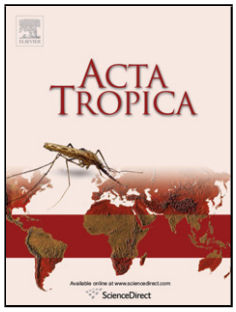

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Progress in research, control and elimination of helminth infections in Asia

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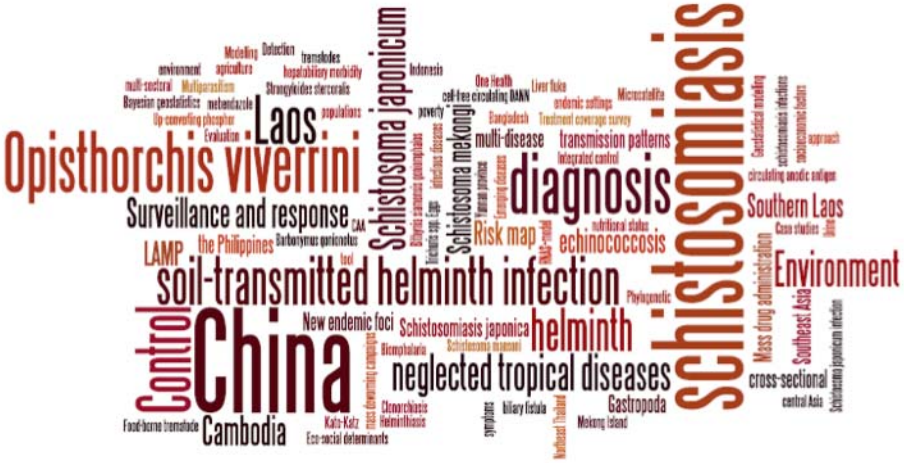
Hightlights

- The Asian helminthiasis network (RNAS+) focuses on innovation, validation, application
- Development of new tools for improved detection, surveillance and monitoring is needed
- Control and elimination approaches must be embedded in strong partnerships
- Integrated and multi-sectorial control approaches are necessary
- P.R. China emerges as a key-player in global health, research and control

Graphical abstract

"Asian-helminth wordl landscape" analysis of all 35 titles and 196 keywords.



A B S T R A C T

Global health has substantially improved over the past 20 years. In low- and middle-income countries, in particular, great strives have been made in the control of communicable diseases, including helminth infections. Nevertheless, the most marginalised communities still suffer from infectious diseases that are intimately connected with poverty and lack of access to essential commodities and services, such as clean water, improved sanitation and sufficient food. A two-pronged approach is thus necessary: (i) intensifying control in remaining high-endemicity areas and pockets of high transmission; and (ii) moving from morbidity control to interruption of disease transmission in low-endemicity areas with the goal of local elimination. The latter will require new tools and strategies, going hand-in-hand with strong partnerships and new strategic alliances. In this special issue of *Acta Tropica*, 35 articles are featured that, together, provide an up-to-date overview of the latest progress made in research, control and elimination of helminth infections in East and Southeast Asia. The first 12 articles expound tools and approaches for improved detection, surveillance and monitoring of helminth infections. Control and elimination approaches for the most important helminth infections are revisited in articles 13-32. The three remaining articles are cross-cutting pieces examining the interface of agriculture, environment and helminth infections and providing a rationale for integrated, multi-sectorial control approaches that are necessary for sustaining helminthiasis control and progressively moving towards elimination. An interesting aspect revealed through an in-depth analysis of the provenance of the 35 contributions is that the People's Republic of China emerges as a key player in global health, which is documented through its prominent role in research and control of helminth infection and networking throughout Asia. Policy implications are discussed and will hopefully shape the future agenda for the control and elimination of helminth infections the world over.

Keywords:
Helminth infection
Research
Control
Elimination
Regional network
Asia

1. Introduction

The publication of the Global Burden of Disease Study 2010 (GBD 2010) provided a comprehensive snapshot of population health in the year 2010 and allowed detailed comparison with the situation 20 years earlier. The comparison is interesting and informative as 1990 serves as the benchmark, against which it will be determined whether the Millennium Development Goals (MDGs) have been achieved in 2015 when the current piece goes live (Dora et al., 2014; Jong-wook, 2003). The good news is that global health has substantially improved over the past 20 years. For example, life expectancy both among males and females has increased in the last two decades and the public health impact of communicable diseases has declined (Lozano et al., 2012; Murray et al., 2012). However, this gain in life expectancy, declining relevance of communicable diseases and changing patterns of risk factors come with a price: although the average citizen now lives longer, this often comes with poorer health, primarily driven by disabilities and co-morbidities among people aged 70 years and above. It must also be noted that health inequalities, specifically the gap between the richest and the poorest people is widening (Barros et al., 2012; Bleich et al., 2012). Importantly though, the aforementioned trends in population health at the global level hide important regional, national and local differences. A deeper understanding of disease and health systems as well as changing patterns at a finer-grained level is necessary to measure local progress towards the MDGs and to prepare for the post-2015 agenda for sustainable development. These issues call for scientific inquiry at local and national levels in order to design specific interventions that are tailored to the needs of the most marginalised communities.

We put our focus on East and Southeast Asia with emphasis on major helminth infections, namely echinococcosis, food-borne trematodiasis (e.g. clonorchiasis and opisthorchiasis), schistosomiasis and soil-transmitted helminthiasis. Historically, and still today, in terms of at-risk population and number of people infected, Asia is a hot bed for major helminthiases {de Silva, 2003 #90; McManus, 2003 #95; Utzinger, 2005 #91; Fürst, 2012 #92; Lai, 2013 #93; Pullan, 2014 #94}. Yet, over the past 20 years, considerable progress has been made in the control of helminth infections over large parts of the continent. For example, a comparison of data obtained in the mid-1990s with data from 2003 reveals substantial declines in the overall infection prevalence of soil-transmitted helminths in Southeast Asia (de Silva et al., 2003). A recent Bayesian-based spatio-temporal analysis, facilitated by a large ensemble of georeferenced soil-transmitted helminth survey data from the People's Republic of China (P.R. China), confirms the declining trend (Lai et al., 2013). Meanwhile, schistosomiasis is at an all-time low in P.R. China. Indeed, there are now less than a quarter of infections compared to the estimated 11 million cases in the early 1950s {Utzinger, 2005 #91; Yang, 2014 #96}. Nevertheless, in the Philippines, progress towards schistosomiasis control has met with mixed success, as there are areas where the disease is still rampant (Bergquist and Tanner, 2010; Ross et al., 2013). Moreover, some helminth infections are emerging, e.g. food-borne trematodiasis and angiostrongyloidiasis (Keiser and Utzinger, 2005; Lv et al., 2008; Yang et al., 2014). Of particular concern is the case of clonorchiasis in P.R. China (Lun et al., 2005; Qian et al., 2013).

