

**Elimination of schistosomiasis  
from low-transmission areas  
Report of a WHO Informal Consultation**

**Salvador, Bahia, Brazil  
18–19 August 2008**



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# Contents

<b>Executive summary</b>	<b>1</b>
<b>Introduction</b>	<b>2</b>
<b>Current status of schistosomiasis: some country and regional situations</b>	<b>3</b>
Where schistosomiasis has been eliminated: Tunisia	3
Where transmission has been interrupted: Morocco	3
Where elimination is feasible: Saudi Arabia	4
Where control is progressing: the Americas	5
Where control is challenging: Sudan	6
<b>Control strategy in low/potential transmission areas</b>	<b>7</b>
Surveillance for schistosomiasis after interruption of transmission: the example of Japan	7
Setting criteria for schistosomiasis control in low-transmission areas: the example of China	7
<b>Clinical aspects of schistosomiasis in low-transmission areas</b>	<b>9</b>
Diagnosis of schistosomiasis in patients with a low-intensity infection	9
Presentation and treatment of schistosomiasis in low-transmission areas	10
<b>Tools for monitoring and surveillance in low-transmission areas</b>	<b>12</b>
Maintenance of a control programme and data reporting in an advanced programme: the example of Brazil	12
Monitoring of schistosomiasis transmission: some theoretical and practical considerations	13
Monitoring of schistosomiasis transmission in the intermediate host: towards implementation of molecular monitoring	14
Monitoring of schistosomiasis transmission in the human host: identification and mapping	15
<b>Recommendations for moving towards the interruption of schistosomiasis transmission in low-endemic areas</b>	<b>17</b>
<b>References</b>	<b>19</b>
<b>List of participants</b>	<b>21</b>



## Summary

Elimination of schistosomiasis is possible in certain areas □ or even countries □ and has already been achieved in some, but there are no agreed criteria for determining elimination of the disease. Elimination will require a combination of methods, including chemotherapy, health education, environmental management, provision of safe water and adequate sanitation. As transmission decreases, however, diagnosis and monitoring of infection become more difficult.

More than 30 international experts and representatives of countries where schistosomiasis has been controlled to different degrees met from 18 to 19 August 2008 in Salvador, Brazil, to look at progress in control, and to discuss and recommend tools and strategies for monitoring schistosomiasis in low-transmission areas and criteria for determining and validating interruption of disease transmission. This report summarizes the discussions and presents the recommendations that emerged from the meeting.

Discussions covered the interruption of transmission in several countries and how this was achieved, diagnosis and clinical presentation in low-transmission areas, and the tools available for monitoring transmission in the human and snail hosts. Although the difficulties of diagnosis in areas of low transmission were highlighted, new molecular tools are being developed that promise improvements in both diagnosis and monitoring of transmission.

It is hoped this report will guide countries in changing from a strategy of morbidity control to one of transmission control, and in moving towards elimination. Guidance on when this might be appropriate can be found in the recommendations and in the experiences of particular countries; nevertheless, the heterogeneous nature of the disease means that each situation is unique and must be assessed individually.

## Introduction

Elimination of schistosomiasis is possible. Several endemic countries have reported no new cases of schistosomiasis in years and now want validation of the interruption of transmission. Other countries have achieved low transmission of schistosomiasis and are seeking guidelines on the tools to use and strategies to follow in moving towards interruption of transmission. Currently, however, no agreement has been reached on criteria for determining elimination of the disease.

Disease *elimination* (as opposed to eradication) is defined as: reduction to zero of the number of new cases (1) of a specified disease in a defined geographical area as a result of deliberate efforts; continued intervention measures are required. Guinea-worm disease, which is actually targeted for *eradication* (permanent reduction to zero of the world-wide incidence of infection caused by a specific agent as a result of deliberate efforts; continued intervention measures are no longer needed), provides a good model for moving towards the elimination of schistosomiasis.

In April 2000, a WHO Informal Consultation on low transmission (2) reviewed schistosomiasis control in 14 countries and discussed the need for more sensitive parasitological and serological diagnostic techniques. The Consultation recommended strategic changes in the approach to transmission control and strengthened surveillance systems with monitoring of incidence in young children. However, no recommendations were made on the criteria for determining interruption of transmission because the country situations were so heterogeneous. In 2007, meetings on the elimination of transmission were held in WHO's Region of the Americas and Eastern Mediterranean Region <sup>1</sup>(3).

The present Consultation involved more than 30 international experts, who met in Salvador, Brazil, from 18 to 19 August 2009. It was convened to review progress in schistosomiasis control in low-transmission areas, and to discuss and recommend tools and strategies for monitoring schistosomiasis in such areas, as well as possible criteria for determining interruption of disease transmission and confirming/validating interruption. The discussions and recommendations of the Consultation are presented in this report.

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<sup>1</sup> Report of an intercountry meeting on strategies to eliminate schistosomiasis from the Eastern Mediterranean Region. Muscat, Oman 6-8 November 2007.

## Current status of schistosomiasis: some country and regional situations

### Where schistosomiasis has been eliminated: Tunisia

Three conditions underpinned the success of efforts to control schistosomiasis (*Schistosoma haematobium*) in Tunisia:

- The decision to eliminate the disease was taken at the highest level. In 1969, the Government of Tunisia decided to eliminate schistosomiasis □ along with malaria and other endemic diseases □ in order to improve the health status of the population, the economy of the country and develop tourism.
- The particular characteristics of the epidemiological situation: each transmission site was isolated and there was only one vector species and no vertebrate hosts other than humans. Transmission of *S. haematobium* was limited to a number of oases that were breeding sites for the vector snail *Bulinus truncates*; about 150 000 people were at risk.
- The personnel recruited to the control teams were all inhabitants of the endemic region (and thus had no linguistic or cultural problems in working together) and showed excellent aptitude for the work.

The objectives of the elimination efforts were to control or interrupt transmission through use of molluscicides, and to treat all infected people.

In 1973, prevalence was 7.2% overall but much higher (up to 70.2%) in some places. Children and young people were particularly affected. A survey based on urine examination of school-age children permitted identification of the transmission sites. Results from a pilot project carried out at one site □ to which the vector never returned □ suggested that the disease could be eliminated from Tunisia. Nearly 75% of sites became negative for *Bulinus truncates* after the first mollusciciding; the remainder required two or more treatments. Most patients were treated in their homes and, with the introduction of metrifonate or praziquantel (PZQ), all cases were cured. The last autochthonous cases occurred in 1981–1982.

Epidemiological surveillance was based on urine examination of selected samples. During the early years, the entire population of 10 oases was examined annually; subsequently, examination was carried out every two years, and was finally limited to school populations. By 1994, many oases had in fact dried up owing to the drilling of artesian wells, which had by then become the principal source of water.

