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Chapter 8

Epidemiology of Imported Bilharzia: Prophylactic and Treatment Options for Children

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Abstract

In its resolution WHA54.19 (2001), the WHO urged Member States "…to ensure access to essential drugs against schistosomiasis…in all health services in endemic areas for the treatment of clinical cases and groups at high risk of morbidity such as women and children, with the goal of attaining a minimum target of regular administration of chemotherapy to at least 75% and up to 100% of all school-age children at risk of morbidity by 2010". However, the number of countries considered endemic for schistosomiasis increased from 77 in 2010 to 78 in 2011 and treatment was only guaranteed in 52 of these countries.

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According to WHO data, in 2012 over 111 million school-age children were in need of preventive chemotherapy.

It is estimated that urinary schistosomiasis (bilharzia) annually affects 200 million people, of whom 120 million remain asymptomatic and at least 200,000 die from related causes. In Spain and in many other European countries, immigrants from areas endemic for S. haematobium regularize their employment status by periodically visiting their countries of origin. This circumstance requires a thorough anamnesis to be conducted, inquiring in each case into the trips made in recent months. This information continues to be the most important element required for a presumptive diagnosis and the factor motivating the search for S. haematobium eggs in a urine sample to confirm the diagnosis.

In January 2008, Spain had 5.2 million registered foreign residents, 11.3% of the total population, as well as a large population that does not appear in any record, but is estimated at over 400,000 people. More than half of these people come from low-income countries and endemic areas for schistosomiasis. These numbers have declined in the last year, partly due to the economic crisis affecting the European Union.

The epidemiology of urinary schistosomiasis and the incidence of infection vary considerably among geographic areas. They are believed to be related to the population density of freshwater snails, especially the species Biomphalaria and Bulinus, the density of cercariae in contaminated water and the frequency of human contact with such water. The snail species involved in the transmission may have prolonged survival at mean temperatures above 18ºC, a circumstance that is considered particularly important in the transmission of the disease.

To date, few published studies on imported schistosomiasis have had an adequate sample size and, in any case, differ in their definition of the diagnosis, clinical presentation and source of infection. In most published series, diagnosis is performed by antibody titer, because the parasite load is usually too low to enable identification in urine. In fact, most chronically infected patients may remain asymptomatic. The epidemiological and clinical impact of schistosomiasis in immigrants from endemic regions differs considerably from that seen in Western visitors to endemic areas. While most infected immigrants remain asymptomatic, with a low parasite load, the exposed Western population more frequently develops Katayama syndrome with more evident clinical signs and symptoms.

This chapter reviews the epidemiology of schistosomiasis in Western countries, the mechanisms involved in its transmission and the prophylactic and treatment options for children affected by it.

Keywords: Imported schistosomiasis, epidemiology in non-endemic areas, diagnosis in children

Introduction

Schistosomiasis is a parasitic disease caused by a trematode helminth of the genus *Schistosoma*. Only six species affect humans: *S. haematobium, S. mansoni, S. japonicum, S. intercalatum, S. mekongi* and *S. malayensis*. It is also termed bilharziasis, after its discoverer, the German doctor Theodor Maximillian Bilharz. In 1851, during his work at the Egyptian Department of Hygiene, he discovered this new class of helminth in the vena cava blood of patients who had died of haematuria.

Bilharzia is a major public health problem that affects approximately 200 million people each year, of whom at least 80% live in Africa [16]. In many Western countries, immigrants from areas endemic for *S. haematobium* regularize their employment status by periodically visiting their home countries, where reinfection may occur. This circumstance requires a thorough anamnesis to be conducted, inquiring in each case into the trips made in recent months. This information continues to be the most important element required for a presumptive diagnosis and is the factor motivating the search for *S. hematobium* eggs in a urine sample to confirm the diagnosis or as part of a serological investigation in cases of long-term haematuria.

The Biological Cycle of the Genus Schistosoma

Schistosoma has a cylindrical body, ending in two oral suckers (See also Chapter 1). There are two main forms of schistosomiasis: intestinal and urogenital. Among the species that parasitise humans, only *S. haematobium* affects the urogenital apparatus, with the other species normally producing intestinal parasitisation (Figure 1). The adult forms are hematophagous, and, in the definitive host, are found in the venous plexuses, especially the mesenteric (*S. mansoni, S. japonicum, S. intercalatum, S. mekongi*) or perivesical ones (*S.haematobium*). The couple migrates here through the capillaries and venules, where the female ponds 100-1000 eggs a day. These eggs, in turn, migrate through the walls of the vessels in which they were deposited, reaching the tissues and then either the intestinal lumen or the urinary bladder lumen. Finally, they emerge in the faeces or the urine, respectively.