The purpose of this presentation is to unfold an umbrella to cover a collection of 35 articles summarising progress in research, control and elimination of helminth infections in East and Southeast Asia. We begin with a historical account of the establishment of a regional network for Asian schistosomiasis. Dating back to the mid-1990s and with an initial geographical focus on P.R. China and the Philippines, the network gained traction in the new millennium, enlarged its geographical outreach and expanded its scope to include other helminth zoonoses. Annual meetings held in different countries in the Far East have not only provided a platform for exchange between researchers, disease control managers and other stakeholders, but were also utilised for specific teaching and training activities. Achievements

of this network are briefly summarised, complementing previous accounts put forth by Olveda et al. (2010) and Zhou et al. (2008a). Next, we present a detailed analysis of the 35 original articles, including provenance of the contributing authors and the main issues covered, graphically represented in an "Asian-helminth wordl landscape". We then present short summaries of the 35 articles, readily grouped into (i) tools and approaches for improved detection, surveillance and monitoring of helminth infections; (ii) control and elimination approaches revisited; and (iii) cross-cutting issues. Finally, we emphasise that P.R. China has emerged as a new major player in global health, discuss policy implications that hopefully will stimulate further dialogue and participate in shaping the future agenda for the control and elimination of helminth infections not only in Asia, but also in Africa and the Americas.

2. A regional network of Asian schistosomiasis and other helminthiases

2.1. Brief historical account

Initiated by the UNICEF/UNDP/World Bank/ WHO Special Programme for Research and Training in Tropical Diseases (TDR), the idea to bring together different stakeholders in a bid to step up the fight against schistosomiasis japonica was first floored at an international workshop pertaining to research, surveillance and control of schistosomiasis japonica in Nanjing, P.R. China in 1996. The plan developed after this meeting marked the beginning of the 'Regional Network on Asian Schistosomiasis' (RNAS), whose primary purpose was to promote intersectoral, interregional and international collaboration for research and control, surveillance, monitoring and evaluation of schistosomiasis japonica.

2.2. Developments and expansion of the network

The first RNAS meeting, facilitated by a TDR-supported project entitled "Establishment of a regional network for research, surveillance and control of Asian schistosomiasis" took place in Tagaytay city, the Philippines in 2000 with participants representing research institutes in Japan, Philippines, P.R. China, Australia, Denmark and Switzerland that resulted in a charter for a network with a focus on research and control of Asian schistosomiasis. Subsequent, annual meetings included international and local member countries. Interest for the activities grew gradually and in 2005, it was decided to expand the vision and reconfigure the network to accommodate additional diseases and new member countries (Olveda et al., 2010; Zhou et al., 2008a). A spectrum of parasitic diseases, such as cysticercosis and food-borne trematode infections (e.g. clonorchiasis, fascioliasis, opisthorchiasis and paragonimiasis) were included, encouraging other countries, endemic for these diseases, such as Cambodia, Lao PDR, Korea, Thailand and Vietnam to become part of the network. Henceforth, the name was changed to the 'Regional Network on Asian Schistosomiasis and other Helminth Zoonoses' ($RNAS^{+}$). The activities were enlarged to include:

- cross-sectional surveys, where researchers developed risk analyses and prediction based on cross-sectional survey data;
- biological investigations where spatial variation and spatio-temporal diversity of biological vectors and pathogens were the objectives;
- assessment of intervention strategies that address transmission, environment and social-economics factors in control of infectious diseases; and
- database management and information sharing.

After focusing exclusively on promoting collaboration among scientists working in the field of schistosomiasis during the first years, the organisation has since strengthened into a wider network that includes a variety of zoonoses and member countries intensely sharing and developing technologies and surveys together. The $RNAS^{+}$ headquarters are currently located in the Research Institute of Tropical Medicine (RITM) of the Philippines. It is registered and approved as a non-profit organisation with the Securities and Exchange Commission of the

Philippines. At the latest annual meeting in 2013, the inclusion of Myanmar increased the number of local RNAS$^+$ member countries to 10. Under the new vision, the network identified its priorities as follows:

- implementation of operational and control-associated research;
- retrieval of data of particular interest for the control of target diseases;
- Identification of knowledge gaps and promotion of innovative synthesis of findings relevant to control of zoonoses in settings characterised by poverty;
- acquainting researchers with the advantages of working via the RNAS$^+$ website as a knowledge management platform for data distribution; and
- encouraging active participation in joint effort to continuously update information on diseases associated with poverty.

2.3. A selection of achievements

Several objectives have been accomplished with particular impact on the regional neglected tropical disease (NTD) control programmes. In brief, RNAS$^+$ has:

- provided assistance to the development of health metrics for the regional offices of the Western Pacific (WPRO) and Southeast Asia (SERO) of the World Health Organization (WHO) (Nakagawa et al., 2015; Qian et al., 2012; WHO/WPRO, 2013);
- coordinated and supported research on the impact of social determinants and economic issues on the epidemiology of helminth zoonotic infections in Cambodia, Lao PDR, Philippines, P.R. China, Thailand and Vietnam (Chen et al., 2013; Schratz et al., 2010; Tambo et al., 2014; Yang et al., 2014; Yang et al., 2015b; Zheng et al., 2013);
- promoted geographical information systems (GIS) and remote sensing for the study of the impact of climate change on RNAS$^+$ target diseases (Lv et al., 2011; Yang et al., 2010; Yang et al., 2006; Zhou et al., 2008b);
- provided opportunities for collaborative study of genetics and the immune responses to better understand the pathology caused and ultimately to apply the new knowledge for the development of new diagnostics, drugs and vaccines {Qian, 2013 #111; Qian, 2013 #112; Xu, 2014 #109; Tong, 2014 #110}; and
- improved and standardised diagnostic capabilities including development of new products and techniques, such as the dipstick dye immunoassay (DDIA) kit and the adaption of novel ultrasensitive diagnostics based on circulating antigens for schistosomiasis japonica (van Dam et al., 2015a; van Dam et al., 2015b; Zhu et al., 2005).

