Epidemiological considerations for development of a schistosome vaccine

Acta Tropica *44*, Suppl. 12, 13–20 (1987)

Schistosomiasis and Other Trematode Infections, Parasitic Diseases Programme,
World Health Organization, Geneva, Switzerland

Epidemiological considerations for development of a schistosome vaccine

K. E. MOTT

The last time that we met to discuss the question of a schistosome vaccine (Mott, 1982), AIDS had not yet been recognized, no one had cloned a schistosome gene and those of you who were dissecting the immune response in experimental models were asking penetrating questions about the direction of your research. Five years ago two million persons had not been treated with praziquantel – let alone the tens of millions of farm animals for parasites other than schistosomiasis.

We are now entering into a new phase of epidemiological assessment of the impact of chemotherapy on infection and disease due to schistosomiasis. I am not certain that this information will help those at the bench to develop a more effective vaccine.

The epidemiology of schistosomiasis has been the object of extensive field investigations for most of this century. Thus its global distribution and characteristics of each form of human infection are well documented in most endemic areas. This general knowledge does not imply that control has been achieved or that implementation is underway in all endemic areas. Even a brief acquaintance of health services in any endemic country will confront an idealist with the profound constraints of public health activities. There are no miracles for control of parasitic diseases. The organization, managerial and infrastructure problems of health services in developing countries are as complex as any aspect of modern biology and probably less amenable to manipulation.

Epidemiological observations on parasitic infections provide a wide-range of baseline information which should be constantly reappraised as new data become available and as fundamental mechanisms are proved or redefined. Epidemiological observations are of limited value in proving cause and effect relationships. Ultimate proof will come by reproducible laboratory experimen-

Correspondence: Dr. K. E. Mott, Chief, Schistosomiasis and Other Trematode Infections, Parasitic Diseases Programme, World Health Organization, CH-1211 Geneva 27, Switzerland

tation. Some of the observations which may be useful in considering vaccine development are:
1. distribution of infection and disease,
2. relationship between prevalence and intensity of infection,
3. status of infection according to age and sex,
4. rates of acquisition and loss of infection,
5. presence of natural/acquired immunity,
6. relationship between human and animal infections,
7. characteristics of parasite complexes,
8. prediction of variables which will measure the efficacy of a vaccine.

1. Distribution of infection and disease. – Schistosomiasis is now endemic in 75 countries more than 200 million persons are estimated to be infected and between 500 and 600 million are exposed to the risk of infection.

Schistosoma mansoni occurs in 53 countries from the Arabian peninsula to Brazil, Surniname and Venezuela. *S. haematobium* is endemic in 53 Eastern Mediterranean and African countries. Of interest in vaccine development is the overlap of both *S. mansoni* and *S. haematobium* in 40 countries as well as the occurrence of *S. intercalatum* in six of these.

Schistosomiasis continues to spread so that transmission is being established in new areas such as São Tomé and Principe, Niger and Oman. On the other hand previously unexposed populations are migrating into endemic agricultural areas and schistosomiasis is being acquired for the first time often with severe clinical consequences as in Botswana and Zanzibar.

From a strategic point of view the World Health Organization has endorsed a global plan of action to reduce morbidity. The plan of action is not uniform – as the epidemiology and distribution of schistosomiasis is not uniform. Most of the countries where schistosomiasis is endemic are designated as "least developed countries". The entire national health budgets of some of these countries are no larger than those of some major European cities.

The feasibility of actual implementation and large scale use of the vaccine must take this into account.

2. Classification of infection. – Quantitation in epidemiological studies is not an end in itself. It serves to aid our epidemiological analysis of the relationship between infection and disease. The positive/negative dichotomy is not sufficient to assess these relationships. There is a general consensus now that clinical and epidemiological studies should classify individuals and populations according to the intensity of infection. The use of quantitative parasitological examinations is now accepted procedure in epidemiological studies. Their relevance in interpretation of data on the human immune response is also being validated. The Kato technique for faecal examinations is widely used. Urine filtration techniques using a variety of filters are also employed in epidemiolog-

ical studies of *S. haematobium* infection. Quantitation does not cover all sins – it may cause them.