Transported in the faeces or urine, the embryo eggs contaminate waters in rivers, lakes and irrigated fields, where in a few hours they hatch and release the miracidia.

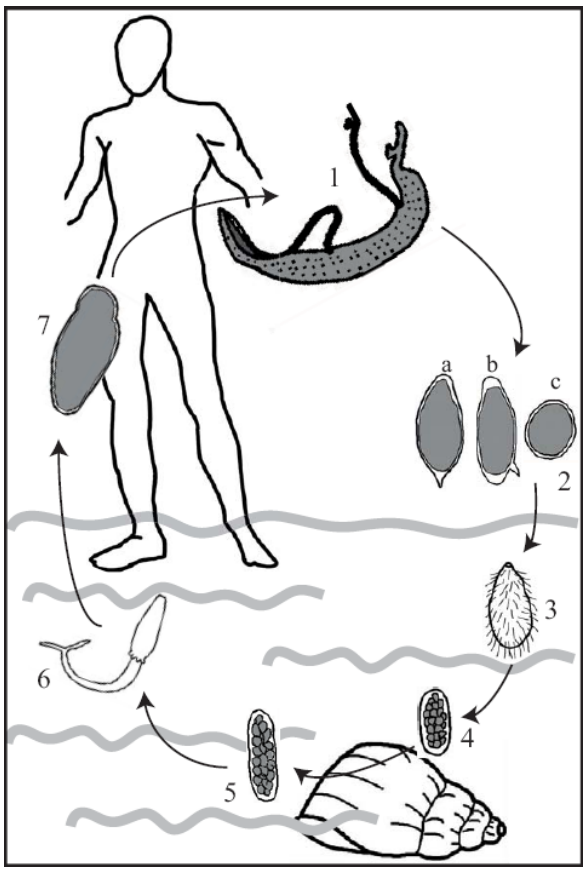

Figure 1. The life cycle of schistosomes, with a morphological description of the different life stages. Adult worms pair (1) living in the definitive human host blood (periportal veins for those species causing intestinal schistosomiasis; peri-bladder veins for those causing urogenital schistosomiasis). Each female lays 20-1000 eggs/day, depending on the species. The eggs (2) are recognizable by their morphology: (a) *S. haematobium* eggs present a terminal spine, (b) *S. mansoni* eggs have a lateral spine; (c) *S. japonicum* eggs are round. The eggs are excreted by either faeces (b,c) or urine (a). Once they reach a freshwater source, they hatch into a free-living ciliated stage called miracidium (3). This one swims towards the mollusc host and penetrates it. Inside the freshwater snails asexual reproduction takes place to increase the number of parasites. Two sequential life stages arise from the miracidium: the mother (4) and the daughter sporocyst (5). This last releases into the water thousands of caudated free living cercariae (6), which are the infective stage for the human host. Cercariae are able to penetrate intact human skin and to develop into a juvenile form: the schistosomulum (7), which migrates undisturbed from the derma to the lungs, where it sexually matures into the adult form (1). This last migrates to the final destination, where it can live for up to 30 years.

The latter penetrate and parasitise certain snails that inhabit the fresh water and constitute the intermediary host. Each species of *Schistosoma* parasitises a particular genus of snail, as follows:

- *S. haematobium*:. Bulinus spp, Physopis spp, Planorbis spp.
- *S. mansoni*: Biomphalaria.
- *S. japonicum*: Oncomelania.
- *S. mekongi*: Tricula aperta.
- *S. intercalatum*: Bulinus.
- *S. malayensis*: Tricula aperta.

Within the snail, the miracidia mature for approximately 6 weeks to become cercariae (with a bifurcated tail and penetration glands), which are then released back into the water. Humans can become infected by walking, bathing or washing in water contaminated by cercariae, which adhere to the skin and penetrate it. In this process, they lose their tails and are transformed into schistosomulae, which reach the bloodstream and are systemically distributed, reaching the lungs and finally the liver, where they mature into the adult form and attach themselves in their definitive location, the mesenteric or vesical venous plexuses, and thus the cycle is completed. The period between the cercariae penetrating the skin and the beginning of egg production from adult worms is 4-7 weeks. Adult worms can live in the venous plexuses for 20-30 years. Direct transmission between persons does not take place, as the participation of the snail in the biological cycle of this trematode is absolutely mandatory [20].

