

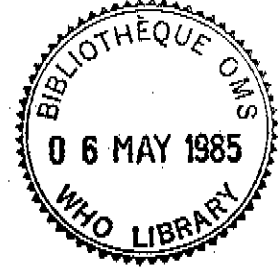


WORLD HEALTH ORGANIZATION  
 ORGANISATION MONDIALE DE LA SANTE

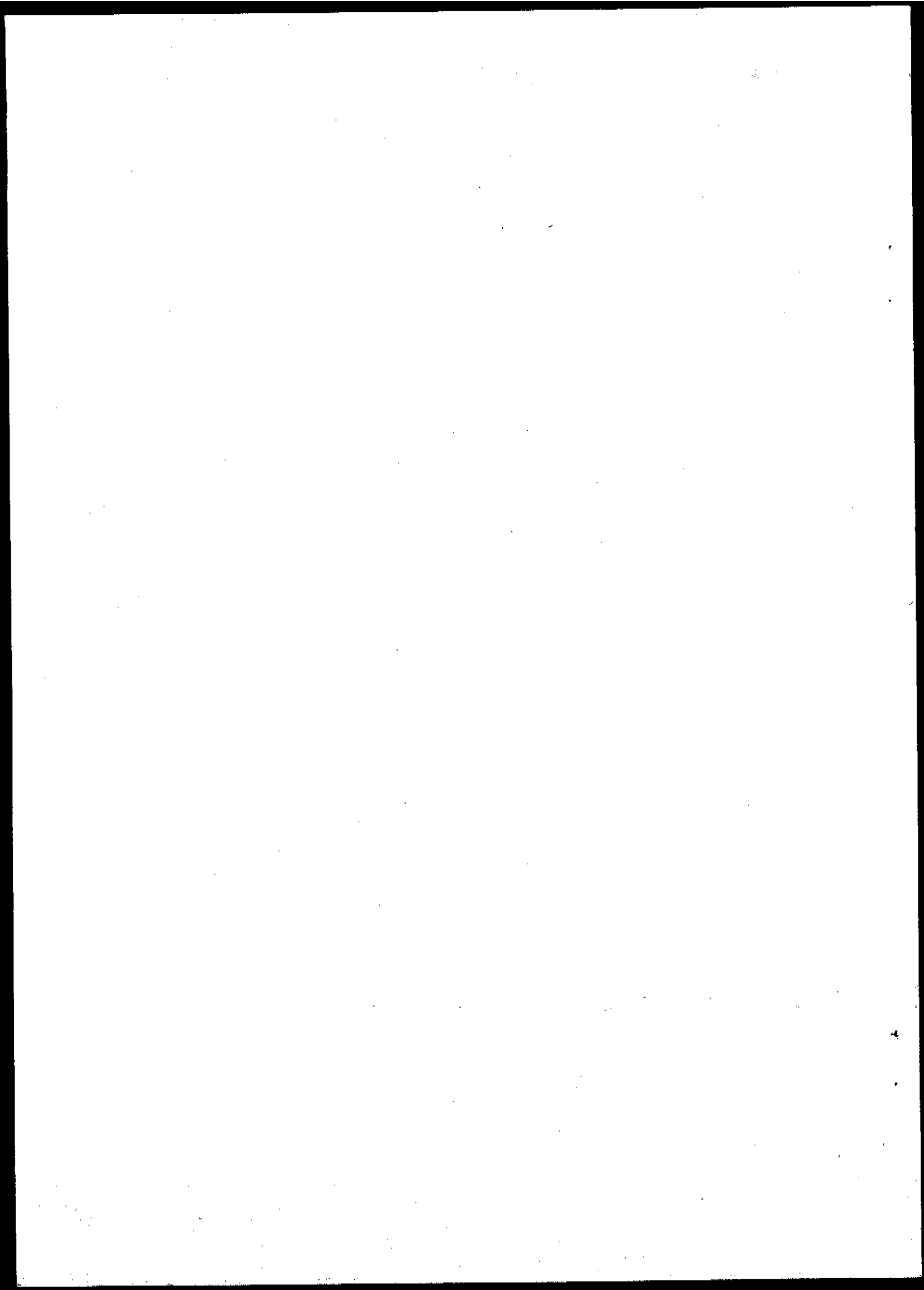
WHO/PVD

*WHO Programme - Pass for 100.000  
 countries - methods  
 of vaccine dev.*

WHO DOC 413



THE WHO PROGRAMME FOR VACCINE DEVELOPMENT





THE WHO PROGRAMME FOR VACCINE DEVELOPMENT

In 1983 the World Health Organization, following the advice of a group of leading scientists, decided to establish a programme concerned with the development of new and improved vaccines against selected infectious diseases. This decision was based on three factors:

- the need to coordinate and encourage national initiatives in vaccine development;
- the responsibility of the Organization to ensure that the great promise provided by modern biotechnology for vaccine development is exploited for the maximum benefit of public health;
- the need to accelerate progress in the control of infectious disease if the goal of "Health for all by the Year 2000" is to be achieved.

This document describes the concept of the WHO Programme for Vaccine Development, its aims and organizational strategy.

The issue of this document does not constitute formal publication. It should not be reviewed, abstracted, quoted or translated without the agreement of the World Health Organization. Authors alone are responsible for views expressed in signed articles.

Ce document ne constitue pas une publication. Il ne doit faire l'objet d'aucun compte rendu ou résumé ni d'aucune citation ou traduction sans l'autorisation de l'Organisation mondiale de la Santé. Les opinions exprimées dans les articles signés n'engagent que leurs auteurs.

CONTENTS

	<u>Page</u>
I. Communicable diseases: a major burden of morbidity and mortality	3
II. The need for vaccines to combat communicable diseases	5
III. Establishment of WHO Programme for Vaccine Development	6
IV. The initial target diseases and their public health importance	8
V. Research strategies for the five target diseases	13
VI. Funding arrangements and allocation of resources	16

Annexes

A	Terms of reference of Scientific Advisory Group of Experts
B	Terms of reference of Steering Committees
C	Allocation of funds in 1983-84

I. COMMUNICABLE DISEASES: A MAJOR BURDEN OF MORBIDITY AND MORTALITY

