

## Introduction

The Ecosystem Health Sciences group covers a wide array of basic and applied research and disease control interventions, mainly focusing on the so-called neglected tropical diseases (NTDs). The research spans from metabolic profiling for enhancing our understanding of complex host-parasite-gut microbial interactions under well-controlled laboratory conditions to risk factor analysis and spatially-explicit prediction of NTDs, which provides decision tools for targeted disease control programmes. Community-based cross-sectional and longitudinal surveys and intervention studies carried out in different eco-epidemiological settings in Africa and Asia serve as the backbone of activities of our group. Research and parasite control activities are facilitated by a broad network of partners within Switzerland, leading research and teaching institutions elsewhere in Europe, the United States and the developing world. Additionally, the unit pursues work within its mandate as a WHO Collaborating Centre for Research and Capacity-Building in Environmental and Tropical Public Health. Field studies are linked to cutting-edge laboratory investigations, and innovative spatial statistical approaches in an iterative fashion. The group is closely interwoven with other units at the STI, namely Biostatistics and Epidemiology (section 7), Health Social Sciences (section 10), Helminth Drug Development (section 6), Parasite Chemotherapy (section 4) and Molecular Diagnostics (section 2), and collaborates across research and service departments, including the Medical Department and Diagnostic Centre. Hence, MSc and PhD fellows are co-supervised, staff and research projects are shared across units and departments, and publications are often co-authored, demonstrating the breadth and depth of the Ecosystem Health Sciences unit.

Key research questions addressed by our group and the network of national and international collaborators are as follows: First, how can the dynamics of multiple species parasitic infections and attributable morbidity be captured, and what is the scope and limitation of  $^1\text{H}$  nuclear magnetic resonance (NMR)-based metabolic profiling for individual diagnosis and the monitoring of disease control programmes? Second, what are key demographic, environmental and socioeconomic determinants of infection risk and resulting morbidity, and how does the combination of epidemiological sample surveys with remotely-sensed environmental data and Bayesian-based geostatistical

modelling improve predictions? Third, to what extent do demographic, ecological and socioeconomic transformations change the frequency and transmission dynamics of NTDs? Fourth, what are the prospects and challenges of health impact assessment of large infrastructure development projects in developing countries and what can mitigation strategies achieve? Finally, what are the feasibility, cost-effectiveness and sustainability of integrated approaches for the control of NTDs?

### 9.1 Metabolic profiling

Although the application of high-resolution  $^1\text{H}$  NMR spectroscopy and multivariate data analysis to infection biology and epidemiology allowed us to gain a deeper biochemical understanding into disease pathology and revealed unforeseen remote mechanisms, the ultimate aim of the metabolic profiling approach was – and continues to be – the development of new tools for accurate diagnosis and monitoring of disease control programmes. Our initial “from-the-field-to-the-bench” approach with urine samples obtained from more than 500 individuals living in a rural part of western Côte d’Ivoire showed that human urinary metabolic profiles are extremely variable, explained by a host of factors, including – amongst others – age, gender, nutritional status, genetic makeup, and infectious diseases as well as non-communicable diseases. In view of our preliminary findings, we conjectured that in typical developing world settings, where multiparasitism is the norm rather than the exception (see section 9.2), metabolic profiling for the extraction of disease-specific biomarkers would be particularly challenging, but might eventually be able to replace a multi-diagnostic approach. Hence, we moved one step back and launched a series of laboratory investigations to characterise whole metabolic changes in rodents to an experimental infection with a helminthic or protozoan infection. In a first step, we characterised the systemic metabolic responses to a *Schistosoma mansoni* infection in the mouse and a *Schistosoma japonicum* infection in the hamster. The key findings of these investigations have been reported in the two previous biennial reports. By now, we have investigated six parasite-rodent models, and applying our metabolic profiling approach to host biofluids and tissue samples facilitated the successful extraction of useful information. Indeed, we have identified common markers of infection, as well as highly specific infection and disease biomarkers.