Epidemiological Questions

According to WHO data [22], with the independence of South Sudan in 2011, the number of schistosomiasis-endemic countries has increased from 77 in 2010 to 78 in 2011. Large-scale treatment is only ensured in 52 of these countries. The rate of transmission of schistosomiasis is considered low in 7 countries and needs to be verified in 19. The figures published by the WHO in its 2012 report [22] indicate that at least 243 million persons required preventive chemoprophylaxis in 2011. Large-scale schistosomiasis control measures continue to require further resources for treatment programmes,

water purification, the provision of health resources and health education and measures to control aquatic snails.

In some countries, the interruption of schistosomiasis transmission can only be achieved through improved hygienic-sanitary conditions and actions to control the aquatic snail population [5]. The WHO, in its WHA65.21 report, acknowledged the progress made in controlling the disease and highlighted the need to verify the results of ongoing programmes to interrupt the transmission of the disease. In 2011, 28 million people received treatment for schistosomiasis, of whom 58% were children aged 5-14 years. Unfortunately, data are only available for treatments performed in 46% of the schistosomiasis-endemic countries. Available data indicate that in 2011, the number of persons treated was 20% lower than in 2010, possibly not due to a lower incidence of the disease, but rather to the fact that 8 countries that reported data in 2010 did not do so in 2011 (Figure 2).

Children, who may play in infected water, and who often suffer a hygiene deficit, are particularly vulnerable. Also at risk are women who carry out domestic tasks, such as washing clothes in these waters. It has been estimated that in chronic cases of vaginal schistosomiasis, the risk of HIV infection is multiplied by three-fold [12].

The WHO strategies for controlling schistosomiasis are centred on reducing cases of the disease *via* periodic, focused treatment with praziquantel. This is a cheap and effective drug, costing only €0.08 per dose. Nevertheless, it may still be expensive for the health administrations of some developing countries. Outbreaks of schistosomiasis can be identified by haematuria screening of schoolchildren and, in cases of epidemic, treating the entire community at risk [4].

The epidemiology of urinary schistosomiasis and the incidence of infection vary widely among geographical areas, but they are considered to be related to the population density of freshwater snails, especially the species *Biomphalaria* and *Bulinus.*

Other relevant factors are the density of cercariae in the contaminated water and the frequency of human contact with such water. The snail species involved in the transmission may have prolonged survival at average temperatures above 18°C, and this circumstance is considered particularly important in the disease transmission. Current opinion is that transmission by both snail species occurs not only in rivers and lakes, but also by means of irrigation systems, which can play an important role in local endemic schistosomiasis.

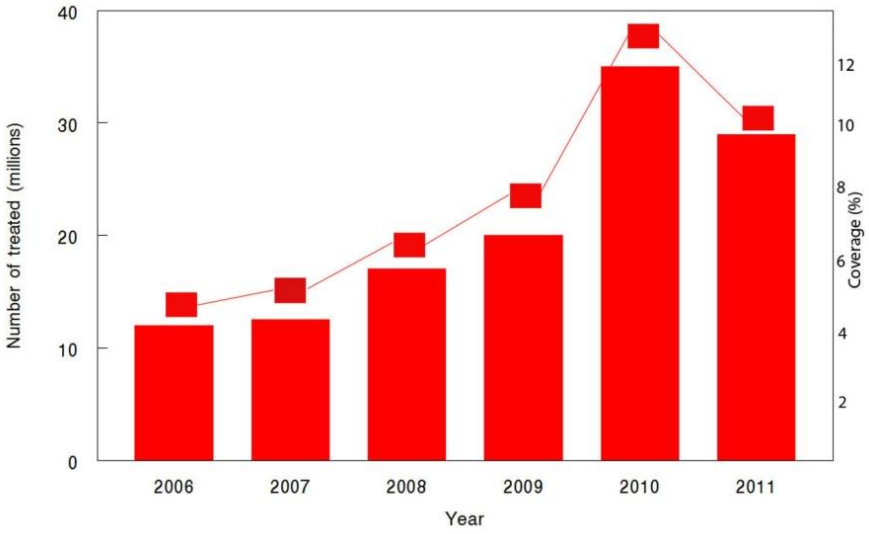

Figure 2. Number of people treated for schistosomiasis and reported coverage of treatment (%), data extracted from WHO Region, 2006–2011.