2.4. Capacity building

More than 10 training courses have taken place as part of the annual meetings, the most important being health metrics, diagnostics, GIS and modelling, sociological and environmental assessment of control programmes, proposal writing, ethics courses and molecular biological tests. With the support of the World Health Organization (WHO)'s Regional Office for the Western Pacific (WPRO), an external quality assessment programme (EQAP) on helminth microscopy and serological diagnosis was established with technical supported by the National Institute of Parasitic Diseases (NIPD) in Shanghai and the Swiss Tropical and Public Health Institute (Swiss TPH) in Basel, which was implemented for three years to promote the capability of regional NTD diagnosis in national laboratories.
The interest for joint projects and international funding has increased that resulted in a multi-country, multi-disciplinary project supported by the International Development Research Centre (IDRC) in Canada. Six member countries developed jointly a project entitled "Innovative strategies for sustainable control of Asian schistosomiasis and other helminth

zoonoses through socio-ecosystem-based Interventions." Through this project, focused on schistosomiasis, clonorchiasis, opisthorchiasis, fascioliasis, cysticercosis and angiostrongyliasis, RNAS^{+} has become involved in a wider collaboration including the development of a "Regional action plan for neglected tropical diseases (NTDs) in the Western Pacific", spearheaded by WPRO.

2.5. Partners and funding

In addition to the major institutes in the 10 member countries, several international partners, such as the Swiss TPH (Switzerland), Copenhagen University (Denmark), Louisiana State University (USA), Brown University (USA), Swedish University of Agricultural Sciences (Sweden), Leiden University Medical Center (Netherlands), the Queensland Institute of Medical Research (Australia), are actively involved with RNAS^{+} through participation at the annual meetings and training courses. With support from national funding and international donor agencies, multi-lateral research projects can be carried out.

3. Collection of 35 articles

3.1. The lay of the land

This special issue of *Acta Tropica* consists of a collection of 35 articles that provide a snapshot of progress in research and control of helminth infections in East and Southeast Asia. There is one review pertaining to freshwater snails in Asia with particular reference to Vietnam (Madsen and Hung, 2015) and nine review-type articles ranging from a critical discussion of health metrics for helminth infection to integrated control using intersectoral collaboration against major helminthiases (Bergquist et al., 2015; Johansen et al., 2015; King, 2015; Nakagawa et al., 2015; Satrija et al., 2015; Xu et al., 2015a; Xu et al., 2015b; Yang et al., 2015b; Zhang et al., 2015). The remaining 25 articles are original contributions covering the value chain from innovation to application and from development and validation of novel diagnostic tools to health policy discussion.

As shown in Fig. 1, the 35 articles are authored by between one (King, 2015) and up to 15 authors (Leonardo et al., 2015). More than three-quarter of the articles have at least five co-authors. The median number of authors per article is seven, indicating that the research covered in this special issue represents highly collaborative work.

<Fig. 1 near here>

Counting up all the authors on the 35 articles reveals a sum of 255. Table 1 shows that most of the authors contributed to a single paper (n=150, 58.8%), while the remaining 24 authors figured on two articles or more, with the maximum of 11 co-authorships by two individuals, one affiliated to an institute in P.R. China and the other in Switzerland.

<Table 1 near here>

The provenance of the 35 articles is shown in Fig. 2a, whilst the provenance of the 255 author-contributions is displayed in Fig. 2b. In the latter analysis, each contribution is given the same weight, and hence, the 255 author-contributions account for 100%. Authors with affiliations to two different countries (e.g. Australia and P.R. China) are accounted half-half to each country. We found that P.R. China is the single most contributing country (n=78.5, 30.8%), followed by Switzerland (n=50, 19.6%), the Philippines (n=29, 11.4%), Thailand (n= 22.5, 8.8%) and Lao PDR (n=17.5, 6.9%). Author-contributions from Asia amounted to 68.4%, whilst author-contributions from Europe, North America and Australia represented 27.8%, 2.9% and 0.8%, respectively. In the article-specific analysis, each of the 35 papers is given the same weight. It follows that articles written by a single or only few authors account considerably more weight to a given country than articles written by many different authors from various countries. Taking this weighing into account, P.R. China remains the

predominant country (27.3%), followed by Switzerland (20.9%), Thailand (10.8%), Lao PDR (8.0%) and the Philippines (6.9%).

<Fig. 2 near here>

3.2. Clouds, radars and spiders

In an attempt to draw the landscape of the 35 articles published in this special issue, we analysed the titles and all 196 keywords. Those terms put forth at least twice (n=83) entered into a cloud and the size of the individual terms was governed by the number of times it was cited. The resulting cloud – customary phrased "Asian-helminth wordl landscape" – is displayed in Fig. 3. Of note, "China" and "schistosomiasis" figure most prominently, which underscores the important historical role that P.R. China played while setting up a regional network that initially focused on Asian schistosomiasis. In the meantime, P.R. China has become a key player in global health (Liu et al., 2014), which is supported by the findings from our in-depth analysis of the 35 articles dissected here. Of note, "Laos" and "*Opisthorchis viverrini*" also figure prominently, thus underscoring the expanding geographical outreach of the regional network that has its roots in P.R. China and the Philippines and its evolving scope, encouraging scientific inquiry and control of other helminthiases. These observations are thus perfectly in line with RNAS being developed into RNAS^{+}.

<Fig. 3 near here>

Finally, we classified the 35 articles into three groups along two main domains. In the first domain, we were interested about the articles' contributions along the value chain from innovation (defined as discovery through promotion and testing of hypotheses) to validation (defined as evidence providing what works) and application (defined as strengthening individual and public health actions, systems and policies). In the second domain, the articles were classified into three main study targets, differentiating between: (i) risk factor analysis and tool development (e.g. diagnostics and drugs); (ii) clinical interventions, modelling, control, surveillance and elimination; and (iii) implications for health policy and network analysis). In each of the two domains, we assigned one point. Whenever an article contributed to two groups in a specific domain, half a point was assigned to each of the two groups.

