The Role of the Scientific Research in the Control of Schistosomiasis in Endemic Areas

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The way the researches established the lines of direction for considering fight against schistosomiasis on the double aspect of transmission and morbidity control is outstanding. Chemotherapy in the morbidity control is emphasized. The research priorities for schistosomiasis control are mentioned.

Key words: schistosomiasis - transmission control and morbidity control - chemotherapy

Scientific investigation is recognizedly the main origin for the discovering of new tools and procedures for the control of schistosomiasis, as it occurs with the diseases in general. Also, it is the more rational mean for evaluating the efficacy, the efficiency, and the effectiveness of any control action. For this reason, the well elaborated control plans have to be articulated with research parallel programmes.

Obviously, there are other ways for the evidence of both facts and its meaning and for the establishment of concepts, without being through the research, understood this "as a scrupulous and systematical investigation for inquirying the reality, with the aim of discovering or establishing facts or principles". Such as the observation at haphazard or resultant from some implanted activity. As an exemple, we quote the observation made by chance, in Ethiopia, of the death of snails, after wear washing using as soap a native plant (*Phytolacca dodecandra*)(Lemma 1965). Although the mass treatment of schistosomiasis with antimonials had not been preceded by researches that showed its efficacy, favourable results about the morbidity were observed (Abdallah et al. 1974). Undeniably, clinical observation is the larger resource of research motivation and for this reason it should not be disregarded. But, without depreciating this importance, it is also essential that the suspicions raised are duely confirmed by the applications of scientific methodology, without improper generalizations. Some facts next mentioned illustrate the importance of such considerations. The aim is not to discuss the obvious importance of the research, but to emphasize how informations that changed proceedings were obtained and to point out some priorities of research for schistosomiasis control.

SCHISTOSOMIASIS CONTROL

Til the 1970s, few countries had met with some success in the control of schistosomiasis. Beside sanitation and education for health of long time results and of dificult implantation, depending on economical development, the strategy for schistosomiasis control was based on the use of molluscicides, with what it was intended to dimninish the population of snails, reducing the transmission of the disease and thus, slowly, influencing its morbidity. The application of the moluscicides took a long time and was complicated if considering the extension of the surfaces to be covered. Thus, except where economical development occurred, or in little foci, under special epidemiological conditions, the reduction of transmission exceptionally met with success and lasted. It was that happened in Japan. The socioeconomic improvements which the rural population of this country has enjoyed have contributed to eradication of the disease. Reduction of the number of rice farmers, changes in farming techniques and living habits, complete control of the water system, and popularization of septic trenches have been decisive factors in interrupting transmission, and in making Japan one of the few countries to have achieved the control of schistosomiasis (Doumenge et al. 1987). Also in Tunisia, the schistosomiasis had been well controlled under orientation of Luis Rey (Rey et al. 1982). Good results had been distinguished in Puerto Rico (Negrón-Aponte & Jobin 1979); Cline (1973) emphasizes that there are reasons to relate them to dramatic socioeconomic advances. In the countries with great endemic areas, during a long time, the control programmes were limited to pilot projects. Beside the use of molluscicides, in some countries like Egypt and China some control programmes were established through mass treatment of populations of endemic areas, by using initially trivalent antimonials.

In the Egypt, Mousa and Ayad (1974) emphasized that the prevalence decline was little and that the dissemination of schistosomiasis was closely linked with the development of and changes in irrigation patterns. More recently, with the increment of control programmes in a large scale, an effective reduction took place in both the prevalence and the infection intensity through the use of health education, chemotherapy, and snail control (Doumenge et al. 1987). In China, since 1950, the control programmes had been increased and in many areas of the country the disease has been even eradicated, often after the implantation of drastic measures for snail elimination and treatment of human and cattle infected.

In Brazil, in despite of, long time ago (Maciel 1925, Pellon & Teixeira 1950) schistosomiasis is being considered as an spreading severe problem of public health, the aim of the Superintendência de Campanhas de Saúde

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Pública (Sucam) (Public Health Campaigns Superintendency) was to block the introduction of schistosomiasis into areas still free of transmission and to reduce the transmission of the disease in selected areas (Pantoja 1974). We should not know how to reach such purpose indeed, since as the a WHO Expert Committee on Schistosomiasis Control (1973) emphasized "long-term results are still lacking". Only in 1967, there were established, under the orientation of Prof. José Rodrigues da Silva, four pilot projetcs (Caatinga do Moura, São Lourenço da Mata, Jacarepaguá, and Belo Horizonte), with the purpose of experimenting with new methods of control.

