The WHO Collaborating Centre for Research and Control of Schistosomiasis at Niamey, Niger

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The Centre de Recherche sur les Méningites et les Schistosomes (CERMES) is a research institute depending on the Organisation de Coordination et de Coopération pour la lutte contre les Grandes Endémies - a West African Organization for Public Health - devoted to the studies on schistosomiasis and meningitis. The staff includes 32 persons with 11 scientists and one financial officer. The activities of the CERMES involving schistosomiasis concern three research units: (a) ecology of human and animal schistosomiasis transmission; the CERMES defined the different patterns of schistosomiasis transmission in Niger (involving African dry savana); in this field, we have shown, (i) the existence of important variability in conditions of transmission of S. haematobium *and, (ii) natural hybridization between parasitic species of the ruminants (*S. bovis *and* S. curassoni*) and genetic interaction between human and animal parasites; (b) definition of morbidity indicators usable for rapid assessment methods, for appraisal of the severity of the disease and for the evaluation of the efficiency of control methods; we have established the correlation between ultrasonographic data and some cheap and simple field indicators; (c) immune response and protective immunity induced by recombinant glutathion S-transferase (Sm28, Sb28 and Sh28) in homologous and heterologous animal models including goats, sheep and non human primates (*Erythrocebus patas*).*

In Niger, we participate in all control programs against schistosomiasis to define control strategies, to supervise operations and to participate in their evaluation with external experts. International collaborations constitute a frame including four laboratories in Africa and six laboratories in developed countries (Europe and USA).

Key words: schistosomiasis - epidemiology - vaccine - control strategies - Niger

The Centre de Recherche sur les Méningites et les Schistosomoses (CERMES) is a research institute depending on the Organisation de Coordination et de Coopération pour la lutte contre les Grandes Endémies (O.C.C.G.E.) - a West African Organization for Public Health - devoted to studies on schistosomiasis and meningitis. The staff includes 32 persons with 11 scientists and 1 financial officer. The annual budget is about US$ 200,000.

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Parasitology

Among problems raised by the study of schistosomiasis, those concerning the ecology of the transmission and the genetic interactions between *Schistosoma* species involving human (*S. haematobium*) or domestic ruminants (*S. bovis* and *S. curassoni*) are more particularly studied by the Unit of population genetic and schistosomiasis transmission.

The studies on the transmission ecology concern (i) experimental research on the *Schistosoma*-bulinid compatibility and, (ii) field surveys on the geographical distribution, population dynamics and actual role of snails involved in the transmission of *Schistosoma*. These studies appear to be essential to the implementation of control measures corresponding to the focus reality.

Also the genetic interactions involve both experimental researches and field surveys on the host recognition by *Schistosoma* (vertebrate and snail), the species identification when mating, particularly interspecies mating and viability of hybrids. These researches allow to apprehend the impact of genes flows on the transmission of parasite species, especially in the area of the extension of the definitive and intermediate host spectre.

The confrontation between field observations and laboratory results showed that in temporary pool foci, there is a wide variability of *S. haematobium* transmission modalities. We can schematically oppose foci of West Niger with those of Centre and East Niger. In West Niger, the main-

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tenance of *S. haematobium* is insured by *B. truncatus* and, in more marginal manner, by *B. senegalensis*, while in Centre and East Niger, *B. globosus* and *B. umbilicatus*, respectively, are the main hosts. In the cattle, *S. curassoni* is transmitted exclusively by *B. umbilicatus* and *S. bovis*, the only *Schistosoma* compatible with the five species of *Bulinus*, concerns apparently only three of them (*B. truncatus*, *B. globosus* and *B. umbilicatus*); the two others (*B. senegalensis* and *B. forskalii*) were never found naturally infested with *S. bovis*.

The analysis of the structure of mixed parasite populations (i.e. consisting in several species) in cattle, or obtained experimentally in ruminants, has clearly shown that *S. bovis* or *S. curassoni* did not show a strict host specificity. Mixed infections led to frequent heterologous mating, although less frequent than expected if randomized. The interspecies mating were fertile and induced large descendants at first generation with good viability both in snails and vertebrates. It has been already proven that human can be infected with such hybrids; so, it is necessary to organize proper field supervision of *Schistosoma* control.

The consideration of (i) the role played by the bulinids in the transmission of *S. haematobium*, (ii) the population dynamics linked with climatic factors (precipitation, temperatures), and (iii) the human behaviour (migration during the dry season, field occupation during cultivation), has allowed to determine the ideal period for a large scale treatment in temporary pool foci. Annual treatments have been performed since 1994, after the end of the transmission and after the pre-patent period. We were not able to carry on large scale treatment. However, results showed a drastic reduction of prevalence and egg excretion three months after treatment in all foci. A second examination of the human population has been undertaken in 1995 after a new transmission period. Some treated people have been re-infected and we observed an increase of prevalence but a lower parasite burden than observed during the first examination. This result demonstrated that treatments, even those given in small part of the population, can induce a strong impact on the transmission in this type of focus.

In parallel to these researches, some other works have been implemented, concerning (i) the evaluation of *Schistosoma* pathogenicity in cattle, (ii) the importance of the urinary schistosomiasis in schools related to the transmission in urban areas.

Epidemiology

The CERMES studies indicators of morbidity (urologic lesions visualised by ultrasonography) related to endemic level and their regression after implementation of control strategies. These researches are undertaken in several regions, including others O.C.C.G.E. countries (Burkina Faso), but they are more particularly developed in the project of urinary schistosomiasis control in the river Niger valley which is supported by European Community.