### Where transmission has been interrupted: Morocco

Urinary schistosomiasis caused by *S. haematobium* was first described in Morocco in 1914. The principal endemic areas were along the ancient trade routes from the Middle East and sub-Saharan Africa. Control activities began in 1977.

The preparatory phase covered the years 1977–1981 and aimed at defining an appropriate strategy and operational approach to implementing the national control programme. This included:

- review of available and published data on schistosomiasis;
- epidemiological surveys and analysis of available data;

- delimitation of the main transmission sites;
- determination of infection intensity;
- development of a snail surveillance system;
- assessment of diagnostic techniques and their use in different operational approaches;
- choice of the most effective drug, treatment schedules, and follow-up;
- determination of appropriate techniques for snail control;
- finalization of guidelines and operational documents;
- compilation of inventory of available human and material resources;
- definition of operational methodology and setting of a timetable for field operations;
- compilation of all components, instructions and activities in a comprehensive guide.

The operational basis for implementing the strategy was provided by the existing infrastructure. Schistosomiasis control interventions were integrated with primary health care activities.

The operational phase covered the years 1982–1993, during which the adopted strategy aimed to control morbidity, infection and transmission by:

- case-detection (selective passive detection, selective active detection, intensive detection, mass screening);
- malacological surveillance (snail monitoring, mollusciciding);
- chemotherapy (individual and mass treatment);
- health education.

By the end of 1992, some foci of transmission had been completely inactivated; others were largely under control and prevalence was gradually falling. In 1993, an elimination programme was developed. The elimination phase has been in progress since 1994; it is based on:

- increasing case-detection in high-risk areas;
- ensuring treatment of all detected cases and wide coverage in the case of mass chemotherapy;
- improving snail surveillance and mollusciciding where necessary;
- strengthening health education;
- developing intersectoral action and improving intersectoral coordination;
- encouraging community participation.

This strategy was modified in 2005 when greater emphasis was put on interventions and surveillance in high-risk areas. No indigenous case has been detected in the country since 2004. By the end of 2008, serological tests and molecular techniques for determining snail infection will be in use to provide additional evidence for the interruption of transmission.

### **Where elimination is feasible: Saudi Arabia**

Saudi Arabia has seen a steady decline in the prevalence of schistosomiasis infection since the early 1980s, when new safe and effective drugs (oxamniquine and PZQ) were introduced and improved methods of laboratory diagnosis and focal snail control became available. In most areas, as the infection rate dropped to about 1%, the use of the vertical approach became less economically justifiable, and schistosomiasis control operations were integrated into the

primary health care system. The general rise in living standards in the country, together with improved sanitation and water supplies, construction of wells in rural areas, and a significant improvement in medical care, means that elimination is now thought feasible in 4 of the 12 endemic areas. In the remaining areas, the strategy used is one of chemotherapy and focal snail control.

Challenges have included:

- lack of leadership for necessary planning and evaluation in some regions, and shortages of laboratory technicians and health inspectors;
- scant attention given to the disease by health authorities, because of the low prevalence;
- lack of cooperation by some communities in providing urine and stool samples;
- population movements;
- non-availability of diagnostic kits and other equipment in many health centres.

### **Where control is progressing: the Americas**

*Schistosoma mansoni* is the only human schistosome present in the Americas. It is to be targeted with intensified efforts for control and possible elimination under a new PAHO initiative for regional elimination of selected infectious diseases by 2015 and PAHO's Health Agenda for the Americas 2008–2017.

Schistosomiasis is endemic in up to eight countries and islands in Latin America and the Caribbean (Brazil, Dominican Republic, Guadeloupe, Martinique, Puerto Rico, St Lucia, Suriname, Venezuela); transmission in the minor foci found earlier in Antigua and Barbuda and in Montserrat may have been eradicated by the volcanic eruption in 1995. Up to 6 million people are infected, most of whom live in north-east Brazil and Venezuela, and 25 million are at risk of infection. Despite these estimates, prevalence and morbidity have decreased in historically endemic countries in the region, with improved sanitation and water supply playing an important role.

Control strategies include the following:

- Large-scale drug administration with PZQ, or individual treatment with family-wide follow-up (widening investigation if indicated).
- Intermediate host control with molluscicides (although environmental laws limit the use of this in some countries, e.g. Brazil).
- Biological control. Success has been achieved by introducing competitor snails for intermediate host control □ they are claimed to be particularly useful in low-transmission areas and when transmission has stopped completely □ but this is no longer an option because of environmental concerns.
- Improved water supply and sanitation.
- Improved health education.
- Package approach for high-risk communities, including mass PZQ administration, health education, improved water supply and sanitation, improved surveillance, integration or coordination with other sectors and stakeholders.

Elimination programmes are confronted by a number of issues. First, the parasitological techniques currently used are not sufficiently sensitive to detect low-intensity infections.

Efficacy can be improved by focusing control efforts, e.g. screening schoolchildren with parasitological techniques and using stool examination results as indicators for identifying schistosome-positive individuals among household members (4). A recent study found that incorporation of serological tests into epidemiological surveillance in low-transmission areas compensates for the underestimation of prevalence based only on parasitological diagnosis (5).

Whether elimination of schistosomiasis will ever be possible without a vaccine is not known, but there are concerns about the sustainability of PZQ treatment for long-term control because of variable efficacy of the drug, high rates of post-treatment reinfection, and the possible development of drug resistance. Vaccine research and development are ongoing in the region.

The impact of global climate change on schistosomiasis remains to be determined. A recent study found that the impact of temperature on disease prevalence and abundance is not straightforward: *S. mansoni* appears not to respond to increased temperatures in a linear fashion. The optimal control strategy could change if there are climatic temperature changes (6).

### **Where control is challenging: Sudan**

Sudan has seen a serious increase in endemicity and prevalence of both *S. haematobium* and *S. mansoni* infections since 1990 as a result of expansion in water resource projects, population movements, and unsuccessful control measures.

One of the main challenges to schistosomiasis prevention and control in the country has been a lack of recognition of the schistosomiasis problem, coupled with a lack of political commitment. While control successes were achieved in some areas of Sudan, funding shortages meant they could not be sustained.

- Appraisal of the epidemiology of the disease, and integration with control programmes for malaria and soil-transmitted helminthiasis).
- Integration into primary health care settings, and extending diagnosis and regular chemotherapy coverage as public health interventions to reach all at risk of morbidity due to schistosomiasis. With morbidity control the preferred strategy, schistosomiasis control has increasingly been integrated into primary health care settings and schools.
- Intersectoral cooperation. Transmission control requires cooperation in control efforts for water supply, sanitation, and environmental management. Snail surveys and focal mollusciciding are necessary to interrupt transmission, especially where there is migration or displacement of populations and where drug supplies are irregular.