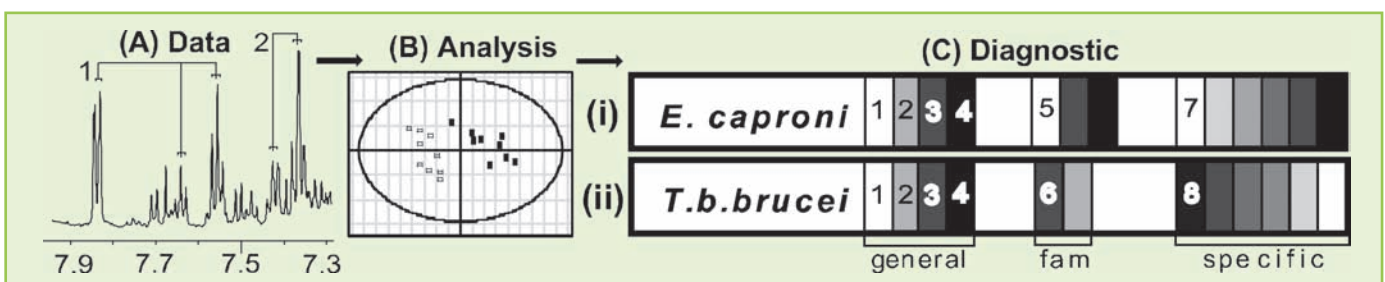


Figure 1: Schematic illustration showing the metabolic profiling approach, consisting of (A) acquisition of spectral profiles from biofluids and/or tissue samples from the host animal infected with a specific parasite

(e.g. *E. caproni* or *T. b. brucei*); (B) data analysis using pattern recognition tools (e.g. principal component analysis); and (C) generation of a panel of candidate biomarkers that give rise to diagnostic potential.

Figure 1 provides a schematic overview of the essence of our metabolic profiling approach. It consists of (A) acquisition of metabolic profiles from biofluids and/or tissue samples from the host, followed by (B) mathematical modelling of the data to establish pre-infection and post-infection phenotypes for a specific parasitic infection. From these models, panels of candidate biomarkers can be identified (C). Infection-induced metabolic changes fall into three categories. First, there are general indices of infectious diseases. Interestingly, the metabolites identified in this category thus far are all known to be produced by gut microbial species and thus reflect changes in the intestinal microflora [hippurate (1); phenylacetylglutamine (2); trimethylamine (3); *p*-cresol glucuronide (4)]. Second, certain metabolites indicate changes in the biochemical pathways of membrane and energy metabolism [e.g. phylogenetically related biomarkers such as choline (5) and lactate (6)]. A third subset of biomarkers consists of highly specific markers of individual parasites [e.g. 5-aminovalerate (7) and methylcrotonate (8)]. We predict that our “metabolic fingerprinting” strategy, although challenging, may prove to be a reliable and robust method for diagnosis and, ultimately, to study responses to therapeutic interventions.

