

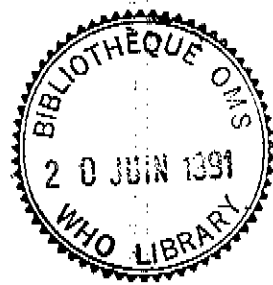


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UNDP/WORLD BANK/WHO SPECIAL PROGRAMME FOR
 RESEARCH AND TRAINING IN TROPICAL DISEASES

15-16 January 1991, Geneva, Switzerland



MEETING ON STRATEGIES FOR THE DEVELOPMENT
 OF A SCHISTOSOMIASIS VACCINE

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Ce rapport exprime les vues collectives d'un groupe international d'experts réuni par le PROGRAMME SPECIAL PNUD/BANQUE MONDIALE/OMS DE RECHERCHE ET DE FORMATION CONCERNANT LES MALADIES TROPICALES (TDR). Il ne représente pas nécessairement les vues du TDR/OMS et, en vue d'une diffusion accélérée, il n'a pas été l'objet d'une mise en forme particulièrement soignée. En outre, les noms géographiques utilisés dans le présent rapport n'impliquent, de la part du TDR ou de l'OMS, aucune prise de position quant au statut juridique de tel ou tel pays, territoire, ville ou zone, ou de ses autorités, ni quant au tracé de ses frontières.

1. INTRODUCTION

Invited from 15 to 16 January 1991 for a TDR consultation at WHO, Geneva, specialists on the immunology of schistosomiasis, together with vaccinology experts and representatives from major donor agencies, discussed research aimed at developing a vaccine against this disease. It was concluded that vaccines are feasible, and moreover that the specific antibody responses which have been shown to correlate with resistance to reinfection in human populations can provide leads for vaccine design. Information on such responses is, however, biased towards infection due to *Schistosoma mansoni*. The primary goal of the TDR-coordinated vaccine programme is to support the production and testing of candidate vaccine antigens including phase I and phase II trials of preparations shown to reduce worm burdens. Notwithstanding the risk of raising unreasonable expectations of short-term gains, it was felt that TDR support of vaccine development as a research priority will contribute to improved schistosomiasis control and, incidentally, provide a paradigm for the development of recombinant vaccines for parasitic diseases worldwide.

The meeting chairman, Professor N. Agabian, opened the first session by asking Dr J.A. Cook to give a brief introductory review of the activities and support given by the Edna McConnell Clark Foundation (EMCF) to research related to TDR. To date, US\$ 53 million had been used for this purpose. Research on schistosomiasis had received approximately US\$30 million, half of which had been spent on vaccine development. Dr Cook concluded that he envisaged future EMCF financial support for vaccine development being channelled through TDR.

Dr A.E. Butterworth reviewed approaches to the study of immunity against *S. mansoni* in humans (fishermen, canal cleaners, adult immigrants) and then presented the findings of longitudinal field studies carried out by his research group during the past 10 years in the endemic area of Machakos in Kenya. These studies had concentrated on the age-dependent, naturally-acquired resistance to reinfection after chemotherapy with praziquantel. He had found that reinfection occurred rapidly in young children but that the prevalence started to decline in the age groups over 12. At this age, the situation in relation to reinfection started to gradually improve so that, at the age of 24, more than 98% of investigated individuals were resistant. Moreover, there was a good correlation between levels of serum antibodies (IgE and to some extent also IgA) and this resistance. The studies were now enlarged to include also parameters such as other isotypes and antibody specificities, cytokines and T-cell responses.

Dr P. Hagan presented data on *S. haematobium* research in the Gambia. He had observed increasing signs of resistance 12 months after chemotherapy in children, 10-14 years of age, whilst there was a high prevalence of infection in children under 10. Two large studies on reinfection after chemotherapy corroborated these findings: children up to 9 years of age were fully sensitive to reinfection, whilst the 10-14 year age group was less sensitive and individuals above 15 were either resistant, even to high exposures of infection, or showed only a low rate of infection. In adults, there was an almost complete resistance to reinfection. Eosinophil counts correlated well with intensity of infection, specific IgE with resistance and IgG₄ with susceptibility to reinfection.