Fig. 4 shows the results of our analysis, displayed in a spider (Fig. 4A) and radar plots (Figs. 4b and 4c). We found that most of the articles were either tagged as validation (0.44) or application (0.39). Innovation, on the other hand, accounted for only 0.17. With regard to study targets, tool development and risk factor analysis was the predominant feature (0.47), closely followed by clinical investigations, modelling, control, surveillance and elimination (0.39), whilst policy implications and networking was rarely addressed (0.14).

<Fig. 4 near here>

3.3. Tools and approaches

King (2015) discusses the common health metrics, namely disability-adjusted life year (DALY) and quality-adjusted life year (QALY), both of which have limitations in their ability to capture the full health impact of helminth infections and other NTDs. While the metrics serve a useful role in cost-effectiveness analysis (CEA), they are limited to disease estimation in a specific region and cannot serve as universal metric for policy planning on a global scale. The donor countries, in particular, still focuses their interests primarily on the "big three" (HIV, tuberculosis and malaria) leading to aggregated DALY scores but underestimate NTD and their impact on health over a lifetime of exposure. King compiles and endorses priorities for more accurate burden assessment for helminth infections and voices his skepticism in the GBD 2010.

The aim of the review-type piece put forth by Johansen et al. (2015) is to elucidate the dilemma of helminth diagnosis, exemplified by zoonotic trematodes. Improved diagnosis is a prerequisite for control, elimination and eradication of many neglected helminthiases. The lack of a 'gold' standard is a continuous obstacle to diagnostic progress. The applied diagnostic methods identifying helminth morphology (microscopy) and host immune responses (serology) exhibit mostly low sensitivity and specificity. Diagnostic sensitivity could be improved by *Opisthorchis* and *Clonorchis* DNA-based techniques, while specificity is still limited. Johansen et al. call for standardised, inter-laboratory test validation, enhanced intersectoral collaboration and establishment of an international One Health diagnostic platform, sharing best practices on diagnosis of helminth zoonoses, which could significantly contribute to control and elimination of these diseases.

Schistosomiasis has been eliminated in five of 12 formerly endemic provinces in the P.R. China with the prevalence reduced in the remaining areas. Tong et al. (2015) report on a risk map of infected intermediate host snails for *Schistosoma japonicum*, i.e. *Oncomelania hupensis*, as detected by PCR-based technology. Applying a loop-mediated isothermal amplification (LAMP) assay targeting 28S rDNA, the authors effectively detected *S. japonicum* DNA in infected and prepatent infected *O. hupensis* snails. By this novel technology, showing a greater sensitivity than nested PCR, the authors generated risk maps indicating higher schistosomiasis transmission in distinct provinces. These risk maps will form a guide for surveillance and response strategies in high-risk areas.

The current status of schistosomiasis in highly endemic areas is difficult to determine by ovum detection applying the standard Kato-Katz technique because of the superficially low parasite load after mass drug administration, while parasite transmission rates are still high. In contrast, cell-free parasite DNA fragments, detected by PCR, exist in the host's body fluids (e.g. blood and urine), appeared a more sensitive diagnostic technology. Kato-Hayashi et al. (2015) conducted population-based studies in the Sorsogon province of the Philippines and documented a higher detection rate of active infection (sensitivity) than the widely used Kato-Katz technique and a serological antibody detection assay. Circulating schistosome DNA could already be detected very early after infection. These results confirm that parasite DNA is a promising diagnostic marker for active schistosome infection, in particular in the case of light infection and for rigorous appraisal of praziquantel efficacy.

The presence of large *Trichuris* spp. eggs in human faecal samples is occasionally reported, addressed either as large variant *Trichuris trichiura* or as *T. vulpis* eggs. Such considerable variability of *Trichuris* spp. ova were not only observed in *T. trichiura*-infected humans but also in *T. vulpis*-infected dogs, respectively. In the frame of a randomised controlled trial conducted in Yunnan province, P.R. China, Steinmann et al. (2015a) observed a large (76 x 34 μm) but not deformed *Trichuris* spp. ova in faecal samples with a prevalence of 6% before and, surprisingly, of 22% after anthelminthic drug administration. Considerably more cases of standard-sized as large *Trichuris* spp. eggs were identified by a novel FLOTAC adaption compared to the ether-concentration technique. No large eggs were observed in the common Kato-Katz thick smears. This observation stresses the importance of attentive microscopic analysis in the laboratory and during in-depth epidemiological and molecular investigation and underscore the need for improved diagnostic tools.

The reduced prevalence and intensity of *S. japonicum* infection in P.R. China warrants the application of highly accurate methods for monitoring the national schistosomiasis control programme verifying whether transmission has been interrupted. van Dam et al.)2015b) have assessed the prevalence of active *S. japonicum* infection by use of an up-converting phosphor lateral-flow (UCP-LF) assay for determination of circulating anodic antigens (CAA) in urine and serum. Applying a combined 'gold' standard, the urine CAA assay showed the highest sensitivity (93%), followed by the serum CAA (77%) and an immuno-haemagglutination

assay for specific antibodies in serum (53%), whilst triplicate Kato-Katz thick smears revealed a very low sensitivity of only 13%. Serum CAA concentrations were about 10-fold higher than in urine and were significantly correlated. The CAA urine assay detected 10% CAA positives and the serum-based CAA assay 12%. In contrast, the Kato-Katz technique revealed only 1.4%. These data have important ramifications for the national schistosomiasis control and elimination programme in P.R. China, particularly in respect to case-finding and intervention strategies. *S. mekongi* is confined to limited foci in Cambodia and Lao PDR, while *S. japonicum* remains the predominant schistosome species in Asia. In a companion paper, van Dam et al. (2015a) report the evaluation of the two circulating schistosome antigens for banked, previously collected, urine samples from *S. japonicum* egg-positive individuals from the Philippines and *S. mekongi*-exposed subjects from Cambodia. They compared the sensitive well-established UCP-LF assay for CAA and the point-of-care (POC)-CCA urine assay in addition to Kato-Katz thick smear examination. This proof-of-concept study highlights the potential usefulness of urine samples for a CAA and CCA diagnostic approach for Asian schistosomiasis. Indeed, *S. mekongi* samples have been for the first time detected by CAA and with less relevance by CCA.