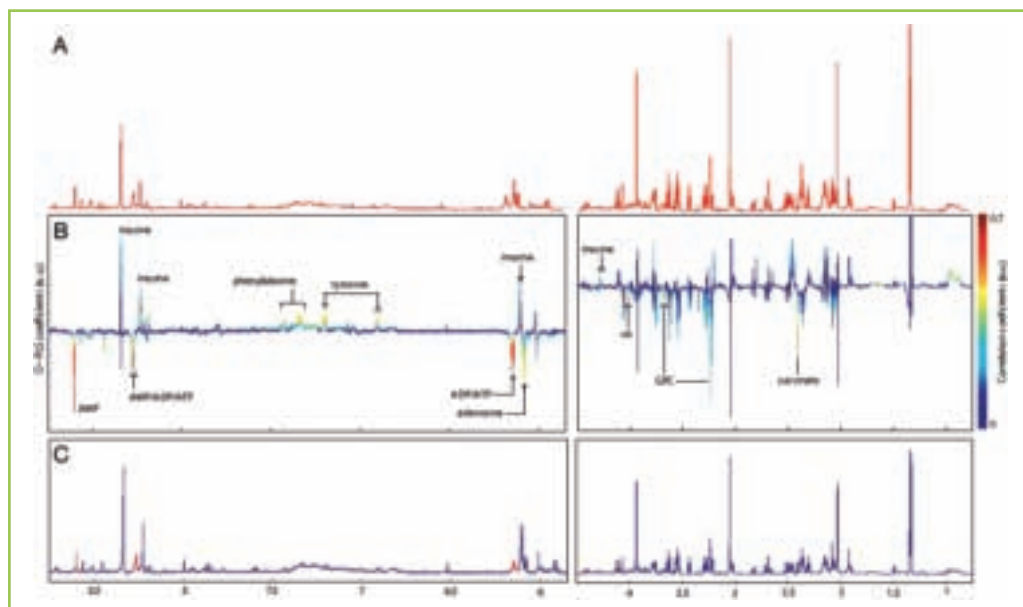
One of the most significant outcomes from this line of research was the early detection of biomarkers in a *Trypanosoma brucei brucei* infection in the mouse, which has shown marked alterations in plasma metabolic profiles already one day post-infection. Elevated plasma concentrations of lactate, branched-chain amino acids (BCAAs) and acetylglucoprotein fragments were noted. Mice infected with *T. b. brucei* were characterised by an imbalance of plasma gluconeogenic (alanine) and ketogenic (valine) amino acids, consistent with differential gluconeogenesis-ketogenesis pathway counterflux, involving stimulated host glycolysis, ketogenesis and enhanced lipid oxidation. Regarding *Plasmodium berghei* – a prominent protozoan model organism that is widely

used by the Parasite Chemotherapy unit – showed the same markers for increased glycolytic activity, for example depleted glucose levels in the plasma and subsequently increased lactate concentrations in plasma and urine, a sign of the high glycolytic turnover of the parasitised erythrocytes.

Our initial work focusing on *S. mansoni* pioneered the metabolic profiling approach in infection biology, and is now being extended to drug treatment profiles of the corresponding biofluids and to other trematode infections, such as *Echinostoma caproni* in the mouse and *Fasciola hepatica* in the rat. Representative 600 MHz spectra obtained from rat biofluids are shown in Figure 2. The direct and remote impact of *E. caproni*, *F. hepatica* and *S. mansoni* was assessed on brain extracts from host animals and revealed clear effects on the metabolic profile of the brains of mice and rats infected with *S. mansoni* and *F. hepatica*, respectively. An infection with *E. caproni* in the mouse, on the other hand, did not result in any perturbation of the mouse brain’s biochemical profile. The metabolic changes reflect the liver pathology, changes in the purine homeostasis and the membrane metabolism, and encourage further studies on the involvement of the brain in parasite infections.

Additionally, we have characterised the faecal metabolome of mice, rats and humans, and our findings provide new insight into differential gastrointestinal functions. For instance, relatively higher levels of uracil, hypoxanthine, phenylacetic acid, glucose and aromatic amino acids were present in aqueous faecal extracts from rats, whereas  $\beta$ -alanine was unique to the rat and glycerol was unique to the human. Human faecal extracts showed a greater interindividual variation than the two rodent species, most likely reflecting the genetic and environmental diversity in natural human populations. Of note, a large number of faecal metabolites were common to the three species, such as short-chain fatty acids and BCAAs.

Figure 2:  
(A) Typical 600 MHz  $^1\text{H}$  NMR spectrum of urine obtained from a rat infected with *F. hepatica*.  
(B) Orthogonal-projection to latent structure (O-PLS) coefficient plots derived from  $^1\text{H}$  NMR spectra of urine individually collected from rats prior to and after an experimental infection with *F. hepatica*, showing the discrimination between pre- and post-infection stages. (C) Statistical total correlation analysis, which is used for metabolite identification and shows biologically and physically related metabolic regions.



## 9.2 Multiparasitism in different eco-epidemiological settings

### Intestinal multiparasitism in south-west China

Two community-based epidemiological studies were carried out among the Bulang people of Menghai county, located in the south-western part of Yunnan province in China (Figure 3). The studies were implemented by



Figure 3: Village of a Bulang ethnic group in Yunnan province, south-western China. (Photo P. Steinmann)

P. Steinmann within the context of his PhD programme, facilitated by a research partnership between STI, the National Institute of Parasitic Diseases in Shanghai and the Yunnan Institute of Parasitic Diseases in Simao. Both studies focused on intestinal multiparasitism and included the collection of multiple stool samples over several days, the use of a suite of diagnostic tools to enhance diagnostic sensitivity, and the appraisal of risk factors for infection by means of a questionnaire that captured demographic, socioeconomic and behavioural information.