Improved capacity is needed at all levels of the health system, but particularly at the periphery, to improve accessibility to drugs and diagnosis, as well as snail control where feasible. Other challenges include the role played by population movements □ particularly migrant agricultural labour □ in the spread of schistosomiasis in Sudan. As well, floods, famine, and civil wars have resulted in massive population movements. New water resource development projects should include a budget item for prevention and control of schistosomiasis and other water-associated diseases, undertake health, environmental, and social impact assessments, and implement measures to prevent transmission of schistosomiasis. Operational research is required to improve intervention strategies, diagnostic techniques, and to facilitate population compliance with control interventions. A final challenge is sufficient funding.

## Control strategy in low-transmission areas

### **Surveillance for schistosomiasis after interruption of transmission: the example of Japan**

Japan has had no locally acquired cases of schistosomiasis (*S. japonicum*) since 1972, although vector snails still persist in two of the three former endemic foci.

Measures that contributed to elimination of the disease included mass screening and treatment, molluscicide application, community participation through health education, and coordination by the Union for Schistosomiasis Control. These control efforts began in 1920.

After the declaration of elimination, follow-up surveillance in the subsequent seven years included:

- snail surveillance by the local government;
- serological testing by the local government;
- regular monitoring of infection in sentinel mice exposed in natural water bodies.

The Government no longer provides funds for surveillance, although small-scale surveillance continues as an integral part of research that covers new diagnostics, drug and vaccine development, field survey using geographical information systems (GIS), clinical studies, and case registration.

Geographical information systems provide an easy, cheap, and precise means to monitor snails in former endemic sites, enabling development of risk maps and identification of sites to be monitored.

In determining the risk of re-emergence, infection in snails can easily be identified using polymerase chain reaction (PCR) and/or loop-mediated isothermal amplification (LAMP) techniques – specific *S. japonicum* DNA is detectable one day after miracidial invasion of the snail. Using this technique, the susceptibility of snails from different areas to the local strain of *S. japonicum* was tested to determine the possibility of parasite exchange with different areas/countries. Snails from China were not susceptible to Japanese strains of parasite, although parasite exchange with the Philippines could not be ruled out □ Japanese snails were not susceptible to schistosome strains from China, but were compatible with parasites from the Philippines.

Among people living in areas where snails are still present, knowledge of schistosomiasis has been found to be declining, although some elderly people still remember the disease.

Academic institutions have proposed a case registration system and maintain a schistosomiasis database (data come from a helminth infections network, from inter-institutional communications, and from case reports at scientific meetings), which can be used as a basis for making recommendations to the Government.

### **Setting criteria for schistosomiasis control in low-transmission areas: the example of China**

China has achieved interruption of transmission in 5 out of 12 endemic provinces and has controlled transmission in 5 others.

There has been a significant reduction in endemicity: since 1950 the number of cases has been reduced by 93% and the area infected with snails by 76%. These achievements are attributed to:

- The original goal: to eliminate the disease from all endemic areas where feasible by integrated approaches, including chemotherapy, snail elimination, environmental modification, health education, and improved sanitation and water supply.
- The sustained commitment and technical support of central and local governments.
- Collaboration of the health sector with various other governmental sectors (notably agriculture, water conservancy, and forestry).

A strategic plan was developed for the national control programme, and a variety of specific protocols were integrated with the plan; these included management, evaluation, and resource mobilization, as well as technical interventions.

National criteria for control of schistosomiasis include:

- *Criteria for infection control*
  - The prevalence rate in residents is less than 5%.
  - The prevalence rate in domestic animals is less than 5%.
  - No outbreaks of acute schistosomiasis occur (fewer than 10 acute schistosomiasis cases, including clinical or parasitologically confirmed cases, occurring within 2 weeks in an administrative village, or fewer than 5 acute cases occurring within 1 week in the same place).
  - Data and files reflecting the changes in human and snail infections at administrative village level are available.
- *Criteria for transmission control*
  - The prevalence rate in residents is less than 1%.
  - The prevalence rate in domestic animals is less than 1%.
  - No acute schistosomiasis cases with local infection are found.
  - No infected *Oncomelania* snails are found for two successive years.
  - Data and files reflecting the changes in human and snail infections at administrative village level are available.
- *Criteria for transmission interruption*
  - No human schistosomiasis case with local infection is found for five successive years.
  - No schistosomiasis case in domestic animals with local infection is found for five successive years.
  - No *Oncomelania* snails are found after careful surveys for two successive years.
  - Data and files reflecting the changes in human and snail infections at administrative village level are available, as well as plans and for surveillance.
- *Certification of schistosomiasis elimination*
  - No new infection in man or domestic animals is detected for five years after reaching the criteria for transmission interruption.

## Clinical aspects of schistosomiasis in low-transmission areas

### Diagnosis of schistosomiasis in patients with a low-intensity infection

Most cases of schistosomiasis are diagnosed by stool examination; however, in low-intensity infections (fewer than 100 eggs/gram of faeces), diagnosis by this means is less sensitive. Ectopic conditions, such as neuroschistosomiasis and genital schistosomiasis, are also found, and stool examination is negative in such cases.

Methods of diagnosis include parasitological (qualitative sedimentation method, and quantitative Kato-Katz), histopathological (rectum biopsy), serological (antigen or antibody detection), and molecular (PCR) methods.

Many antibody detection assays are available for schistosomiasis, such as the cercarian reaction (fresh cercariae), circumoval precipitation test (fresh eggs), haemagglutination test (adult worm antigens), indirect immunofluorescence test (adult worm and infected liver section), and immunoenzymatic assays (enzyme-linked immunosorbent assay – ELISA; competitive enzyme immunoassay – CELISA; Western blot). Antibody detection is less sensitive in low-intensity infections: among other things, results are affected by previous treatment, by cross-reactivity with other parasites, and particularly by antibody persistence after infection “cure”.

In a comparison of parasitological and serological methods in 268 individuals (7), the prevalence (based on number found infected by the different methods) varied from 6% for with stool examination, to 47% and 39% for two immunoenzymatic tests (ELISA and immunofluorescence IgM respectively). In another comparative study (8) of parasitological and serological procedures in the water rat (a wild reservoir indicator of *S. mansoni* in Rio de Janeiro), the sensitivity and specificity of the Kato-Katz method were 50% and 100% respectively, of Western blot 86.6% and 89.1%, and of ELISA 96.6% and 84.4%. Autopsies performed on the rats suggested that stool examination is not a sufficiently sensitive technique to use in areas of low endemicity or in low-intensity infections.

Efficacy trials (supported by WHO/TDR) of a number of serological assays, including SEA SMP-ELISA (soluble egg antigen, sodium metaperiodate-ELISA), MAMA (*Schistosoma mansoni* adult microsomal antigen) Western blot, and MAMA FAST dipstick) are being carried out in five regional reference laboratories to ascertain individual test sensitivity and specificity with parasitologically confirmed clinical samples. Preliminary results showed the MAMA Western blot to work well in all laboratories; specificity and sensitivity of the other tests varied from one laboratory to another.