Karagiannis-Voules et al. (2015) employed Bayesian geostatistical models to spatially align the socioeconomic predictors at an individual level with the soil-transmitted helminth infection data compiling household-level socioeconomic data relevant for sanitation, drinking-water, education and nutrition. The authors found that the risk of soil-transmitted helminth infection, in particular for *Ascaris lumbricoides* and *T. trichiura* from 2000 onwards was considerably lower than in surveys conducted earlier. Surprisingly they did not find any significant association between soil-transmitted helminth infection and socioeconomic proxies. Individual information of both, infection risk and potential predictors are needed. The presented soil-transmitted helminth infection risk estimates for Cambodia can be used for prioritising control efforts, spatially designing new surveys and serve as a benchmark for long-term surveillance.

Xu et al. (2015b) examine the application of modelling tools in the epidemiological study of schistosomiasis japonica during the past 20 years and explore the application of enhanced models for surveillance and response considering the many changes of social, ecological and environmental factors involved in control activities. The authors combined GIS techniques with conceptual models analysing risk factors, predicting schistosomiasis prevalence for optimisation of control strategies. The authors update the information for decision-makers in the national elimination programme but, in spite of the new modelling techniques introduced, many questions remain.

Lv et al. (2015) evaluate the results of subadventitial cystectomy treatment of liver hydatidosis in 153 patients with hydatid disease from Shihezi University, P.R. China during 2006-2010. Biliary fistulas and cystobiliary communication are the most common morbidity following liver surgery. The authors describe the surgical procedures performed on hydatid cysts of the liver, postoperative complications and general management. They state that subadventitial cystectomy represents an effective and safe surgical approach to treatment with lower rates of recurrence, complications of the residual cavity and biliary fistula.

Bergquist et al. (2015) discuss the basic issue of surveillance and response as promising tools and approaches for the elimination stage of NTDs. Ensuing from the London Declaration, based on the WHO roadmap of January 2012, on how to control/eliminate many of the NTDs by 2020. The authors refer to progress in polio and dracunculiasis but mention also the hazard of disease outbreaks like Ebola epidemic. Discovery, investigation and interruption of continuing transmission are major purposes. They emphasise the need of (i) standard definitions for disease identification and reporting; (ii) detection, examination and confirmation of suspected outbreaks and investigation of pockets of ongoing, newly

established or re-established transmission; (iii) analysis of collected data for monitoring and outbreak investigations; and (iv) selection and implementation of appropriate response-packages tailored to the particular features of given transmission hotspots. For controlling NTDs, tools of recognition and discovery such as sensitive diagnostics, spatial epidemiology and health metrics must be applied and adapted to work hand-in-hand with strengthening surveillance. Caveats include temperature and changing water systems are the main drivers of the shifting distribution of many diseases.

3.4. Control approaches revisited

Zhang et al. (2015) review the epidemiology, risk, transmission and control of echinococcosis in central Asia (Mongolia, Kazakhstan, Kyrgyzstan, Tajikistan, Uzbekistan, Pakistan and Iran), and in particular P.R. China, comprising cystic echinococcosis (CE) caused by *Echinococcus granulosus* and alveolar echinococcosis (AE) by *E. multilocularis*. Highest prevalences of CE and AE occur in Chinese Tibet and the hyper-endemic situation is largely associated with social factors including limited community knowledge of echinococcosis, animal production, home killing of livestock, and feeding of dogs with uncooked offal. Echinococcosis control programmes are generally fragmented and uncoordinated. Thus, monthly deworming of dogs with praziquantel represents a key measure to control the *Echinococcus* parasites, however, has proven difficult. Additional control measures including health education, domestic livestock animal treatment/vaccination and dog vaccination are needed in CE-endemic areas to accelerate progress.

Ecological information on the intermediate hosts of the liver fluke *O. viverrini* remains limited, while epidemiology and parasitic incidence in humans are well studied. Wang et al. (2015) reported on factors affecting the distribution and abundance of the first intermediate host, *Bithynia siamensis goniomphalos* snails. Snail population and distribution are affected by biotic and abiotic factors. The authors described snail compositions and diversities across different habitat types. *B. s. goniomphalos* snails were more dominant in rice paddy habitats and were negatively correlated to *Filopaludina* snail populations indicating possible influence of species interaction. Rice planting practices regulate snail population dynamics at rice paddy habitats. This study provides new ecological insights into the factors affecting *Bithynia* snail distribution and abundance. It bridges the knowledge gap in *O. viverrini* disease ecology and highlights the potential effect of anthropogenic irrigation practices on *B. s. goniomphalos* snail ecology.

Opisthorchiasis is an important public health problem and a major cause of cholangiocarcinoma in the Greater Mekong subregion, including Cambodia, Lao PDR, Thailand and Vietnam. Humans acquire the infection by consumption of raw or undercooked cyprinid fish containing infective metacercariae. Donthaisong et al. (2015) examined the infection of *Barbonymus gonionotus* fish by *O. viverrini* cercariae, the site of cyst formation of the cercariae and development to the metacercariae. The authors showed that *O. viverrini* metacercarial recovery rate are related to infection rate in fish and increased with the age as well as the size of the fish and that most of metacercariae encysted in fish body.

Attwood et al. (2015) present an update on the distribution and phylogenetics of *Biomphalaria* snail populations in Guangdong province, P.R. China reporting that *B. straminea* were discovered in Hong Kong in 1973. In view of the renewed interest in these invasive snails, a morphological and DNA-sequence based phylogenetic study was undertaken for seven populations of *Biomphalaria* snails collected in Guangdong. Morphologically and phylogenetically, five of the populations clustered more closely with *Biomphalaria kuhniana* than with *B. straminea*. In explaining the current distribution of the snails, multiple colonization events, each establishing a new local snail population near to maritime international container ports, were considered more likely than the spread of snails

from Hong Kong to P.R. China. The conclusions is that any risk of *S. mansoni* transmission in P.R. China is more likely to stem from multiple parasite importation in the intramolluscan stage, than from transmission by migrant workers from South America or Africa. The authorsemphasise that the current expansion of container ports in Brazil and Venezuela, and the increase in trade with P.R. China, imply the risk of imported schistosomiasis, and therefore surveillance around major ports in P.R. China, together with further research, are necessary.