The first study aimed at elucidating the extent of intestinal multiparasitism among a representative population sample of 215 individuals from a single village. Soil-transmitted helminths (*Ascaris lumbricoides*, hookworm and *Trichuris trichiura*), food-borne helminths (e.g. *Taenia* spp.) and intestinal protozoa were investigated. Additionally, emphasis was placed on *Strongyloides stercoralis*, arguably one of the most neglected intestinal helminths. The diagnostic performance of the Kato-Katz method, an ether-concentration technique for screening sodium acetate-acetic acid-formalin (SAF) conserved stool, the Koga agar plate method and the Baermann technique were also assessed. It was found that intestinal multiparasitism is common among this population. Indeed, up to six intestinal parasite species were found in some individuals after screening three stool samples by different methods. Overall, eight helminth and seven intestinal protozoa species were diagnosed among the study population, and the prevalence of each of the three common soil-

transmitted helminths exceeded 85%. *S. stercoralis* was found among 11.7% of the study participants, with males aged  $\geq 15$  years at highest risk of infection. *Blastocystis hominis* was the most prevalent intestinal protozoan (20.0%). Parasite infestation was universal; over 80% of the individuals harboured at least three intestinal parasites concurrently (Figure 4). The infection intensities were predominantly light for hookworm and *T. trichiura*, but moderate for *A. lumbricoides*. Of note, 30% of the young children (4–9 years) harboured high-intensity *A. lumbricoides* infections ( $\geq 50,000$  eggs/g of stool), while the prevalence of heavy infections was only 7.2% across the older age groups. As expected, the examination of multiple stool samples increased the diagnostic sensitivity of the employed tools, most notably for hookworm and *S. stercoralis*. For these parasites, the recorded prevalence almost doubled if three instead of a single stool specimen were collected and examined. For hookworm diagnosis, the Koga agar plate method performed particularly well. The combination of different tools also increased the overall sensitivity.

The second study was an open-label randomised trial. The safety and efficacy of single-dose oral tribendimidine was compared to an equal dose of albendazole in a population with high rates of intestinal multiparasitism. A total of 123 individuals participated in this trial, and both drugs were administered to 5- to 14-year-old children at a dose of 200 mg, while a dose of 400 mg was given to  $\geq 15$ -year-old individuals. The study focused on common soil-transmitted helminths but – for the first time ever – the effect of tribendimidine against *S. stercoralis* and *Taenia* spp. was also assessed. Multiple stool samples were collected from every study participant at baseline, and again 2–4 weeks after treatment. All samples were screened for helminth eggs as described above. Both single-dose oral albendazole and tribendimidine were highly efficacious against *A. lumbricoides* (cure rate albendazole: 100%; cure rate tribendimidine: 92.3%) and, moderately, against hookworm infections (albendazole: 69.6%; triben-

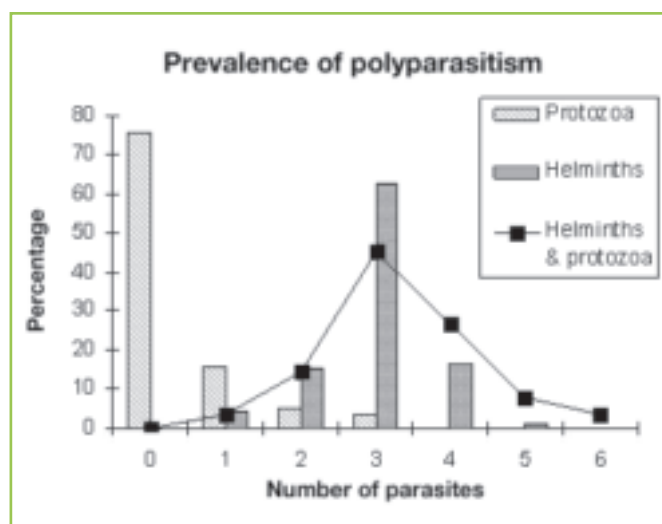


Figure 4: Frequency of no, single- and multiple-species parasitic infection among 215 study participants from Nongyang village in Yunnan province, south-western China.