Communicable diseases, complicated by malnutrition and other adverse socioeconomic factors, continue in the present decade to contribute greatly to the unacceptably high levels of morbidity, mortality and disability, particularly in the under-five age group, in all developing countries. It is estimated that five million deaths occur per year from diseases which can be prevented by vaccines available today, and that another five million people are being crippled, blinded or mentally retarded as a result of the same diseases.

More than 30% of deaths in children in their first five years are due to acute diarrhoeas of viral and bacterial etiology, resulting in as many as three to five million deaths annually. Acute respiratory infections, primarily pneumonias, are another major killer, with a worldwide estimate of 2.2 million deaths per year. Malaria continues to take its heavy toll, with some 150 million people suffering from acute malaria annually. On the basis of studies in the past, it can be estimated that about one million children die every year from malaria in tropical Africa alone. Tuberculosis and leprosy still remain major public health problems in developing countries. Viral haemorrhagic fevers, in particular that associated with dengue virus, have a major impact in several countries.

Sexually transmitted diseases are everywhere on the increase with a general shift towards the teenage group. The rising incidence of the associated complications has high social and economic costs. Some 80% of the world's estimated 28 million blind people live in developing countries where the main causes of blindness are mostly avoidable or curable. Protozoa and helminths cause a broad spectrum of diseases of major socioeconomic importance. The number of persons at risk from these diseases is enormous: 600 million are at risk for schistosomiasis and 200 million from filariasis or onchocerciasis. There are still real threats of epidemics and pandemics of viral and bacterial origin. Of increasing concern are acquired microbial resistance to chemotherapeutic agents and vector resistance to chemical pesticides that impede progress in disease reduction and increase costs of control operations. Rapid urbanization and the expansion of travel and population movement and of trade in human and animal foods within and between countries have all increased the risk of introduction of diseases from one country or region to another.