Freshwater snails have received attention for their role as intermediate hosts for trematodes causing a spectrum of diseases ranging from schistosomiasis to food-borne trematodiases. To facilitate specific measures, an overview of the snail families and their medical and veterinary importance in Asia, Madsen and Hung (2015) present the current situation with the main focus on Vietnam. They discuss the importance of controlling these snails with minimal impact on biodiversity in their aqueous habitats pointing out that we are only at the threshold of thinking on how to approach this critical question.

Steinmann et al. (2015b) claim that the current global strategy for soil-transmitted helminthiasis control emphasising mass drug administration fails to address the root social and ecological causes. This research group designed a 5-year multi-intervention trial in Yunnan province, P.R. China testing three different interventions that were rigorously implemented for three years, whilst the follow-up, which included annual albendazole distribution, lasted for two more years. Before the third round of treatment, the prevalence of *A. lumbricoides* was reduced by only 2.8% in the annual treatment arm, whilst bi-annual deworming combined with latrine construction and health education resulted in a prevalence reduction of 53.3%. All three control approaches significantly reduced the prevalence of *T. trichiura* and hookworm, with the highest reductions achieved when mass drug administration was combined with sanitation and health education. However, the prevalence of *T. trichiura* remained at 30% regardless of the type of intervention. The findings presented support the notion that in high-endemicity areas, sustainable control of soil-transmitted helminth infections necessitates measures to reduce faecal environmental contamination to complement mass drug administration. However, elimination of soil-transmitted helminthiasis will not be achieved in the short run even with such a rigorous approach, and probably requires improvements in living conditions, changes in hygiene behaviour and more efficacious anthelminthic drugs and treatment regimens.

Mass drug administration in combination with health education is the mainstay of control for multiple helminth infections, which are very common in communities of southern Lao PDR. Phongluxa et al. (2015) assessed knowledge perceptions and practices of rural communities related to endemic helminthiasis and their control during a mass drug administration campaign. Their results show that opinion leaders and villagers were well aware of the importance of attending mass drug administration and appreciated that the deworming drugs were provided free of any charge. However, anticipated adverse events of praziquantel were identified as a major barrier for participation. Most leaders had a good knowledge on severe schistosomiasis though only a few of them described its cause correctly. However, they knew only little about the disease consequences of liver fluke and soil-transmitted helminth infections. It was understood that consumption of raw or insufficiently cooked fish, frequent physical contacts with Mekong River water and low number of latrines. Mass drug administration was found to be widely accepted in affected communities. Avoiding severe schistosomiasis was the main motivation to comply. Participation rates increased significantly when drugs were provided free of charge in the villages. The conclusion is that perceived illness drives participation in mass deworming campaigns in Lao PDR.

Strongyloides stercoralis is a neglected helminth infection potentially leading to a systemic infection in immunocompromised individuals and information on this infection is

scarce. Vonghachack et al. (2015) assessed *S. stercoralis* infection and the associated risk factors and symptoms on the Mekong Islands in southern Lao PDR and found that males were at higher risk than femals. Urticaria and body itching was associated with *S. stercoralis* infection. Infection with *O. viverrini*, *S. mekongi*, and hookworm were very common. In contrast, very few infections with *T. trichiura*, *A. lumbricoides* and *Taenia* spp. were detected. The majority of helminth infections were of light intensity but, nevertheless, heavy infection intensities were observed for *O. viverrini*, *S. mekongi* and hookworm. *Strongyloides stercoralis* is highly endemic on islands of Khong district, Champasack province. The national helminth control programme should no longer neglect the presence of this helminth infection.

Bless et al. (2015) found a high prevalence of large trematode eggs in Cambodian school-aged children. Their study aimed to assess the prevalence of large trematode eggs in the stools of children attending the affected school, identify potential risk factors for infection Large trematode eggs were observed in about 50% of the stools of >200 school-aged children. Two blood serum samples from children were positive for *Fasciola hepatica* in a first enzyme-linked immunosorbant assay (ELISA), but were negative in a confirmation immunofluorescence antibody test. Applying the polymerase chain reaction (PCR) technology, only one tested positive for *Fasciola* spp. and none for *Fasciolopsis buski*. The consumption of raw aquatic plants and fermented fish sauce were significantly associated with large trematode eggs in the stool. *Fasciola* spp. flukes were observed in about 20% of cattle livers. The prevalence of fascioliasis in cattle droppings was very high. The low prevalence of schoolchildren that tested positive for *Fasciola* spp. with specific molecular diagnostics and that had no diagnostic evidence of *F. buski* strongly indicates that the majority of microscopically observed large trematode eggs are from *Echinostoma* spp. An *Echinostoma*-specific PCR analysis could not be performed. *Fasciola* spp. transmission from cattle to human is possible and public health services need to be alerted accordingly.

Ayé Soukhathammavong et al. (2014) assessed hepatobiliary morbidity using abdominal ultrasonography related to *O. viverrini* infection. They report that although *O. viverrini* prevalence is high, cholangiocarcinoma is scarce in Lao PDR. However, the presence of hepatobiliary lesions, suggestive of cholangiocarcinoma, was diagnosed in five patients (1.2%). Tumour markers (i.e. interleukin-6, plasminogen activator inhibitor and carbohydrate antigen 19-9) were within normal range. The number of cholangiocarcinoma suspected liver masses and hepatobiliary morbidity diagnosed among clinically asymptomatic adult patients in *O. viverrini*-endemic areas presents a major public health concern in Lao PDR. However, definitive diagnosis is urgently needed to gauge the burden of this deadly disease in Lao PDR.

Northern Cambodia and southern Lao PDR are highly endemic for *S. mekongi* and Nickel et al. (2015) investigated and validated *S. mansoni* antigens for the detection of anti-*S. mekongi* antibodies in human sera collected from a region in Lao PDR highly endemic for *S. mekongi*. They report that *S. mansoni* antigens can be used for the diagnosis of *S. mekongi* infections. A high sensitivity (>90%) was calculated for a combination of ELISA and immunofluoresent assay as compared to the detection of *S. mekongi* eggs in stool samples.