Examination of *one gram* of stool probably represents less than 0.3% of the total daily output of *S. mansoni* eggs in the stool (Bradley, 1965). The stability of *S. mansoni* egg count from day to day and month to month has been shown and thus quantitative stool examinations can reliably classify infected persons (Barreto et al., 1978). The limitation, however, is in the comparative analysis. The coefficient of variation in a period of three days is about 70%. Any conclusions derived from comparison of egg count categories which are close together should be supported with the appropriate statistical analysis and significance testing.

3. Status of infection according to age and sex. – In most epidemiological studies some differences in prevalence and intensity of infection between sexes have been reported. This is not surprising in view of the different habits and customs. These differences have generally been explained by water contact patterns. Perhaps as epidemiological studies continue some intrinsic differences between sexes may become apparent – as has been noted for example in the higher rate of alcoholic cirrhosis in women as compared to men.

On the other hand, evidence is more convincing about the role of age as determinant of the epidemiological pattern of schistosomiasis in a population. In the younger age groups acquisition occurs at a rapid rate and depending on the species the older age groups tend to excrete fewer eggs and even if prevalence does not decrease intensity of infection does.

4. S. haematobium – epidemiological characteristics. – The prevalence/intensity relationship of *S. haematobium* infection is well known (Fig. 1). Wilkins and his colleagues (1984) have begun to publish their observations. These include:

- the mean life span of *S. haematobium* is about 3.4 years,
- persons of all ages acquire new infections – *not* just children,
- egg counts are higher in children,
- egg counts tend to be very stable in older persons,
- egg counts increase rapidly in children but also decrease rapidly with age,
- in a 3-year period of observation 50% of egg output has been from infections acquired during that period,
- older persons tend to have less water contact.

Again it appears that water contact and the life span of the adult worm could explain these usual distributions of prevalence and intensity.

The question has been raised[1] as to why the frequency of pneumonitis and cor pulmonale is so rare in *S. haematobium* infection. If the dogma of anatomy

[1] An observation by Dr. Chen Ming Gang, Medical Officer, Schistosomiasis Unit, Parasitic Diseases Programme, WHO.

