., 2006; Singer and Castro, 2007; Utzinger et al., 2009). It is in this connection important to further our understanding of the epidemiology of the NTDs, so that multi-pronged, setting-specific and integrated approaches can be deployed to make a durable impact against them, which, in turn, would improve health, equity and well-being.

Here, an overview is provided of two special thematic volumes of the *Advances in Parasitology* pertaining to the epidemiology and control of

NTDs in Southeast Asia and neighbourhood countries. Short prefaces are setting the scene for each volume leading up to the centre piece of 25 comprehensive reviews. These reviews summarise the latest available information on the diagnosis, epidemiology, pathogenesis, prevention, treatment, control and elimination of NTDs. Particular consideration has been given to schistosomiasis, lymphatic filariasis, food-borne trematodiases, echinococcosis and cysticercosis/taeniasis. Less common parasitic diseases that can cause epidemic outbreaks (e.g. capillariasis and trichinellosis), helminth infections affecting the central nervous system (e.g. angiostrongyliasis and gnathostomiasis) and the issue of multi-parasitism are also discussed. The cutting-edge '-omics' sciences are reviewed, including genomics, proteomics, transcriptomics and metabonomics. Several chapters focus on cross-cutting themes, such as capacity strengthening through existing networks, for example Regional Network of Asian Schistosomiasis and other Zoonotic Helminthiasis (RNAS^{+}), exploring links between the NTDs and ethnic minority groups, discussing the role of the social sciences, current challenges in estimating the regional and global NTD burden, development and application of geospatial health technologies and modelling a potential impact of climate change on helminthic diseases. Given the importance of an accurate diagnosis, adequate patient management and large-scale control of helminthiases by means of preventive chemotherapy, separate reviews pertaining to diagnosis and drugs have been prepared. It seems, at least for some of the NTDs discussed here, that vaccines are needed along with other preventive and curative measures to ultimately achieve local elimination, and hence a separate vaccine review is presented. The 25 chapters have been prepared by 69 experts, the majority of whom based in Asia. Most of the chapters are multi-authored, demonstrating the breath and depth of the existing partnerships between universities, research institutions and disease control managers in disease-endemic countries of Southeast Asia and abroad.

1.2. TWO THEMATIC VOLUMES OF THE *ADVANCES IN PARASITOLOGY*

1.2.1. An idea originating in the ancient city of Lijiang

The original idea of this project stems from two meetings, held back-to-back, in September 2007 in the ancient city of Lijiang, Yunnan province, People's Republic of China (P.R. China). Summary reports are available both for the 7th RNAS^{+} meeting (Zhou et al., 2008a) and the 1st International Symposium on Geospatial Health (Zhou et al., 2009). Six oral presentations from these two meetings were selected for publication in a special section of *Parasitology International*:

- Leonardo et al. (2008) summarising results from a prevalence survey of *Schistosoma japonicum* in two areas of the Philippines, where control of schistosomiasis proved particularly challenging;
- Wu et al. (2008) pursuing a retrospective analysis of the effect of floods on the transmission of *S. japonicum* in the Yangtze River valley of P.R. China;
- Garjito et al. (2008) describing the past and current epidemiological situations of schistosomiasis in Indonesia;
- Lin et al. (2008) performing an in-depth investigation of the diagnostic accuracy of the widely used Kato-Katz technique, concluding that single thick smears considerably under-estimate the prevalence of *S. japonicum* in settings characterised by low-infection intensity;
- Attwood et al. (2008) presenting phylogenetic data of *Neotricula aperta*, the only intermediate host snail of *Schistosoma mekongi*, to understand the past, present and potential future distributions of schistosomiasis in Cambodia and Lao People's Democratic Republic (Lao PDR); and
- Conlan et al. (2008) reviewing the scarce data currently available regarding taeniasis and cysticercosis in Lao PDR, and calling for new research, including standardised community-based surveys.

Additionally, three oral presentations focusing on the spatial distribution of *S. japonicum* and its intermediate host snail *Oncomelania hupensis* within a single county (i.e. Eryuan in Yunnan province) and the spatio-temporal distribution and changing patterns of both human and bovine schistosomiasis japonica across P.R. China were published (Steinmann et al., 2007; Wu et al., 2007; Yang et al., 2009).

The two meetings convened in Lijiang were attended by over 100 scientists and disease control managers primarily from Asia, but collaborators from Australia, Europe and North America and invited guests from Africa also participated. It was the largest RNAS^{+} meeting held thus far, which shows the increasingly important role of the network in strengthening local and regional co-operations and facilitating exchange of expertise and experiences pertaining to the epidemiology and control of NTDs in Southeast Asia and neighbourhood countries. The African colleagues were invited to stimulate their thinking about how to render the recently established Research Network for Schistosomiasis in Africa (RNSA) more visible and vibrant.

1.2.2. Action towards collaboration and partnership in an enabling environment

When contacted in October 2008, Drs David Rollinson and Simon Hay, the editors-in-chief of the *Advances in Parasitology*, were open to our proposal of producing a major piece pertaining to the NTDs in Southeast Asia.

Their colleagues at Elsevier, Narmada Thangavelu, the development editor, and Lisa Tickner, the publisher, agreed to go along with this idea. Once the depth and breath of the 25 chapters became obvious (e.g. two of the submitted manuscripts were 100+ double-spaced DIN A4 pages long), it was clear that our endeavour needed to be split into two separate volumes.

Before summarising the structure and main thrust of these two volumes, we must firmly acknowledge Drs Rollinson and Hay and their colleagues at Elsevier for their tireless efforts in moving the project along and for keeping us on track with regard to content as well as time. We also highly appreciate the editors and production staffs' patience, as the ultimate delivery of this umbrella piece was delayed by a few weeks. We express our deep gratitude to the many external referees who provided peer-review comments in a timely and constructive fashion. The huge scientific freedom, coupled with a lean, yet highly efficient, publishing environment and the existing collaboration and partnership were the key features that kept us motivated throughout this 18-month project. A big THANKS to all parties involved!