Environmental management, such as the provision of a safe water supply, the disposal of refuse, waste water and excreta, the securing of adequate housing, the safeguarding of the environment from chemical pollution etc., would undoubtedly reduce the burden of communicable diseases. However, the development of these control measures is, of necessity, a slow process. In urban centres they represent a large capital investment while, in the vast peri-urban and rural areas of the third world, environmental management is a part of overall development.

Related to environment is the control of vectors transmitting disease. Chemical control has been used for many years with excellent results and will continue to be used in the future. Owing to the development of resistance to insecticides, vector control is being oriented towards integrated control; involving the use of chemical, biological and environmental measures in optimal combination that can be implemented by the community itself, again as a part of overall development and, of necessity, a long-term process.

New drugs and antibiotics for prophylaxis and therapy will, of course, continue to be developed, but many will lose their efficacy as the infecting organisms become resistant.

Vaccines are amongst the most potent means ever devised against communicable diseases and provide the greatest hope for a substantial reduction in the toll of these diseases. It is clear therefore that WHO should endeavour to ensure that the most effective vaccines possible be made available to Member States, according to their needs.

II. THE NEED FOR VACCINES TO COMBAT COMMUNICABLE DISEASES

The very impressive scientific developments in the biomedical sciences which have occurred in recent years provide the prospect of new, more effective vaccines against those communicable diseases for which at present there are either no vaccines or for which existing vaccines are less than satisfactory.

These developments include identification of protective antigens by the use of monoclonal antibody techniques and their production by recombinant DNA technology and peptide synthesis. In addition, there is much new information on the functioning of the immune system which provides a basis for rational vaccine design.

### III. ESTABLISHMENT OF WHO PROGRAMME FOR VACCINE DEVELOPMENT

In October 1983, WHO held a meeting on New Approaches to Vaccine Development. The meeting was attended by eminent scientists in microbiology, immunology, biochemistry, vaccine production and vaccine control. A major recommendation from the meeting to the Director-General was for the Organization to establish with urgency a programme for vaccine development. The Director-General responded positively to this recommendation, agreeing that the gathering momentum of biotechnological research provided WHO with the opportunity to play a crucial role in encouraging, coordinating and developing priorities on new vaccines so that the great potential of recent progress was harnessed for the maximum benefit of all countries. WHO could take advantage of its unique position of being deeply involved in all problems of communicable diseases in the developing world and having at the same time knowledge of scientific achievements in the most privileged countries. The same general view was expressed by the Advisory Committee on Medical Research at its October 1983 session.

As a result, a small group of eminent scientists met in December 1983 to outline the scope, priorities and management of the Programme. It will be closely related to other WHO programmes that are also based on modern biological research (e.g. the Special Programme for Research and Training in Tropical Diseases, the programme for Diarrhoeal Diseases Control and the Special Programme of Research, Development and Training in Human Reproduction.

Having considered the organizational aspects and what should be the initial activities of the Programme, the group recommended that the Programme on the Immunology of Tuberculosis (IMMTUB) that had been initiated early in 1983 should become part of the Programme for Vaccine Development. The group called for the establishment of five steering committees (SCs), each to cover one aspect of the Programme, as follows:

Tuberculosis  
Acute respiratory viruses  
Dengue  
Encapsulated bacteria  
Hepatitis A

The following points were emphasized:

1. Progress in vaccine development requires a multi-disciplinary approach that must use to the maximum the recent advances in molecular biology, biochemistry and immunology.
2. It is important that the Programme should remain involved in research efforts until the stage where the vaccines have been found applicable and effective in the context of WHO programmes, especially the Expanded Programme on Immunization (EPI).
3. Since the development of vaccines in most areas is intimately related to the development of diagnostic tools (including reagents), such activities, when appropriate, should be considered as part of the Programme.
4. Although there is already a great deal of activity in the area of vaccine development, WHO has a unique role to play. One example is to ensure a close link between laboratory research and field activities, especially in developing countries.

