Immuno-epidemiology of *Schistosoma mansoni* Infections in a Recently Exposed Community in Senegal

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Schistosoma mansoni *was introduced in the Senegal basin around 1988, due to man-made ecological changes. Since 1991, we investigate a recent but very intense focus, Ndombo, a village near the city of Richard Toll where the outbreak was first described. Four cohorts, each a ramdom sample (±400 subjects each) from this community, were examined and followed up after treatment, starting at 8 month intervals over a 2-year period. Each cohort is examined parasitologically (Kato-Katz), clinically, serologically (circulating antigen and antibody profiles); treated with praziquantel 40 mg/kg; followed up 6-10 weeks, one and two years after treatment; and monitored for water contact patterns and local snail densities. In the first cohort, the prevalence was 91%, with a mean egg count of 663 epg. Prevalences are near 100% in all age groups, but egg counts decline strongly in adults. Antigen detection in serum and urine confirmed that the egg counts genuinely reflect variations of worm burdens, not e.g. of worm fecundity. This is surprising, as in this focus acquired immunity in adults should not have yet developed according to current hypothesis. The antigen detection assays (CAA/CCA) showed high sensitivity and quantitative power, and promising perspectives as a research tool and possibly as a method for non-invasive diagnosis and screening in urine. Epidemiological in subsequent cohorts were highly similar, although seasonal variations were observed possibly due to transmission fluctuations.*

Anti-AWA and anti-SEA IgE levels increased with age, while IgG4 peaked in the age-group 10-19 years and correlated well with egg counts. The levels of IgE and IgG4 increased strongly between cohorts, indicating a dynamic immunological situation, but no immediate impact on infection levels.

Morbidity was little specific: abdominal discomfort was reported by 61%, diarrhoea by 33% of the subjects; mild hepatomegaly was found in 16%, splenomegaly in 0.5%. No relation to egg counts was observed for any symptom. This mild morbidity may be due to the recent nature of the focus.

In the first cohort, the percentage of people with negative egg counts ten weeks after treatment was only 18%, though egg counts declined strongly. Antigen detection confirmed these results. Praziquantel treatement provoked transient but impressive side effects (colics, vomiting, urticaria, oedema), the occurrence of which correlated with intensity of infection. Cure rates in subsequent cohorts were followed up shorter after treatment but remained low. Reinfection nevertheless appears limited. This lower drug efficacy may be due to very rapid reinfection and/or to the lack of immunity in the population, but also reduced susceptibility of the local parasite strain must be considered and studied.

Key words: *Schistosoma mansoni* - immunology - epidemiology - morbidity - chemotherapy - praziquantel - Senegal

Schistosoma mansoni was introduced in the in the Senegal river basin around 1988, due to man-made ecological changes (Talla et al. 1990, Diaw et al.1991, Talla et al. 1992, Stelma et al. 1993, Gryseels et al. 1994). Since 1991, we investigate the community of Ndombo, in the center of the outbreak. Of particular interest are immuno-epidemiological patterns in such a recently exposed community, where, in contrast to normal endemic situations, age and history of exposure are not confounded: all age groups (above five years) have in principle been exposed to the parasite for the same period. Acquired immunity, which would be expressed only after many years of exposure (Butterworth et al. 1987, Hagan 1991), should thus not yet play an important role. It is of great interest to

This study is supported by the Commission of the European Communities under the programme for Science and Technology for Development - STD2 (TS2-0145-NL) and STD3 (TS3-CT91-0041), and is associated with the ESPOIR programme for research and control of schistosomiasis in Northern Senegal

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investigate whether typical epidemiological features of schistosomiasis, such as age-related prevalences and intensities of (re)infection (high in children, low in adults), attributed to acquired immunity in adults, are present or not in this community. The situation provides a unique opportunity, so to speak, to test the "null hypothesis" of acquired immunity in schistosomiasis mansoni, for which available epidemiological evidence is in fact still debatable (Gryseels 1994).

This paper summarizes our findings so far in the project, which is still in progress. These results are already intriguing from the immuno-epidemiological point of view, moreover some unexpected results with chemotherapy have been obtained.

MATERIALS AND METHODS

We perform our studies in Ndombo, a traditional community of about 4,000, near Richard Toll, in the "epicentre" of the epidemic schistosomiasis outbreak. The study area and village are described in detail elsewhere (Stelma et al. 1993, Gryseels et al. 1994).