dimidine: 52.2%). The efficacy against *T. trichiura* was low (albendazole: 11.7%; tribendimidine: 0). Among 57 individuals who had received tribendimidine, the prevalence of *S. stercoralis* was reduced from 19.3 to 8.8% (observed cure rate 54.5%), and that of *Taenia* spp. dropped from 26.3 to 8.8% (observed cure rate 66.7%). Similar prevalence reductions were noted among the 66 albendazole recipients. Taking into account “new” infections discovered at treatment evaluation, the difference between the drug-specific net *Taenia* spp. cure rates was highly significant in favour of tribendimidine. These infections were most likely missed pre-treatment due to the lack of sensitivity of the available diagnostic tools. No significant adverse effects of drug administration were noted.

The results of the two studies further underscore that intestinal multiparasitism is the norm in rural communities of the tropics, and call for control programmes delivering regular anthelmintic treatment in order to prevent morbidity, as well as health education and improvements in water supply and sanitation to curb transmission and re-infection. Our epidemiological studies also showed that the collection of multiple stool samples, as well as differential diagnosis employing complementary tools are paramount for the comprehensive evaluation of intestinal multiparasitism. Single-dose oral tribendimidine can be employed for intestinal helminth control in such settings. Its efficacy against *A. lumbricoides* and hookworm was confirmed, and the noted effects against *S. stercoralis* and *Taenia* spp. warrant further investigations.

#### Food-borne trematodiasis and schistosomiasis in Laos

Since September 2005 we have been carrying out a research project in Laos with an emphasis on food-borne trematodiasis and schistosomiasis. The overarching goal of this project is to contribute to the design of effective control strategies to combat these neglected diseases. The research activities were designed to analyse the characteristics and dynamics of multiparasitism due to hepatobiliary and intestinal trematodes in Laos, and to estimate its community-attributable burden. It is anticipated that our research and control activities will generate and strengthen the evidence-base for designing and implementing effective and sustainable control programmes.

In a first step, we addressed the issue of multiple trematode infections. In an in-depth study performed in the provinces of Savannkhet and Champassak, we examined stool samples from 97 patients who presented at hospitals and were suffering from hepatobiliary and intestinal symptoms. Patients were purged, and the entire stool produced within the next 24 hours was examined for adult trematodes. We found a large number and diversity of food-borne trematodes. *Opisthorchis viverrini* was the predominant trematode species; it was found in 95 patients, followed by *Haplorchis taichui* found in 76 patients in all age groups (Figure 5). Moreover, in three patients we recovered *Echinochasmus japonicus*, which is gener-

