plexity of the health service system so as to improve the performance of activities in its area of competence.

- To formulate the type of training for each level.
- To use—as needed at each level—the resources available for training: in-service training, workshops, courses at a distance, INE courses, courses for public health graduates, and special basic and refresher training courses.
- To promote access for management levels to courses of practical content that will enable them to process and analyze data for application in the health field, and to promote access for personnel at operational levels to courses stressing the importance of proper data generation.
- To maintain a system of continuing education in occupational training and assure access to it at the levels of higher complexity.
- To strengthen the documentation centers (INE, public health schools, health secretariats, and PAHO) with updated bibliographies, and to circulate the most important material.

General Research Guidelines

- To carry further the analysis of mortality and its trends as an approach to the diagnosis of the health situation and to improve the quality of data.
- To evaluate the information on morbidity, particularly as to its quality.
- To explore other data sources and classification criteria.
- To study risk factors so as to take preventive action against modifiable conditions, and to devise predictive instruments for the purpose of identifying high-risk population groups for special care. Risk factors for some harmful conditions identified could be used in intervention strategies or to verify their local importance.
- To evaluate the impact of intervention measures and the use made and functioning of health services, activities, and technologies.

Malaria Vaccines: State of the Art

Background

Despite the remarkable results of the intensive efforts made against malaria between the 1950s and the 1970s, the disease has remained a major health problem in many tropical and subtropical countries.

The situation during the past 15 years clearly shows that the worldwide elimination of malaria cannot be achieved with currently available means, and the present antimalaria strategy is therefore based on realistic concepts of malaria control within the general strategy of primary health care.

However, even at modest target levels of malaria control, the same constraints that aborted global malaria eradication will continue to operate, namely financial and administrative difficulties as well as technical problems. The latter include widespread resistance of anopheline vectors to insecticides, the occurrence and spread of chloroquine resistance and the increasing development of multidrug resistance of *Plasmodium falciparum* in large tropical areas, the exophilic behaviour of certain anopheline vectors, and factors associated with human ecology such as migration and social attitudes. These obstacles have made the traditional antimalaria armamentarium less effective.

In reaction to this most unsatisfactory and dangerous situation, the UNDP/World Bank/WHO Special Program for Research and Training in Tropical Diseases in cooperation with the Malaria Action Program has planned and implemented research aiming at the improvement of malaria control. Part of this program pursues the development or improvement of tools and methods of the traditional type, while another part is devoted to the exploration of innovative approaches such as vector control through biological agents, and the control of the malaria parasite through vaccines.

Research on immunization against malaria has made outstanding progress over the past years so that there is a distinct possibility that malaria vaccines will play a role in malaria control in the not too distant future.

Current Approaches to Malaria Vaccine Development

Until approximately six years ago, before the advent of the cell fusion (hybridoma) technique for the production of specific monoclonal antibodies, most research towards malaria vaccines was based on the use of whole parasites as antigens. Although this approach proved to be successful with whole, inactivated sporozoites of *P. falciparum* and *P. vivax* in man, it has been realized that the quantities of antigen required were quite substantial. This has been ascribed to the simultaneous challenge by a multitude of antigens, the
The gene encoding the protective sporozoite antigen of *P. falciparum* has been cloned and the antigen produced in *Escherichia coli*. The immunodominant epitope has been synthesized chemically and the possibility of producing the antigen in vaccinia and other genetically engineered microorganisms is being explored. Several putative protective antigens of the asexual erythrocytic stages of *P. falciparum* have been identified and the genes coding for some of these have been cloned. The target antigens of transmission-blocking immunity have been identified and gene cloning is in progress. It is therefore clear that several candidate antigens/vaccines will become available for evaluation before long.

### Cautions and Reservations

The development of malaria vaccines is an entirely new area, and much of the current enthusiasm in this field is based on optimism and hope. There is good justification for this attitude on the basis of experimental studies, but this does not exclude the possibility of failure in producing vaccines which are cheap and well tolerated and do confer high protection of long duration. A variety of technical questions are also awaiting solutions, namely the selection of suitable carriers and, if so required, adjuvants.

Probably all these problems will be adequately solved given sufficient time, but even then caution is required with forecasts regarding the operational availability of malaria vaccines since there is a long way from the essential preclinical development to the completion of Phase III trials in humans, i.e., the moment that a vaccine can be registered.