Antigen-detection tests include the circulating cathodic antigen (CCA) and circulating anodic antigen (CAA) urine and serum tests, detection of DNA in the faeces by PCR, and detection of coproantigen by ELISA. The latter two techniques look promising and could prove useful in the future (though not as field tests) since most clinical laboratories have started to standardize procedures for PCR.

In two cases of genital schistosomiasis, eggs were found only by histopathology and rectal biopsy, not by with stool examination. After treatment, antibody titres tended to decrease. IgG1 has been found to be a good isotype for antibody testing.

Detection of schistosome DNA using PCR may offer another diagnostic approach. The DNA of *S. mansoni* has been detected in human serum and faeces by PCR (9). This is a good test for use

with faeces, and is under development using other methods for extraction; PCR-ELISA is also being developed to make it simpler to run.<sup>2,3</sup> Specific amplification of DNA for the identification of *S. haematobium* is also being applied to human urine samples (10).

In areas of low schistosomiasis endemicity, where parasitological diagnosis may be insensitive, better tests and diagnostic approaches, including characterization of sensitive and specific antigens (recombinants and peptides, need to be validated and standardized, with uniformity of assays among studies and control programmes,.

## **Presentation and treatment of schistosomiasis in low-transmission areas**

In Brazil, clinical and epidemiological studies have found hepatosplenic schistosomiasis in areas of high prevalence. It was therefore postulated that a reduction in the overall prevalence of infection would eventually lead to a reduction in the morbidity due to hepatosplenic schistosomiasis.

When the Brazilian schistosomiasis control programme was planned in the 1970s, reduction of hepatosplenic schistosomiasis was made the main objective; other aspects of morbidity were considered to be less important. At the time, interruption of schistosomiasis transmission was not considered possible. The vertical programme implemented from 1976 to 1979 took an integrated approach that included education activities aimed at prevention of the disease, construction of sanitary facilities, provision of potable water in every municipality, and mass chemotherapy with oxamniquine (OXM). Mass chemotherapy meant that all individuals were treated in any community where the prevalence of schistosomiasis exceeded 50%. The programme reached 8 of the 13 states then considered to be endemic. A total of 11 254 847 individuals were treated for schistosomiasis from 1976 to 1997 and more than 12 million people have now received treatment since the beginning of the programme.

There is general agreement within the medical community in Brazil that the morbidity of schistosomiasis has declined significantly since the launch of the mass chemotherapy programme in the 1970s. This conclusion is based on:

- a 47% reduction in mortality due to schistosomiasis between 1977 and 1994;
- a 50% reduction in the number of patients with schistosomiasis admitted to hospital in Brazil between 1984 and 1997;
- a consistent decline in the number of patients operated on for portal hypertension as well as a reduction in the percentage of individuals with hepatosplenic schistosomiasis described by pathologists in autopsy series.

The mechanism by which treatment diminishes or prevents hepatosplenic schistosomiasis is unknown.

Morbidity was successfully controlled and, with the reduction in overt morbidities such as hepatosplenic schistosomiasis, other hidden aspects of morbidity, such as acute schistosomiasis,

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<sup>2</sup> Gomes LI et al. *PCR-ELISA assay for diagnosis and estimation of parasite burden of schistosomiasis mansoni*. Poster presented at: 11th International Symposium on Schistosomiasis, 20–22 August 2008, Salvador, Bahia, Brazil (hosted by the Centro de Pesquisa Gonçalo Moniz, FIOCRUZ).

<sup>3</sup> Marques LHS et al. *Further development of the polymerase chain reaction for the detection of Schistosoma mansoni DNA in human stool samples*. Poster presented at: 11th International Symposium on Schistosomiasis, 20–22 August 2008, Salvador, Bahia, Brazil (hosted by the Centro de Pesquisa Gonçalo Moniz, FIOCRUZ).

pulmonary hypertension, glomerulonephritis, neuroschistosomiasis, and ectopic schistosomiasis, began to receive proper attention. These aspects of the disease had been neglected. Even with very low transmission, there is still severe morbidity from these sequelae of infection.

These pathological presentations require new diagnostic and treatment algorithms. Diagnosis of low-intensity infections has been discussed previously, but it should be added that new imaging techniques are useful for detecting these forms of disease.

The manifestations of the complications of the disease, particularly at its chronic stage, and their treatment are outlined below.

### **Chronic schistosomiasis**

*Hepatosplenic disease* is treated with PZQ or OXM.

In *hepatosplenic schistosomiasis*, the liver may vary from almost normal in some cases to severely fibrotic in others. Even with very light fibrosis, the patient may have severe portal hypertension; a marker for portal hypertension (oesophageal varices, for example) is therefore needed. Hepatosplenic schistosomiasis is treated with PZQ or OXM (with different scenarios for patients with portal hypertension and oesophageal varices). Occasionally surgical treatment may be required (oesophagogastric devascularization with splenectomy to destroy the venous collaterals that transport blood from the high-pressure portal system into the veins of the oesophageal submucosa). Other methods of treatment include endoscopic sclerotherapy, and the use of beta-blocking agents (to prevent bleeding). Fibrosis of the liver is easily seen using magnetic resonance imaging (MRI).

*Lung involvement* is common in chronic schistosomiasis. In Brazil, *pulmonary hypertension* is found in 10% of patients with hepatosplenic schistosomiasis. Diagnosis has improved with the computed tomography (CT) scan, but treatment of pulmonary hypertension is still a challenge. The standard approach includes anticoagulant therapy with warfarin, and promising results have also been obtained with sildenafil; drug treatment has to continue for life. In some cases, the only option is a lung transplant.

The importance of *neuroschistosomiasis* in endemic areas should be emphasized. Prompt diagnosis (which has improved with the use of MRI) and treatment are critical. The condition is treated with ivermectin, followed by PZQ + methylprednisolone, followed by prednisone.

There is no effective treatment for *glomerulonephritis*, which persists after cure and even after administration of steroids; it results in renal failure and necessitating kidney transplantation.

## Tools for monitoring and surveillance in low-transmission areas

### **Maintenance of a control programme and data reporting in an advanced programme: the example of Brazil**

Transmission of schistosomiasis persists in vast areas of Brazil. The disease affects some 6 million people, a significant number of whom are affected by its advanced forms, and about 25 million people live in areas where there is risk of transmission. However, elimination of schistosomiasis appears feasible in 5 of 14 states.

The severity of the schistosomiasis problem led the Ministry of Health in 1975 to set up a special programme for schistosomiasis control, which has been undergoing progressive decentralization since 1993. The programme has a permanent expert committee and regularly publishes handbooks reflecting the recommendations of a technical advisory committee. Priority areas for research in schistosomiasis are kept updated by researchers and supported by the Ministry of Health.