5. In the light of the limited but, it is expected, increasing resources available for the Programme, it is important that WHO should (a) use its good offices in order to minimize duplication of the national efforts put into vaccine development and (b) establish a flexible management structure for the Programme, adapted and modified as the Programme develops and additional resources become available.

To provide continuous technical management of the Programme, its periodic review and scientific guidance, a Scientific Advisory Group of Experts (SAGE) was established. At an initial meeting of this group in June 1984 terms of reference for its own activities and for those of the individual SCs were formulated (see Annexes A and B).

To ensure the scientific independence of the Programme, it was agreed that both members of SAGE and of the SCs should be appointed for a fixed number of years and that decisions, especially those related to the funding of research proposals, should be taken by the SC members by secret ballot. The WHO staff participating in the meetings do not have voting rights.

The Global Advisory Committee on Medical Research (GACMR) is the advisory body to the Director-General on all research activities. A brief report on the activities of the Programme, as outlined in the yearly SAGE report, will be submitted to GACMR.

At the end of the first five years of operations the Director-General will appoint an external independent committee to review the Programme.

#### IV. THE INITIAL TARGET DISEASES AND THEIR PUBLIC HEALTH IMPORTANCE

##### 1. Tuberculosis

Tuberculosis still ranks as a major health problem in many developing countries. Morbidity statistics for this disease are available from more than 100 countries, encompassing about three-fifths of the world's population. Each year well over a million new cases of tuberculosis are reported and this is probably only a fraction of the actual number of new cases. An index of the annual risk of infection, can be estimated and expresses the risks of tuberculosis within the community. Unlike morbidity and mortality notifications, this index has the advantage of being objective and reliable, since data for its calculation are collected independently of the routine reporting procedures for tuberculosis. There appears to be an almost constant ratio between the annual risk of tuberculosis infection and the annual incidence of smear-positive tuberculosis (i.e. infectious tuberculosis) in developing countries: every 1% of the risk of infection seems to correspond to about 50-60 new smear-positive cases of pulmonary tuberculosis per 100 000 general population.

In 1977, in Europe, the incidence of smear-positive tuberculosis is calculated to have been 24 per 100 000; in the United States of America, and Canada, 7 per 100 000; and in Oceania, 12 per 100 000. For Africa, a 3% annual risk of infection corresponds to a smear-positive incidence of 165 per 100 000; for Latin America, a 1.5% annual risk of infection corresponds to 80 per 100 000; for Asia (excluding China), a 2% annual risk of infection (possibly too low) corresponds to 110 per 100 000. Overall, in 1977, out of a world population of over 4 100 million, from four to five million cases of smear-positive pulmonary tuberculosis might have developed (a global incidence of about 100 per 100 000). The number of new smear-negative pulmonary cases (especially among children) and of extrapulmonary cases might have been about another four to five million. It is estimated that between two and three million persons die from tuberculosis each year in the world.

The most effective means of tuberculosis control is a combination of case-finding and chemotherapy, considered as an entity as case-finding is a prerequisite for diagnosis and cure.

Bacteriology, based on microscopical examination of direct smear, has so far played a key role in diagnosis. It is possible to foresee that diagnosis could be simplified by use of modern immunological techniques. Chemotherapy is effective but it is lengthy - over a year - and only a small proportion of patients adhere to the regimen. There are now a number of highly-effective, well-tolerated regimens of 6-9 months, but they are much more expensive than the standard regimens.