With respect to exposure to schistosomiasis, there are considerable differences between the local population and foreign workers or immigrants on a holiday visit to their countries of origin. Among the latter, exposure tends to be occasional, short-term and related to recreational water activities.

The GeoSentinel Surveillance Network carried out a transversal study of affected travellers who had visited endemic schistosomiasis areas between 1997 and 2008. The GeoSentinel is a worldwide communication and data collection network for the surveillance of travel related morbidity. Confirmed cases were communicated in 12 countries belonging to this worldwide surveillance network. In a total sample of 25,240 people, some 410 persons (16‰) were found to be suffering from schistosomiasis; 37% were European, 24% North American, 24% Asian and 15% from Oceania. Over 80% of those affected had acquired this disease in Africa, mainly in sub-Saharan Africa. There were some differences depending on demographic characteristics and the type of travel. Male travellers and travellers aged under 45 years were more likely to be diagnosed with schistosomiasis than with another illness. When the data were controlled for age and sex, those traveling for missionary or other volunteer work were twice as likely to be diagnosed with schistosomiasis than were tourists and other types of travellers. Business travellers were less likely to be diagnosed with schistosomiasis than were

tourists and other types of travellers. Individuals traveling as expatriates, regardless of the type of travel, were twice as likely to be diagnosed with schistosomiasis as those staying for shorter times and staying in hotels. Attending a pre-travel health care consultation was also associated with being diagnosed with schistosomiasis. 63% of the 401 travellers, who were infected with schistosomiasis, on their return attended a GeoSentinel clinic within six months of return, with a median time-to-presentation of six weeks (interquartile range IQR 2–12 weeks); the median duration of travel for this group was 13 weeks (IQR 4–33 weeks). 110 (27%) travellers attended a GeoSentinel clinic more than 6 months after their return. Time to presentation was 6-24 months for 73 travellers (18%), 3-4 years for 16 (4%), and five or more years for 18 (4%). 41% of the 319 travellers who were asymptomatic at presentation were diagnosed with schistosomiasis. The most commonly reported symptoms were gastrointestinal, fever, urogenital and fatigue. Returned travellers with schistosomiasis were more likely to present with fever than those who were ruled out for schistosomiasis. Those with *S. haematobium* and *S. mansoni* infections presented with more respiratory symptoms than did those ruled out for schistosomiasis. Moreover, returned travellers with schistosomiasis who were seen within six months of travel more often presented with fever and respiratory symptoms compared with those who presented later [13].

Imported travel-related infections were also studied in a retrospective and descriptive study of travellers returning from the tropics and attended at the Tropical Medicine Unit, Infectious Diseases Department of Hospital Ramon y Cajal in Madrid (Spain) during the period January 1989 to November 2006. A total of 2982 travellers were analysed; 1387 had travelled to Sub-Saharan Africa and 44 of these were diagnosed with schistosomiasis (3%). 98% of the patients with schistosomiasis had travelled to Sub-Saharan Africa and only 2% to other geographical areas [20].

Many centres in Australia routinely screen African refugees for schistosomiasis using serology, and in some cases with faeces and urine examination for schistosome eggs. A seroprevalence of 38% was reported for 653 African refugee adults and children arriving in Australia, predominantly from Liberia, Burundi, Tanzania and Sudan. A multivariate analysis of the Newcastle data showed that schistosomiasis serology was much more likely to be positive among those from East Africa (OR 14.5) and West Africa (OR 5.5) than those from the Sudan region (OR 1.0) [10].

In most published series, diagnosis is performed by antibody titer, because the parasite load is usually too low to enable identification in urine. In fact,

most chronically infected patients may remain asymptomatic. The epidemiological and clinical impact of schistosomiasis in immigrants from endemic regions differs considerably from that seen in Western visitors to endemic areas. While most infected immigrants remain asymptomatic, with a low parasite load, the exposed Western population more frequently develops Katayama syndrome with more evident clinical signs and symptoms.