### Expected Contributions of Malaria Vaccines to Malaria Control

Current indications are that the three types of malaria vaccine will become available for field testing and that each will possess its own functional characteristics. A sporozoite vaccine, if fully effective, would prevent the successful establishment of plasmodial development in the host and thus induce sterile immunity. Parasitaemia, asexual or sexual, would therefore not occur; clinical illness would not supervene and the subject would remain incapable of infecting mosquitoes. A vaccine of this type if applied to human populations sufficiently widely could effectively interrupt the natural transmission of malaria, irrespective of the prevalent endemic level. However, subjects effectively immunized against sporozoites would probably remain susceptible to challenge with asexual erythrocytic stages of the parasite and, following such challenge, i.e., transfusion of infected blood, would show para-
sitaemia and clinical illness and would develop gametoctyaemia and become infectious to mosquitoes. The operational indications of the sporozoite vaccine will largely depend on the duration of protection. In determining the operational indications, it will be important to assess the role of natural challenge as a potential booster of protective immunity.

An asexual erythrocytic stage vaccine is expected to induce an immunity which operates by restricting the replication of asexual blood stage parasites without necessarily inducing sterile immunity. Consequently its function will be to reduce the morbidity and mortality due to malaria. However, persons immunized by this type of vaccine will probably remain susceptible to sporozoite infection and the parasite’s development in the liver will occur unimpeded; low grade asexual parasitaemia may occur and gametocytogenesis may evolve normally so that immunized persons would remain capable of infecting mosquitoes. Asexual blood stage vaccines, therefore, seem unlikely, if used alone, to achieve the interruption of transmission of malaria in any endemic area.

Asexual blood stage vaccines would be used in highly susceptible groups in endemic areas to induce a level of immunity that would prevent serious illness following infection. The objective would be to confer a degree of protection equivalent to that which develops only after several infections in endemic areas. Infection might boost the vaccine-induced immune response.

The third type of vaccine will operate by inducing in the human host serum antibodies which effectively block the fertilization of females by male gametes within the mosquito gut or inactivate the fertilized zygote or the ookinete. Such transmission-blocking vaccines seem capable of interrupting malaria transmission at the mosquito level, but will neither protect the human host against sporozoites, hepatic forms, and asexual blood stages nor prevent the development of gametocytamia. However, they are expected to reduce the overall rate of malaria transmission in endemic areas and thereby play an important role in malaria control. Such vaccines would be used in combination with a protective vaccine against sporozoites and/or asexual erythrocytic stages.

Of the three different types, only the asexual blood stage vaccine would seem likely to induce an immunity similar to that acquired by populations living in highly endemic regions. The most appropriate circumstances for the use of an asexual blood stage vaccine on its own may, therefore, be in areas of high endemicity where it may be used specifically for the young children of the community, particularly those under four years of age who bear the burden of malaria morbidity and mortality. The aim here would be to induce in the young child by limited vaccine administration an immunity which would eliminate serious morbidity and mortality, while still permitting reinfection and gametocytogenesis which would continue to boost the vaccine-induced immunity.

Sporozoite and transmission-blocking vaccines, which might be used with the aim of interrupting transmission, will both need to be administered to all ages in as complete a coverage as possible to be effective. Repeated vaccination at such intervals as are required to maintain effective immunity would also be necessary until interruption of transmission is achieved. Both sporozoite and transmission-blocking vaccines may have special application in limiting the epidemic spread of malaria, while the sporozoite vaccine seems especially suitable, as an adjunct or a replacement of personal drug prophylaxis, for the protection of non-immunes who enter endemic areas for occupational or recreational reasons, particularly in areas where drug-resistant parasites are prevalent. A sporozoite vaccine could also be used for the protection of young children in highly endemic areas, although booster doses may be required. Such usage could with time reduce natural infections and require extended vaccination of other, older groups.

Eventually, when all three vaccine types are available, their use in combination may be desirable. However, it must be realized that epidemiological, economic and logistic considerations may impose the use of single rather than multiple vaccines. Apart from the specific requirements of safety and efficacy assessment, such factors will also demand that all vaccine types be tested and evaluated independently in field circumstances before their use in combination is tested.

**Ethical Aspects of Malaria Vaccine Trials**

All trials should be conducted in accordance with the principles laid down by the World Medical Assembly of 1975 on Ethics and Human Experimentation and this aspect of the studies will be paramount. Informed consent of volunteers must be obtained in every case during Phase I-III trials. In tropical countries this means that the information should be given to the volunteer in writing or translated into a language and form that are well understood by each person concerned. In trials involving infants or children informed consent should be obtained from relatives in accordance with national legislation.

Each trial protocol should be agreed upon or prepared by the principal investigator involved, signed by him and approved by a local/national ethical committee. The safety of the volunteers in the trial is the primary consideration of the ethical committee in giving its approval of the study and of the principal investigator in carrying it out. However, the relevance of
the study and the chance of acquiring useful knowledge from it must also be considered before approving any new project.