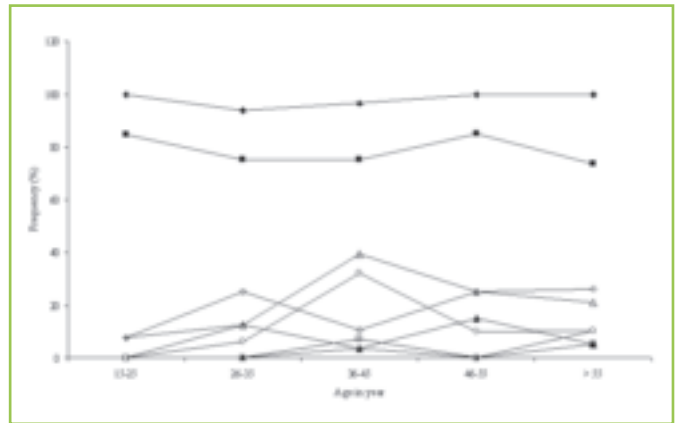


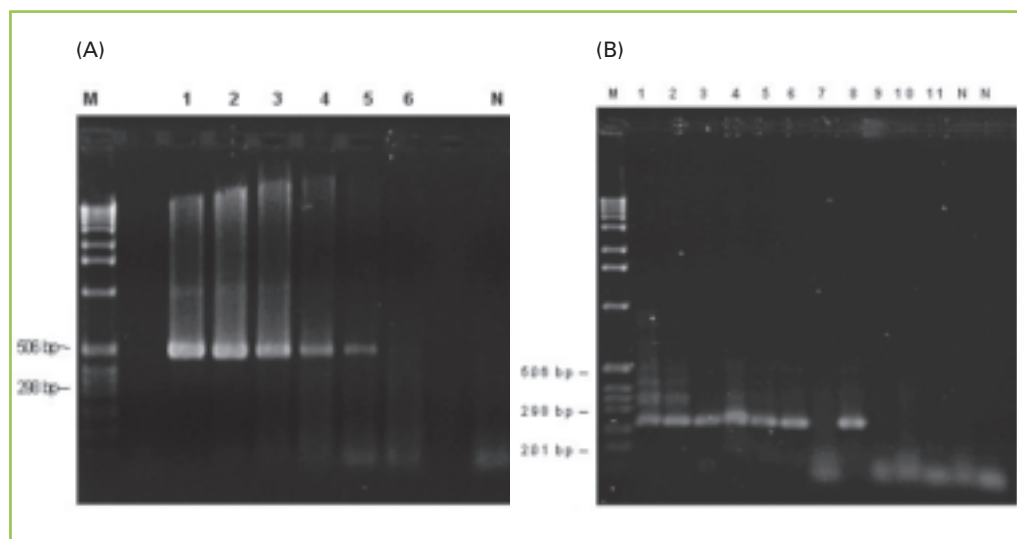
Figure 5: Age-prevalence curves for *O. viverrini* (◆), *H. taichui* (■), *E. japonicus* (□), *T. saginata* (◇), *P.s. bonnei* (Δ), *P. molenkanpi* (○), *H.s. pumilio* (▲) and *H.s. yokogawai* (\*), as revealed by a purging study among 97 patients with self-reported intestinal symptoms in Lao PDR.

ally considered a rare parasite. Indeed, to our knowledge this is the first report of this parasite in Laos. Our results have direct public health implications, and emphasise that the control of *O. viverrini* warrants attention. Indeed, an infection with *O. viverrini* – if left untreated – can lead to liver cancer. One issue which considerably complicates the control of opisthorchiasis is the difficulty to readily distinguish the eggs of *O. viverrini* from those of other food-borne trematodes that are often co-endemic in the same settings and population strata. Hence, the significance of developing and validating species-specific diagnostic tools for common food-borne trematodes cannot be emphasised enough.

In collaboration with the Molecular Diagnostics unit, we have developed a polymerase chain reaction (PCR) technique to identify *O. viverrini* infection in stool samples. A primer for *O. viverrini* was identified and validated. It proved to be highly specific for the diagnosis of *O. viverrini* infections without any significant cross-reactions with other common parasites, including *H. taichui*. In the meantime, our PCR technique has already been validated with stool samples from an *O. viverrini*-endemic community examined with several parasitological stool techniques (Figure 6).

In the Khong district of Champassak province, the southernmost province of Laos, infections with *O. viverrini* are highly prevalent. Moreover, in this part of Laos, *Schistosoma mekongi* is also endemic, which implies that co-infections occur. In the nearby Munlapamock district, however, only *O. viverrini* is endemic, whereas in the mountainous district near Attapeu, *S. mekongi* is absent and *O. viverrini* affects only a small fraction of the population. In a cross-sectional community-based survey in these three settings, we have screened the local population for intestinal parasites, investigated parasite associations, and assessed liver morbidity. Our study revealed significant hepatobiliary morbidity in connection with *O. viverrini* infection, such as enlarged intrahepatic bile ducts. The degree of morbidity increased with the intensity of infections. Co-infection with *O. viverrini* and