Important Aspects for Diagnosis

According to all health care protocols for immigrant children, the presence of *S. haematobium* should be considered in cases of persistent haematuria. This is also applicable to children born in Western countries from immigrant families, who periodically visit their home countries. We have observed such a case, of a child with Spanish nationality, born from immigrant parents [19]. There are increasing references to urinary schistosomiasis diagnosed among immigrants living in Western countries [6, 11].

The disease is acquired by contact with fresh water contaminated with *S. haematobium* cercariae. In non-sensitized subjects, the penetration of cercariae through the skin may cause transient pruritic dermatitis. 3-4 weeks later, there is a febrile reaction with headache, joint pain, swollen liver and spleen, diarrhoea and eosinophilia, known as the Katayama syndrome. In 37% of patients with acute schistosomiasis, symptoms appear 3 weeks after exposure (3.1 ± 2.7 weeks). Fever is the most prevalent symptom, followed by respiratory symptoms and rash. Only 9.5% of cases present the full range of symptoms of acute schistosomiasis. 20% of patients have chronic schistosomiasis at the time of diagnosis, and the lag time from exposure to diagnosis ranges from 4 months to 3 years. Moreover, 47% of infected patients remain asymptomatic [8].

The immune response to early-stage schistosomiasis may be Th1-type, developing to Th2 after egg laying by mature worms [2]. The Th2 response is controlled by the IgE response, which stimulates the eosinophils to release cytokines against the schistosome. During infection, as well as the IgE response, IgG4 infection occurs, which potentially blocks the effect of other immunoglobulins. In the host, the most intense inflammatory response does not take place against the schistosome antigens, but rather against the eggs trapped in the tissues, which provoke the formation of mucosal granulomatous hyperplasias, together with nodules and polyps that tend to ulcerate and bleed

[7, see also chapter 2]. T cell-mediated immunity is crucial to the development of resistance to schistosome re-infection.

Initially, parasitisation may be asymptomatic, followed by haematuria which is more intense at the end of urination and may be accompanied by dysuria. The existence of haematuria at the end of urination is related to the presence of viable eggs deposited on the bladder wall, related to lengthy processes with the presence of granulomas in the bladder submucosa and distal ureter [18]. Advanced stages of the disease may give rise to hydronephrosis caused by ureteral obstruction and peri-vesical calcifications. In repeated and severe infections, the ureteral wall mucosa is also affected, and obstructive uropathy and hydronephrosis may evolve.

Eosinophilia is a nonspecific finding observed in 57% of cases. In patients with symptoms of acute schistosomiasis or Katayama syndrome, the prevalence of eosinophilia may be slightly higher, up to 61% in some series [3]. The correlation of eosinophilia with positive serological data can be relatively low (19%), while with negative serological data it is somewhat higher (43%). In patients with chronic schistosomiasis, eosinophilia is uncommon. Direct microscopic examination of urine reveals schistosome eggs in only 22% of patients with urinary schistosomiasis, and in Western countries this has a low correlation (13%) with positive serological data [3].

In our society, schistosomiasis screening for people at risk should be done as a serological test, conducted at least 6 weeks after potential exposure to contaminated water. In this period, the absence of antibodies against schistosomes virtually excludes the possibility of infection. When schistosome serology is positive, the identification of eggs in urine is indicated, although the low sensitivity of this test needs to be taken into account [21].

Treatment and Prophylaxis

For over 20 years, the most effective means of controlling the disease has been chemoprophylaxis with praziquantel. In endemic areas, the WHO recommends collective treatment of the population with praziquantel (Table 1 lists the recommended treatment strategies [5]). In addition, many African countries such as Ghana have concentrated efforts to combat schistosomiasis by controlling the vectors (snails) in the rivers.

The treatment of choice is praziquantel at a dose of 40 mg/Kg per day in two doses, every 12 hours. With this dose, the 6-week cure rate is 88%; the administration of a second dose of praziquantel at 4-6 weeks increases the cure

rate to 100% [9]. During the immature stages, schistosomes are moderately refractory to praziquantel, but their sensitivity to treatment increases with maturity and egg laying. In consequence, during the first 10-12 weeks after *S. haematobium* infection, praziquantel may not be useful [17].