Four randomly selected cohorts of ± 400 subjects are surveyed, starting at eight months intervals, and followed up after treatment. By considering each cohort as representative of the same community, a longitudinal study is approximated as closely as ethically possible; follow-up of cohorts without treatment would, indeed, obviously not be acceptable. Each cohort is examined parasitologically, clinically, and serologically (circulating antigen and antibody profiles); treated with praziquantel 40 mg/kg; and followed up 6-12 weeks, one and two years after treatment.

Parasitology is based on egg counts in duplicate 25 mg Kato slides on two stool samples, converted into eggs per gram faeces (epg). Serum and urine samples are collected and examined according to Deelder et al. (1989) and De Jonge et al. (1990) for the presence and concentration of Circulating Anodic Antigen (CAA) and Circulating Cathodic Antigen (CCA). Serum is also examined by sandwich ELISA for IgG subclasses, IgE, IgM, and IgA against crude Soluble Egg Antigen (SEA) and Adult Worm Antigen (Van Dam et al. in preparation).

At each survey, a clinical examination and a medical history are taken (Polderman 1988, Stelma et al. 1994a), and after treatment side effects of treatment are monitored (Stelma et al. 1994b). Additional ultrasound studies take place in selected cohorts and surveys, according to methods described by Kardorff et al. (1994).

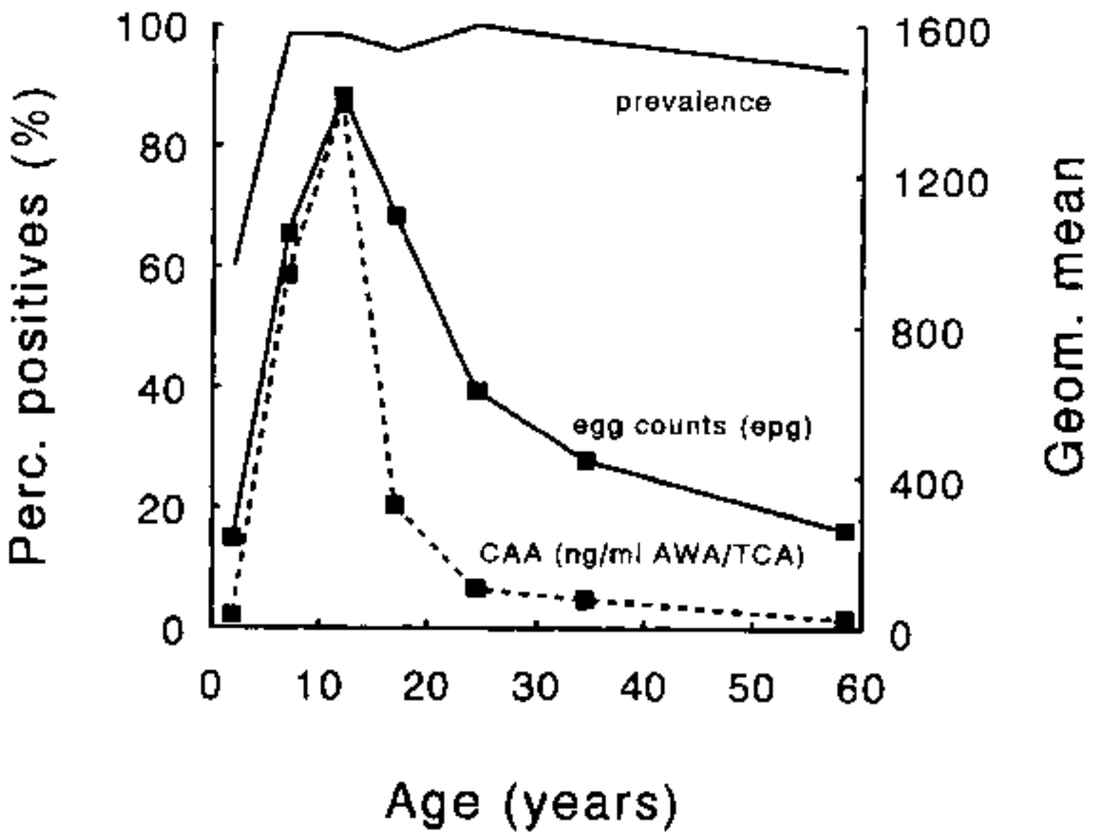
Transmission takes place mainly in a canal, and adjacent creeks and marshes, which link the inland lake of Guiers with the Senegal river, and feeds the sugar cane plantations of Richard Toll; these are also by far the main water source for all purposes in the community. Though there are some dug wells in the village.

Quantitative transmission studies are performed at the five main transmission sites along the canal and the creeks in the village. Direct, individual quantitative water contact observations, are made each month during a one-week period, from 6 am to 6 pm daily. Snail densities and cercarial shedding rates are measured every fortnight.