Professor G.F. Mitchell reviewed observations in *S. japonicum* infections in the Philippines and China. Reinfection after chemotherapy, based on egg counts, was quite high even in adults (70% after 18 months) but detailed serological investigations and studies on children had not yet been carried out. Animal experiments, however, had shown significant differences when

compared with infections due to *S. mansoni*: rats infected with high doses of *S. japonicum* looked healthy and had no eggs in the faeces, possibly due to anti-embryonation immunity; mice injected with *S. japonicum* irradiated cercariae were not protected against challenge although the same strain of mice showed up to 90% protection in the *S. mansoni* system; and *S. japonicum* infected mice treated with praziquantel were easily reinfected. Professor Mitchell also felt that faecal egg counts were less reliable in indicating infection due to *S. japonicum* than in infection due to *S. haematobium* or to *S. mansoni*.

Professor D.G. Colley introduced the general discussion of acquired immunity in humans by stating that encouraging results had been presented but he cautioned that many aspects have still to be studied. Several such points were raised, e.g. vaccine administration, oral vaccination, length of immunity, the poly-parasite situation in endemic areas, etc. In summing up the discussion, Professor Colley felt that there was agreement that:

- (a) development of improved indicators for measurement of worm burdens in humans is a priority;
- (b) vaccination of communities exposed to infections should be combined with chemotherapy. However, the opinions as to in which order this should be done were not uniform;
- (c) criteria for vaccine assessment should be considered in a clinico-pathological context using modern approaches, e.g. ultrasonography.

The meeting went on to review approaches to antigen presentation and immune recognition. Dr K. Lövgren presented data on how immune responses could be improved by preparing the antigen in the form of so-called immunostimulating complexes (ISCOMs). In this technique, the antigen molecules are attached by hydrophobic interaction to a Quil A glycoside matrix of plant origin. ISCOMs have already shown promising results in veterinary medicine and their suitability for improving the immune response to viral vaccines in humans is currently under study. Emphasizing the complicated interaction between parasite infections and the host immune system, Dr S. Buus reviewed the updated knowledge of immune recognition by B- and T-cells with special reference to unresponsiveness, e.g. defects in antigen processing, in MHC binding and in T-cell repertoires. Dr J. Young discussed the use of live vector delivery systems in general and of BCG in particular. He specifically referred to safety aspects, the importance of T-cell stimulation and the advantages of oral application.

Following this session, several aspects of immune response modulation were brought up for discussion. Microencapsulation, ISCOMs, liposomes, proteosomes and live vectors, all represent novel approaches offering the prospect of effective and affordable vaccines for widespread use. Although attenuated live vectors, such as BCG, Salmonella and Vaccinia, are sufficiently well known to permit considering their use in practice, it was felt that their potential risk to the human recipient would warrant further research. The avipox viruses, on the other hand, produce only abortive infection in humans and thus present a negligible risk. Peptide-based or mixed vaccines, T-cell subsets, cytokines and B-cell markers were also touched upon and it was thought that the use of the severe combined immunodeficiency (SCID) mouse could be worth considering for experimental studies of human immunity. The importance of being able to fine-tune immune response by using various ways of antigen presentation, including different adjuvant preparations to ensure prolonged contact between the antigen and the immune system, was emphasized. Although anti-idiotypic

vaccines have attractive features including the capacity to produce a relatively high degree of protection, this type of vaccine was thought to be impractical for large-scale production and distribution. Professor G. Ada led the discussion and closed the session by listing some important requirements. He felt that an acceptable vaccine should:

- (a) activate cells for antigen presentation;
- (b) generate a high yield of B- and T- memory cells;
- (c) include several epitopes to overcome variation; and
- (d) the antigen should persist after administration.

Professor A. Capron described his research strategy towards vaccination. In the *S. mansoni* system, immunization of experimental animals (mice, rats, baboons, patas monkeys) with schistosome glutathione-S-transferase (GST) reduced not only the worm burdens (mediated by IgE antibodies) but also worm fecundity and egg viability (mediated by IgA antibodies). The identification of a major T-helper cell epitope (amino acid sequence 115-131 of this antigen), important for the IgE response, had led to the proposal of producing a synthetic peptide vaccine consisting of a GST "octopus" (eight copies of this sequence coupled to a lysine core) in combination with other molecules.