Figure 6: Detection limit of *O. viverrini* DNA by (A) pPCR and (B) nPCR on agarose gel (1.5%) stained with ethidium bromide. Lane M, DNA size marker (1 kb DNA ladder, Merck); lane N, negative controls containing no DNA. Primary primers in (A) were tested in 10-fold serial dilutions with *O. viverrini* DNA:  $7.5 \times 10^4$  pg (lane 1),  $7.5 \times 10^3$  pg (lane 2), 750 pg (lane 3), 75 pg (lane 4), 7.5 pg (lane 5), 0.75 pg (lane 6). Size of the amplicon, 508 bp. Panel (B) shows nested primers amplifying pPCR product of serial dilutions of *O. viverrini* DNA: 75 pg (lane 1), 7.5 pg (lane 2), 0.75 pg (lanes 3–5),  $7.5 \times 10^{-2}$  pg (lanes 6–8),  $3.75 \times 10^{-2}$  pg (lanes 9–11). Size of the amplicon, 226 bp.



*S. mekongi* resulted in further elevated morbidity levels; individuals with a co-infection were at a 70-fold higher risk of liver fibrosis than those with a single *O. viverrini* infection. The study participants were treated with a single 40-mg/kg oral dose of praziquantel, and two follow-up studies at yearly intervals were carried out. Based on this cohort study we were able to investigate the resolution of hepatobiliary-related morbidity due to *O. viverrini* and *S. mekongi*. Data analysis and interpretation is under way and will further strengthen the evidence-base on how often praziquantel should be administered to reduce liver pathology.

Another aspect of our work is deepening our understanding of risk factors for trematode infections. It is commonly assumed that lower socioeconomic strata carry an elevated risk for schistosomiasis and other trematodiasis. In our cross-sectional survey in the Khong district, we administered a questionnaire to assess people's socioeconomic status. We then employed principal component analysis to investigate housing characteristics and household-based assets. Our analysis revealed that an infection with – and morbidity due to – *S. mekongi* was significantly associated with socioeconomic status. Interestingly, *S. mekongi* infection was positively associated with socioeconomic status, indicating that the populations with *S. mekongi* infection are wealthier than those without infections. This observation can be explained by the fact that schistosomiasis-endemic areas in Laos are favourite tourist destinations, and hence the local communities have other opportunities to make an earning than by the subsistence farming observed in neighbouring districts.

#### **Soil-transmitted helminths and *S. stercoralis* in Zanzibar, Tanzania**

Within a newly established research partnership between the STI, the Natural History Museum in London and the Helminth Control Team of Zanzibar, a cross-sectional survey and an in-depth study pertaining to the epidemiology of soil-transmitted helminthiasis, with a par-

ticular focus on strongyloidiasis, were launched (Figure 7). The two main objectives of these epidemiological investigations were (i) to assess the relative importance of *S. stercoralis* versus other soil-transmitted helminths in school-aged children, and (ii) to compare the performance of different techniques for diagnosing soil-transmitted helminths, placing emphasis on *S. stercoralis*. It is important to note that a national helminth control programme had already been initiated in Zanzibar in the mid-1990s, and hence repeated rounds of mass drug administration had been carried out using albendazole, ivermectin, mebendazole and praziquantel.

For assessing the prevalence of *S. stercoralis* and other soil-transmitted helminths, one stool sample from a total of 336 children from six districts in Zanzibar was examined during the cross-sectional survey, and three stool samples from a total of 342 children from two primary schools (Chaani and Kinyasini) were analysed using different methods. The most prevalent helminth species was *T. trichiura* (48% in the in-depth study), followed by hookworm (23%) and *A. lumbricoides* (17%). The preva-



Figure 7: Newly established research partnership between STI, the Natural History Museum (London, UK) and the Helminth Control team of Unguja, Zanzibar. (Photo H. Marti)

lence of *S. stercoralis* was considerable lower (11%), but infections were observed among school-aged children in most of the districts. For all the parasites investigated, infection intensities were generally low. The comparison of our data obtained in the schools of Chaani and Kinyasini in 2007 with available data from the mid-1990s – before mass drug administration campaigns had started – revealed a considerable decline both in the prevalence and infection intensity of soil-transmitted helminths.

