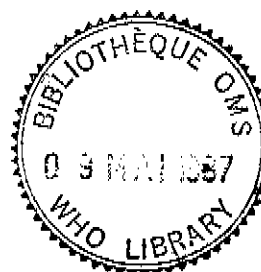




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REPORT ON
 INFORMAL DISCUSSIONS ON AIDS VACCINE EFFICACY
 TRIALS IN HUMAN POPULATIONS

Geneva, 15-16 December 1986

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1. Issues related to AIDS vaccine development

The World Health Organization has recognized a responsibility to assume a lead role in global efforts to combat the pandemic of infection with the human immunodeficiency virus (HIV). Current prevention and control efforts are focused primarily on health education and communications and on HIV antibody screening of blood for transfusion. However, a safe and effective vaccine to prevent HIV infection would be a significant addition to prevention programmes. In anticipation of the need for clinical testing of candidate vaccines, the WHO Programme on AIDS organized an informal meeting, held in Geneva from 15 to 16 December 1986, to discuss AIDS vaccine efficacy trials in human populations.

Dr Halfdan Mahler, Director-General of the World Health Organization, welcomed the participants, stressed the importance of scientifically rigorous human efficacy trials of any vaccine and emphasized that failure to prepare in advance for such trials involving AIDS vaccines could seriously delay vaccine availability to the entire world. The participants were asked to identify areas of potential concern in clinical trials and to make recommendations to WHO about its role in helping to anticipate and address these issues.

Dr F. Mhalu (Tanzania) chaired the meeting, and Dr L. Kallings (Sweden) and Dr C. Quinnan (USA) served as rapporteurs.

1.1 Current status of AIDS vaccine development

The prospects for development of a vaccine to prevent HIV infection appear encouraging. However, substantial uncertainty remains since no vaccine against retroviruses of the lentivirus group has been shown to be effective. Laboratory efforts to develop candidate vaccines are in progress in several countries.

Among the structural antigens of HIV, epitopes of the envelope antigen are considered likely to be important in protective immunity. Antigenic variation in this protein may result in a need for a multivalent vaccine. A number of laboratory preparations derived from the envelope protein gene have been produced, including proteins produced in *Escherichia coli* and animal cells by recombinant DNA techniques, recombinant live viruses (e.g., vaccinia and adenovirus), synthetic peptides and anti-idiotypic monoclonal antibodies. Efforts to develop HIV-specific immune globulin are also in progress. These laboratory preparations are in various stages of *in vitro* or animal testing. Some laboratory preparations induce neutralizing antibodies in small animals and primates. Several laboratory preparations are being tested in chimpanzees, since the quality of the immune response induced is likely to be similar to that in man, and chimpanzees may serve as a useful model for viral challenge studies. Current progress of testing in animals suggests that some laboratory preparations could become available for preliminary testing of immunogenicity and safety in humans (phase I clinical trials) during 1987.

However, the development of a vaccine of proven efficacy and safety, should it be feasible, is a long-term objective that, at best, will take several years to accomplish. Success will be dependent upon many factors, including:

- (a) Appropriately designed clinical trials;
- (b) Meticulous laboratory and clinical evaluation;
- (c) Inclusion of appropriately defined target groups in vaccine development programmes;
- (d) Resolution of complex ethical, legal and socio-political issues

1.2 Design of clinical trials

The stages of vaccine development involve both preclinical and clinical studies. Before clinical trials can begin, products intended for immunization of human beings should be tested *in vitro* for composition, purity and stability. Immunogenicity and absence of unacceptable toxicity should be demonstrated in appropriate animal models. Clinical trials of vaccines are then generally conducted in phases.

Phase 1 trials are open studies conducted in a small number of healthy adult volunteers (10-20 individuals) to exclude serious unexpected toxicity. Normally, immunogenicity is also evaluated on a limited basis.

Phase 2 trials involve larger numbers of healthy volunteers (100-200 individuals) and are intended to extend knowledge on immunogenicity and adverse effects. Phase 2 trials also define optimal dosing as well as spacing of repeated injections. These trials are usually randomized and are often double-blinded.

Phase 3 trials are intended to determine vaccine safety and the extent to which a vaccine provides protection against disease. In the case of an HIV vaccine, protection against infection could also be determined. The size of the study population is determined by the estimated incidence of infection within the group during the study period and the level of protective efficacy required of the vaccine. These trials are usually randomized, concurrently controlled (e.g., placebo), and double-blinded.

The major objectives of efficacy studies for AIDS vaccine need to be precisely defined at the onset (e.g., prevention of infection, prevention of disease). The laboratory and clinical parameters chosen to measure efficacy should be selected on the basis of practicality and relevance to the size of the study and its duration, as well as their biological significance. Randomized, placebo-controlled studies are likely to be essential, but alternative study designs may be of value. When placebo-controlled studies are used, the need for placebos must be justified. However, the decision to conduct a study that is not placebo controlled should also be carefully explained. Study size and duration are inter-related and can be estimated once efficacy parameters and numbers of potential subjects in individual target groups are known. Specific study sites will need to be defined and programmes established for volunteer recruitment, counselling, clinical and laboratory evaluation, and follow-up. Plans regarding study design, size, duration, and site will need to account for the possibility that multiple candidate vaccine preparations may be available. The clinical evaluation of several candidate vaccines will need to be closely coordinated to ensure comparability of the data.