Dr V. Houba informed the participants about a recent assessment of strategies for schistosomiasis vaccine development carried out by WHO (Microbiology and Immunology Support Services) at the request of EMCF. He distributed a draft report, based on the views of nine non-schistosomiasis experts in vaccine research, reviewing the updated strategies for vaccine development provided by 12 leading institutions in the field of schistosomiasis. The main conclusions were summarized as follows:

- (a) In spite of widely available, highly effective and safe chemotherapy, a vaccine is needed and its development and production are feasible.
- (b) Rather than identifying new vaccine molecules, detailed research on those already available, or combinations of these antigens, would be useful. Persistence of antigens may be important for vaccine efficacy.
- (c) Studies should focus on finding out whether or not immune responses in resistant individuals differ from those observed in subjects susceptible to infection. Since there is still a large gap in knowledge about the role of T-cells in resistance, the study of their effects should be included.
- (d) The criteria for vaccine assessment in humans have to be considered in a clinico-pathological context. It would be necessary to develop simple, accurate and non-invasive methods of measuring the protection achieved (worm burdens) by vaccination.

Leading the discussion after this session, Dr P.H. David raised the question as to whether the current concept of vaccination for partial protection would influence the transmission of the infection and whether mathematical modelling could be useful in this connection. Observing that the main vaccine candidates had been identified by antibodies, he wondered if T-cells could be used for selection of antigens. Concluding that these questions need to be investigated, the session ended on the note that the animal models do not actually reflect the situation in man. Although the SCID mouse might provide some answers, it was agreed that further important information has to come from human trials.

In the final session, Dr P. Reeve summarized the conditions necessary to finalize the preclinical stage of vaccine development. He did not feel that there were any major problems concerning the actual processes of development for a recombinant schistosomiasis vaccine but he underlined that several strategic issues must first be resolved before detailed planning of a schistosomiasis vaccine for humans can begin. In addition, economic, regulatory and liability issues are connected to the choice of expression vectors or synthetic system, antigen presentation and adjuvants including currently available live delivery vectors.

Drs D.I. Magrath and J. Dunne discussed the regulatory considerations for clinical trials, conditions of "good manufacturing practice" for pilot-scale production and other conditions for vaccine licensing. It was pointed out that ethical issues concern both the use of animal models and clinical trials. The predictive value of experimental models must be justified and stringent rules should apply in selecting animals for testing of vaccines. At the clinical-trial stage, it would be necessary to devise a protocol for estimation of protection and amelioration of symptoms. The risk for hypersensitivity reactions and disease potentiation would also need to be addressed. The age for vaccination would have to be decided in close collaboration with agencies responsible for other vaccination schemes, e.g. the WHO Expanded Programme for Immunization (EPI).

Dr Mott discussed vaccination in the context of control programmes, emphasizing the particular need for strengthening health services in countries with a high prevalence of schistosomiasis in order to ensure vaccine delivery. He supported his analysis with the following information:

- (a) in seven of the 39 African countries where the prevalence of schistosomiasis in the exposed population is greater than 52%, the capacity of delivering three-dose vaccines to children over one year of age is minimal;
- (b) in countries with over 45% coverage of three-dose vaccines, the total population is smaller, the population at risk for schistosomiasis is smaller, and the prevalence of schistosomiasis among the population at risk is lower than in other countries;
- (c) the prevalence of schistosomiasis is comparatively lower in countries with the highest coverage of a single-dose vaccine in children less than one year of age; and
- (d) in seven of the 37 African countries where the prevalence of schistosomiasis is 55% or more, the coverage with a single-dose vaccine is lower than in the remaining countries.

Dr T. Godal informed the participants that the development of a schistosomiasis vaccine is regarded as a high-priority project of the TDR programme. He mentioned that mixing rationale with a little empiricism had brought unexpected bonuses in other areas of TDR-supported research.

