Schistosomiasis

Disease Burden

Schistosomiasis, also known as bilharziasis, is second only to malaria in public health importance. It is estimated that 200 million people worldwide are infected with the snail-transmitted, water-borne parasitic helminth, and that 20 000 deaths are associated with the severe consequences of infection, including bladder cancer or renal failure (Schistosoma haematobium) and liver fibrosis and portal hypertension (S. mansoni). In sub-Saharan Africa where schistosomiasis constitutes an important public health problem, a survey in 2000 of disease-specific mortality reported that 70 million individuals out of 682 million had experienced haematuria and 32 million dysuria associated with S. haematobium infection. It was estimated that 18 million suffered bladder wall pathology and 10 million hydronephrosis. Infection with S. mansoni was estimated to cause diarrhoea in 0.78 million individuals, blood in stool in 4.4 million and hepatomegaly in 8.5 million. Using the very limited data available, mortality rates due to non-functioning kidney (from S. haematobium) and haematemesis (from S. mansoni) have been estimated at 150 000 and 130 000 per year, respectively. Although these are global estimates of the schistosomiasis disease burden, the public health impact of schistosomiasis in the field has been poorly evaluated and is still subject to controversy. Apart from a few situations where schistosomiasis is or was recognized as an obvious public health problem, as in Brazil, China, Egypt, the Philippines, northern Senegal and Uganda, the disease is often not a priority for health authorities. Moreover, the

lack of a simple clinical case definition does not enable rapid identification of the disease by health personnel.

High rates of schistosomiasis occur near bodies of fresh water. Environmental changes linked to water resource development, population movements and population growth have led to the spread of the disease to previously low or non-endemic areas, particularly in sub-Saharan Africa. The building of the Diama dam on the Senegal River for example introduced intestinal schistosomiasis into both Mauritania and Senegal. Refugee movements and population displacements in the Horn of Africa introduced intestinal schistosomiasis to Somalia and to Djibouti. In contrast, successful schistosomiasis control has been achieved in several countries in Asia, the Americas, North Africa and the Middle East. Schistosomiasis has been eradicated from Japan and some of the islands in the Lesser Antilles. Four national control programmes (Brazil, China, Egypt, and the Philippines) have demonstrated that concerted control efforts together with economic development can decrease morbidity to low levels. Chemotherapy was central to these successes. The current drug of choice, praziquantel, reverses pathology in as little as six months after treatment in S. haematobium infections. The cost of praziquantel has decreased significantly over the past 20 years. Nevertheless, large scale use of praziquantel can impose a heavy burden on health systems. In addition, concerns remain over the potential threat of the emergence of praziquantel-resistant parasites.

Parasitology

The three major species of schistosomes, S. mansoni, S. haematobium, and the S. japonicum complex (including S. japonicum and S. mekongi) are distinguished by their snail vectors, location within the host

vasculature, and egg morphology. S. haematobium is found in the Middle East and Africa, including the islands of Madagascar and Mauritius. Intestinal schistosomiasis due to S. mansoni, is now found in the Arabian peninsula, most African countries north of the equator (Egypt, Libya, Sudan, Somalia, Mali, Senegal, Mauritania), as well as in Brazil, some Caribbean islands, Suriname and Venezuela. S. japonicum is endemic in China where bovines are the main reservoir, as well as in Indonesia and the Philippines (with dogs and pigs as reservoir). S. mekongi is mostly found in Cambodia and Laos, along the Mekong River.

Asexual reproduction of the parasites occurs in fresh-water snails that release in the water large numbers of free-swimming larval schistosomes known as cercariae. The cercariae are attracted to the human skin through which they penetrate then lose their tail upon entry to become schistosomulae which migrate through the blood stream and the lung of the host until they reach the liver.

Schistosomules differentiate in the liver into male and female schistosomes that migrate through the portal vasculature to settle in the mesenteric or bladder venules where they lay eggs. The latter exit from the body in faeces or urine and hatch in fresh water, giving birth to miracidia that swim via the action of their cilia until they find a suitable snail host in which they will give rise to thousands of progeny.