THE BASIC ACHIEVEMENTS

Dead worms - The toxicity of the antimonials discouraged its use in large scale. Many deaths occurred. Many diseased gave up the treatment and, in the Egypt, according to Sherif (1964), this happened in 80%. Besides, some authors referred the finding in humans (Coutinho & Coelho 1940, Coutinho et al. 1944), and experimental (Magalhães Filho 1955) of dead worms in the liver and lungs, surrounded by extensive necrotic area after antimony therapy. Such findings led some authors even to counterindicate the specific treatment, generalizing the risk verified by the findings in some necropsies. The reaction of the dead worms were minimized by Amaury Coutinho (1974) who individualized the toxic reactions produced by the drugs by separating them from the severe and sometimes lethal reactions attributed to the dead worms. With the advent of new schistosomicide drugs not much toxic, millions of individuals were treated and no accident due to worms death was reported.

Reinfection after treatment and worm burden - In endemic areas, as many individuals were reinfected after the parasitological cure, is was thought that there was no sense in doing specific treatment, including with drugs not always well tollerated, without snail ellimination or the adoption of measures that avoided the contact with foci of infection. The field study, carried out in Canabrava (Bina & Prata 1974) showed, for the first time, the behaviour of the whole population of an endemic area after specific treatment, followed by another treatment one year later than those that were reinfected, without application of another control measure. Before the mass treatment, there were 46.3% of individuals avoiding *Schistosoma mansoni* eggs, but the infection was of 82%, also considering the positivity of the skin test. Two years after the second treatment, the prevalence was of 19%, being smaller in all the age groups, but mainly among the older ones (Fig. 1), as it has already been observed by Rodrigues da Silva (1958). The individuals under the age of 20 years were reinfected in a greater proportion. The form of the prevalence curve is similar to that before the treatment, but the peak, followed by the inflexion occurred in the age group of 10-14 years, instead of that of 25-29 years as it was before the treatment. The treatment anticipates a natural tendency for spontaneous cure which occurs with the age progression (Bina & Prata 1974).

Another aspect extremely significant is that in the reinfection after the treatment generally the individuals present reduction of the number of eggs in the stool (Kloetzel 1963, Prata et al. 1980, Sturrock et al. 1987).

Safe and single dose treatment - The schistosomiasis control campaigns with schistosomicides which began in the Egypt in 1922 (Abdallah et al. 1974), initially with volunteers became afterwards compulsory. In China the treatment has been done in large scale (Mao & Shao 1982). Mass treatment attempts have been done also in Sudan and Zimbabwe (Clarke 1960).

In Brazil, in several opportunities, the specific treatment was used as control measure in schistosomiasis (Prata 1976). Initially, with antimonials, in selected groups, in little communities, comprehending about hundred thousand individuals in the 1962-1971 decade.

The possibility of using chemotherapy for mass treatment did not increase with the appearance of niridazole,

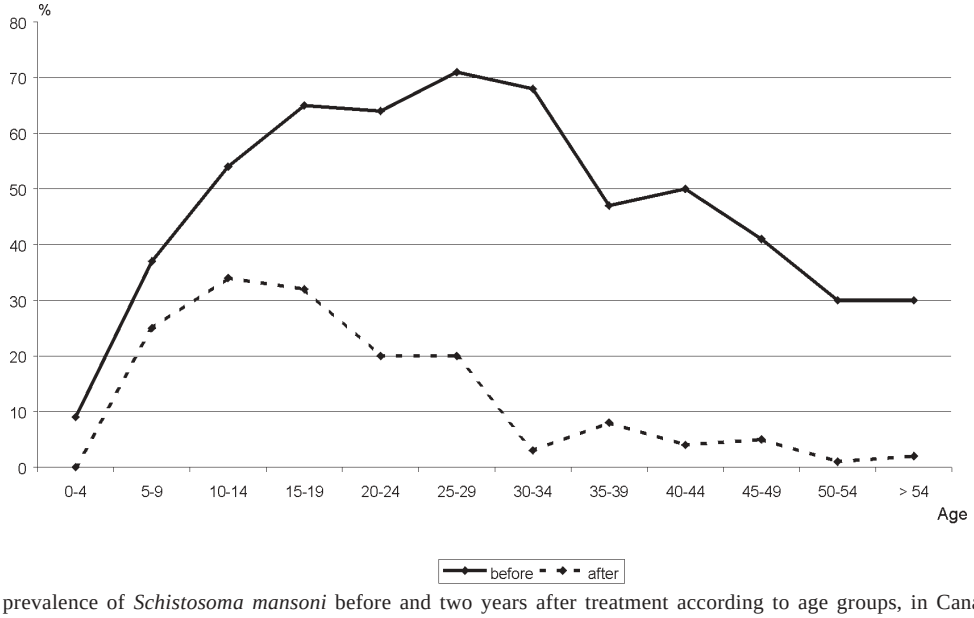

Fig. 1: prevalence of *Schistosoma mansoni* before and two years after treatment according to age groups, in Canabrava.