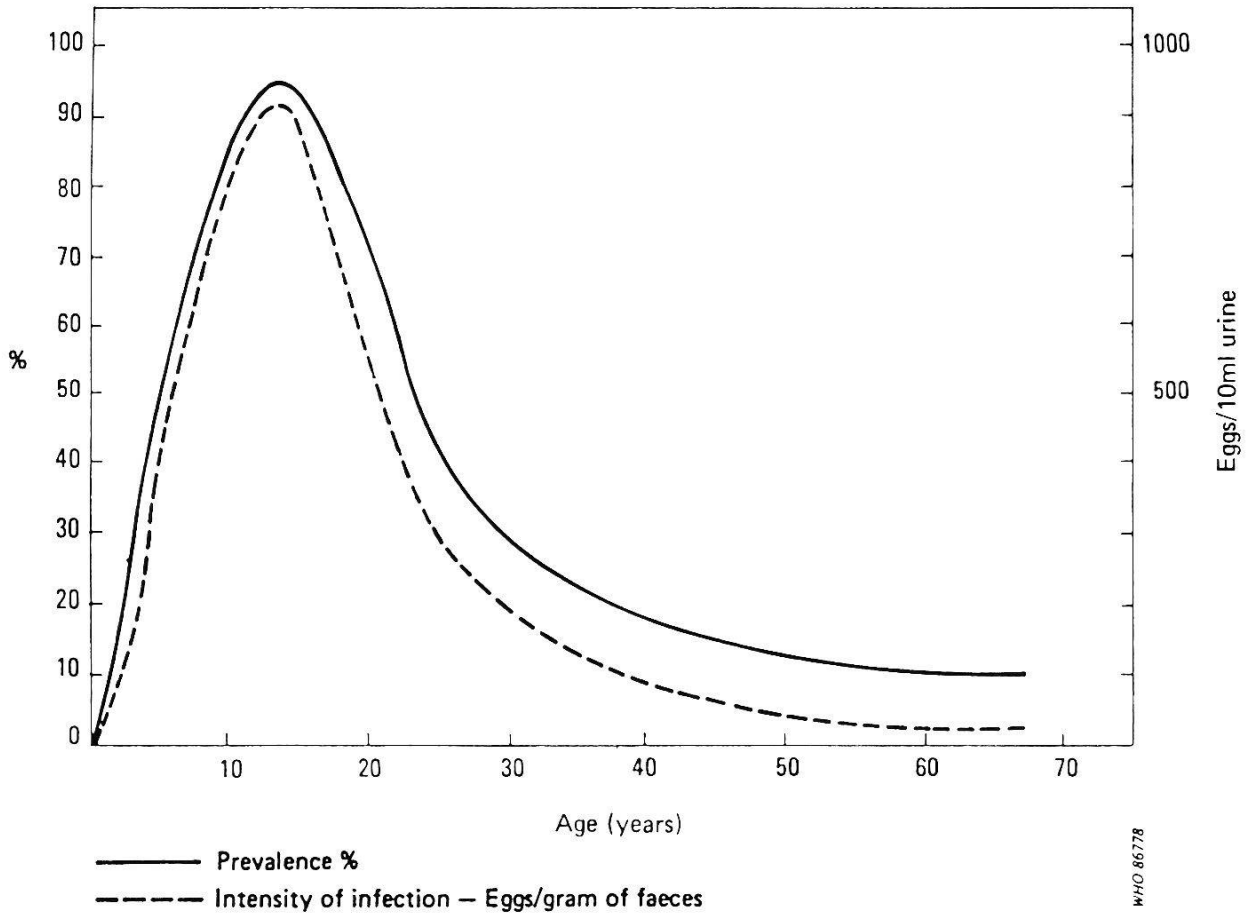

Fig. 1. A generalized distribution of prevalence and intensity of *S. haematobium* infection. With permission, previously published in: Clinics in Tropical Medicine and Communicable Diseases vol. 1, no. 3 (1986).

and physiology is correct, the *S. haematobium* eggs should have direct access to the lungs via the vesical veins through the inferior vena cava. Yet in spite of high rates of pulmonary granuloma in *S. haematobium* infection at autopsy, cor pulmonale does not evolve frequently. Forsyth proposed that metrifonate acts against the adult worm by paralyzing it and allowing the worm to be swept to the lungs where it is killed by immune mechanisms. One wonders why there is no consistent clinical pulmonary sequelae after treatment or in the natural history of infection.

5. S. mansoni – epidemiological characteristics. – The typical age prevalence distrubution of *S. mansoni* infection is quite familiar (Fig. 2). The peak prevalence ranges from 10 to 24 years of age and the peak intensity of infection usually occurs earlier. The slope in the older age groups is less than observed in *S. haematobium* infection.

There is now general agreement that in the endemic areas the life span of the adult worm is about 5 years and there are many similarities between the distribution of *S. mansoni* and *S. haematobium* in a population.