1.2.3. Nuts and bolts

Figure 1.1 provides 'an umbrella view' of the 25 chapters covered in volumes 72 and 73 of the *Advances in Parasitology*, which, together form an understanding of the epidemiology and control of NTDs with particular emphasis on Southeast Asia and neighbourhood countries. Each volume consists of a short preface; the first by Dr. Yu Sen-Hai, a former director of the National Institute of Parasitic Diseases (IPD), Chinese Center for Disease Control and Prevention (China CDC) in Shanghai, and the second by Dr. Robert Ridley, the current director of the Special Programme for Research and Training in Tropical Diseases (TDR). The 25 comprehensive reviews cover a vast territory reflecting the principles of 'translational medicine' as they describe the move from the bench to the field and clinical medicine, from the molecular to the spatial and systemic, and from basic science to operational research and integrated control. The most important results are summarised in Section 1.3 along with implications for the control and elimination of NTDs at a local, regional and global scale.

Three chapters are single-authored pieces (Attwood, 2010; King, 2010b; McManus, 2010), but the remaining 22 chapters underscore the collaborative approach with two contributions prepared by 11 authors each (Schratz et al., 2010; Yang et al., 2010) (Fig. 1.2A). Interestingly, almost four out of five chapters (76.9%) were prepared by scientists and disease control managers from Asia in partnership with authors from the industrialized countries in Europe, the United States and Australia

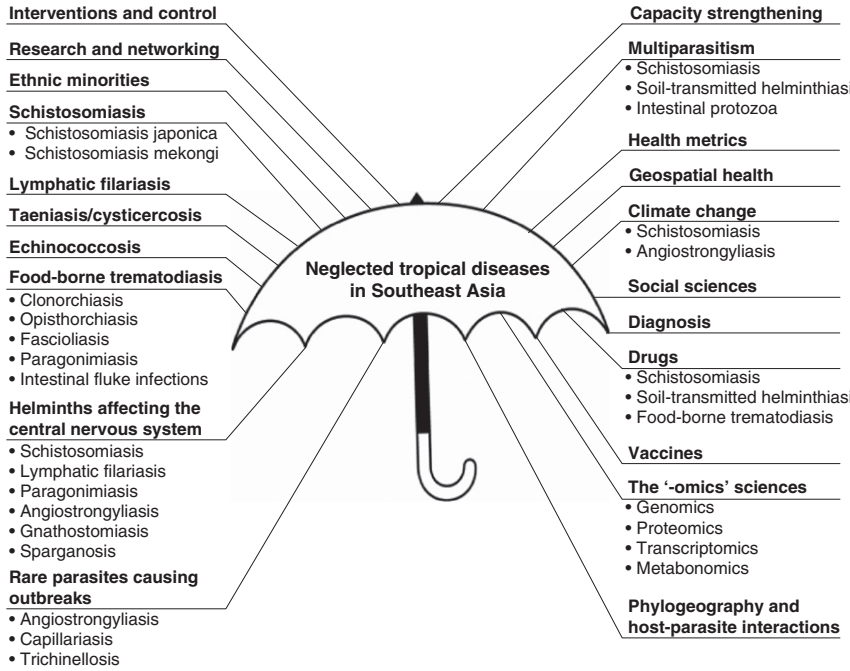

FIGURE 1.1 Umbrella showing the overall structure and main topics covered in two special thematic volumes of the *Advances in Parasitology* pertaining to the NTDs in Southeast Asia and neighbourhood countries (volume 72, left-hand side; volume 73, right-hand side).

(Fig. 1.2B). These collaborations and partnerships have partially been facilitated by the RNAS^{+} network established in the late 1990s and involved in corralling the expertise needed to produce the present two volumes (Leonardo and Bergquist, 2002; Zhou et al., 2002, 2008a). Gender stratification reveals that 26 of the contributing authors (37.7%) are females (Fig. 1.2C). This percentage is considerably higher than that found in a 2003 analysis of gender composition of editorial boards of six leading general-medicine journals, which reported only 23% females (Keiser et al., 2003).

Figure 1.3 shows the results of a geographical analysis according to author affiliation. Two-thirds of the contributing authors are affiliated with universities, research institutions and disease-control organizations in Southeast Asia and neighbourhood countries. P.R. China represents the highest number of contributing authors ($n = 21.5$, i.e. 31.2%; of note, if an author is affiliated with two different countries, each country counts as half, which explains the figure 21.5), followed by the Philippines ($n = 13$, i.e. 18.8%). In most cases, the lead was taken by a colleague based in Asia and the majority of the senior authors are affiliated to universities,