but a great progress was verified with hycanthone (Katz & Pellegrino 1967) which made possible the treatment with a single dose (Figueiredo & Prata 1969). Treatments had been accomplished in several localities (Katz et al. 1970, Bina & Prata 1970, 1974) with research purpose and in Public Health programmes (Pizza & Campos 1974). However, the evidency that the drug may produce severe toxic hepatitis (Andrade 1974) and the suspicions, although not substantiated (WHO 1972), that it would produce teratogenic, carcinogenic, and mutagenic effects discouraged the use of hycanthone as a mass treatment drug. Yet, concomitantly, oxamniquine was being developed (Foster 1973) and the clinical trials (Prata et al. 1973) soon revealed its excellent efficacy, also in a single dose. The pains caused by the injection made impossible, initially, the use of the drug in large scale. Nevertheless, it was soon verified that the medication used by oral via, also in a single dose, was equally effective and very well tolerated. Short time after, praziquantel appeared (Seubert et al. 1977) efficacious and with good tolerance (Katz et al. 1979, Prata et al. 1982) and useful for the treatment of the hematobium schistosomiasis (Davis et al. 1979) and japonicum (Santos et al. 1979). Thus, the specific treatment became the main measure for the schistosomiasis control.

Morbidity assessment - The severity of mansoni schistosomiasis, in a certain locality, is usually evaluated by the percentage of patients over 5 year age with hepatosplenomegaly. There is no consensus about what is an hepatosplenic patient. When the spleen is voluminous and the liver is consistent and larger in the left lobe there is no doubt. This occurs at the interpretations of a palpable spleen only in inspiration, that should not be included in the hepatosplenic form (Prata 1970). The hepatosplenic form appears only after the age of 5 years, in inhabitants of endemic areas, usually 5-15 years after the initial infection. In a paper on its development (Prata & Bina 1968), we see that it happens slowly in patients with the form either hepatointestinal or intestinal and that by the clinical examination, since it begins to appear, it takes at least three years for being well defined as hepatosplenic form. Only individuals with repeated contacts with the infection foci develop the hepatosplenic form of the disease, probably increasing the parasite burden and breaking the apparent equilibrium between deposition or removal of eggs put on the tissues (Coelho et al. 1994).

The hepatosplenic form is more frequent in areas with higher prevalence of the disease (Pessoa & Barros 1953) and larger quantity of eggs eliminated by the population (Costa 1983). Often it occurs in the members of a same family (Tavares-Neto 1987). It attacks mainly the young individuals corresponding the age groups with larger elimination of eggs by the stool. It is associated with the development of periportal fibrosis described by Symmers.

The ultrasonography is better than clinical examination for characterizing Symmers' fibrosis although requires equipment and specialized staff.

The reversibility of the hepatosplenomegaly - There were reports that the treatment carried out in some populations could diminish the prevalence of severe clinical forms and the complications in the schistosomiasis. In accordance with Abdallah et al. (1974), in the Egypt, about one to one and a half million patients were treated per year, what, although not having controlled the transmission, lowered the prevalence and resulted in outstanding decrease in the severity of complications in the schistosomiasis, certified by the diminution in the number of surgical complications and cases with hepatic fibrosis and cor pulmonale. Sette (1953), in Catende, verified the diminution of hepatosplenic individuals in the population treated 10 years before by Jansen (1946). Dias (1952) accepted the possibility of the hepatosplenomegaly reversion only when it was moderate, since when well developed the lesions would be irreversible. The predominant idea was that the treatment benefits would occur in the prevention of severe forms (Silva 1957, Kloetzel 1967), what was demonstrated by Bina (1981). Posteriorly (Bina & Prata 1983), it was well proved that the hepatosplenomegaly may improve and even desappear after specific treatment and that the progress may occur even in patients with a history of previous treatment and long time established hepatosplenomegaly (Dietze & Prata 1986). In these last two works mentioned, carried out in inhabitants of endemic areas, 93 hepatosplenic individuals were treated with oxamniquine, which results are presented in Table I. Thus, the treatment of the patients, besides influencing on the cycle of schistosomes life, either reducing the number of or eliminating the worms, acts on the lesions in the human organism, preventing its development or causing the regression of those already existing.