The objectives and strategies of the schistosomiasis control programme (SCP) are to reduce prevalence in hyperendemic areas; reduce morbidity and mortality; prevent and reduce the spread of schistosomiasis; and eliminate transmission in isolated areas with low-intensity transmission. Measures implemented by the SCP to control schistosomiasis transmission are:

- early diagnosis and treatment of *S. mansoni* carriers;
- search for and control of intermediate hosts;
- health education for the population exposed to risk;
- sanitation procedures to change household and environmental factors favourable to transmission.

In non-endemic areas, schistosomiasis cases are detected in the primary health care units, and are notified and reported through the national notifiable diseases information system (Sinan).

In endemic areas, schistosomiasis cases are detected by coproscopic survey performed by the SCP. Cases detected are registered in the SCP's operational information system, which issues reports about the diagnosis (including eggs/gram of faeces, treatment of cases). This information system also issues reports on intermediate host surveillance and reports at various levels according to degree of endemicity.

Trends seen in the SCP indicators are:

- Proportion of carriers detected in parasitologic surveys performed by the SCP fell by 34% (from 23.0% to 6.0%) between 1977 and 2005.
- Disease-specific hospital admission rates fell by 67% (from 2.5 to 0.4 per 100 000 inhabitants) between 1988 and 2005.
- Disease-specific mortality rate fell by 54% (from 0.7 to 0.2 per 100 000 inhabitants) between 1977 and 2005.
- The average age of death due to schistosomiasis increased by 13 years (from 42 to 55) between 1977 and 1998.

The principal causes of difficulty encountered in controlling schistosomiasis have included:

- Insufficient sensitivity of methods: it continues to be difficult to identify individuals with low-intensity infection.
- Inadequate efficacy of drugs: carriers are treated but not cured, and thus contribute to continued transmission.
- Wide dissemination of snail hosts and difficulties in controlling them with molluscicides.
- High costs associated with the provision of adequate sanitation and safe water supply.
- The long time needed for health education to take effect and for communities to join control programmes.
- Unsatisfactory involvement of municipal authorities in schistosomiasis control.
- Complexity of the transmission cycle, necessitating the involvement of sectors other than the health sector to achieve permanent control.
- Insufficient resources to cover all endemic areas with regular schistosomiasis control activities.

### **Monitoring of schistosomiasis transmission: some theoretical and practical considerations**

The true nexus of schistosomiasis transmission is where humans and intermediate host snails come together at the waterside. This is where human sewage pollutes the environment with parasite eggs that cause snail infections, and it is here that people come into contact with infectious schistosome cercariae.

Current schistosomiasis control policy is based, in part, on simplified mathematical models of parasite transmission which suggest that drug treatment alone, particularly if focused on school-age children, should be sufficient to eliminate parasite transmission. However, when programme results are examined closely in operational research, it is evident that even after mass treatment campaigns there remain a number of high-risk villages where treatment appears to have had little impact on parasite transmission (11). Parasite transmission in high-risk areas may not be significantly altered by current large-scale treatment programmes (although these are a first step towards reducing the global burden of the disease).

Transmission is maintained by the aggregation of heavy infection among a small number of inhabitants, their contact with water at certain sites, and by their travelling between water sites. Such individuals are often termed “superspreaders”, and their disproportionate influence must be considered in the design of control and elimination programmes.

Monitoring of transmission ideally requires accurate measures of who is infected, where and when water contamination and snail infection are happening, and where and when human infection is happening. The most sensitive monitoring tools are needed in areas of very low endemicity.

Using current diagnostics to detect interruption of transmission may be uncertain or slow. Standard parasitological testing, based on *Schistosoma* egg detection in faeces or urine, is particularly insensitive for detecting low-level or light infections and, as morbidity control reduces parasite burden, becomes a relatively poor gauge of infection elimination. There are significant limits to antigen testing techniques, and although antibody tests do offer a sensitive measure of any past exposure to infection by *Schistosoma* spp., they do not distinguish between present (active) and past (inactive) infection. Measuring very low rates of transmission, when

no positive results are detected, presents a constant statistical challenge with ever-larger sample sizes being needed as the disease becomes rarer.

Water contamination can be detected by observation of human water-use and defecation/urination activities, by miracidia counts in water, and by snail infection rates. Detection of snail infection by PCR (or related isothermal nucleic acid detection systems) may become the more useful water sampling and testing approach.

Measurement of snail-to-human transmission potential can be generally estimated from human water-contact activity, by measuring host snail abundance at water-contact sites and snail production of cercariae, or by direct measures of cercarial abundance in water.

Integration of snail reduction with population-based treatment can eliminate infection over time, but the process may take several decades.

Sensitive and specific methods now exist for monitoring both the human and snail aspects of the transmission process. Currently, molecular detection of snail infection combined with serological testing in children is probably the most useful approach in the final phases of schistosomiasis elimination.

### **Monitoring of schistosomiasis transmission in the intermediate host: towards implementation of molecular monitoring**

Available DNA amplification techniques can detect schistosome infection in snails and are suitable for use in large-scale monitoring of residual post-control schistosomiasis transmission and for certifying elimination.

The PCR technique is tried and tested for detecting *S. haematobium*- and *S. mansoni*-infected snails (and is also applied to the vectors of lymphatic filariasis and onchocerciasis), and assays for detecting both species are available. The PCR positivity rate in snails has been shown to correspond to infection prevalence in humans living in nearby communities. The PCR reaction mixture is now available as a freeze-dried preparation for extended storage at room temperature.

The LAMP assay, a new and very sensitive DNA amplification method that is more user-friendly than PCR, is being developed for schistosomiasis. Although field laboratories will need to be upgraded to incorporate LAMP capacity, the technique is suitable for use in the field because the equipment required is simpler than that for PCR. It is hoped that LAMP reagents will also soon be available freeze-dried and with a long shelf-life.

The LAMP assays now under development for monitoring infected snails are based on amplification of the same repeated sequences as those targeted for amplification by PCR. For detecting *S. haematobium* these are the DraI (12, 13) repeated sequence, which is group-specific, and the new sequence Sh110/SmSL (15), which is species-specific. So far, amplification of the Sm1□7 (15) repeated sequence of *S. mansoni* is possible by PCR, with the LAMP version to follow.

The first step in the implementation of molecular monitoring is to select sites for snail collection. Criteria for site selection will probably include intensity of water-contact activity. Selected sites should be well marked by global positioning system (GPS) and mapped.

Logically, snails should be collected during the known transmission season. If sufficient numbers are collected, one or two collections per season are practical. Snail collection should be standardized by using standard nets and a standard collection time or number of net dips. Snail numbers required to certify elimination should be determined □ in practice they will depend on snail prevalence and the catch per collection.

Once collected and identified, the snails need to be preserved, labelled, and shipped to the molecular monitoring laboratory. They can be preserved (by a simple procedure) for two years in a condition suitable for DNA extraction and subsequent PCR.