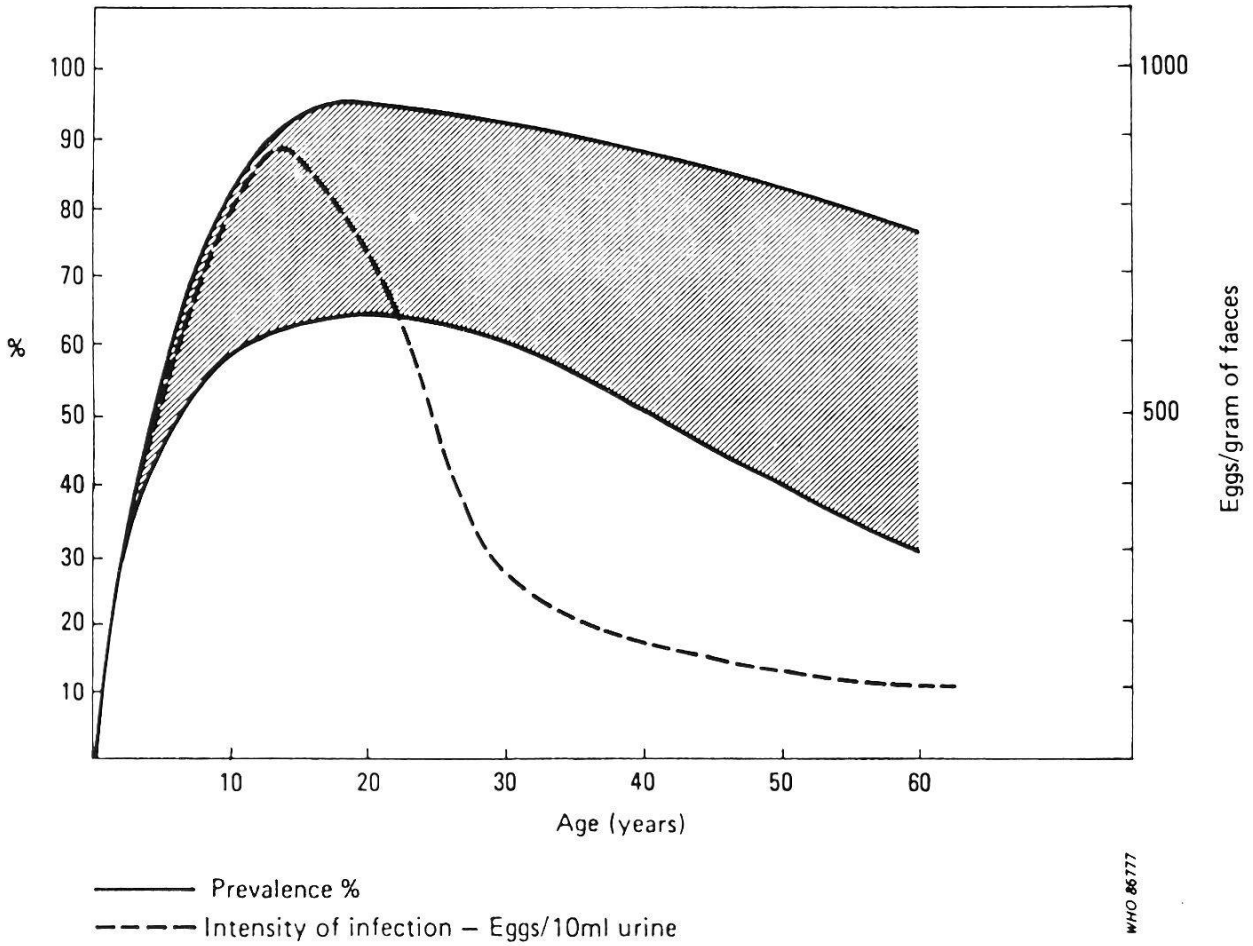

Fig. 2. A generalized distribution of prevalence and intensity of *S. mansotobium* infection. With permission, previously published in: Clinics in Tropical Medicine and Communicable Diseases vol. 1, no. 3 (1986).

6. Mixed infections. – Epidemiological investigations in areas of mixed *S. mansoni* and *S. haematobium* infections would be useful to clarify their interrelationships. The studies of El Alamy and Cline (1977), Saladin et al. (1983), Kazura et al. (1985) and Granier et al. (1985) have all published the data of each infection irrespective of the presence or absence of the other infection in each person. The data from single infections could be separated from that of mixed infections to determine if both the prevalence and intensity of infection of the single infection is different from that of the same parasite in mixed infections. A similar analytical approach may be useful in serological studies. With the Western blot technique and two-dimensional electrophoresis it should be possible to look at these interrelationships as well.