The second day was largely devoted to the study of different key questions. The participants were allocated to three study sections and the results of their elaborations were discussed in a final plenary session. The following conclusions and recommendations were reached:

2. EPIDEMIOLOGICAL EVIDENCE FOR RESISTANCE

In studies of human infection due to *S. mansoni*, resistance correlates well with the level of IgE antibodies against unpurified adult worm antigens. Preliminary data indicate that there is also a correlation with IgA responses against these antigens and that specific IgA responses to the *S. mansoni* GST antigen (Sm28) correlate with resistance. In contrast, IgM and IgG₂ antibodies against carbohydrate epitopes expressed in several schistosome life-cycle stages correlate with the high susceptibility of young children to reinfection after treatment and may act as blocking antibodies. IgG₄ antibodies against Sm28, or other adult worm antigens, may also act as a blocking mechanism.

In studies of *S. haematobium* infections, IgE specific for adult worm antigens (and egg constituents) show a correlation with resistance, while IgG₄ antibodies against the same antigens correlate with susceptibility. In this case, there is no correlation between IgM and susceptibility but in children, aged 8-13 years, the level of peripheral blood eosinophils correlate directly with resistance.

To date, the specific antibody responses in individuals infected with *S. japonicum* have not been assessed and thus should be encouraged.

Furthermore, functional analyses of cell-mediated responses have not been adequately assessed in infections due to any of the schistosome species infectious to humans.

3. CANDIDATE VACCINE MOLECULES

A limited number of vaccine candidates have reached the stage at which development with the objective of trials in humans might be considered. At the moment, this group includes the glutathione-S-transferase (GST) enzyme family, paramyosin or Sm97, and triose phosphate isomerase (TPI). Furthermore, there are many additional schistosome antigens of potential utility, at various stages of development and testing. Different types and characteristics of antigens to be selected for continued development were discussed and the following recommendations were made:

- 3.1 Priority should be given to protein antigens, presumably recombinant ones, rather than carbohydrate vaccines.
- 3.2 Synthetic peptides were considered particularly useful in permitting the selection and use of only those epitopes deemed advantageous and the construction of molecular designs in which those epitopes are presented in immunogenic arrays. Although initial trials could involve the use of full-length recombinant proteins, continued development of appropriate multiple epitopic constructs would be useful. Study designs should include considerations of potential genetic restrictions of host immune responses which might be encountered with these materials.
- 3.3 The development of vaccine antigens relying on criteria other than those of immune responses to natural infections might provide alternative vaccination strategies. Currently, however, there is neither positive nor negative evidence to suggest that stage-specific vaccine targeting would lead to more effective immunization.
- 3.4 There is evidence that the host may develop beneficial anti-fecundity and anti-egg responses, separable from the immunopathological reactions

leading to granuloma formation. Since these beneficial immune responses may well fit into the ultimate efficacy of a combined vaccine, research in this area should be further encouraged. Nevertheless, the primary goal remains the development of candidate vaccines capable of reducing the worm burdens normally elicited by reinfection.

- 3.5 The role of IgA is intriguing and deserves serious study. Its antigen targets, as well as those of IgE, and their distribution in different life cycle-stages, should be identified. Such antigens would be considered as vaccine candidates, should transfer experiments clearly demonstrate the protective efficacy of these antibody classes.
- 3.6 The expression vector providing the most effective production for any given candidate vaccine antigen should be determined and selected on a molecule-specific basis. Effective production would usually be the production of the antigen in its native conformation and in useful amounts.

4. IMMUNE RECOGNITION AND ANTIGEN PRESENTATION

Given the evidence correlating antibody responses and resistance to reinfection, the following research objectives were recommended with particular reference to induction of preferential individual isotypes:

- 4.1 There is no requirement to induce MHC I restricted cytotoxic T-cell responses but other studies of T-cell regulation involved in the defence against schistosome infection is needed, e.g. further correlative studies to test the possible role of T_{H1} -like effects with macrophage activation in humans.
- 4.2 At the moment, priority should be given to induction of antibody responses, in particular of those immunoglobulin classes shown to correlate with natural resistance to reinfection. Although IgE and IgA responses have been implicated in this connection, the possibly protective role of certain IgG isotypes (such as IgG₁ and IgG₃) should not be excluded.
- 4.3 Research should focus on antigens which selectively stimulate useful immune responses as opposed to those which also result in the production of antibodies that block desirable immune responses or which promote pathology.