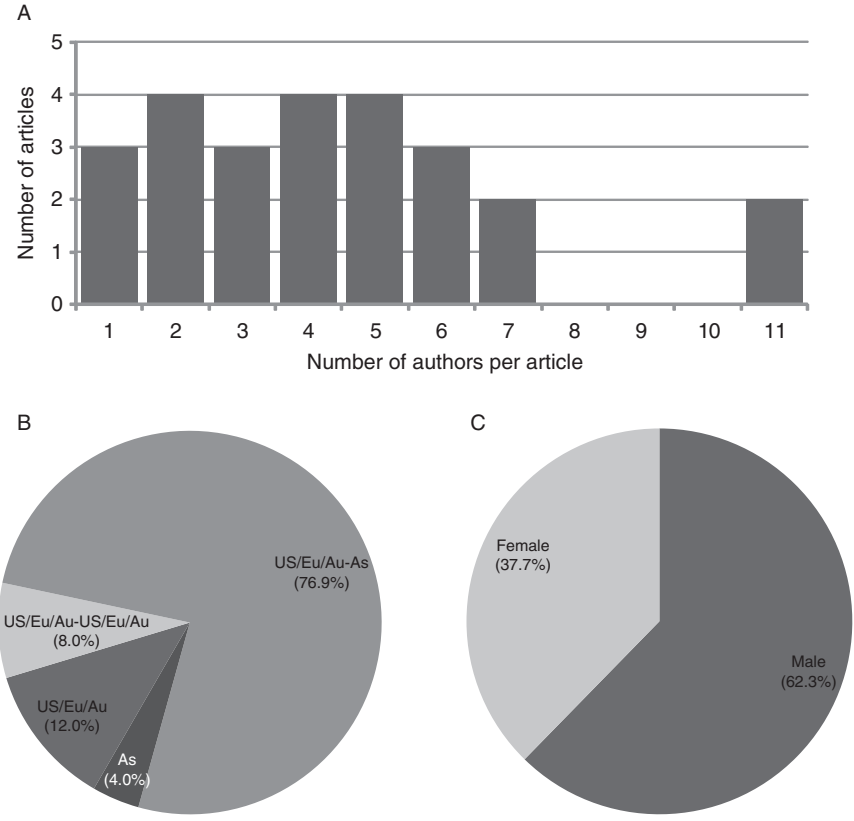

FIGURE 1.2 Bibliometric analysis of 25 reviews published in two special thematic volumes of the *Advances in Parasitology* pertaining to the NTDs in Southeast Asia. Depicted are (A) the number of articles according to the number of authors in each chapter, (B) collaboration and research partnerships stratified by different regions of the world (key: As = Asia, Au = Australia, Eu = Europe, US = United States of America) and (C) gender composition of the 69 contributing authors.

research institutions and disease control organizations in Asia. Many of the reviews represent long-standing research partnerships as the contributing authors have been collaborating for years within institutions that bridge the North–South gap. This is in contrast to findings obtained after an analysis of 2348 full-length articles, published between 2000 and 2002 in six leading tropical-medicine journals, where 48.1% of the contributing authors had affiliations in countries with a high human development index, whereas only 13.7% of the authors came from countries with a low human development index (Keiser et al., 2004). However, the articles of three previous, similar special issues of core parasitology and

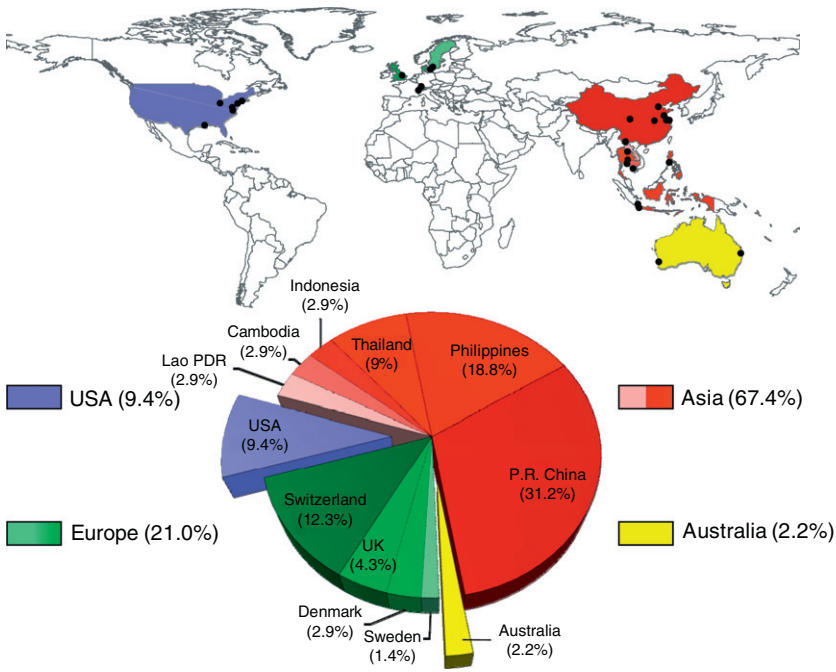

FIGURE 1.3 Geographical analysis, stratifying the 69 authors contributing one or several chapters to these two volumes of the *Advances in Parasitology* by their affiliations. Countries are highlighted with different grey shades to differentiate between Asia, Australia, Europe and the United States. The towns of the contributing authors' affiliations are highlighted with white dots. Of note, if an author is affiliated to two different countries (e.g. P.R. China and Switzerland), each country is counted half.

tropical-medicine journals also show a high representation of authors from the developing world, for example the overview of the control of schistosomiasis in P.R. China, published in *Acta Tropica* (Utzinger et al., 2005), the commemoration of 100 years of research and control of schistosomiasis in Brazil also put forth in *Acta Tropica* (Bergquist, 2008) and, most recently, a special issue of *Parasitology* reviewing and updating the epidemiology and control of schistosomiasis in sub-Saharan Africa (Stothard et al., 2009).

1.3. PROGRESS MADE IN RESEARCH AND CONTROL OF NTDs

1.3.1. The global landscape

Notable progress in the field of NTD control is multi-factorial with the Internet, public–private partnerships built around drug donation programmes and scientific networks as the more prominent new facets

(Hotez et al., 2007; Moran, 2005; Moran et al., 2009; Morel et al., 2005, 2009). When the 'World Wide Web' was launched in 1989, it marked the beginning of the 'world wide use' of the Internet that had so far been of limited service. However, Berners-Lee, then working at CERN, saw it as the solution to the need for information sharing across time and space (see http://www.ted.com/talks/tim_berners_lee_on_the_next_web.html). Although the approach first seemed to amount to putting the carriage before the horse as this need was neither widely perceived nor pronounced, but Berners-Lee foresaw its enormous potential and it is now obvious that without the 'Web', practical applications would have continued to lag common needs in spite of an ever increasing rate of scientific advances. Still, the difficulty of locating and managing the wealth of scientific articles is frustrating and today's searching, analysing, organizing and sharing new findings, bibliographic management in short, underline the importance of management and linking of data as well as translating scientific breakthroughs into policy briefs, so that they become of practical use.