Intestinal parasitic infections are common in Lao PDR. Sayasone et al. (2015b) show that repeated stool sampling and use of multiple techniques enhance the sensitivity of the diagnosis. They investigated the accuracy of the Kato-Katz technique in relation to varying stool sampling efforts, and determined the effect of the concurrent use of a quantitative formalin-ethyl acetate concentration technique (FECT) for helminth diagnosis and appraisal of concomitant infections. Diagnosis was carried out by light microscope by a team of experienced laboratory technicians. Analysis of three stool samples with Kato-Katz plus a single FECT was considered as diagnostic 'gold' standard and resulted in prevalence estimates of hookworm, *O. viverrini*, *A. lumbricoides*, *T. trichiura* and *S. mekongi* infection of

78%, 65%, 33%, 26% and 24%, respectively. Further, Sayasone et al. (2015a) conducted a cross-sectional study to assess and quantify the relationship between single and multiple species helminth infection with clinical and self-reported morbidity indicators and nutritional status in southern Lao PDR. Hookworm and *O. viverrini* were the predominant helminth species, while the prevalence of *S. mekongi* in the surveyed children was low. Multiple species helminth infections were recorded in >40% of the study cohort. The strong associations between helminth infections and intestinal morbidity lead the authors call for concerted efforts to control helminth infections, which in turn might improve children's health and development.

The prevalence of schistosomiasis and soil-transmitted helminthiasis has decreased significantly in P.R. China, particularly after 2005 when the national control programmes were reinforced by forming of integrated control strategies. Xu et al. (2015a) investigated the prevalence of zoonotic helminthiases, including clonorchiasis and echinococcosis and concluded that either are these infections underestimated or have in fact increased due to changes in social and environmental factors. The authors claim that more funding is needed to support further studies on helminthiases and scientific advancements need to be translated into improved or novel interventions to accelerate the control of helminthiases.

Qian et al. (2015) investigated potential new schistosomiasis foci in P.R. China finding that the disease might still be endemic in 12 provinces. They note the distribution of snail-breeding sites has not been reduced significantly in spite of an otherwise successful control programme and report that also total number of new acute cases did not diminish. The fact that surveillance showed a majority of these acute schistosomiasis cases in mobile populations (e.g. fishermen and migrant workers) leads to the conclusion that continuous surveillance with an emphasis on snails must be enhanced in potential risk areas.

On the current status of schistosomiasis japonica in Indonesia, Satrija et al. (2015) report that the disease continues to be endemic in the three isolated areas in Central Sulawesi province, although the control programme has successfully reduced the prevalence during the period of 1982–2005. However, human prevalence surveys reveal that the prevalence has tended to increase in the period of 2008–2011. In 2008, schistosomiasis was also found in a fourth setting, i.e. the adjacent Bada valley.

Schistosomiasis is endemic in 28 provinces in the Philippines, mainly in the south-eastern part. However, Leonardo et al. (2015) report that, in 2002 and 2005, respectively, two new endemic foci were reported in the most northern part of the country, i.e. in Gonzaga and Cagayan and also in Calatrava and Negros Occidental in the centre. Stool examinations and snail studies confirmed the endemicity in these areas in 2008/2009. Proximity of snail habitats to human habitation including higher snail density and snail infection rate were felt to be responsible for the high prevalence found in these new places. Migration was blamed for the spread of the disease, at least into Gonzaga and Calatrava. Risk maps revealed the distribution of snails in Gonzaga and Calatrava, indicating differences in elevation among the snail sites that would need to be further investigated. The authors hypothesized that the snail intermediate host has been in these sites for sometime but discovered only lately.

The so-called Lawa project deals with integrated opisthorchiasis control. Despite a long history of control, *O. viverrini* infection remains common in the north-eastern provinces and Sripa et al. (2015) describe a new control strategy using an ecohealth/One Health approach. As a result, the infection rate in the more than 10 villages surrounding the study area, the Lawa Lake, has declined to approximate one third of the average of 50% as estimated by a baseline survey. Hence, this liver fluke control programme has been termed “Lawa model” and is now recognised nationally and internationally. The integrated control programme using a community-based, ecosystem approach with local scale-up regionally has been particularly successful, and hence activities have expanded to other parts of Thailand, and neighbouring

Mekong countries.

In a companion paper, the team led by Sripa has developed an ultra-sensitive diagnostic approach; Arimatsu et al. (2015) based on LAMP. The sensitivity and specificity were shown to be higher than microscopic egg examination, however, specific amplification from other parasites could not be ruled out. By using hydroxyl naphthol blue-LAMP, *O. viverrini* microsatellite 6 could specifically amplify DNA from the rest of the genome, which was not possible for other parasites such as *C. sinensis*, *O. felineus*, *Centrocestus caninus*, *Haplorchis taichui*, *Fasciola gigantica* and *Haplorchoides* spp. The detection limit of the test is 1 ng genomic DNA, which is 1,000 times better than the ITS1-LAMP, but targeting microstellites also showed more specific detection.

3.5. Cross-cutting issues

Hafiz et al. (2015) applied qualitative and quantitative methods to identify challenges related to monitoring mebendazole treatment in Bangladesh's national deworming programme that targets school-aged children. A treatment coverage cluster survey revealed that bi-annual primary distribution of the drug is an effective strategy. However, particularly low coverage was seen amongst non-school attending children, most likely due to the lack of national policy to effectively target this vulnerable group. On the other hand, it was found that the majority of households and schools have access to latrines and safe drinking water.

The effectiveness of schistosomiasis control interventions are, among other factors, governed by the social-ecological context. Yang et al. (2015b) screened residents in 26 villages of Yunnan province P.R. China for *S. japonicum* infection with a serological assay and stool examination for sero-positive individuals. Applying Bayesian multilevel models with spatial random effects the authors identified as eco-social determinants the absence of a sanitary stall house for livestock and presence of living and infected intermediate host snails in close proximity. The authors conclude that a Bayesian multilevel modelling approach will contribute to a better understanding of the epidemiology, control and eventual elimination of schistosomiasis.