5. PASSIVE TRANSFER EXPERIMENTS

Current conclusions regarding human resistance against schistosomiasis, based on correlative community-based studies, can now be directly investigated by passive transfer studies in human subjects. Such studies could be carried out in treated young (susceptible) children who cannot avoid subsequent exposure to natural reinfection, using pooled plasma from naturally-infected adult donors screened for high levels of specific IgE and/or IgA, or of IgE-, IgA- or IgG-enriched fractions. A similar strategy could be used for testing the protective effect of antibodies induced by vaccination in non-endemic adult volunteers participating in phase I clinical trials.

6. VACCINE DELIVERY SYSTEMS

As information accumulates regarding the advantages of any specific protective immune response induced by the candidate vaccine, suitable delivery systems should be chosen to provide preferential stimulation of those responses. Safety aspects would need further investigation, particularly with reference to the potential risk to the recipient of live delivery systems. The criteria for ultimate delivery systems should include ease of incorporation into existing immunization programmes and ease of passage through regulatory stages. The cost of vaccine delivery should be considered but it should not be a factor in determining the most effective way of inducing immunity. The following recommendations were made:

- 6.1 The stimulation of long-lived antibody responses with a simple immunization schedule should be sought. In the case of peptide-based vaccines requiring carriers, preference should be given to the use of proteins derived from the schistosome so as to achieve boosting by natural infection.
- 6.2 In the case of a non-infectious type of vaccine, a standard formulation already acceptable to licensing authorities, such as, for example, an alum-precipitated recombinant antigen or a peptide-carrier complex, would be preferable.
- 6.3 Single-dose methods of immunization would need to be developed for stimulation of IgE responses since multiple administrations could risk inducing anaphylactic reactions in a proportion of the population being vaccinated.
- 6.4 If evidence can be obtained for a strong correlation between resistance and specific IgA levels with a particular antigen, priority should be given to inducing mucosal immunity by intranasal or oral antigen administration. Such vaccine candidates could include certain control release preparations, e.g. conjugates and/or fusion products with the beta subunit of cholera toxin, and live vectors such as adenovirus, BCG and Salmonella .
- 6.5 Efforts should be made to achieve multiple stimulation, for example, by including both B- and T-cell epitopes.

7. PRECLINICAL TESTING

A great deal of knowledge on the effects of schistosomes in experimental animals has been collected but no particular animal model is known to correspond well to the situation in the human hosts. However, taken as a whole, results from the different animals used provide important information which may apply to the immunological mechanisms operating in man.

- 7.1 Mice are useful in examining different aspects of pathology, both in vaccinated and challenged mice and in vaccinated, previously treated animals, and provide a stringent test of vaccine efficacy. Mice could also be used to examine potential anti-fecundity effects. The potential use of SCID-mice for adoptive transfer studies with human cells should also be explored.
- 7.2 Rats can be used for studies of vaccine immunogenicity and efficacy.

- 7.3 Baboons might be considered for assessment of the safety aspects of vaccination with reference to the risk of inducing autoimmunity with candidate antigens resembling "self".

8. SELECTION OF SITES FOR VACCINE TRIALS IN HUMANS

The definition of specific vaccine trial sites would require input from the local authorities. The most suitable locations would be those where established links have already been made and where some information regarding the epidemiology of infection are available. Countries where trials could be contemplated would include Brazil, Burundi, Egypt, Kenya and The Gambia. One potentially suitable site for phase II trials has been identified in Northern Senegal, where schistosomiasis is currently spreading in an immunologically naive population. Close cooperation would be needed with on-site health care staff whose involvement at an early stage should be encouraged.