Vaccine Development Phases

Preclinical development

The primary purpose of preclinical studies of advanced candidate experimental vaccines is to produce information on which to base a decision on whether to proceed with Phase I clinical trials (such preclinical studies are therefore often referred to as Phase 0). In addition, the data obtained are frequently used to improve or modify the experimental product and to gain insight into expected results in humans. Evidence is required which supports the proposition that the experimental vaccine is safe for use in man and that it will produce functional immunity. Requirements depend upon the type of vaccine and method of manufacture but in general are based on specific analyses and on in vitro and in vivo tests which characterize, as far as possible, the product in terms of content, purity, sterility, immunogenicity and toxicity. The experimental vaccine proposed for clinical trials should be produced in accordance with Good Manufacturing Practice and tested following the guidelines published by WHO and by national regulatory authorities.

Clinical and Field Trials of Malaria Vaccines

The overall objectives of malaria vaccine trials are the assessment of the safety, tolerability, and efficacy of the vaccines in individuals of different age, ethnic or geographical origin and malaria experience, as well as the determination of optimum conditions for the induction and maintenance of functional immunity. Furthermore, the epidemiological impact of immunization against malaria should be determined, including assessment of the acceptability of and compliance with immunization procedures in communities or population groups exposed to malaria risk.

The following phases of clinical and field trials have been defined:

Phase I. Trials, initially carried out in healthy adult male non-immune volunteers, will take place under close medical scrutiny and be sited in areas where malaria is not endemic. The objective of these trials will be to assess human local and systemic tolerability and immune responses to a malaria antigen(s) which has been shown to be safe and immunogenic during preclinical (Phase 0) studies. The test vaccine will be administered to determine the optimal dosage schedules for Phase II trials. The trials may also include comparison with a carrier, if included in the vaccine(s) and with a placebo, and will be double blinded whenever feasible. The conduct of such trials should comply with local/
section, the test provides also a *Plasmodium* species diagnosis of the sporozoites. For better applicability the original radioimmunoassay has been adapted to the use of enzyme markers.

Antigen detection tests and DNA probes hold considerable potential for improving and simplifying malaria diagnosis. While in an earlier phase of development, sensitive methods are already in field evaluation, preliminary results of which are encouraging.

(Source: Statement on the Development of Malaria Vaccines, Document WHO/MAP/TDR, 1985.)

---

**Biotechnology: Its Potential for Health in Latin America and the Caribbean**

The knowledge that has been explosively produced in recent years in microbiology, molecular biology, biochemistry, genetics and other disciplines has set off an unprecedented development of biotechnology and given it an increasingly important part to play in the socioeconomic advancement of countries. Judicious application of the latest discoveries in gene-splicing, the production of monoclonal antibodies, protein engineering, etc., to the solution of problems in the fields of health, food production, energy and the environment has given birth to technologies that have made themselves felt in the industrialized countries. The effort to control diseases and conquer health has already scored triumphs whose implications are publicized almost daily in the mass media.

Biotechnology is a general term that includes any technique that uses living organisms (parts of organisms or products obtained from such organisms) to produce or alter products, to improve animals or plants or to develop microorganisms for specific purposes.

One important feature of biotechnology is its interdisciplinarity, for it relies on the basic sciences, although popular lore and tradition have been decisive factors in many biotechnological advances. Since the dawn of civilization, human societies have deliberately selected organisms for the improvement of crops, livestock, the quality of foods, and the preparation of fermented products. As biology has elucidated the functioning of the cell, and particularly its molecular and regulatory mechanisms, it has become possible to develop more efficient production processes.

One of the outstanding features of biotechnology is that the entire process can go forward at different levels of scientific and technical knowledge. Between the popular lore of traditional biotechnologies and the basic knowledge of modern science there is a whole gamut of degrees of biotechnological sophistication.

Traditional biotechnological processes arose out of empirical practices such as the production of fermented liquids and bread. Today, the advances made in cell biology, molecular genetics and biochemistry have spurred the development of a modern, or new biotechnology (NBt). This is the name given to the use of organisms modified by the recombinant DNA (rDNA) technique. With this technique the genetic makeup of organisms can be changed at will. NBt also embraces procedures based on cell fusion, which include the fusion of plant protoplasts and the production of hybridomas that secrete monoclonal antibodies.

Whereas traditional biotechnology selects plants, animals and microorganisms created by cures of varieties or gene transfers mediated by natural mechanisms, NBt switches the specific genes that code for a desired character through direct chemical manipulation of the chromosomes of the donor and recipient species. In this way interspecific barriers are surmounted and chimeras can be developed that express foreign genes on a high-yielding industrial scale. Thus, insects can be obtained that express mammalian genes, plants that express microbial genes, bacteria that express human genes, fungi that express components of viruses of higher mammals, and viruses that express proteins of other species of virus.

The cell (or viral) genome can also be dissected to obtain organisms without the genes that make them pathogenic. This opens up a new strategy for the production of vaccines and new methods for the control of animal and plant diseases based on the substitution of modified microorganisms in certain ecological niches.