Schistosomiasis

An estimated 170 million people in sub-Saharan Africa, and a further 30 million in North Africa, Asia and South America, suffer from schistosomiasis, which is generally associated with rural poverty. The global burden of death and chronic disability is high – perhaps 20 million with severe disease and an estimated 200 000 deaths in 2003 – and may well be underestimated, since schistosomiasis-related conditions such as anaemia and low growth rate may not be recognized as resulting from the disease. Most infections are caused by Schistosoma mansoni, S. haematobium or S. japonicum, with two other species (S. intercalatum and S. mekongi) contributing less to the case load.

Humans are infected when they enter or come in contact with schistosome-infested water. Schistosomiasis is primarily a disease due to extreme poverty – people get infected because they do not have access to safe water supplies and proper sanitation. The disease is maintained under these conditions because infected people release schistosome eggs in their excreta. After reaching water, the eggs hatch into larvae that infect aquatic snails, where they develop further until they are released as free-swimming immature parasites (cercariae) that can penetrate the skin of human hosts and develop into adult worms. People acquire the infection during the course of routine domestic, agricultural or occupational duties. The adult worms lodge in blood vessels of the intestinal or urinary (for S. haematobium) systems. After mating, female worms produce eggs that are deposited in the liver, bladder or other tissues, depending on the infecting species, and are released in excreta to complete the cycle. The manifestations of disease are due to chronic inflammatory reactions induced by the eggs.

Control of the disease currently relies on chemotherapy, either of high-risk groups (e.g. schoolchildren, irrigation workers) at the community level, or of individuals with diagnosed infection. When effective diagnosis and chemotherapy are allied with health education, provision of adequate sanitation and potable water, and snail control, transmission of the disease can be essentially eliminated (as in, for example, Japan, parts of China and Brazil, and the Caribbean islands). In sub-Saharan Africa, in contrast, it is estimated that schistosomiasis is second only to malaria as a cause of morbidity among tropical diseases.

Rapid diagnosis in the field, especially of intestinal schistosomiasis, remains difficult. Current treatment is based mainly on a single drug, praziquantel, which was introduced over 25 years ago. Praziquantel is safe, well tolerated and effective as a single-dose treatment. However, treatment failures have been reported, and it is likely that increasing resistance of parasites to the drug accounts for some of these cases. Oxamniquine can be used as an alternative anti-schistosomal drug, but it is not effective against S. haematobium. Repeated infection induces some degree of immunity in humans, so an effective vaccine could offer a promising alternative to chemotherapy or be used in conjunction with it, but so far no such vaccine is available.

Towards improved treatment

Diagnosis

Intestinal schistosomiasis can be difficult to diagnose, especially in areas of low disease transmission. TDR and its par-
People become infected when they come into contact with schistosome-infested water, as here, where men emptying a fish trap expose themselves to infection. Credit: WHO/TDR/Crump

Researchers have drawn up protocols for evaluating rapid diagnostic tests for detection of *S. mansoni* and/or *S. haematobium*. The evaluation will be undertaken at four different sites during 2005. Urinary tract infection due to *S. haematobium* is more easily diagnosed, as there is a good correlation between infection and the presence of blood in the urine. This correlation has been validated at the community and district level, and if it can be scaled up, could provide a basis for future extension of community-directed treatment to a national level.

**Medication**

In most countries, the standard dose of praziquantel is 40 mg/kg per treatment. Because treatment failures have been observed, and in some cases associated with a need for higher drug doses to kill the parasite isolated from the patient, the safety and efficacy of a higher dose of praziquantel are being studied in TDR-supported clinical trials at four sites in Asia, Africa and South America. Drug combinations may also help to improve treatment success rates and prevent the development of resistance. The combination of artemether and praziquantel is being tested in clinical trials in China and Egypt. However, as recommended by a TDR-convened expert committee, use of this combination is not planned in malaria-endemic areas because of the risk that it might induce resistance to artemisinins in malaria parasites. A protocol for testing a combination of oxamniquine and praziquantel has recently been prepared, and if approved, will be the basis for Phase I clinical trials to start in 2005. A separate proposal to test triclabendazole, an anthelmintic drug that is active against *Fasciola* parasites, in patients co-infected with *Fasciola* and schistosomes is currently under review.