If the 'Web' was the key for connection and information exchange, public–private partnerships play a seminal role for funding, advocacy and fostering control efforts (Maudlin et al., 2009; Molyneux, 2006; Savioli et al., 2002; Widdus, 2005). In retrospect, the collaboration between Merck & Co, the Mectizan Donation Program, WHO and the African Programme for Onchocerciasis Control (APOC) for the control of onchocerciasis in the late 1980s did not only help people with, and those at risk for, onchocerciasis, but also ushered in the very idea of public–private partnerships (Peters and Phillips, 2004; Sékétéli et al., 2002). This way of thinking led to increased integration with regard to NTD control (Brady et al., 2006; Fenwick, 2006; Lammie et al., 2006). As a consequence, control approaches are becoming less vertical, although integration of NTD control programmes, thus far, heavily rely on specific, preventive chemotherapy (Anonymous, 2004; Hotez et al., 2006, 2007, 2009; Reddy et al., 2007; Smits, 2009; WHO, 2006a). However, in order to achieve sustainable control of the NTDs, more integrated approaches are necessary, for example by further strengthening existing health systems and fostering inter-sectoral collaboration between, among others, the health, agriculture, education, financial and water resources sectors (Ehrenberg and Ault, 2005; Holveck et al., 2007; Singer and Castro, 2007; Utzinger and de Savigny, 2006; Utzinger et al., 2003; 2009). This is no news, rather good public health sense, backed up by historical evidence. Charles W. Stiles, for example, who was instrumental during the Rockefeller Sanitary Commission-led efforts against hookworms in the southern United States, concluded that the elimination of hookworm disease should be based on ''20% thymol and Epsom salts [treatment] combined with 80% sanitation [prevention]'' (Stiles, 1939). This conclusion, we believe, is as important today as it was many decades ago, and it is in this

connection that we welcome thinking and action beyond deworming (Anonymous, 2004; Utzinger et al., 2009; Wang et al., 2009a,b).

International donor agencies now find it useful to work directly with pharmaceutical companies and private foundations as mentioned by Bergquist and Tanner (2010). This trend is growing and the last decade has seen the establishment of numerous global partnerships in the public health sector that address challenges such as the 'big three' (The Global Fund to Fight AIDS, Tuberculosis and Malaria, 2010), as well as deficiencies with respect to child and maternal health, nutrition and access to clean water and improved sanitation (Wahlqvist and Kuo, 2009; WHO and UNICEF, 2010). These new partnerships have not only raised the profile of health in general, but also generated unprecedented, financial resources now spilling over into the field of the NTDs. However, formidable challenges remain, as a result of the lack of readily available rapid assessment techniques for mapping the co-endemicity of multiple NTDs, as well as the diversity of disease control approaches and governance structures (Brooker et al., 2009; Kolaczinski et al., 2007; Liese et al., 2010; Sturrock et al., 2009; Utzinger and de Savigny, 2006). Of particular note is the *Global Network for Neglected Tropical Diseases (the Global Network in short; http://globalnetwork.org/)*.

1.3.2. Regional advances: Southeast Asia and neighbourhood countries

1.3.2.1. Epidemiology and control of worms: then and now

Not only does Southeast Asia harbour all cases of schistosomiasis japonica (Zhou et al., 2010a), schistosomiasis mekongi (Muth et al., 2010) and the majority of food-borne trematode infections (Keiser and Utzinger, 2009; Sripa et al., 2010), but also one-third of the world's intestinal helminthiases (Hotez and Ehrenberg, 2010), a quarter of the global burden of lymphatic filariasis (Sudomo et al., 2010), and a multitude of less common parasitic infections that can produce outbreaks (Odermatt et al., 2010) or invade the central nervous system (Lv et al., 2010). Moreover, multiparasitism is the norm rather than the exception, although detailed investigations on the epidemiology, risk factors and clinical implications of multiple species helminth and intestinal protozoa infections are lacking (Ezeamama et al., 2005; Pullan and Brooker, 2008; Steinmann et al., 2008, 2010). Considering that Southeast Asia and the Western Pacific Region is also home to a very large number of marginalised, vulnerable population groups, control activities are a priority (Schratz et al., 2010). The epidemiology of many parasitic helminths is different from that of most other infections. For example, the risk an infected person (or animal reservoir host) carries for others is a direct function of the number of worms present

in the definitive host, that is the intensity of infection (Anderson and May, 1985). This important issue, highlighted by a family of life cycles collected at the back of volume 1, is the key to unravel our 'wormy world' and has important ramifications for control.

We have moved a long way since 'this wormy world' was first minted in the late 1940s (Stoll, 1947), or have we? In fact, it must be stated that, in spite of vast amounts of new knowledge coming from the development and application of mathematical modelling, molecular biology and the '-omics' sciences, the old appraisal of the wormy world still stands and the various helminth infections still exist much as they did more than 60 years ago when Norman R. Stoll delivered his keynote address to the American Society of Parasitologists (Bethony et al., 2006; Brooker and Utzinger, 2007; Bundy and de Silva, 1998; Crompton, 1999; Hotez and Ehrenberg, 2010; Keiser and Utzinger, 2010). Stoll (1947) did not mince his words when calling for parasitic diseases to be brought under control. However, the task is far from straightforward, since behavioural, cultural, demographic, ecologic, economic, environmental, political, scientific and social factors have derailed efforts until the present time. The elimination of lymphatic filariasis from P.R. China (Lammie et al., 2007; WHO, 2006b) may be the turning point the scientific community and public health experts have been waiting for.