Most of the morbidity associated with Schistosomiasis occurs when eggs remain trapped in the intestinal or bladder wall or in the liver, eliciting the formation of granulomas and fibrosis. In the liver, fibrosis leads to portal hypertension and splenomegaly. The most severe forms of the disease are due to S. japonicum.

Mechanisms of pathology in schistosomiasis

The host immune response against schistosome eggs is the basis of chronic pathology in schistosomiasis. Granulomatous lesions form around eggs that are lodged in host tissues (especially the liver), and this can lead to a generalized fibrosis.

Studies of *Schistosoma mansoni*-infected individuals in Kenya have demonstrated a significant correlation between hepatosplenomegaly (liver and spleen enlargement) and the production of the cytokine, tumour necrosis factor - alpha (TNF-alpha). This supports studies in mice, which have shown that **TNF-alpha is a key signal in granuloma formation**. This primes local immune responses, stimulating granuloma formation in response to interaction between an intercellular adhesion molecule (ICAM-1) and its cognate integrin receptor which is a leucocyte functional antigen (LFA-1). It has also been shown that a vascular cell adhesion molecule (VCAM-1) is able to act as back-up in the absence of ICAM-1.
TNF-alpha has also been implicated in the induction of egg laying by female worms, and the TNF-alpha receptor on the worm has been identified.

Immunization studies of mice with *Schistosoma mansoni* egg antigens plus the cytokine interleukin-12 (IL-12) have provided further insights into the mechanisms of pathology:

- **IL-12 is involved in regulating both granuloma formation and fibrosis**

- **TNF-alpha is involved in regulating granuloma formation** (but not fibrosis)

Interferon-gamma (IFN-gamma) is involved in regulating fibrosis (but not granuloma formation). Secretion of IFN-gamma is increased when synthesis of TNF-alpha is blocked.

These results suggest that distinct mechanisms may be involved in controlling the inflammatory response and fibrosis.

Other studies in mice have shown that **immunization with the *S. mansoni* egg antigen p40 reduces granuloma formation**. This is accompanied by a reduction in IFN-gamma secretion.

Vaccine

The administration of radiation-attenuated cercariae to laboratory animals provided protection against experimental S. mansoni infection by blocking the migration of the parasite out of the lung. IFN-γ and Th1 cellular immune responses appear to play a key role in this process.

Great attention has been paid to the use of antigens from schistosomules, with disappointing protection results so far. Somewhat better results have been obtained with antigens that are shared between schistosomules and schistosomes, such as the 63 kD parasite myosin, the 97 kD paramyosin, the 28 kD triose phosphate isomerase (TPI), a 23 kD integral membrane protein (Sm23), and the 26 and 28 kD glutathione-S-transferases (GSTs). In recent Phase I and II clinical trials, the 28 kD S. haematobium GST (Sh28GST) developed by Institut Pasteur de Lille (France), was safe and showed good immunogenicity in human volunteers in France, Niger and Senegal.

The Schistosomiasis Vaccine Development Programme (SVDP), based in Egypt and supported by USAID, has focused on two S. mansoni antigens:

paramyosin and a synthetic peptide construct containing multiple antigen epitopes (MAP) from the triose phosphate isomerase (Bachem Company, Los Angeles, USA). Another candidate vaccine, which is developed by FIOCRUZ (Rio de Janeiro, Brazil), is based on the use of Sm14, a 14 kD fatty acid-binding S. mansoni protein with cross-reactivity with Fasciola hepatica. In mice, Sm14 provided a 67% protection against challenge with S. mansoni cercariae and full protection against F. hepatica metacercariae.

None of the above candidate vaccines has, however, been able so far to provide more than a partial reduction in challenge-derived worm burdens relative to non-immunized controls. It is hoped that better success can be achieved using cocktails of recombinant antigens.

Another approach to vaccination against schistosomiasis has been to target the fecundity of the female schistosome in order to diminish egg excretion. Success with this approach has been reported in mice and large animal reservoir hosts, including pigs and water buffaloes, using S. japonicum 26 kD GST and paramyosin. The suggestion was made, and the hope entertained, that vaccination of the reservoir host might be sufficient to reduce S. japonicum transmission to humans.