Changes in the natural environment and agricultural systems associated with economic and industrial development, including population dynamics (growth, urbanization, migration), are major causes resulting in the persistence, emergence and re-emergence of infectious diseases in developing countries. Yang et al. (2015a) review emerging and re-emerging diseases such as schistosomiasis, dengue, avian influenza, angiostrongyliasis and soil-transmitted helminthiasis with respect to environmental and agricultural changes. The authors show direct and indirect effects of global warming on the transmission of *S. japonicum*. As research priority the authors propose (i) the identification of an appropriate set of metrics of infectious diseases and environmental/agricultural factors; (ii) the definition of risk factors, quantitatively and qualitatively, due to infectious diseases and the environment; (iii) the establishment of models to evaluate the proportion of a particular disease that is influenced by a single or interacting risk factors; and (iv) the design of disease-related policies and programmes for decision-makers.

NTDs are a diverse group of diseases caused by a variety of pathogens whose local prevalence are intimately linked to conditions of poverty being most prevalent diseases among the 2.7 billion people who currently live on less than US$ 2 per day. Nakagawa et al. (2015) discuss in a position article the feasibility of implementing multi-disease, multi-sectoral intervention packages for helminth NTDs in the Western Pacific Region. The authors present suggestions as practical guides including (i) key activities routinely implemented in helminth NTDs control programmes in the WHO Western Pacific Region; (ii) examples of health programme activities; and (iii) non-health-sector programme activities. These key activities and information required for multi-disease, multi-sector control interventions. The

benefits of multi-disease, multi-sectoral approaches could go beyond immediate health impacts by contributing to sustainable development, raising educational attainment, increasing productivity and reducing health inequities. Only concerted efforts will allow reaching the goal of eliminating NTDs and ultimately achieve good health for all.

4. Outlook

There is a need to translate research findings into control applications. This is particularly true for the NTDs that primarily affect poor and marginalised communities. Hence, dissemination of key findings and new technology through networking play an important role. RNAS$^+$ is well placed in this endeavour and will utilise its strategic alliances to make joint efforts and thus contribute to reduce the burden and impact of NTDs among the most vulnerable populations, such as children and women of childbearing age. The mission of RNAS$^+$ is to steer research progress onto specific targets and to harness new findings into easily accessible repositories, including (i) foster communication between scientists and control authorities; (ii) disseminating advanced research methodology; and (iii) be the primary centre for specific research, such as assessment of health metrics, surveillance, diagnostics and Bayesian-based risk profiling introducing global standards and developing cutting-edge technologies in the region.

Thanks to support from various donors and concerted efforts of its partners, RNAS$^+$ emerged as a successful model in Asia with prospects to replicate this model elsewhere to have a more global outreach. Indeed, RNAS$^+$ features on multi-lateral and sectorial cooperation to achieve a common goal, and its working mechanism with the theory of change could be used to extend to other regions in the NTD arena. At the regional level, working as a virtual organization of researchers and control officers in the endemic settings of Southeast Asia, RNAS$^+$ is playing an increasingly important role in this conversion (Horstick et al., 2010; Zhou et al., 2015; Zhou et al., 2010a, b). Its responsibilities are divided along disease systems into the fields of epidemiology, molecular biology, population genetics and ecohealth/One Health. It extends cooperation with other regions beyond WPRO and SERO, namely AFRO (in Africa) and PAHO (in the Americas) along the different NTDs.

In the future, RNAS$^+$ will make further efforts to maintain and intensify its dialogue with various stakeholders (e.g. scientists, research administrators, policy makers and residents in endemic areas) to improve public health and alleviate poverty. In the future, interaction between changing patterns of agriculture, environment and infectious diseases of poverty should be explored in more depth. The focus should remain on emerging/re-emerging target diseases, including Asian schistosomiasis and other important helminth zoonoses (i.e. cysticercosis/taeniasis, echinococcosis and food-borne trematodiasis), while new efforts are warranted to also look at non-communicable diseases, as Southeast Asia and other parts of the developing world are going through rapid epidemiological transitions. Hence, integrated projects combining the health, agricultural and environmental sectors with a focus on NTD elimination along the Mekong basin will be urgent priorities in the near fugture. The way to cooperate with other regional network, such as the Regional Network on Schistosomiasis in Africa (RNSA) and the African Network on Drugs, Diagnosis and Vaccine Innovation (ANDI) will be further explored in order to accelerate the global elimination programme on NTDs. These efforts will contribute to further global health and we conjecture that particularly P.R. China is well placed in this endeavour. Indeed, as emphasised by Liu et al. (2014), P.R. China plays a distinct role in global health, along four main domains: (i) deploying medical teams through P.R. China's health aid; (ii) construction of health facilities and other infrastructure; (iii) donation of drugs and equipment; and (iv) training personnel and supporting malaria control, mainly in Africa and Asia. As shown in our detailed analysis of the 35 articles featured in the current special issue, a fifth domain emerges: P.R. China's growing role in

research and control of NTDs in Asia with ongoing efforts to adapt the models to Africa and the Americas.

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953 **Figure captions**
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955 **Fig. 1.** Histogram showing the number of authors per article in a collection of 35 papers
956 forming the current special issue of *Acta Tropica* pertaining to research and control of
957 helminth infections in Asia.
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959 **Fig. 2.** Provenance of 35 articles (a) and the 255 author-contributions (b), stratified by country
960 affiliations, of the current special issue of *Acta Tropica*. (1, China; 2, Philippines; 3, Thailand;
961 4, Lao PDR; 5, Japan; 6, Indonesia; 7, Cambodia; 8, Bangladesh; 9, Singapore; 10, Vietnam;
962 11, Switzerland; 12, Sweden; 13, Netherlands; 14, Denmark; 15, UK; 16, Italy; 17, Norway;
963 18, USA; 19, Canada; 20, Australia).
964
965 **Fig. 3.** Cloud tag based on titles (n=35) and keywords (n=191) of the current special issue of
966 *Acta Tropica*.
967
968 **Fig. 4.** Spider plot (a) and radar plots of the two main domains along which the 35 articles
969 published in this special issue of *Acta Tropica* have been analysed; namely, value chain from
970 innovation to application (b) and study topic (c)
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Table 1. Number of contributions by individual authors to the 35 articles published in this special issue of *Acta Tropica* pertaining to research and control of helminth infections in Asia

Authorship(s)	No. of authors	Cumulative authors
1	150	150
2	8	166
3	4	186
4	3	198
5	2	210
6	1	220
7	1	226
8	0	233
9	0	233
10	0	233
11	2	255