In paying tribute to Stoll's seminal piece, two important papers published in the late 1990s (Bundy and de Silva, 1998; Crompton, 1999) pointed out that the public health significance of helminth infections is far greater than generally acknowledged. Along with the availability of inexpensive, safe and efficacious anthelminthic drugs that can be administered by non-health personnel after minimal training (Savioli et al., 2002; WHO 2006a), this contributed more than anything else to pave the way for the current large-scale control programmes. As mentioned before, international agencies are joining forces with private foundations and industry to manage human helminth infections targeting all the major helminthiases. Apart from the Mectizan Donation Program and APOC, the Bill and Melinda Gates Foundation (BMGF; http://www.gatesfoundation.org), the United States Agency for International Development (USAID; http://www.usaid.gov) and other aid organizations are working in union supporting specialized programmes as for example the Schistosomiasis Control Initiative (SCI; http://www.sci-ntds.org/) and the Global Network to realize the MDGs (http://www.un.org/millenniumgoals/) of sustainable poverty reduction. These activities are now becoming more integrated, targeting several diseases concurrently in many countries (Fenwick, 2006; Fenwick et al., 2009; Lammie et al., 2006; Smits, 2009; Utzinger et al., 2009). Thus, optimism over the prospects for control is no longer misplaced and the new movements in

'this wormy world' of ours remind us of the need to tackle the 'unremittingly corrosive' burden of helminth infections (Stoll, 1947).

Hence, an important issue of volumes 72 and 73 of the *Advances in Parasitology* is to boost interest in research on, and concerted control efforts against, helminth infections that dominate the disease spectrum in many parts of Southeast Asia and other parts of the world (Bethony et al., 2006; Hotez and Ehrenberg, 2010; Hotez et al., 2008). Much space has been devoted to the epidemiology and control of Asian schistosomiasis (Attwood, 2010; Bergquist and Tanner, 2010; Muth et al., 2010; Xiao et al., 2010; Zhou et al., 2010a), which makes sense from public health and economic points of view. Additionally, after lymphatic filariasis, *S. japonicum* may become the second major parasite infection to be eliminated in P.R. China (Wang et al., 2009a). Historically, judging from the absolute numbers of infected people, the schistosomiasis problem seems to have been worse in P.R. China than in the Philippines (Bergquist and Tanner, 2010). The big difference in cross-country, average prevalence that can be calculated (2% in P.R. China versus 8.6% in the Philippines) does not say more than that a comparatively smaller part of the latter country was endemic than the former. In the first decade of the new millennium, we find that the situation still holds, but the figures have changed even more to the advantage of P.R. China ($<0.1\%$ versus 0.6% in the Philippines). Although this again may mainly reflect that the former country has managed to reduce the extent of the endemic areas more than the latter, the bottom line is that both countries have reduced the number of people infected with *S. japonicum*, even in the face of strong population growth.

The analysis by Zhou et al. (2010a) not only reveals the importance of integrated control approaches for sustaining the advances achieved in schistosomiasis control to date, but also the need for flexible control approaches and innovation. It is in this connection more than just interesting to learn that Chinese farmers are spearheading the march into the industrial society by exchanging tractors for their water buffaloes (Wang et al., 2009a). Since it has been shown that domestic animals contribute more to sustain transmission than humans (Gray et al., 2009; Wang et al., 2005), this move will lower the risk of transmission of schistosomiasis, at the same time as it on balance might reduce the release of greenhouse gases (Zhou et al., 2008b). However, the current biggest hurdle for further progress are remaining pockets of high transmission, and compliance for repeated preventive chemotherapy (Guo et al., 2005) critically depends on a deeper understanding of people's perception and beliefs of schistosomiasis and practises to prevent and control the disease (Vandemark et al., 2010), a better appreciation of the 'true' burden of schistosomiasis (King, 2010b) and more sensitive diagnostics (Johansen et al., 2010) and rigorous surveillance.

Apart from the presence of *S. japonicum* in P.R. China, the Philippines and in limited foci in Indonesia (Zhou et al., 2010a), *S. mekongi* in Cambodia and Lao PDR should be noted, as this type of schistosomiasis is particularly aggressive with severe organ involvement and a high mortality rate if left untreated (Muth et al., 2010). Prior to 1999, transmission of *S. mekongi* was thought to be restricted to a 300 km section of the Mekong River between Khong Island in Lao PDR and Kratié in Cambodia. The range of both the parasites and its intermediate host snail *N. aperta* are now known to be much larger, with the snail found across central Lao PDR and eastern Cambodia and the parasites also occurring in two additional river systems of eastern Cambodia (Attwood, 2010; Attwood et al., 2004). The distribution of *N. aperta* outside the specific conditions of Mekong River has already raised the estimated population at risk by more than a factor 10 (Attwood et al., 2008), but its wider tolerance indicates that the new figure of 1.5 million might still be an underestimation. Indeed, Attwood (2010) argues that the current absence of *S. mekongi* from most of Lao PDR can be due to reasons other than any ecological barrier. If he is correct, it is conceivable that the invasion of much of Lao PDR by *S. mekongi* is just a question of time. Major water resources development and management (i.e. construction of large hydroelectric dams and expansion of irrigation systems) might further exacerbate the risk of *S. mekongi* in Lao PDR (Erlanger et al., 2008).

No discussion on trematode infections would be complete without examining the food-borne trematodiases, particularly as many of these infections only occur in Southeast Asia (Keiser and Utzinger, 2009). *Clonorchis sinensis*, with an estimated 35 million infections, is the predominant species and clonorchiasis is considered as an emerging infectious disease (Lun et al., 2005; Keiser and Utzinger, 2005, 2009). The estimated number of infections with *Paragonimus* spp. and *Opisthorchis viverrini* are 20.7 million and 10 million, respectively (Keiser and Utzinger, 2009). There are a host of intestinal flukes such as *Fasciolopsis buski*, the echinostomes and the *Heterophyidae*, which are among the most neglected of the NTDs, although some of these infections are fatal (Sripa et al., 2010).