RESULTS

The first cohort counted 422 individuals, of which 91% had positive egg counts and the mean egg count was 663 epg. The percentage of people excreting over 1000 epg was no less than 41%, and some individuals excreted up to 24,000 epg. The prevalence remained nearly 100% in age groups above 5 years. However, quantitative egg counts peaked strongly in those aged 10-14, at 1409 epg, and declined to 632 epg the age group 20-29 and 266 epg in the age group over 40 (Fig.). There was no substantial difference between women and men. More detailed data have been published elsewhere (Stelma et al. 1993).

Data of cohorts 2, 3 and 4 are still being analyzed, but preliminary results are summarized in Table. As compared to cohort 1, similarly high prevalences were recorded. In cohorts 2 and 3, examined in spring and autumn, egg counts were substantially lower, particularly in adults, as compared to cohort 1 and 4, which were both examined in the hot summer season. Antigen detection results from the first cohort confirm and reinforce the parasitological data. Ninety-four % of the subjects were positive in the serum CAA ELISA, 83% in the serum CCA ELISA and 95% in the urine CCA ELISA; CAA in urine was less sensitive, and



Age-related prevalences and intensities of infection, as measured by faecal egg counts and serum levels of Circulating Anodic Antigen (CAA).

TABLE

Egg counts in subsequent cohorts

	Cohort 1	Cohort 2	Cohort 3	Cohort 4
Study period	August 91	April 92	January 93	August 93
epg > 0	91 %	85 %	83 %	85 %
epg > 1000	41 %	26 %	25 %	39 %
GM 5-19 years	1188	870	676	1445
GM >20 years	463	220	214	363
GM overall	646	347	380	676
Total examined	422	403	405	420

GM = geometric mean eggs per gram (epg)

was negative in half of the urine samples. Fig. shows that antigen levels, and serum CAA in particular, followed the same age-related pattern as egg counts, with a peak in adolescents and a strong decline in adults. Positivity rates for all assays increased with rising egg counts, and circulating antigen concentrations in both serum and urine correlated well with egg counts. If both egg counts and serum CAA are considered 100% specific, and their combined results taken as a gold standard for the presence of infection, then urine CCA and serum CAA determination in a single specimen were at least as sensitive as repeated egg counts (96% and 95% for the antigen assays, versus 94% for 2 x 2 Kato slides), and substantially more sensitive than a single Kato slide (81%). More detailed results of antigen detection in this study population are reported elsewhere (Polman et al. accepted for publication).

Age-related antibody profiles from the first and consecutive cohorts will be published in detail elsewhere (Van Dam, in preparation). IgE (both against AWA and SEA) showed a significant increase with age, while IgG4 peaked in the age-groups 10-15 and/or 15-19 years. A strong correlation between IgG, IgG1, IgG4 against both crude antigens with pre-treatment egg-load was observed. Anti-SEA IgE showed a weak inverse correlation with pre-treatment egg-load. Preliminary results indicate that levels of IgE and most IgG subclasses against both AWA and increase between subsequent cohorts.

Morbidity was surprisingly low, or at least little specific. Of the subjects in the first cohort, 61% reported abdominal pain, 33% diarrhoea; only 16 % showed mild hepatomegaly and only a few mild children had mild splenomegaly cases. These symptoms showed, however, no statistically significant relation to presence or intensity of infection (Stelma et al. 1994a).

Routine treatment of the first cohort with praziquantel 40 mg/kg resulted in somewhat of a surprise. Of 298 re-examined subjects, 82% were still positive for *S. mansoni* in the Kato slides 12 weeks after treatment. However, the frequency of heavy infection and mean egg counts declined by over 80%. Again, antigen levels confirmed the parasitological results: 90% or more of the subjects remained positive in both the serum CAA and the urine CCA ELISA, at 10 days and 12 weeks after treatment (for more details see Stelma et al. 1994b). One year after treatment, cohort 1 showed relatively mild reinfection rates after this initial poor result, with e.g. mean egg counts in children (5-19 years) at 358 epg as compared to 1188 epg pre-treatment.

Treatment also resulted in unusually impressive, though always transient side effects (Stelma et al. 1994b), particularly acute (bloody) diarrhoea and abdominal cramps, which were not only reported but also convincingly observed. These gastrointestinal side-effects correlated well with intensity of infection, and may be due to a massive death, paralysis or shift of worms in the mesenterical veins rapidly after absorption of the drug. More sporadically, also reactions of apparently allergic nature, such as urticaria and oedema, were observed; particularly a few cases with generalized acute oedema a few hours after treatment were remarkable and required corticoid treatment.