7. Post intervention epidemiology. – Controversy still reigns over the reasons for the lower cure rate observed in children as compared to the cure rates in adults in endemic areas. This has been reported in Brazil after treatment with hycanthone (Katz et al., 1978) in Upper Volta after treatment of *S. mansoni*

infection with oxamniquine (Boudin et al., 1982). It has also been observed in Zanzibar after treatment of *S. haematobium* infection with metrifonate (Mgeni, 1984).

These observations have been the basis for the emphasis on school age children in national control programmes. In large-scale programmes, diagnosis and treatment at short intervals is being made available to this age group through school surveys or local health units.

8. Zoonotic relationships. – The relationship of human schistosomiasis and animal schistosomes is far from being fully described. There are two areas in Africa where field investigations have indicated that there may be important epidemiological interrelationship between human and animal schistosomiasis. In the Senegal River Basin schistosomes with terminal spined eggs, *S. bovis* and *S. curassoni* infect cattle, sheep and goats (Rollinson and Southgate, 1985; Vercruysse et al., 1985). *S. curassoni* infection is found almost exclusively in goats. Since these zootic infections occur in *S. haematobium* areas, there has been speculation that these parasites could hybridize and that the hybrid schistosomes may be found in man. Until now the terminal spined eggs in stool of infected humans in this region have been identified as *S. haematobium.* As modern biological techniques are applied, perhaps this conclusion will be altered.

9. Parasites complexes. – Both epidemiological and clinical studies tend to support the view that each major *Schistosoma* species infecting man is a complex of parasites. The range of response of *S. mansoni* to oxamniquine is one evidence of the biological variation within the species. The variations in snail infectivity, pathology caused in experimental animals and even the morphology of the eggs are such that new techniques of molecular biology should further define these differences. The significance of these observations to vaccine development is unexplored.

10. Polyparasitism. – In all endemic countries polyparasitism is ubiquitous and causes significant disease. In five villages in Chad with between 200 and 400 persons between 7 and 16 different parasitic and infectious deseases were detected at one time. Furthermore up to 6 different parasites were found in the same individual (Buck et al., 1978). Some epidemiological studies on schistosomiasis have shown positive correlation with other infections, such as *Trichuris* and *S. mansoni* infection in children (Lehman et al., 1976). The clinical and epidemiological interpretation of these observations remain relatively unexplored.

11. Serological cross reactivity and intercurrent infection. – The purification of *Schistosoma* antigens has greatly improved the specificity of serological tests.

However, crude schistosome antigens have been shown to cross-react with sera of a wide range of parasitic infections. The seroreactivity of *Schistosoma* antigens was reviewed by McLaren and Daper (1978):

Antibodies which react to S. mansoni antigens[2]
a) Infections with non-trematode worms:
Ascaris
Necator americanus
Trichuris
Taenia
Wuchereria bancrofti
Loa Loa
Onchocerus volvulus
b) following exposure to cercariae of animal schistosomes
c) following exposure to or infection with human schistosomes other than *S. mansoni*
d) presence of an active infection with *S. mansoni*
e) following recovery from an infection with *S. mansoni*

In addition a wide range of other bacterial and parasitic infections cross-react with *Schistosoma* antigens (Kagan and Pellegrino, 1961):

Clonorchis
Paragonimus
Hydatid
Ascaris
Taenia saginata
Syphilis
Trichinella spiralis

The importance of serological cross-reactivity to the possible interference of an intercurrent infection is unknown.

When preparing this paper I thought that I would compile a large literature on the interference between of intercurrent viral infections with both dead and live vaccines against the childhood illnesses. My search was in vain. On the other hand hypothesis that enteroviral infections could interfer with oral live virus polio vaccinations and that malaria interferred with tetanus vaccinations has not altered the operational recommendations of the expanded programme of immunization. Thus any remarks about the possible interference or interrelationship between intercurrent homologous or heterologous parasitic infection on an epidemiological basis would be speculative.

12. Conclusion. – Epidemiological observations strengthen the argument for the feasibility of the development of a vaccine for schistosomiasis. On the other hand, careful epidemiological assessments will be required in designing field trials to evaluate its efficacy.

[2] McLaren M., Draper C. C.: Ann. trop. Med. Parasit. *72*, 243–253 (1978).