To identify infected snails, PCR can be applied for amplification of the DraI repeat for group-specific identification of *S. haematobium* and the Sh110/SmSL repeat for species-specific identification of *S. haematobium*. In contrast to the sensitive DraI PCR, the latter test still requires validation by testing sufficient numbers of infected field snails. For identification of snails infected with *S. mansoni*, PCR amplification of the Sm1□7 repeat, which is very sensitive, can be used. Amplification of Sm1□7 is also used in Brazil for coprodiagnosis.

Pool screening of snails should be applied, as it is to filarial vectors in filariasis elimination projects. For certifying elimination it is necessary first to determine the pool test sensitivity and then to decide how many negative pools need to be tested.

The relationship between snail PCR positivity rates and human infection prevalence in a low-endemic pilot area should be determined; the effects of the control intervention on the rate of infection in snails and people should be determined subsequently.

To examine operational requirements for large-scale monitoring, a pilot laboratory in an endemic area should be adapted for molecular monitoring, and the required supplies and personnel must be ensured. This should be associated with well-structured technology transfer, including preparation of protocols and training, and examination of operation costs. PCR laboratories that undertake monitoring of residual post-control filariasis transmission can probably also be used for monitoring of infected snails.

## **Monitoring of schistosomiasis transmission in the human host: identification and mapping**

Some general points to consider in monitoring transmission in the human host in low-transmission areas are outlined below. Where prevalence is low, there is lower intensity of infection and lower morbidity, and hence surveillance must be more active than passive.

The various types of transmission situations include known sites of active transmission (e.g., Brazil, China, Egypt), and historical transmission sites, where there was transmission in the past but there is no active surveillance (e.g. some Caribbean Islands).

The distribution of schistosomiasis is very focal; there are two main approaches to finding out where the infected people are. One is to use data already available in the public domain, such as satellite images and socioeconomic and geographical data, which can be used to make predictions about possible transmission sites (“synthetic” mapping). This type of mapping of transmission is relatively low-cost because existing data are used for modelling. The other approach is biological mapping, using tests to detect schistosomiasis in faeces, blood, or urine. Biological mapping of transmission is likely to target school-age children, who play an important role in transmission and are accessible and compliant to control interventions.

Of the different biological tests, the Kato-Katz method – which has long been used for intestinal schistosomiasis and also detects other soil-transmitted helminth infections – loses sensitivity in areas of low intensity. In these areas, sensitivity can be increased by collecting a greater number of stools or increasing the number of slides/stool. A commercial kit – Helm Teste (Bio-Manguinhos) – is available in Brazil. In Australia, some institutional review boards do not approve protocols that use the Kato-Katz because of worker exposure to fresh stools. Other stool-based diagnostic tests include the classic concentration methods, stool PCR or antigen detection, the magnetic bead assay, and two new techniques, one based on inclusion of the miracidia and the other based on a gradient of solutions.

Urine-based tests for *S. haematobium* include the urine filtration test for haematuria and PCR.

Of the blood-based tests, detection of antibody does not provide evidence of cure, nor is it good at assessing intensity of infection. There may also be specificity issues and variations between and within laboratories in the antigen preparations. However, antibody-detection methods are more sensitive than antigen-detection tests.

Antigen-detection assays are good for differentiating active infection from cured infection and from reinfection, and for assessing intensity of infection. Traditionally, antigen detection has been performed on sera. However, tests for detection of circulating antigen in the urine have recently become commercially available – although they do raise some specificity concerns as individuals with urinary tract infections may give false-positive results. Moreover, the tests are relatively expensive compared with the parasitological techniques. These tests need to be evaluated in relation to other assays.

In a study designed to assess *S. mansoni* infections in children aged 1–15 years ( $n = 484$ ), the CCA urine test detected infection in at least as many children as the Kato-Katz test but not quite as many as the ELISA test for antibodies to adult worm antigens. The results using the urine assay were obtained much more quickly than the results of stool or antibody testing (Secor E, unpublished data).

Different types of test are suitable for different transmission situations. Antibody detection is fine for areas with unknown transmission but less useful in areas with ongoing treatment programmes. While the point-of-contact antigen-detection strip test is more expensive than parasitological methods, the costs of fuel for repeat visits, microscopes, training etc. involved in these techniques must be taken into consideration. The sensitivity of immunological assays is less affected by low-intensity infections than that of stool-based assays.

Despite the availability of these tools, new and better tools are needed. The characteristics of an ideal test would include a set of recombinant diagnostic antigens for use in sensitive and specific antibody-detection techniques, a point-of-contact test format, and antibody reactivities that disappear following treatment and can utilize saliva as the test sample. Appropriate sampling schemes for low-transmission areas need to be devised. In addition, modelling of the lower limit of transmission pressure (prevalence  $\times$  intensity) necessary to maintain the life cycle would be useful.

## Recommendations for moving towards the interruption of schistosomiasis transmission in low-transmission areas

The meeting recommended that efforts be made to move towards interruption of schistosomiasis transmission and the certification of transmission elimination, while maintaining management of patients, in low-transmission areas with less than 5–10% prevalence as determined by egg positivity.

An “area” is defined as the administrative level responsible for the health situation in that location or situation (e.g. municipality, district, local government area).

“Transmission elimination” is defined as zero incidence in children (no new locally transmitted cases) as determined by serology and no evidence of infection in sentinel or collected snails for five years; it must be based on active surveillance for case-finding.

Achieving interruption of transmission is likely to require increased local environmental interventions to break the cycle of transmission. The overall period of surveillance and intervention may be more than 20 years.

The tasks to begin surveillance are outlined below:

- Make an inventory of available and needed assets for augmented schistosomiasis control.
- Map the human population, water sites, snail population, and presence of infection.

### Monitoring transmission in the human host

1. Carry out annual surveillance of a statistically valid sample of schoolchildren in all primary schools in target areas. Use parasitological tests initially (three samples each) until no new cases are detected; then test serologically until no new conversions are seen for five years. In addition, no autochthonous cases should be detected in health centres, and no infected snails should be found in intensive sampling.
2. When any child positive for schistosomiasis is detected, treat the child, survey the child’s village of residence, and treat active cases.
3. In villages/communities with a past history of transmission, carry out additional community-based surveys three times during the programme.
4. For surveillance in low-risk villages, screen 10% of patients in the local health centre; notification of schistosomiasis cases is mandatory.
5. Support the active surveillance phase by comprehensive interventions involving:
  - health education;
  - mollusciciding/habitat modification to reduce water contamination and contact with infested water;
  - sanitation, provision of safe water, and safe irrigation practices.

This will require intersectoral cooperation by ministries of health, education, land, water, agriculture, livestock, and veterinary services, and an adaptive management approach based on local decision-making about what interventions to implement.