In the first study period (August-November 1991) *Biomphalaria pfeifferi* populations were found in amazing, almost unmeasurable densities: thousands of snails could easily be scooped in a few minutes. Moreover, in each site over 20% of the snails shedded human schistosome-type cercariae. Snail counts then decreased strongly: in December 91 - February 92, no *B. pfeifferi* were found, and for over the rest of 1992, a total of only 63 specimens (33% positive) were collected. Pre-

liminary water contact data patterns show that bathing and fetching water account for over 80% of the water contacts; frequency nor duration appeared to be strongly related to age.

DISCUSSION

Prevalences and intensities of *S. mansoni* infection in our study area are extremely high, particularly if it is considered that the first case was diagnosed only in 1988; there is also further evidence that the parasite has not been introduced much earlier. In a few years time this has become one of the most intense foci ever described: a sad record indeed, and another example how difficult it is to predict, let alone prevent, the effect of ecological changes on disease transmission. Considerable efforts have been made to assess the impact of recent dam and irrigation building activities in this area. Although a few warnings had been issued concerning a possible extension of *S. haematobium*, since long endemic in the area, nobody had foreseen that *S. mansoni* would be so dramatically introduced. Probably a small isolated colony of *B. pfeifferi* from Lac de Guiers spread through a hydrological system which, due to the closing of a dam near the mouth of the Senegal river, had suddenly become much less brackish (Gryseels et al. 1994).

Apart from providing essential data to the health authorities for the assessment of the situation and the control of the disease, our studies may contribute significantly to our understanding of the immune resistance in human schistosomiasis. In most if not all "normal" endemic foci, prevalences and intensities of (re)infection are consistently higher in children than in adults.

Whether this is due to age-specific water contact patterns, or to immunity acquired through years of exposure, has long remain debated. Recent evidence from careful reinfection studies indicate, but do not yet unambiguously demonstrate, that indeed "acquired immunity" plays a major epidemiological role: after treatment, children are reinfected much more rapidly than adults and than can be explained by differences in water contact, while some serological markers which develop with age appear to be associated with susceptibility to reinfection (Butterworth et al. 1987, Hagan 1991).

The major problem with interpreting these studies is that, even if actual water contact and transmission data are painstakingly measured (a methodological nightmare on its own), "history of exposure" over the years before the observations cannot be quantified nor be dissociated from age itself. A retrospective, cross-sectional study in groups of immigrants, moving into an endemic areas in Brazil, indicated that prevalences declined in adults a few decades after settlement in the endemic area; this suggested the development of some form of protective immunity after years of exposure, independently of age (Kloetzel & da Silva 1967). However, the study population was small and not well defined (Gryseels 1994). In a similar situation in Burundi, prevalences and intensities of infection continued to increase with duration of exposure, even 20-30 years after settlement, though reinfection rates after treatment were indeed much higher in children than in adults (Gryseels 1984, Gryseels et al. 1987, Gryseels 1991, Gryseels et al. 1991, Gryseels 1994).

The Ndombo project offers a unique opportunity to test current hypotheses, according to which acquired immunity should not, or at most partially have developed even in adults of this recently exposed community. Evidently, all members of the population are susceptible to infection and exposed to (intense) transmission, as prevalences quickly reach and remain 100% from age five onwards. On the other hand, intensities of infection, measured either by egg counts or by antigen levels decreased strongly after the age of 20 years. The antigen data show that the reduction of infection intensities in adults reflects a true reduction of worm loads, not of worm fecundity or increased tissue retention of eggs. Water contact data are still preliminary, but so far do not appear to explain these observations. If this would be confirmed, and neither exposure nor acquired immunity explains the observed infection patterns, than the possibility may have to be (re?)considered that *inherent* age factors are responsible for the reduced susceptibility of adults to infection. Such factors may range from skin thickness and penetrability, to age-related neuro-endocrinological interactions with the immune system. The hypothesis, which would actually explain most of the above described epidemiological patterns (Gryseels 1994), would obviously shed new light on the epidemiology and control of schistosomiasis, and on current efforts to develop a vaccine. "Slowly" acquired immune responses may still play a role in later endemic stages, and our immunological data so far do indicate that serological profiles do evolve over time.

The preliminary results data from cohorts 2, 3 and 4 do confirm the broad epidemiological patterns, in spite of increasing serological immune responses. The differences between the first and fourth "high-transmission" cohorts on one hand, and the spring/winter cohorts 2 and 3 on the other, suggest that seasonal transmission peaks are quite strongly reflected in infection patterns. This would be quite surprising, as a substantial spontaneous attrition of worms must then be assumed.