The morbidity induced by *S. haematobium* in children living close to rice fields of the river Niger valley has been evaluated by ultrasonography in 11 primary schools (673 examinations). A very high morbidity level has been observed in some of them, the prevalence of hydronephrosis aspects reaching 42%. Echographic investigations permitted to define rapid assessment methods based on the visual aspect of urine of school children to evaluate the morbidity. It has been applied in 64 villages of the zone, allowing to precise the strategy of praziquantel distribution (mass distribution or selective treatment).

The regression of lesions of the urinary tract after chemotherapy is supervized by ultrasonography in hyperendemic areas. Children received a standard dose of praziquantel after a clinic, parasitologic and echographic examination in January 1995. Since, a monthly follow up has been performed to observe the regression of renal and vesical lesions in parallel with the evolution of the other parasitological findings. Data would allow to determine the periodicity of treatments related to the regression of lesions, and to the rapidity of re-infection. The importance of indirect indicators for the appraisal of control strategies, especially the microscopic or macroscopic haematuria, will be confirmed. One observes that the treatment was 100% efficacy on the basis of parasitology, the prevalence of abnormal indirect indicators decreased regularly and, moreover, the prevalence of urinary tract lesions decreased dramatically one month after the treatment. On the other hand, at individual level, we observed that some lesions aggravated even after correct treatment.

Immunology

The Experimental Vaccine Unit is in charge of the evaluation of the immunogenicity and the efficiency of new vaccines. Regarding vaccines against schistosomiasis, researches undertaken at CERMES consist in vaccine trials in small ruminants and primates against the human urinary schistosomiasis (*S. haematobium*) and against schistosomiasis of ruminants (*S. bovis* and *S. curassoni*) using candidate vaccines to measure the efficiency and the tolerance. Our objectives are to improve methods of vaccination (choice of the adjuvant, route of the administration) and to propose a vaccine protocol applicable in the fields (number and

interval of booster injections).

Four antigens have been tested in goats (rSb28GST, rSm28GST, rSh28GST and SbSWAP which is the crude antigen of *S. bovis* adult worm). The injected antigens have released, after the second shot, an IgG response in all animals. The main difference concerned the response which is immediate and prolonged with the Complete Freund Adjuvant (CFA), more progressive and temporary with the Muramyl-Di-Peptide Adjuvant (MDP). Following injection with CFA, the immunological response was homogeneous although the MDP induced very heterogeneous specific antibody titres.

Trials with *S. bovis* antigen have shown that the vaccination significantly reduced the parasite burden, more in goats than in sheep. But, faecal excretion was paradoxically higher in sheep than in goats. Individual variations, both in vaccinated animals and in control, did not allow to conclude on an anti-fecundity effect because the number of excreted eggs and the number of intra-uterine eggs was fairly modified after vaccination. These results confirmed therefore that the immunization protocol using the rSb28GST, with CFA, seemed to concern the survival of the parasite rather than its fertility.

We try currently several protocols of infestation by oral route. This way of infection has been certainly underestimated regarding its importance in the transmission of parasite. Two modes of infestation have been tried, the first used a massive and unique dose, the second used a small but repeated dose, weekly for several months.

During the first protection test, animals were previously immunized by groups of three, using one of the three recombinant antigens (Sm28, Sh28 or Sb28) or the crude antigen of adult worm of *S. bovis* (SbSWAP). The infestation was performed using 2,000 cercariae administered in the drinking water. The interval between the last immunization and the infestation reached four weeks. We did not observe any protection, neither in terms of parasite burden, nor in terms of egg excretion, nor in terms of intra-uterine eggs. The second protection test included the infestations by oral route with fractionated doses (100 cercariae every week for five months). It simulated the better, in practice, to natural transmission conditions. The immunization was obtained after two injections at six weeks interval using five different doses (10-25-50-100-200 μg per injection) of rSb28GST with MDP adjuvant. Furthermore, in this case, the infestation was carried on 642 days after the immunization. Minimum doses were sufficient to reduce by half the faecal excretion.

Concerning the urinary schistosomiasis, we have carried on the first trials of immunization with the new rSh28GST recently cloned by the Centre d'Immunologie et de Biologie Parasitaires (CIBP) of the Institut Pasteur de Lille (Professor Capron). This antigen has been injected in patas monkeys according to six different protocols. The choice of the various adjuvants aimed to describe the different possibilities offered by the experimental model: the CFA was used as positive control, the B.C.G. and the aluminium hydroxide were authorized in human, and the liposomes, which could be (i) administered by oral route, an easier administration route in human, and (ii) able to induce an IgA response. The IgA isotype has been implied in *Schistosoma* anti-fecundity mechanisms.

We carried on a large scale experience in completely homologous conditions using 30 patas monkeys. The Sh28GST has been cloned using a strain from Niger. Two groups received the antigen associated with CFA or B.C.G. The B.C.G. has been chosen because of its wide global coverage (> 80%). The use of B.C.G. as adjuvant in human is effective with both the anti-*Leishmania mexicana* and the anti-leprosy vaccinations.

Experiments carried on in CERMES have confirmed the protection potential of candidate vaccines in all models that we used. Recombinant proteins seemed able to alter the development of the parasite by inducing either a reduction of parasite burden or an inhibition of the fecundity of parasites. We have also observed a reduction of the transmission and a clinic improvement of subjects protected. The good tolerance of the studied vaccine allows to envisage the trials in human in a near future.

Documentation and Training

The CERMES plays an important role in Niger to insure the training of the laboratory staff and the young physicians. Each year, we give courses and practices to pupils of the National School of Public Health. About ten medical thesis have been prepared in our laboratory.

The library of the CERMES comprises many books and article reprints, mainly in the schistosomiasis and meningitis area. We subscribed to about 20 international journals as well as to MedLine®. Our collaboration network spreads essentially on West African countries but comprises also European and North American laboratories.

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