## **Monitoring transmission in the snail host**

6. Maintain classical methods for identification of snail infections. In addition, introduce molecular tools to identify foci of transmission.
7. Use sentinel snails, where available, to help validate interruption of transmission; protocols should be developed, through operational research, for use of sentinel snails to monitor the infectivity level of the community.
8. Validate the hypothesis, through operational research, that reduction in infection prevalence in humans is reflected in changes in snail infection prevalence.

## **Certifying transmission elimination**

9. Confirm elimination of transmission by external audit of the surveillance data; if findings are validated, the area will be certified.
10. Following certification, vigilance for new transmission/reintroduction should continue for 10 years, starting with active surveillance of humans and snails and progressing to passive surveillance, with mandatory notification of cases to public health authorities.

## **Operational research issues**

11. Validate the urine circulating antigen test in low-transmission areas.
12. Validate PCR-based egg-detection assays in low-transmission areas.
13. Develop a protocol to monitor the incidence of infection.
14. Develop a serological test that effectively detects incidence and does not cross-react with other infectious agents. This test should be highly sensitive and specific and in a rapid test format that can be produced in large quantities.
15. Develop a protocol to evaluate the effectiveness of treatment.
16. Develop and validate models to predict the threshold necessary to interrupt transmission and develop a sampling scheme able to detect this threshold prevalence.
17. Find and treat cases in both active surveillance and health care settings.
18. Validate the new diagnostic techniques for detection of schistosomiasis in faecal specimens.

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## List of participants

### Temporary advisers

Dr Ibrahim ABBASI

Department of Biology, Faculty of Science and Technology, Al-Quds University,  
P.O. Box 20002, Jerusalem, Israel  
Tel: +972 2 279 9753; mobile: +972 542 019 505; e-mail: iabbasi@science.alquds.edu

Professor Mutamad AMIN

Research and Grants Unit, Ahfad University for Women, P.O. Box 167, Arda, Omdurman,  
Khartoum, Sudan  
Mobile: +299 1212 8870; fax: +249 187 579111; e-mail: mutamadamin@hotmail.com

Professor Ronald BLANTON

Center for Global Health & Diseases, Case Western Reserve University, 2103 Cornell Road,  
Cleveland, OH 44106-7286, USA  
Tel: +1 216 368 4814; fax: +1 216 368 4825; e-mail: reb6@case.edu

Professor Rodrigo CORREA-OLIVEIRA

Laboratory of Cellular & Molecular Immunology, Centro de Pesquisas René Rachou □ FIOCRUZ,  
Av. Augusto de Lima 1715, 30190-002 Belo Horizonte, Minas Gerais, Brazil  
Tel: +55 31 3349 7777; fax: +55 31 3295 3115; e-mail: correa@cpqrr.fiocruz.br

Dr Margareth Maria GONÇALVES, Department of Immunology, Institute of Microbiology,  
Federal University of Rio de Janeiro, Av. Trompovsky s/n □ Cidade Universitaria,  
21941-590 Rio de Janeiro, Brazil

Tel: +55 21 2562 6747; fax: +55 21 2560 8344; e-mail: margmaria@micro.ufrj.br

Dr Jiagang GUO, National Institute of Parasitic Disease, China Center for Disease Control,  
207 Rui Jin Er Road, Shanghai 200025, China

Tel: +86 21 6466 2182; fax: +86 21 5465 0863; e-mail: guojg@sh163.net

Professor Joseph HAMBURGER,

Department of Parasitology, Kuvim Center for the Study of Infectious & Tropical Diseases,  
Hebrew University of Jerusalem, P.O. Box 12272, 91120 Jerusalem, Israel  
Tel: +972 2 675 8082; fax: +972 2 675 7425; e-mail: hambu@cc.huji.ac.il

Dr Naftale KATZ

Laboratory of Schistosomiasis, Centro de Pesquisas René Rachou □ FIOCRUZ,  
Av. Augusto de Lima 1715, 30190-002 Belo Horizonte, Minas Gerais, Brazil.  
Tel: +55 31 3349 7813; fax: +55 31 3295 3115; e-mail: nkatz@cpqrr.fiocruz.br

Dr Charles KING

Center for Global Health & Diseases, Case Western Reserve University, 10900 Euclid Avenue,  
Cleveland, OH 44106-7286, USA  
Tel: +1 216 398 3667; fax: +1 216 368 4825; e-mail: chk@cwru.edu

Mr Mohamed LAAZIRI

Formerly Director of Planning & Financial Resources, Ministry of Health, Secteur 21, Bloc R13,  
Hay Riad, Rabat, Morocco  
Tel: +212 377 10562; mobile: +212 616 54177; e-mail: mlaaziri@yahoo.fr

Dr José Roberto LAMBERTUCCI

Department of Internal Medicine, Faculdade de Medicina da Universidade Federal de Minas  
Gerais, Av. Alfredo Balena 190, 30130-100 Belo Horizonte, Minas Gerais, Brazil  
Tel: +55 31 3337 7781; fax: +55 31 3409 9820; e-mail: lamber@uai.com.br

Dr Nobuo OHTA

Division of Environmental Parasitology, Tokyo Medical and Dental University,  
1-5-45 Yushima, Bunkyoku, Tokyo 113-8519, Japan  
Tel: +81 3 5803 5191; fax: +81 3 5803 5191; e-mail: matata.vip@tmd.ac.jp

Dr Jose Mauro PERALTA

Department of Immunology, Institute of Microbiology, Federal University of Rio de Janeiro,  
Av. Trompovsky s/n □ Cidade Universitaria, 21941-590 Rio de Janeiro, Brazil  
Tel: +55 21 2562 6747; Fax: +55 21 2560 8344; E-mail: peralta@micro.ufrj.br

Dr Otávio PIERI

Laboratory of Eco-epidemiology & Control of Schistosomiasis & Soil-transmitted  
Helminthiasis, Oswaldo Cruz Foundation □ FIOCRUZ, Av. Brasil, 4365,  
21040-900 Rio de Janeiro, Brazil  
Tel: +55 21 2560 6474; email: opieri@ioc.fiocruz.br

Dr Ana RABELO

Laboratory of Clinical Research, Centro de Pesquisas René Rachou, Fundação Oswaldo Cruz □  
FIOCRUZ, Av. Augusto de Lima 1715, 30190-002 Belo Horizonte, Minas Gerais, Brazil  
Tel: +55 31 334 97782; fax: +55 31 329 53115; e-mail: ana@cpqrr.fiocruz.br

Dr Mitermayer Galvao REIS

Laboratório de Patologia e Biologia Molecular, Centro Pesquisa Gonçalo Moniz, Fundação  
Oswaldo Cruz, Rua Waldemar Falcão, 121, Candeal, 40296-710 Salvador, Bahia, Brazil  
Tel: +55 71 3176 2202; fax: +55 71 3176 2289; e-mail: miter@bahia.fiocruz.br