It is worth to note that the antigen detection assays, applied for the first time as an operational epidemiological tool in this study, have provided

very useful supplementary information, showing that the reduction of egg counts in adults is indeed due to a reduction of worm loads. Also the poor cure rates obtained with praziquantel, which might otherwise be explained by persistent egg excretion, rapid reinfections or development of prepatent infections, was confirmed by the antigen detection assays: at ten days after treatment, antigens from killed worms should have been cleared, whereas newly acquired worms would not yet shed these glycoproteins. Clearly, antigen detection as a direct measure of worm burden is at least a promising tool for (immuno-)epidemiological studies and monitoring, including possible vaccine trials and drug resistance assessment. Another possible promise of antigen detection is the development of an easy screening technique based on the detection of circulating antigens, e.g. with a reagent strip assay in urine, which would in particular facilitate screening of *S. mansoni* and *S. japonicum*. This study demonstrated a high sensitivity of both the serum CAA and the urine CCA-ELISA. Especially the latter opens interesting perspectives for non-invasive screening.

Severe morbidity appears not to have developed yet in this recent focus (Stelma et al. 1994). Intestinal symptoms and complaints were frequent, but could not be related to egg counts, in spite of their extremely high levels. There was virtually no severe organomegaly in the study population, and this was confirmed by ultrasound studies (Rouquet et al. 1993, Kardorff et al. in preparation). So chronic liver disease may not yet have developed, it is surprising that the high intensities of infection do not give rise to more direct, inflammatory liver and spleen enlargement. The specific early immune status must explain this lack of reactive disease. In any case, close monitoring of the morbidity situation is necessary to plan timely intervention if severe chronic pathology would start to develop.

The unexpectedly poor results of standard praziquantel chemotherapy have had international echoes, as they have been interpreted as possibly the first indication ever of schistosome resistance to praziquantel - quite a fearsome prospect for currently advocated control strategies which rely heavily on chemotherapy. However, it must be emphasized that intensities of infections were still substantially reduced, and this is the main objective of community treatment. Cure rates were low also when only lower egg count groups were considered, or when they were compared to those obtained in other intense foci (Polderman et al. 1988, Stelma at al. 1994). However, results with schistosomicides do vary between areas, possibly due to parasite strain differences (Davies). The high pretreatment intensities, the intense transmission, and low levels of immunity may all partly or wholly explain the results. Also the unusually strong side effects can probably be explained by the intensity of the infections and the specific immune status of the population.

The possibility of drug resistant parasite strains, even if considered remote, should, however, not wholly be discarded: it would have quite important consequences for control, locally but at the longer term possibly also internationally. A scientifically interesting hypothesis would be that a schistosome pair at the low end of the normal susceptibility range would have been at the origin of a rapidly expanding clonal parasite population, which inherited this (genetic?) trait as a whole. Here lies quite a challenge for parasite geneticists and biochemists.

In conclusion, the opportunity of studying the immunology and epidemiology of schistosome infections in such a recently exposed community clearly opens exciting perspectives to shed further and possibly unexpected light on old questions and assumptions in schistosomiasis, with far-reaching consequences for research and control. In all this scientific enthusiasm, however, we should not forget that our primary duty and objective lies with the suffering population, and that our efforts must first and foremost serve to improve the local health situation and control strategies in general. If anything, our studies so far show, first of all, that hampering with ecological equilibria is opening a box of pandora, and that once again health services are left to pick up the pieces left by macro-economic planners. Clearly, such situations must be avoided and attitudes changed once and for all; national and international health and development instances should not be satisfied with lip services, but plan development with the genuine needs, interests and expectations of the communities as a prime objective. Secondly, our results show that we are still far from understanding the nature and dynamics of human resistance to schistosome infections, and hence from the rational development of any vaccine candidate. Lastly, the results of chemotherapy in this focus, whatever the explanations, show once again the basic weakness of chemotherapy for helminth control: without serious and lasting accompanying measures to reduce transmission, or (endlessly) repeated chemotherapy, full reinfection will occur sooner or later, as long as the ecological determinants of the equilibrium between human and parasite populations have not been modified.

ACKNOWLEDGMENTS

To Dr JP Hervé, Dr P Handschumacher and colleagues (ORSTOM, Dakar), Dr P Verlé and Dr A Kongs (VVOB, Flemish Cooperation of Belgium, St. Louis),

Prof A Capron and colleagues (Institut Pasteur, Lille), and our colleagues at the Department of Parasitology in Leiden, for their logistic and scientific support. To Mr M Diop, Mr A Yague, Mr N Sy, Mr A Taye for technical assistance and to the population and authorities of Ndombo for friendly cooperation.

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