When three rather than a single stool sample were examined by the Kato-Katz method (for *A. lumbricoides*, hookworm and *T. trichiura*), the Koga agar plate method (for hookworm and *S. stercoralis*) and the Baermann technique (for *S. stercoralis*), we observed striking increases in the prevalence of the various parasites (e.g. an increase of 161% for hookworm when considering the results of the Kato-Katz method). Additionally, stool samples were preserved and subsequently analysed by the newly developed FLOTAC method. This investigation was possible owing to our recently established collaboration with Prof. G. Cringoli and his team at the University of Naples in Italy. Prof. Cringoli has developed the FLOTAC apparatus – a new multivalent technique for diagnosing parasites in veterinary medicine – and we have now launched a series of investigations to broadly validate the FLOTAC method for human helminths and intestinal protozoa. With stool samples from Zanzibar we were able to demonstrate that the FLOTAC method is indeed more sensitive for diagnosing soil-transmitted helminths than the Kato-Katz method; a single FLOTAC revealed higher prevalences of soil-transmitted helminths than multiple Kato-Katz thick smears, confirming previous results from Côte d'Ivoire.

In summary, our results demonstrate that soil-transmitted helminths, including *S. stercoralis*, are still highly prevalent among school-aged children in Zanzibar. Periodic mass-drug administration of ivermectin and mebendazole/albendazole significantly reduced the prevalence and intensity of helminthic infections. But this strategy needs to be complemented with preventive measures, includ-

ing health education, water supply and sanitation, if the achievements are to be consolidated and transmission control the ultimate goal. Investigations on the prevalence of *S. stercoralis* and other soil-transmitted helminths in entire communities of Zanzibar are currently under way. Finally, our results underscore previous observations which indicate unanimously a low sensitivity of widely used parasitological methods to detect low-intensity soil-transmitted helminthic infections, and highlight the potential of the FLOTAC method as a supportive diagnostic tool for laboratories with adequate technical equipment. It remains to be investigated whether the FLOTAC method can also be used to diagnose *S. stercoralis*, and to compare the results with those obtained from already standardised methods for diagnosing this neglected parasite. Finally, work is under way in Côte d'Ivoire to validate the FLOTAC method for diagnosis of *S. mansoni*, and in Kyrgyzstan for diagnosis of *Enterobius vermicularis*.

### Demographic and ecological transformations

The Ecosystem Health Sciences group was involved in two projects that looked at the effect of demographic and ecological transformations on health-related issues. In the first study, under the leadership of Prof. X. Zhou at the National Institute of Parasitic Diseases in Shanghai, we attempted to predict the potential impact of climate change on schistosomiasis transmission in China. We developed a biology-driven model based on the results of laboratory investigations, historical accounts of intermediate host snail distribution in China, and climate models. Estimated temperature increases in China of 0.9°C by 2030 and 1.6°C by 2050 enabled predictive risk mapping. We forecasted an expansion of schistosomiasis transmission into currently non-endemic areas in the north, with an additional risk area of 783,883 km<sup>2</sup> by 2050, translating to 8.1% of the total surface area of China. We issued a strong call for rigorous monitoring and surveillance of schistosomiasis in a future warmer China.

The second main research activity pertained to health impact assessment (HIA) of large infrastructure develop-

Figure 8: A systematic investigation of the peer-reviewed literature revealed that only 6% of the health impact assessment (HIA)-related studies had an explicit focus on low- and middle-income countries, whereas the remaining 94% of the published work focused on high-income countries. We have coined this finding the “6/94 gap in HIA”.



ment projects. Specifically, we were able to follow up on HIA-related research relating to the Nam Theun 2 hydroelectric project in central Laos and to finalise our baseline health and socioeconomic appraisal of two communities that will be affected by the project. Additionally, we carried out the first systematic review by asking the following question: Where in the world have HIAs been carried out? Our review revealed 237 HIA-related publications, only 6% of which had a focus on the developing world. We termed this huge disparity the “6/94 gap in HIA” (Figure 8). In fact, this gap is even worse than the widely known 10/90 gap in health research (i.e. 10% of health research funding goes to diseases that cause 90% of the global burden of disease). These findings emphasise that HIAs of infrastructure development projects in low-income countries are urgently needed.

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