TABLE I

Hepatosplenomegaly after treatment of schistosomiasis mansoni by oxamniquine

	Patients	
Results	Nr	%
Improvement [a]	67	72
No alteration	17	18.3
Worsening	9	9.7
Total	93	100

a: with disappearance 30 (33.3%)

TRANSMISSION CONTROL AND MORBIDITY CONTROL

In 1976, Brazil initiated the Programa Especial de Controle da Esquistossomose (Pece) (Special Programme of Schistosomiasis Control) (Machado 1979), with the aim of eliminating the transmission and reducing the prevalence to less then 4%. A group of researchers (Aluízio Prata, Amaury Coutinho, Frederico Simões Barbosa, José Rodrigues Coura, Luiz Caetano, and Naftale Katz invited by the Sucam for analysing the Pece, in 1979, stated (Report 1981): "emphasized the following postive aspects of chemotherapy in large scale: rapid and outstanding reduction of the prevalence; reduction of parasite burden; probable prevention of the hepatosplenic forms and the clinical improvement of the treated individuals". In 1982,

the aim of Brazil's programme became that of controling morbidity more than transmission and preventing the spreading of the disease to new areas. For this, the results of field studies carried out in Brazil, and mentioned above, were decisive. In 1985, the World Health Organization (WHO 1985) began to considering that the prime purpose of the schistosomiasis control is either to reduce or eliminate the morbidity or at least the severe forms of the disease. On the occasion, the WHO's Manager of Schistosomiasis Service was Dr KE Mott who knew well the works carried out in Brazil.

Thus, in the schistosomiasis control programmes, we must consider the two purposes: transmission control and morbidity control. In large scale and at short term specific treatment is the best tool to schistosomiasis control. Some following patterns illustrate our experience on the results and restraints of the application of some procedures used at large term in the schistosomiasis control.

Schistosomiasis control of transmission by repeated treatment - In a locality hyperendemic with a population of about four hundreds individuals, having a lagoon as water supply resource as well as of infection by *S. mansoni*, there were performed repeated monthly treatments with a single dose of oxamniquine, after the initial mass treatment (Prata et al. 1980). The positivity of stool test was of 71.2% and, considering the skin test, the schistosomiasis prevalence increased to 83.2%. The average of *S. mansoni* eggs per gram of stool among the positive was of 638. After 20 months, the prevalence lowered to 3.7%, oscilating til 10% in the 40th month to becoming to 3.7% in the 41st month, thus remaining til the 47th month (Fig. 2). The age group that required of a larger number of treatments was that of 5-19 years. The great mobility of the population and the dificulty in identifying the candidates for selective treatment did not permit to reduce the prevalence below 3.7%.

Schistosomiasis control through molluscicide - In the endemic area of Taquarendi, for a period of nine years, in the attempt of interrupting the schistosomiasis transmission, applications of Bayluscide were made several times a year (Barreto & Prata 1971). After three years, the reduction of schistosomiasis prevalence in all age groups (Fig. 3) and of the parasite burden was verified. The results after nine years were not very different (Table II). There was no exhaustion of the infection at the worm death, which may have a life longer than one may suppose, as showed by Coura (1974). A reduction was verified in the parasite burdens over 1000 eggs per gram of stool. The prevalence of hepatosplenic individuals in the population followed did not show a remarkable reduction. Among the patients with hepatosplenomegaly, there were progression of the disease in 2.9% and regression in 4.6% ($p > 0.05$) (Bina 1995).

Schistosomiasis control by health education and other measures - Of all the experimental control projects that we have in hyperendemic areas of schistosomiasis,