Fifteen million people with lymphatic filariasis live in Southeast Asia. This disease is not only interesting from a scientific point of view but also, in particular, it represents a parasitic disease that has recently been eliminated in P.R. China. When Dr. Chan, Director-General of WHO, in a ceremony in early October 2008 in Beijing congratulated P.R. China for its success in having eliminated this parasitic disease as a public health problem, it was a turning point, not only in the fight against lymphatic filariasis but also for all major parasitic diseases. Dr. Chan noted the crucially important role of the Global Alliance to Eliminate Lymphatic Filariasis (GAELF), which was established as a result of the 1997 World Health Assembly (WHA) resolution 50.29, calling for worldwide

elimination of lymphatic filariasis as a public health problem by 2020. It is of interest to be able to follow the activities of the Chinese lymphatic filariasis control project, which started 60 years ago and chronicled in considerable depth by Sudomo et al. (2010). It is encouraging to note that the elimination activities in the surrounding countries where lymphatic filariasis is still endemic are also registering major progress (WHO, 2006b, 2009) and 2020, the target year for its final elimination, seems realistic.

Neurocysticercosis, the most serious form of *Taenia solium* infection, is considered the most preventable cause of epilepsy in the developing world (Lv et al., 2010; Sinha and Sharma, 2009; Willingham and Engels, 2006; Willingham et al., 2010). Although theoretically easy to control, there is a lack of information on the burden and transmission of the disease, partially explained by the unavailability of high-quality diagnostic tools in field-applicable formats. The presence, distribution, public health importance and economic relevance of cysticercosis need to be better documented in Southeast Asia in order to bring it to the attention of affected communities, decision makers and funding bodies alike.

1.3.2.2. DALYs and QALYs

During the September 2007 RNAS$^+$ meeting, held in Lijiang, P.R. China, a training workshop focussing on general and region-specific issues of disease burdens was part of the agenda (Zhou et al., 2008a). This issue is at the heart of elimination discussions and the most recent RNAS$^+$ meeting, which took place in October 2009 in Vientiane, Lao PDR, called attention for concerted efforts to estimate the global burden of food-borne trematodiasis. Indeed, no burden estimates are currently available for the major food-borne trematode infections (Hotez et al., 2006; Keiser and Utzinger, 2009). This is all the more surprising as the causative agents of *opisthorchiasis (i.e. O. viverrini*) and clonorchiasis (i.e. *C. sinensis*) are established risk factors for cholangiocarcinoma (Keiser and Utzinger, 2009; Sripa, 2008; Sripa et al., 2007, 2010). The burden of NTDs is vastly higher in Southeast Asia than previously recognised, but the impact of these diseases is difficult to pin down as it includes parameters above the simple number of people infected by a particular infection. Although the DALY metrics (Murray and Lopez, 1996) was a huge step forward from simple mortality figures, weaknesses of this approach have been pointed out (King, 2010a; King and Bertino, 2008; King et al., 2005). It is emphasised here that the DALY metrics is not always helpful, particularly not with regard to chronic diseases such as schistosomiasis and multiple species helminth infections (King, 2010b). Moreover, disability weights, as employed in the initial global burden of disease (GBD) studies by Murray and Lopez (1996), were based on expert opinion. With regard to schistosomiasis, very low disability weights were assigned, that is 0.005–0.006 on a scale from 0 (i.e. perfect health) to 1

(i.e. death). Recent investigations challenge these disability weights and speculate that the actual disabilities due to chronic schistosomiasis japonica are more than one or even two orders of magnitude higher (Finkelstein et al., 2008; Jia et al., 2007).

The quality-adjusted life year (QALY) seems to better capture the impact of helminthic infections that are characterised by subtle morbidities and long-term chronicity. First experiences with standardised, self-rated quality of life questionnaires have been presented for echinococcosis on the Tibetan Plateau (Budke et al., 2005) and chronic schistosomiasis japonica in P.R. China (Jia et al., 2007). However, there is controversy about how accurately QALYs reflect preferences for health care in other situations, for example in industrialised countries. The debate regarding the use of QALYs in countries at various levels of development has been reviewed (Neumann and Greenberg, 2009). Although this discussion may appear academic, the appreciation of the link between long-term, parasite-mediated inflammation, impact on the course and outcomes of pregnancy, impaired physical and cognitive development during childhood and poor work performance at older age is critical. For example, the QALY highlights evidence of great importance for decision makers such as choosing preventive over curative intervention. Health metrics is gaining in importance and occupies today, together with diagnostics, which strongly influences the appreciation of the 'true' burden of disease (Johansen et al., 2010), a decisive position how to proceed with regard to the diseases at hand.

1.3.2.3. Diagnostics, drugs and vaccines

Chemotherapy-based control programmes significantly reduce the prevalence and intensity of infection and NTD-related morbidity. Hence, preventive chemotherapy is promoted as a rapid impact strategy and has been suggested as a highly cost-effective public health intervention (Hotez et al., 2006, 2007, 2009; Molyneux et al., 2005; WHO, 2006a). Whilst progress in morbidity control due to NTDs through large-scale administration of drugs is laudable, some authors have argued that this success hindered progress in research and development of new drugs, diagnostics and vaccines (Bergquist et al., 2009; Caffrey, 2007; Cioli, 1998; Keiser and Utzinger, 2007; Utzinger et al., 2007). Preventive chemotherapy not only runs the risk of having to be continued indefinitely, but also of inducing drug resistance without the long-term protection a vaccine can offer as complementary intervention (Bergquist et al., 2005; 2008; McManus and Loukas, 2008; Utzinger et al., 2009). Facing the problem that long-term drug treatment represents a continuous expense and risk for drug resistance development, a new goal of vaccine development has been proposed (Bergquist et al., 2005; Bergquist and Lustigman, 2010), that is the integrated drug–vaccine approach. This aims at reposting vaccines

from stand-alone tools to adjuncts to chemotherapy. Thus, rather than inducing sterilizing immunity, the new role of vaccination would be to introduce a long-term component into control programmes, thus reducing the likelihood of transmission and re-infection, and lowering the risk of drug resistance development and spread.