Prevention of disease by vaccination can in many cases be a practical and cost effective means of reducing morbidity and mortality. BCG vaccination has been widely employed and has proved effective in some trials. However, following an extensive trial in South India, doubts have arisen about its efficiency in tropical countries. For this reason, a joint Indian Council of Medical Research/WHO scientific working group on vaccination against tuberculosis recommended that further research should be undertaken.

## 2. Acute viral respiratory diseases of childhood

Communicable diseases of the respiratory tract are a major cause of morbidity and mortality all over the world. For this reason, the Twenty-ninth World Health Assembly (1976) decided that WHO, during its Sixth General Programme of Work beginning in January 1978, should expand its activities to include the control of these diseases. To this end, WHO has endeavoured to provide more precise and complete information on the magnitude of the problem and the relative contributors of different infectious agents to its etiology.

Unfortunately, since morbidity data on acute respiratory diseases are available from very few countries, it is not possible to present a comprehensive picture of the morbidity from respiratory diseases in the world. Nevertheless, it may be estimated that about 2.2 million deaths from acute respiratory diseases occur throughout the world every year. In children aged 0-14 years acute respiratory diseases account for 20% (range: 9-27%) of all deaths. However, the highest mortality for that group of diseases is reported for infants below one year of age. In this group the death rate in some countries exceeds 2000 per 100 000 live births.

The common respiratory diseases of childhood are caused by viruses of the paramyxovirus group, principally parainfluenza virus types 1, 2 and 3, classified in the genus Parainfluenza, and respiratory syncytial (RS) virus, classified separately in the genus Pneumovirus. It has been estimated that 50% of cases of severe croup and bronchiolitis and 24% of cases of pneumonia could be prevented if effective vaccines against these agents were available. Epidemics of severe respiratory disease associated with RS virus infection occur annually in infants worldwide, with variable morbidities and mortalities. Parainfluenza virus type 3 is associated with acute respiratory disease in children, but is more sporadic in its incidence. Parainfluenza virus types 1 and 2 are also associated with severe respiratory illness with a more variable seasonal incidence. The genetic, immunological and epidemiological relationships between the three parainfluenza viruses with each other and with other parainfluenza viruses, such as type 4 which infects but does not appear to cause disease in man, and SV5 implicated in persistent infection in man, require further study.

RS virus and the parainfluenza viruses appear to be ubiquitous and no community appears to be free of disease caused by these agents. It is also becoming apparent that RS virus at least is a cause of acute respiratory illness in the elderly and in the immune compromised. The need for effective vaccines is clear, but conventional approaches to vaccine development have been frustrated by the instability and the poor growth potential of most of these agents. The need to administer such vaccines to children in their first months of life adds further constraints, particularly on the development and testing of live vaccine.

Previous attempts to develop RS virus vaccines have been unsuccessful. A formalin-inactivated vaccine did not protect and subsequent natural infections frequently took a more severe course than in unvaccinated individuals. Cold-adapted and temperature-sensitive variants of RS virus have been developed and tested as live vaccines, but all have been unsatisfactory on account of under-attenuation, over-attenuation or genetic instability. Considerable ignorance remains regarding the pathogenesis of RS virus infection in infants. RS virus and parainfluenza virus type 3 infections are unique in that reinfection is common and even high levels of serum

neutralizing antibody are not necessarily protective. Recent advances in molecular biology, specifically the ability to molecularly clone individual virus genes and to obtain monoclonal antibodies, have circumvented some of these problems and opened up new approaches to the development of viral vaccines.

### 3. Dengue

Flaviviruses and their vectors are now spread over a very large area of the world. While yellow fever virus has been confined to sylvan foci in Africa and South America, infection by dengue viruses is now common also in urban areas where Aedes aegypti is present.

For some time dengue was considered as a minor disease of no serious public health importance. In recent years, it has become clear that dengue virus infections can cause a shock syndrome especially in children that, if not treated at the onset, can cause death in a great number of the children affected.