Because praziquantel has been such an effective drug, there has been very little research directed at finding new treatments for the disease, giving rise to the risk that resistance to praziquantel becomes widespread while treatment options remain very limited. In 2003, TDR allocated funds for screening compounds for anti-schistosomal activity to two laboratories. After validation of the screening methods, over 600 compounds were evaluated for their activity against adult worms in vitro; the activities of a few selected compounds, including new synthetic artemisinin analogues, are being further evaluated in infected mice.
Towards a vaccine

Lack of funding severely curtailed TDR’s direct involvement in schistosome vaccine development during the past biennium. In 2003, TDR organized a meeting on the future of schistosome vaccine development. The participants recommended that development of the two most advanced vaccine candidates – Sm14 from S. mansoni, which has entered a Phase I clinical trial, and Sh28GST from S. haematobium, for which a Phase III trial is planned – should continue. TDR contributed to the clinical monitoring of the Sh28GST Phase II trial. At least six other candidates show some degree of efficacy in animal models of schistosomiasis and also merit further attention. An electronic network to facilitate communication between scientists working on schistosome vaccines has been set up and linked to the TDR website.

New knowledge

TDR continued to support the schistosome genome network website, and the genomes for S. mansoni and S. japonicum have been published. Many thousands of expressed sequence tags (ESTs) from S. mansoni and S. japonicum have been characterized. Among the gene products identified or better characterized with TDR support during the biennium are phosphoenolpyruvate carboxykinase, an immunogen of S. mansoni eggs; Sm-p40, an antigen involved in egg-induced pathology, in which new T-cell epitopes were identified; and several known or novel proteins whose roles in the architecture of the schistosome tegument were clarified. The possible role of human macrophage inflammatory protein 1a (MIP-1 α) in the pathogenesis of the disease was further investigated.

The genetic structure of natural S. mansoni populations, knowledge of which may bear on reasons for some treatment failures, is being investigated in an endemic area of Brazil using microsatellite markers. Several studies dealing with the influence of health sector reforms or gender on access to treatment, or social and environmental influences on disease prevalence, were funded in China. It appears that reforms encouraging user fees in the Chinese health sector have limited access to treatment for poorer people.

Capacity building

Many of the studies mentioned above, and especially those carried out in disease-endemic regions, have a research capacity strengthening component. TDR provided specific support for capacity building to the projects aimed at improving treatment by increasing the dose of praziquantel. After issuing a call for proposals to carry out this work, TDR provided support for developing the selected proposals, including protocols and preparations for scientific, technical and ethical review of the projects, training in good clinical practice and the conduct of clinical trials. The studies will be carried out in Brazil, Mauritania, the Philippines and Tanzania. Support for developing the proposal to evaluate triclabendazole as a potential anti-schistosomal agent was also provided. TDR maintains its close links with the Regional Network for Research, Surveillance and Control of Asian Schistosomiasis, a multicountry partnership which has helped to spread the use of tools such as remote sensing and geographic information systems for schistosomiasis control. TDR, with the Schistosomiasis Control Initiative (SCI), the Schistosomiasis Research Programme (SRP), and the Danish Bilharziasis Laboratory (DBL), is supporting the establishment of another regional schistosomiasis research network in Africa.

37 www.nhm.ac.uk/hosted_sites/schisto/
www.genedb.org/genedb/smansoni/imdex.jsp


40 The International Journal of Health Planning and Management, 2004, 19(suppl. 1). (Several articles in this special supplement deal with health sector reforms in China.)