In endemic areas, reinfection after praziquantel treatment is common. Today, it is recognized that reinfection with *S. haematobium* is closely related to the IgE/IgG4 balance [7]. Although at present there is no evidence of the existence of strains resistant to praziquantel, a reduction in susceptibility to the drug has been reported [17]. Praziquantel combines safety and low price, and is active against the adult stages of schistosomes. One of the major limitations of praziquantel is its non-efficacy against immature stages, which is related to treatment failure and a higher frequency of reinfection. Large-scale schistosomiasis control programmes depend on the use of praziquantel, and there is concern that its continued use could lead to the development of resistance in the parasite.

Table 1. WHO recommended treatment strategy for schistosomiasis in preventive chemotherapy

Prevalence* in school-age children (SAC)	Treatment Group	Target Group	Treatment Frequency
≥50%	A (High)	Treat all SAC and adults at risk	Once every year
≥10% and <50%	B (Medium)	Treat all SAC and adults at risk	Once every 2 years
≥1% and <10%	C (Low)	Treat all SAC	Once every 3 years (twice during primary schooling age)

**Determined by parasitological methods*

The schistosomicide activity of artemisinin was discovered in the 1980s. Its activity is directed against the immature stages of the parasite, and so this would complement the therapeutic activity of praziquantel. This has led some authors to propose the combined use of praziquantel and artemisinin as a treatment strategy for schistosomiasis. In this respect, Pérez del Villar and co-workers [14] conducted a systematic review, analysing the available data on the safety and efficacy of artemisinin in the treatment and prophylaxis of schistosomiasis, examining 50 articles of the 261 published on the question. Seven studies compared artemisinin with praziquantel and reported a lower

cure rate for artemisinin. Four studies evaluated the combination of artemisinin and praziquantel *versus* praziquantel alone. In urinary schistosomiasis, the patients treated with the combination presented higher cure rates than those treated with praziquantel alone (OR=1.84, 95% confidence interval (CI) 1.01-3.36, p=0.047). These observations are also applicable to *S. mansoni* and *S. japonicum*. Three studies compared artemisinin and sulfadoxine-pyrimethamine with praziquantel alone, and found that the cure rate for the combination therapy was significantly lower than that for praziquantel alone. Finally, five studies compared artemisinin with a placebo treatment and observed a better response with the artemisinin (OR=0.11, 95% CI 0.06 - 0.22, p=0.001).

The side effects most frequently described after the use of artemisinin are epigastric pain, headache, nausea and vomiting. Nevertheless, all studies agree that both praziquantel and artemisinin are in general well tolerated.

At present, it is concluded that artemisinin used as the sole treatment option is not recommended, as it is mainly effective against the immature forms of the parasite, and its cure rates are lower than those of praziquantel. Furthermore, its use in combination with praziquantel raises the question of whether more widespread use could facilitate the emergence of resistance in the treatment of malaria.

The above considerations regarding treatment reflect the need to achieve approaches that are more specific and which provide long-term protection against schistosomiasis. The development of a vaccine strategy seems appropriate though it would need longer times to be achieved. Although several vaccine candidates have been proposed, the antigen glutathione S-transferase 28 kDa (Sh28GST) has been well characterized, and the immunization of diverse laboratory animals with this antigen has produced a significant decrease in the fertility of the parasite, and the safety of the procedure has been demonstrated [1]. Some studies have shown that resistance to reinfection is associated with the presence of antibodies to 28GST, capable of inhibiting the 28GST enzymatic activity of the parasite. Riveau and co-workers [15] published a phase I clinical trial focusing on the safety and tolerability of recombinant Sh28GST vaccine, adjuvated with aluminium hydroxide (rSh28GST) in humans. For ethical reasons, the authors recruited an adult population, although it seems clear that children would constitute the ideal population for this vaccine. These authors concluded that the recombinant vaccine (rSh28GST) adjuvated with aluminium hydroxide was both safe and tolerable for adults.

Conclusion

There are increasing references to urinary schistosomiasis diagnosed among immigrants living in Western countries. The schistosomiasis screening for people at risk should be done as a serological test, conducted at least 6 weeks after a potential exposure to contaminated waters. In this period, the absence of antibodies against schistosomes virtually excludes the possibility of infection. Should the schistosome serology be positive, the identification of eggs in urine would be indicated, although the low sensitivity of this test needs to be taken into account. The treatment of choice is praziquantel. Although at present there is no evidence of the existence of strains resistant to praziquantel. In endemic areas, reinfection after praziquantel treatment is very common. Therefore in school children the frequency of prophylactic treatment with praziquantel should be adjusted to the prevalence of the disease in their environment.

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