By considering the fact that sustained work on vaccine development over many years, notably in the fields of hookworm infection, leishmaniasis, malaria, onchocerciasis and schistosomiasis, effective vaccines are becoming more credible, particularly as experiments in animal models have shown strong promise and several prototype anti-parasite vaccines are entering clinical trials. Additionally, the transmission-blocking approach, that is vaccination of reservoir host animals, has been successful even up to the point of provisional registration of a pig vaccine aiming at breaking the transmission of cysticercosis in humans (Rickard et al., 1995). Several other vaccines also mark a promising step in the whole progress of vaccine development, for example, the immunological control of *Fasciola* in sheep and cattle is within reach and this might have spillover effects on human schistosomiasis (Tendler and Simpson, 2008). In addition, highly effective, recombinant vaccines have already been developed for the prevention of *Taenia ovis* in sheep, *T. saginata* in cattle, *T. solium* in pigs and *Echinococcus granulosus* in livestock (Lightowlers, 2006). Indeed, transmission-blocking *S. japonicum* vaccines are already in field trials and have shown good results (Da'dara et al., 2008; McManus et al., 2009, 2010). The current accumulation of molecular data and expansion of parasite sequence databases are providing a fresh start by permitting a more rational approach to vaccine discovery and development. Therefore, it is likely that a range of new vaccines can be expected during the next few years. A strong move forward in this field would be facilitated if international donor organizations and private foundations could agree on a joint, major NTD vaccine initiative (Bergquist and Lustigman, 2010).

The global strategy for the control of helminth infections have two, not mutually exclusive and sequential goals, that is morbidity control, followed by elimination as a threat to public health. Clearly, over the past decade, particularly so in areas where helminthiases are highly endemic, the focus has been on the former (WHO, 2006a), but we are now turning to the latter in some parts of the world as new drugs and optimised administration of old ones have worked together to significantly reduce morbidity (Bergquist et al., 2009). The definitive review of anti-schistosomal drugs in P.R. China is presented by Xiao et al. (2010) who summarise the past 60 years of research and development in this field. Whilst praziquantel remains the drug of choice against schistosomiasis, the artemisinins and related compounds have been developed for 'chemoprophylaxis', because these drugs—best know for their anti-malarial properties—are able to prevent

the development of egg-laying patent schistosome infections. A second comprehensive review focuses on the current drugs against soil-transmitted helminthiases and food-borne trematodiases and discusses the latest findings with the cyclooctadepsipeptides, monepantel, nitazoxandide and tribendimidine, which might become the next generation of anthelminthic drugs (Keiser and Utzinger, 2010).

In any event, while regular administration of anthelminthic drugs to school-aged children and other people at high risk of morbidity serves as the backbone of interventions in the endemic areas, development of new diagnostics and vaccines has been somewhat put on the backburner due to the excellent efficacy and safety profiles of drug treatment (Bergquist and Lustigman, 2010). However, not only should we think about the need for concerted efforts to discover, develop and deploy the next generation of anthelminthic drugs, but also think how vaccine development can be brought to the fore and how a strategy based on integrated approaches can be forged.

1.3.2.4. The '–omics' sciences

Huge progress has been made over the past 20+ years in the area of the '–omics' sciences, including genomics, proteomics, transcriptomics and metabolic profiling in this wormy world, as reviewed for the *Advances in Parasitology* by Ju et al. (2010) and Wang et al. (2010). For example, we now dispose of the full genome sequences of multiple helminth species, including *S. japonicum* (*Schistosoma japonicum* Genome Sequencing and Functional Analysis Consortium, 2009). Moreover, the global metabolic responses of the hamster to an experimental infection with *S. japonicum*, the hookworm species *Necator americanus* and a co-infection with both parasites concurrently have been characterised (Wang et al., 2006, 2009c; Wu et al., 2010). Results obtained from the '–omics' sciences offer new insights into early events in the evolution of animals and co-evolution of host–parasite systems, will guide a more rationale approach for drug and vaccines target identification, and hence assist the research community in the development of new tools and strategies for the control and elimination of NTDs (Berriman et al., 2009; *Schistosoma japonicum* Genome Sequencing and Functional Analysis Consortium, 2009).

1.3.2.5. Geospatial health technologies

The development of geographical information systems (GIS) together with remote sensing and spatially-explicit risk mapping and prediction provides powerful tools to further our understanding of the frequency and transmission patterns of NTDs, which, in turn, can improve the efficiency of interventions and integrated disease control (Bergquist and Rinaldi, 2010; Clements et al., 2008; Simoonga et al., 2009; Yang et al., 2005).

Geospatial health technologies are also crucial for surveillance, particularly for disease control programmes as they shift the emphasis from morbidity control to transmission control and ultimately elimination. Malone et al. (2010) show the strengths of using a GIS approach for collating, storing and queering of data and displaying disease risk maps, which can be used for several purposes, such as identifying epidemiological risk factors and detection of 'hot spots' for disease transmission. The potential impact of climate change on helminth infections, with two case studies pertaining to angiostrongyliasis and schistosomiasis in P.R. China, is discussed by Yang et al. (2010). The authors employed biology-based models and speculate that predictive capabilities might be further enhanced by expanding these biology-based models to include also ecological and socio-cultural aspects, similar to recent experiences made with dengue (Arunachalam et al., 2010).

Spatially-explicit modelling of helminth infections has not only opened the door for improving forecasting regarding transmission patterns, but also provided predictive maps on how to improve communication between different stakeholders, decision makers and the public. Thus far, however, no organization on a national level has stepped to the forefront with a comprehensive response that provides for an integrated reporting structure that enables timely data collection and assessment, and promotes rapid communication with key organizations and the public. On the other hand, the thematic guide to social science applications of remote sensing, published by the Center for International Earth Science Information Network (CIESIN), shows that the utility of remote sensing can be broadened to include also the social sciences (de Sherbinin et al., 2002).