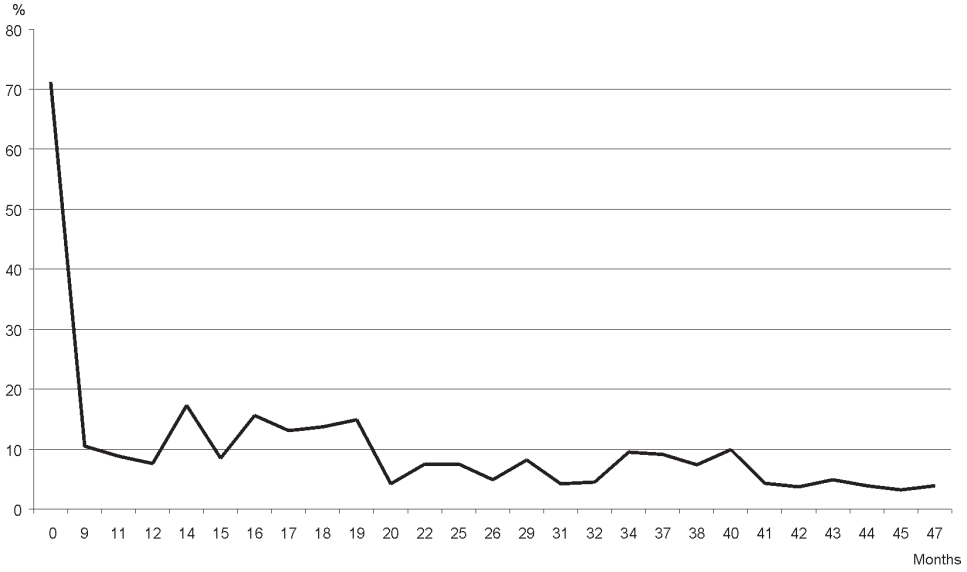

Fig. 2: percentage of positive stool examinations of *Schistosoma mansoni*, before mass treatment with oxamniquine and, months later, under selective and repeated treatments, in Nova Esperança.

TABLE II

Schistosoma mansoni eggs in the stool and hepatosplenomegaly after repeated use of molluscicide

	S. mansoni eggs in stool			Hepatosplenomegaly
Molluscicide	Positive %	Geometric median/gram	> 1000%	%
Before	73.1	309	19.7	10.5
After three years	51.6	182	5.4	9.4
After nine years	55	177	3.1	7.7

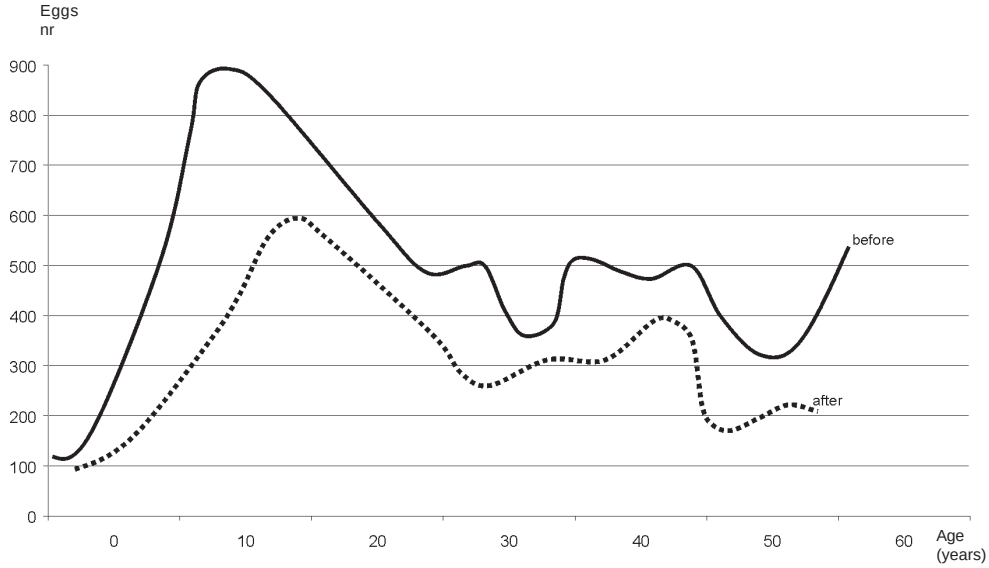

Fig. 3: *Schistosoma mansoni* egg count before and three years after the interruption of the transmission by niclosamide, in Taquarandi.

no one presented better results than that of Brejo do Espírito Santo, which data are in phase of publishing, in collaboration with Raiza Ruiz Guevara. During three years, the only control measure that we established in the area was the education for health with the support of the Movimento Brasileiro de Alfabetização de Adultos (Mobral) (Brazilian Movement for Adults Alphabetization). Later on, after more than one decade, the water supply was initiated and, more recently, the latrine installation, electric fittings, and selective specific treatment. We have never used molluscicide in the area. The results may be observed in the Fig. 4 and in Table III. Barbosa (1971) also reported that schistosomiasis mansoni was effectively controlled in a project in an area in which control measures were limited to environamental sanitation and community health education program. Barbosa (1974) emphasized that the decreasing of the infection rates is a progressive phenomenon which is also occurring in some other areas of Northeast Brazil and considered the economic and social transformation which is taking place in the country as the more significant factor of modifications in health. Although we agree, such socioeconomical changes did not occur in Brejo do Espírito Santo, and in some projects that we have in the same area we did not verify the same results in both prevalence and morbidity of the schistosomiasis.