Dengue virus infections have caused serious outbreaks of epidemic proportions in some of the South-east Asian countries. Morbidity patterns for severe dengue disease are illustrated by a WHO report on children hospitalized or dying of dengue haemorrhagic fever/dengue shock syndrome (DHF/DSS) in tropical Asia. In Thailand in 1977, DHF/DSS was the second leading cause of hospitalization of children and among one of the leading causes of death from communicable diseases. While some years ago severe cases of dengue infection were restricted to a few countries in South-east Asia, recently a large number of severe cases have been reported from Cuba where in a few months a quarter of a million cases were reported. It is estimated that dengue infection is present in countries with populations totalling 342 million and that a further 1,500 million people live in areas with recent dengue activity.

Unfortunately, there are no animal models for dengue and the immunopathological mechanisms causing DHF/DSS are poorly understood. There are four serotypes of dengue virus which are antigenically very close to each other but are different enough to elicit only partial cross-protection. The most outstanding features of the epidemiology of DHF/DSS are that: (a) the syndrome usually occurs in persons with pre-infection dengue antibody, and (b) the infecting virus precipitating the attack is usually dengue type 2. There has been increased activity of dengue viruses in many parts of the world causing apprehension, especially in areas where DHF/DSS has not been experienced.

The almost ubiquitous distribution of A. aegypti in some of the most densely populated areas of the world demands mosquito abatement on a scale that exceeds realistic budgeting unless innovative methods are used. Reasonably cost-effective control of A. aegypti and of dengue transmission might be achieved if public education and legal sanctions were combined with an ecologically sound mosquito abatement programme.

In the Americas an extensive programme for the eradication of A. aegypti for the elimination of urban yellow fever was launched before the 2nd World War. The reintroduction of A. aegypti into many Caribbean and Central American countries within the past two decades is sobering evidence that country-level eradication of A. aegypti will demand endless vigilance unless eradication of the species is carried out on a global basis. For this reason a dengue vaccine would open the way to the control of dengue diseases.

#### 4. Diseases caused by encapsulated bacteria

Five genera of encapsulated bacteria are major causes of morbidity and mortality among infants and young children in almost all countries.

During infancy and early childhood, different strains of streptococci, particularly group A and certain serotypes of the pneumococcus and of Haemophilus influenzae are major causes of infections of the upper respiratory tract. In most developing countries, such infections are one of the major causes of death in early childhood.

Throughout childhood, endemic meningitis is a constant threat. Strains of Neisseria meningitidis, Streptococcus pneumoniae and Haemophilus influenzae that elaborate certain capsular polysaccharides each account for approximately one third of cases. In every major city in the developing world, thousands of cases of childhood meningitis are treated every year. Without antibiotics, death is certain. Antibiotics are costly and a major economic drain on the resources of hospitals in the developing world.

Epidemic meningococcal meningitis is superimposed on the background of endemic meningitis. Caused by meningococci elaborating certain capsules (group A or, rarely, group C), epidemics spread in slow waves affecting older children and adults in addition to the infants and young children that are at risk in meningitis endemic areas.

Cellulitis and abscesses caused by staphylococci and streptococci are a neglected cause of morbidity in many developing countries. Treatment of serious staphylococcal infection may require the use of expensive antibiotics. Staphylococci cause serious infections such as endocarditis, osteomyelitis and pyomyositis, whilst streptococci precipitate acute rheumatic fever or acute glomerulonephritis.

Childhood burns are prevalent in many under-privileged countries where such children occupy a high proportion of beds in paediatric hospitals. The possibility of preventing colonization of burns by Pseudomonas sp. with a LPS vaccine has been demonstrated.

Clearly, prevention of disease caused by these encapsulated bacteria is of the highest priority. Vaccines that use the purified capsular polysaccharides and are administered by parenteral injections have been developed and have proved effective in preventing disease, especially meningococcal meningitis, in groups of adults in developed countries. These vaccines are safe, but they are not generally immunogenic under two years of age. Because of this, they cannot be used in EPI programmes; they have been used in the developing world mainly to contain epidemics of meningitis. The duration of immunity provided by these vaccines is short, being no more than one year in infants who can respond to a few polysaccharides. They provide no secondary or herd immunity.