9. SELECTION OF SUBJECTS FOR VACCINE TRIALS

- 9.1 Preliminary safety testing (phase IA trials) should be carried out in healthy young male volunteers living in non-endemic countries.
- 9.2 Further safety testing (phase IB trials) should be conducted in a rural poly-parasitized population in which there was known to be no schistosome infection. Army recruits, for example, might provide one target group. These trials were felt to be important to safeguard against hypersensitivity reactions which might be induced as a result of cross-reaction with other helminths.
- 9.3 Preliminary efficacy testing (phase II trials) should initially be conducted in infected people who have already been treated. The presence of blocking antibodies in very young children might influence the response to the vaccine, so the best target would be the group between 8 and 10 years of age who would also be likely to have a high (and fairly uniform) exposure to reinfection. Older children or young teenagers would be unsuitable for vaccine testing due to a probably high degree of naturally-acquired resistance. Immunologically-naive immigrants to endemic areas, or residents in new endemic foci, constitute alternative target groups. Due to the unknown, but potential, risk of pathology, cercarial challenge in immunized volunteers was considered unacceptable.
- 9.4 Extensive clinical trials (phase III) and post-registration field research (phase IV) were not discussed but would follow in due course.
- 9.5 The recruitment of humans, particularly children, into any trial phase needs to be specifically addressed as an ethical issue. To that end, all clinical trial protocols should be submitted to the WHO Secretariat Committee on Research Involving Human Subjects (SCRIHS) and trials should only start after they have been cleared by this body.

10. VACCINE EVALUATION

The development of a product to be used for vaccination against schistosomiasis would ultimately need to be licensed in each country of use. For this purpose, all preclinical and clinical data, including information on the specific indications for the vaccine and the population groups targeted for

receipt of it, would need to be presented to the appropriate national regulatory authority. To achieve this, double-blind placebo trials were deemed necessary but professional statisticians would be consulted at an early stage to advise on the details of any clinical study. Evaluation of the effects of vaccination would rest on the following considerations:

- 10.1 Vaccine efficacy would be judged by egg counts; in intestinal schistosomiasis by repeated Kato stool examinations and in infections due to *S. haematobium* by multiple urine filtration tests.
- 10.2 A strong recommendation was made to involve antigen-detecting assays, e.g. the circulating (schistosome) anodic antigen (CAA) assay. However, this assay would need to be validated by other groups and to be made more widely available. The need for a standardized kit type of immunoassay was emphasized.
- 10.3 Clinico-pathological studies, including ultrasonography, should be included for evaluation of progress or regress of pathological lesions due to schistosomiasis.

11. GENERAL CONCLUSIONS

Currently available information primarily relate to *S. mansoni* and the above-mentioned aspects therefore mostly concern this species. Since epidemiological and immunological studies have shown clear evidence of resistance in adults naturally exposed to *S. haematobium* it was recommended that research on this species be given particularly high priority. Further study at the molecular level was recommended in order to identify suitable homologous vaccine candidate molecules from this species. Considerably less is known about *S. japonicum* infections and more basic studies will be required in this case.

Since the schistosome parasite does not replicate in the human host and the pathological damage sustained is directly proportional to the number of eggs retained in the host, it was concluded that even a partially protective vaccine would be useful. However, the required level of protection needed for a significant impact on morbidity remains to be investigated.

Candidate vaccine antigens selected for phase II vaccination trials would be required to undergo exhaustive testing in experimental animal models prior to human studies but it was recommended that passive transfer studies in humans be considered to be conducted directly. It was further recommended that all candidate vaccine molecules be submitted for WHO/TDR sponsored, comparative, independent vaccine testing, singly or in combination, in standardized laboratory model systems. The following criteria should be met for any preparation worthy of consideration for such accelerated evaluation.

- 11.1 The antigen, or its immunogenic portion(s), should have been chemically defined. In the case of protein antigens, this would involve cloning, expression and DNA sequence analysis.
- 11.2 It should have been shown to induce reproducible and significant reduction in worm burdens and/or fecundity after challenge infection in more than one existing rodent model.
- 11.3 Evidence of immune responses against the putative immunogen correlating with resistance to reinfection in humans would be desirable.

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