Barreto M. L., Silva J. T. F., Mott K. E., Lehmann J. S. jr.: Stability of faecal egg excretion in *Schistosoma mansoni* infection. Trans. roy. Soc. trop. Med. Hyg. *72*, 181–187 (1978).

Boudin C., Moreau J. P., Dupouy-Camet J.: Tentative d'interruption de la transmission de *Schistosoma mansoni* dans une communauté rurale de Haute-Volta par chimiothérapie de masse à l'Oxamniquine en trois cures bimestrielles. Cahiers ORSTOM: Série Ent. méd. Parasit. *20*, 69–75 (1982).

Bradley D. J.: The measurement of bilharziasis: prevalence and schistosomal egg output. Bull. WHO *33*, 503–508 (1965).

Buck A. A., Anderson R. I., MacRae A. A., Fain A.: Epidemiology of poly-parasitism. I. Occurrence, frequency and distribution of multiple infections in rural communities in Chad, Peru, Afghanistan and Zaire. Tropenmed. Parasitenk. *29*, 61–70 (1978).

El-Alamy M. A., Cline B. L.: Prevalence and intensity of *Schistosoma haematobium* and *S. mansoni* infection in Qalyub, Egypt. Amer. J. trop. Med. Hyg. *26*, 470–472 (1977).

Granier H., Granier-Filloux F., Granier-Guionie M., Couprie B., Same-Ekobo A., Apprioo M., Tribouley J., Ripert C.: Etude épidémiologique des bilharzioses intestinale et urinaire dans la région de Tala Mokolo (Monts Mandara-Nord, Cameroun). Méd. trop. *45*, 27–33 (1985).

Kagan I. D., Pellegrino J.: A critical review of immunological methods for the diagnosis of bilharziasis. Bull. WHO *25*, 611–674 (1961).

Katz N., Zicker F., Rocha R. S., Oliveira V. B.: Re-infection of patients in schistosomiasis mansoni endemic areas after specific treatment. Rev. Inst. Med. trop. S. Paulo *20*, 273–278 (1978).

Kazura J. W., Neill M., Peters P. A. S., Dennis E.: Swamp rice farming: possible effects on endemicity of schistosomiasis mansoni and haematobia in a population in Liberia. Amer. J. trop. Med. Hyg. *34*, 107–111 (1985).

Lehman J. S. jr., Mott K. E., Morrow R. H. jr., Muniz T. M., Boyer M. H.: The intensity and effects of infection with *Schistosoma mansoni* in a rural community in northeast Brazil. Amer. J. trop. Med. Hyg. *25*, 285–294 (1976).

Mgeni A. F.: A primary health care approach to schistosomiasis control in Zanzibar. X. International Congress of Tropical Medicine and Parasitology, Calgary, Canada 1984.

Mott K. E.: Epidemiological considerations for parasite vaccine development. Pontificae Academiae Scientiarum Scripta Varia *47*, 5–23 (1982).

Rollinson D., Southgate V. R.: Schistosome and snail populations: genetic variability and parasite transmission. In: Ecology and genetics of host-parasite interactions, p. 91–109. Linnean Society of London, 1985.

Saladin B., Saladin K., Holzer B., Dennis E., Hanson A., Degrémont A.: A pilot control trial of schistosomiasis in Central Liberia by mass chemotherapy of target populations combined with focal application of molluscicide. Acta trop. (Basel) *40*, 271–295 (1983).

Van Wyck J. A.: The importance of animals in human schistosomiasis in South Africa. S. Afr. med. J. *63*, 201–203 (1983).

Vercruysse J., Southgate V. R., Rollinson D.: The epidemiology of human and animal schistosomiasis in the Senegal River Basin. Acta trop. *42*, 249–259 (1985).

Wilkins H. A., Goll P. H., Marshall T. F. de C., Moore P. J.: Dynamics of *Schistosoma haematobium* infection in a Gambian community III. Acquisition and loss of infection. Trans. roy. Soc. trop. Med. Hyg. *78*, 227–232 (1984).