Dr Luis REY

Universidade Federal do Rio de Janeiro, Caixa Postal 70024, R. Prudente de Moraes 307/801,  
2242-041 Rio de Janeiro, Brazil  
Tel: +55 21 522 7620; e-mail: luisreybrasil@gmail.com

Dr David ROLLINSON

Wolfson Wellcome Biomedical Laboratories, Department of Zoology, Natural History Museum,  
Cromwell Road, London SW7 5BD, England  
Tel: +44 20 7942 5181; fax: +44 20 7942 5518; e-mail: D.Rollinson@nhm.ac.uk

Dr Ronaldo SANTOS DO AMARAL

Epidemiological Surveillance Department (DEVEP), Secretariat of Health Surveillance (SVS),  
Ministry of Health, Setor Comercial Sul, quadra 4, bloco A, Edifício Principal, 2º andar,  
CEP 70-304-000 Brasilia, Brazil  
Tel: +55 61 321 38132; fax: +55 61 321 38129; e-mail: ronaldo.amaral@saude.gov.br

Dr William Evan SECOR

Division of Parasitic Diseases, Centers for Disease Control & Prevention, 4770 Buford Highway  
NE, Mailstop F-36, Atlanta, GA 30341-3724, USA  
Tel: +1 770 488 4115; fax: +1 770 488 4253; e-mail: was4@cdc.gov

Dr Mamadou Souncale TRAORÉ

Département d'Enseignement et de Recherche (DER) en Santé Publique, Faculté de Médecine  
de Pharmacie et d'Odonto-Stomatologie (FMPOS), B.P. 1805, Hôpital du Pt G, Bamako, Mali  
Tel: +223 222 52 77; fax: +223 222 96 58; e-mail: traorem@afribonemali.net

Dr Mohamed Mostafa YOUSSEF

Department of Endemic Disease Control, Ministry of Health & Population, P.O. Box 1048689,  
3 Magless El-Shaab Street, Cairo 11516, Egypt  
Tel: +2 227 947 199; fax: +2 227 984 187; e-mail: mohamedmostafayh@netscape.net

## **Consultant**

Dr Nina MATTOCK

6 Chemin du Jura, 1233 Bernex, Switzerland  
Tel: +41 22 757 0431; e-mail: ninamattock@freesurf.ch

## **WHO staff (Regional Offices)**

Dr Zaida YADON

Regional Adviser, Communicable Diseases Research-Brazil-Brasilia, Pan American Health  
Organization, Setor de Embaixadas Norte Lote 1, 70800-400 Brasilia, DF, Brazil  
Tel: +55 61 3251 9500; Fax: +55 61 32519591; e-mail: yadonzai@paho.org

## **WHO staff (Headquarters)**

Dr Lester CHITSULO

Scientist, Preventive Chemotherapy & Transmission Control, Department of Control of  
Neglected Tropical Diseases, World Health Organization, Geneva, Switzerland  
Tel: +41 22 791 3862; fax: +41 22 791 4777; e-mail: chitsulol@who.int

Dr Janis LAZDINS-HELDS

Coordinator, Drug Development & Evaluation for Helminths & Other Neglected Tropical  
Diseases, Special Programme for Research & Training in Tropical Diseases, World Health  
Organization, Geneva, Switzerland  
Tel: +41 22 791 3818; fax: +41 22 791 4774; e-mail: lazdinsj@who.int

## **Invited but unable to attend**

Dr Steven AULT

Regional Adviser, Communicable Diseases, Pan American Health Organization, 525 23<sup>rd</sup> Street  
NW, Washington, DC 20037, USA  
Tel: +1 202 974 3896; fax: +1 202 974 3663; e-mail: aultstev@paho.org

Dr Riadh BEN-ISMAIL

Regional Adviser, Tropical Diseases & Zoonoses, WHO Eastern Mediterranean Regional Office,  
Abdul Razzak Al Sanhoury Street, P.O. Box 7608, Nasr City, Cairo, Egypt  
Tel: + 20 2 276 5280; fax: +20 2 670 2494; e-mail: ismailr@emro.who.int

Dr Omar DOS SANTOS CARVALHO

Centro de Pesquisas René Rachou, Fundação Oswaldo Cruz □ FIOCRUZ, Av. Augusto de Lima  
1715, 30190-002 Belo Horizonte, Minas Gerais, Brazil  
E-mail: omar@cpqrr.fiocruz.br

Dr John Patrick EHRENBERG

WHO Regional Adviser, Malaria, Vector-borne and other Parasitic Diseases, P.O. Box 2932,  
Manila 1099, Philippines  
Tel: +63 2 528 9730; fax: +63 2 521 1036; e-mail: ehrenbej@wpro.who.int

Dr Dirk ENGELS

Coordinator, Preventive Chemotherapy & Transmission Control, Department of Control of  
Neglected Tropical Diseases, World Health Organization, Geneva, Switzerland  
Tel: +41 22 791 3824; fax: +41 22 791 4777; e-mail: engelsd@who.int

Dr Alan FENWICK

Department of Infectious Disease Epidemiology, Faculty of Medicine, Imperial College London,  
St Mary's Campus, Norfolk Place, London W21PG, England  
Tel: +44 20 7594 3287; fax: +44 20 7262 8140; e-mail: a.fenwick@imperial.ac.uk

Dr Wang LIYING

Division of Schistosomiasis Prevention & Management, Department of Diseases Control,  
Ministry of Health, 1 Xizhimenwai Nanlu, Xicheng District, 100044 Beijing, China  
Tel: +86 10 6879 2372; fax: +86 10 6879 2342; e-mail: wangly@moh.gov.cn

Dr Likezo MUBILA

Scientist, Division of Disease Prevention & Control Unit for Other Tropical Diseases,  
Parirenyatwa Hospital, P.O. Box BE 773, Harare, Zimbabwe.  
Tel: + 263 4 706951; Fax: + 263 4 746000; e-mail: MubilaL@zw.afro.who.int

Dr Jean-Pierre POINTIER

Laboratoire Ecosystèmes Aquatiques Tropicaux et Méditerranéens, UMR 5244 CNRS-EPHE-  
UPVD, Biologie et Ecologie Tropicale et Méditerranéenne, 52 avenue Paul Alduy, University of  
Perpignan, 66860 Perpignan cedex, France  
Tel: +33 4 68 66 21 92; fax: +33 4 68 50 36 86; e-mail: pointier@univ-perp.fr

Dr Patricia WILKINS

Bacterial Zoonoses Branch, Division of Parasitic Diseases, Centers for Disease Control &  
Prevention, 1600 Clifton Road, Mailstop D-11, Atlanta, GA 30333, USA  
E-mail: pma1@cdc.gov

Professor Xiao-Nong ZHOU

National Institute of Parasitic Disease, Chinese Center for Disease Control, 207 Rui Jin Er Road,  
Shanghai 200025, China  
Tel: +86 21 647 38058; fax: +86 21 643 32670; e-mail: ipdzhouxn@sh163.net