Given the magnitude of the problem, the limitations of existing solutions and the development of new technologies, multidisciplinary, international efforts to develop a new approach to vaccine prevention of these diseases are urgently needed.

## 5. Hepatitis A

Infectious hepatitis caused by hepatitis A virus is a self-limiting but clinically important disease of world-wide distribution with a particularly high prevalence among the young in developing countries. The disease occurs frequently among people travelling from countries of low prevalence to those where the disease may be endemic. Infection may result in particularly severe clinical consequences in both children and adults whose health is compromised by nutritional deficiencies or chronic infection, such as malaria or schistosomiasis. In emerging nations where infection may no longer occur commonly in very early infancy, the disease occurs more frequently because infection at a later age results in more overt disease.

In temperate zones, epidemic waves have been observed with peaks in late autumn and early winter. In many tropical countries, the peak of reported disease tends to occur during the rainy season with low incidence in dry periods. A superimposed cyclic epidemic pattern with peaks every 5-10 years has been observed in several countries with long records of reporting. Control of the disease is seen as making an important contribution to the primary health care goal of WHO.

Though passive immunization by the administration of human immunoglobulin provides short-term protection, active immunization is seen as the only strategy capable of universal routine prophylaxis. However, hepatitis A virus grows poorly in cell cultures and conventional approaches to vaccine development are unlikely to yield products which are sufficiently inexpensive to be widely used in countries other than the highly developed. The hepatitis A virus is a member of the picornavirus family and the recently derived information on the molecular biology and antigenic structure of other members of this group, for example, poliovirus, provides hope that the application of modern biotechnological approaches will lead to the development of new vaccines against hepatitis A.

## V. RESEARCH STRATEGIES FOR THE FIVE TARGET DISEASES

The research strategies outlined below have been elaborated by the SC for the individual area of the Programme and approved by SAGE. In many cases, these are heavily dependent on the new biotechnologies as outlined above.

### 1. Tuberculosis

The strategic plan for research on the immunology of tuberculosis was prepared during an informal consultation held in Boston, USA from 7 to 9 February 1983. It was recommended that research should be conducted on the following subjects:

1. Molecular biology
2. Monoclonal antibodies
3. Immunoregulation in human tuberculosis
4. Experimental immunology of tuberculosis
5. Cloning of mycobacteria.

Concerning the other components of the Programme, at its meeting in June 1984, SAGE approved the following lines of research, proposed by the SC.

### 2. Acute viral respiratory diseases of childhood

- (a) Molecular cloning of individual genes of parainfluenza virus type 3 and respiratory syncytial virus.
- (b) Nucleotide sequencing of the genes specifying the immunologically important polypeptides (presumed to be the two surface glycoproteins and the nucleoprotein) and subsequently the other genes and inter-cistronic regions.
- (c) Expression of cloned viral genes in prokaryotic systems (to produce high yields of unprocessed polypeptides) and eukaryotic systems (for modified proteins).
- (d) Production and characterization of monoclonal antibodies for definition of epitopes and for use in affinity chromatography for purification of viral polypeptides.
- (e) Characterization of the function and immunogenic potential of individual virus proteins.
- (f) Study of the protective immune response with emphasis on the role of cell-mediated immunity.
- (g) Support of other initiatives, i.e. development of live attenuated viruses, cell receptors, etc.

### 3. Dengue

The main aim is to produce second generation vaccines by using the following approaches:

- (a) Biochemical definition of principal neutralizing antibody-inducing epitopes on the virus glycoprotein.