1.3 Laboratory and clinical evaluation

To facilitate interpretation of data from several testing sites on vaccine immunogenicity, adverse effects, and efficacy, a standardized set of laboratory and clinical evaluations will be needed. Evaluation of immunogenicity will include measurement of serologic and cell-mediated responses to vaccine. The ability to distinguish vaccine vs natural infection induced immune responses is important. Detection and evaluation of adverse effects will be based on information obtained from the history, physical examination, and haematologic, immunologic, and clinical chemistry laboratory testing. A less detailed assessment of safety will be required for Phase 3 trials. However, Phase 3 trials should include evaluation of a variety of viral, immunologic and clinical parameters to allow determination of the immunologic responses that correlate best with protective efficacy.

Standardization of laboratory and clinical evaluations is essential. Standardization efforts should include the use of uniform procedures and reporting parameters (e.g., laboratory units) as well as the development and distribution of standard reagents.

1.4 Definition of target groups and their inclusion in clinical trials

Issues relating to selection and preparation of vaccine recipient groups for testing include:

1. criteria for inclusion into or exclusion from a study;
2. use of high-risk or low-risk populations in Phases 1, 2 and 3;
3. high risk populations of particular interest;
4. the geographic location of studies; and
5. the background data on study population required before studies begin.

1. Medical criteria to be considered for entry into studies can be divided into general health status and evidence of prior infection with HIV or HIV-related retroviruses. Participants in all three phases should be in good general health. Since the primary goal of a vaccine is to prevent HIV infection in vaccine recipients, only persons without evidence of prior infection with HIV or HIV-related retroviruses should be included as study subjects.

2. Degree of risk of acquiring HIV infection is a selection criterion: the desired degree of risk will probably vary among Phases 1, 2 and 3. Phase 1 participants should generally be of low risk so that measures of immunogenicity will not be confused by prior exposure or by intercurrent natural infection around the time of vaccination. Phase 2 participants may need to include both low- and high-risk persons, low-risk persons for assessment of immunogenicity and high-risk persons because safety should be assessed in this group before starting phase 3 studies. Phase 3 studies will generally require high-risk persons so that sample sizes and duration of study can be limited.

3. Among persons at potentially high risk of exposure to HIV, there are several groups of interest: sexually active young adults of both sexes, pre-adolescents about to enter the sexually active age group, young children at risk for infection by injection and blood transfusion, and newborns at risk for perinatal infection. These groups may be included in a single Phase 3 study or tested separately.

4. Geographic site requirements will probably differ for Phases 1, 2 and 3. Technical issues important in site selection include availability of necessary health care and laboratory personnel and facilities, and of adequate numbers of subjects with appropriate health, education, and risk characteristics. Testing candidate vaccines in several geographic settings (e.g., tropical and temperate zones) and in several populations (e.g., intravenous drug users, heterosexuals, homosexual men) may also be necessary.

5. Background data on study populations are required before Phase 3 studies can begin. These data should include the prevalence and incidence of HIV infection in the study population as well as an assessment of residual risk for uninfected persons in a particular high-risk group. The assessment of residual risk is important because uninfected persons in high-incidence, high-prevalence populations may be resistant to infection in some way or at low risk of infection because of behaviour to avoid exposure and therefore not truly at risk.

1.5 Ethical, legal and socio-political issues

The development and testing of any candidate AIDS vaccine should follow a standard procedure which takes ethical, legal and socio-political considerations into account. Pre-clinical laboratory and animal testing should always precede clinical trials. Clinical trial participants should always be volunteers who are free of coercion by their government, employer, or academic superior, and who have given informed consent. Studies in children should be preceded, whenever possible, by all appropriate tests in adults. All study plans should have been reviewed by an ethical committee and should contain provisions for liability coverage as appropriate to the local conditions, in the event of adverse reactions to vaccine.

In addition to following these general guidelines, AIDS vaccine study plans should take into account issues related to the following four areas:

- (1) study design
 - (a) use of placebos;
 - (b) use of inducements to participants (e.g., free medical care)
- (2) study location
 - (a) the health infrastructure and research regulation levels required for a country to be considered as an appropriate site for Phase 1, 2 or 3 studies
- (3) subject selection and protection
 - (a) appropriate timing and special requirements and ethical considerations in connection with studies in children;
 - (b) education of study participants about HIV infection, AIDS and the potential risks of participation;

- (c) education of study participants and potential participants rejected because of HIV infection about behaviour changes important for reduction of (re)-infection and transmission;
 - (d) maintenance of confidentiality of study participants;
 - (e) potential for discrimination against study participants who develop serum antibody to HIV as the result of vaccination
- (4) ethical and legal review
- (a) need for prior review of study protocols and monitoring by, at a minimum, the vaccine producer, the country of the producer, and the country in which the vaccine will be tested;
 - (b) the need for representation of members of high-risk groups on vaccine study review boards.
 - (c) liability issues.

2. Review and conclusions

2.1 General concepts

The following general concepts were arrived at regarding evaluation of candidate AIDS vaccines:

1. Efforts to develop AIDS vaccines establish a new era in vaccine development.
2. Testing of candidate AIDS vaccines is going to be complex, difficult and time-consuming. An AIDS vaccine for general use will not be available, if at all, before 1991 and is unlikely to be available before the mid-1990's.
3. Given the complexity of the problem, including ethical and social dimensions, along with the paramount global importance of developing a safe and effective AIDS vaccine, international cooperation and collaboration and open information exchange are essential in the evaluation of candidate AIDS vaccines.
4. There is an urgent need for advance planning of clinical trials of potential AIDS vaccines.

2.2 Recommendations to the World Health Organization

It is recommended that WHO establish, as soon as possible, a mechanism to ensure the open exchange of scientific, social, and ethical information necessary for advance planning and international collaboration in the clinical testing of candidate AIDS vaccines, with particular attention to Phase 3 trials.

ANNEX 1

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