TABLE III

Prevalence and new cases of hepatosplenic schistosomiasis in Brejo do Espírito Santo, 1976-2002

	Hepatosplenomegaly			
	Prevalence		New cases	
Year	Nr	%	Nr	%
1976	126	7.1		
1985	78	4.7	21	26.9
1989	34	3.4	5	14.7
2002	36	2.5	2	5.6

RESEARCH PRIORITIES FOR SCHISTOSOMIASIS CONTROL

Epidemiology: distribution; prevalence; economic impact of control.

In the area of epidemiology, we need more studies on the distribution and prevalence of schistosomiasis at national extent, to be used for orientation in preparing the control programmes. More information on the economical impact of the control are required for the establishment of priorities.

INTERVENTION TOOLS

Chemotherapy: optimization of current drugs; new drugs; praziquantel in pregnancy and during lactation; formulation to prevent cercaria penetration; rapid and good test to detect reinfection; marker of morbidity.

We need to optimize the current drugs: (a) to manufacture tablets with lesser quantities of medicament, as much oxamniquine as praziquantel, for a better division of the doses; (b) to formulate praziquantel for children; and (c) to know more about the use of praziquantel in pregnancy and during lactation.

The drugs that we have for the treatment of the schistosomiasis are excellent, but it would be better if new drugs appeared, in case of problems with the existent ones. There was a formulation in the phase of clinical trial to prevent the penetration of cercariae, but we had not more information about the matter. It would be important to have available a preparation for cutaneous application that may prevent the penetration of cercariae, thus protecting the individuals who are exposed to the risk of infection.The greater priority would be the development of a rapid and good test to detect reinfection and also for the diagnosis of infections associated with the low parasite burden, in order to facilitate the application of schistosomicides in

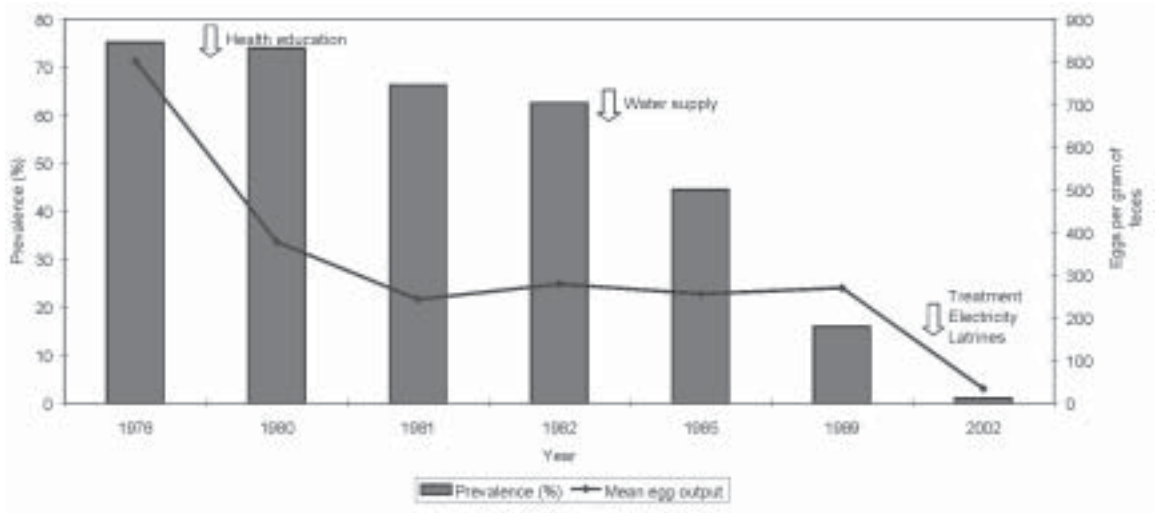

Fig. 4: *Schistosoma mansoni* prevalence and worm burden, according to control actions established in Brejo do Espírito Santo.

selective treatment. It is necessary to establish other markers of morbidity, including evaluating the importance of neurological behaviour in the schistosomiasis.

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