1.3.2.6. Capability strengthening, teaching and training

In order to successfully deal with the current challenges in Southeast Asia and neighbourhood countries with respect to the NTDs and to prioritise research and control efforts, it is important to understand the role of scientific networks. This issue is discussed by Olveda et al. (2010) who present the $RNAS^{+}$ as a model for other similar initiatives. The potential of network analysis has also been emphasised for the strategic planning, implementation and management of a programme pertaining to research, development and capacity building of NTDs in Brazil (Morel et al., 2009). The process of successfully embedding research into the health systems of developing countries calls for input from international research institutions and the participation of competent national scientists with local experience and expertise. The role of applied social sciences as a resource for capacity strengthening, teaching and training for research and control of NTDs discussed by Vandemark et al. (2010) complements recent reviews on the social sciences for an

enhanced understanding of the epidemiology and control of NTDs (Aagaard-Hansen et al., 2009; Huang and Manderson, 2005).

The infrastructure to improve the control programme of helminthiases is presented by Zhou et al. (2010b) and Malone et al. (2010) in terms of capability strengthening, training and teaching in epidemiology. These papers emphasise that not only the choice of model for research capacity building is an issue of the resources needed but it is also obvious that the results depend on the level of maturity of the national disease control programmes. Three models were proposed to be used in capacity strengthening in the region through (i) existing networks, (ii) international partnership and (iii) current infrastructure of operational research. Apart from RNAS^{+}, the two existing networks in Southeast Asia in the field of tropical medicine are the TROPMED Network of the Southeast Asian Ministers of Education Organization (SAMEO) and the Asian Collaborative Training Network for Malaria (ACTMalaria). International partners in the region are encouraged to integrate their activities with regard to existing programmes as this would facilitate and improve efficiency, effectiveness and delivery in the capacity building as well as health interventions. This is the trend of a new type of collaboration in which international donor agencies work together with commercial, pharmaceutical companies and private foundations, such as the BMGF (Hotez et al., 2007).

TDR' new strategy to deal with challenges arising from the impact on health of NTDs, emerging and re-emerging infectious diseases and climate change has translated into the idea of fostering an effective global research effort on infectious diseases of poverty. Stakeholder consultation in disease-endemic countries is an integral part to govern and prioritise the research agenda. Support for the development of networks that can be sustained in accelerating critical research and management skills in disease-endemic countries is emphasised in the quest to strengthen the capacity of endemic countries for research. For example, implementation of a geospatial health infrastructure in Southeast Asia will mainly depend on robust training programmes for health workers active in different institutions, for example Ministries of Health (MoH), non-governmental organizations (NGOs) and other health organizations involved in research and geospatial health operational applications (Leonardo et al., 2007). Under the auspices of the Global Network for Geospatial Health, a 'training node' entitled the 'International School of Geospatial Health', has been established to offer standardised short courses at IPD in Shanghai. Similar units at the Research Institute for Tropical Medicine (RITM) in the Philippines, the University of the Philippines and the Mekong Institute in Khon Kaen, Thailand have been established for training health workers who are in need of geospatial health technologies for disease risk mapping and surveillance of control programmes. At the same time,

training courses on zoonotic helminthiases in the region have been arranged, often in connection with RNAS^{+} meetings, to take advantage of the availability of regional and international experts (Zhou et al., 2010b).

1.3.2.7. Regional and international collaboration

Rapid and reliable communication between national and international public health agencies is essential to promptly mount an effective response to the threat of infectious diseases. In zoonotic tropical diseases, communication between public health and veterinary communities—including those dealing with domestic animals, wildlife and other animals such as zoo animals—is often weak, which hinders tracking of emerging infectious diseases. Current systems neither allow nor facilitate rapid communication. Moreover, information on disease outbreaks is not directly shared between countries, federal agencies, states or laboratories, whether on the local, provincial or regional level, and the private sector has no vehicle for sharing information with human health or veterinary professionals.

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. Olveda et al. (2010) summarise how a small bid for research on schistosomiasis japonica a decade ago eventually developed into a major regional network (i.e. RNAS^{+}). This network led to a new vision not only for the general strengthening of research capabilities in the sub-region, but also for furthering efforts to close the gap between research and control, and hence fostering integrated and inter-sectoral collaboration and disease control efforts.

1.4. CONCLUDING REMARKS

The regional progress noted in the 'war on the worms' and other NTDs in the latest decade cannot only be credited to the current economic upswing in many of the Southeast Asian countries. It is to a large part due to the activity of local and regional networks that have not only been able to raise unprecedented funding by tapping emerging public–private partnerships, now joining forces to roll back 'this wormy world', but also to make good use of this new funding. The financial support issuing from the new collaboration between international donor agencies, private foundations and pharmaceutical companies is big enough to make a clear difference for control activities.

It is important to appreciate that the regional networks have contributed strongly to the advances through furthering collaboration between

the research community and disease control managers. These networks have also played an important role in analysis for strategic planning, implementation and capacity building. The success in embedding research into the endemic countries' health systems can be ascribed to input from international research institutions and the participation of competent scientists with local experience and expertise. Indeed, the authorship configurations of the 25 reviews in these two thematic volumes of the *Advances in Parasitology* attest to the collaborations forged between the North and the South as well as between the West and the East.

Chemotherapy-based morbidity control dominates the fight against helminth infections and, in the case of lymphatic filariasis, it seems credible that success can largely be achieved by mass drug administration alone. In other cases, for example schistosomiasis, the integration between various control tools and inter-sectoral collaboration is needed to achieve elimination. The strong progress of the national schistosomiasis control programme in P.R. China relies as much on snail control as on chemotherapy and it is plausible that the high level of re-infection in the remaining endemic areas in P.R. China and elsewhere requires an integrated approach that includes a vaccine. While praziquantel can be relied on for cure of infection, snail control and transmission-blocking vaccines are needed to reduce the risk of re-infection.

Above all, the recent elimination of lymphatic filariasis from P.R. China is a turning point in the 'war on the worms'. However, this advance does not only support the likelihood that the achievement can be repeated in other countries but it also raises the hope that other NTDs can be eliminated as a public health problem in the foreseeable future. This is therefore not the time to rest on the laurels but to step up vigilance to root out remaining problems and then focus on surveillance to counteract any re-emergence and to deal with post-transmission squeals of chronic diseases that will be with us long after the infections have been eliminated.

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