- (b) Definition of epitopes, which induce the formation of neutralizing versus enhancing antibodies by using monoclonal antibodies.
- (c) Viral genome sequencing; cDNA cloning.
- (d) Experimental studies of potential vectors, such as bacteria or viruses other than dengue.
- (e) cDNA cloning of 17D yellow-fever virus to study its possible use as a vector, by substituting gene sequences coding for epitopes capable of inducing dengue neutralizing antibody.

#### 4. Diseases caused by encapsulated bacteria

The Programme will concentrate on developing vaccines against N. meningitides with a principal focus on oligosaccharide (LOS) antigens. The main goal is to develop an infectious replicating vector, engineered to express antigens which induce protective immunity in children. The strategy includes:

- (a) Epidemiological studies of epidemic/endemic disease, with emphasis on immune responses to N. meningitides and other organisms with antigenic determinants shared with virulent Neisseria.
- (b) Development of standardized isotype-specific serological tests for bacteriocidal (protective) antibody.
- (c) Biochemical and structural analyses of relevant LOS antigens defined by monoclonal antibody and shown to be involved in protective immunity.
- (d) Studies of bacterial genetics to define methods of transferring genes for oligosaccharide expression to potential vector organisms.

#### 5. Hepatitis A

- (a) The collection of well-characterized strains of hepatitis A viruses of diverse geographical and epidemiological origin.
- (b) Studies towards an improved understanding of the pathogenesis and primary sites of replication of the virus.
- (c) Establishment of a panel of monoclonal antibodies against hepatitis A virus strains for use in virus characterization and antigen analysis.
- (d) Identification of critical antigenic sites of the virus relevant to protective immunity using a combination of selection of non-neutralized mutants in the presence of monoclonal antibodies and recombinant DNA technology.
- (e) Molecular cloning and sequencing of the complete genomes of carefully-selected hepatitis A strains to determine the genetic basis of antigenicity and virulence.
- (f) Development of experimental vaccines using antigens prepared by controlled gene expression and synthesis of oligopeptides.

- (g) Rescue of infectious hepatitis A virus by transfection of cDNA clones to construct experimental attenuated vaccine strains by specific modifications of the virus genome.
- (h) Study of both humoral and cell-mediated immunity to hepatitis A infections.

VI. FUNDING ARRANGEMENTS AND ALLOCATION OF RESOURCES

On establishing the Programme for Vaccine Development in 1983, the Director-General provided as the initial driving force for the Programme the total amount of \$ 1 million from his development fund to be used to support research. A further \$500,000 was provided for 1985 for the support of research. Additional WHO funds were made available for the administration of the Programme including meetings of SAGE, SCs, etc.

These WHO funds were mobilized on the assumption that (a) the Programme would eventually be funded from extrabudgetary resources and (b) some time was needed to mobilize these resources.

The Programme on the Immunology of Tuberculosis has been funded in the greater part by funds made available from the Norwegian support through the WHO Expanded Programme on Immunization for tuberculosis.

In 1984 the Japanese government contributed \$100,000 to the Programme.

The Programme is at present seeking support from governments and foundations. It is the intention of SAGE that the funds required to allow the programme to develop should increase to cover a budget of \$3-4 million per year.

ANNEX A

TERMS OF REFERENCE OF SAGE

1. To provide for the continuing scientific review of progress in the development of vaccines, particularly those which are important in developing countries.
2. To provide essential knowledge in the various scientific disciplines bearing on vaccine research and development.
3. To recommend (a) diseases for vaccine development, (b) priorities for basic and clinical research.
4. To recommend the establishment of research Steering Committees (SC), each to be concerned with vaccines for individual or groups of diseases (see terms of reference for SC).
5. To carry out annual formal review of the functioning of each SC with regard to:
  - (a) scientific priorities;
  - (b) appropriateness of scientific membership;
  - (c) quality of research;
  - (d) innovation;
  - (e) productivity and rate of progress;
  - (f) budgeting effectiveness and needs.
6. To recommend the allocation of funds to the SC.
7. To encourage and coordinate collaborative efforts through the SC for:
  - (a) exchange of reagents and other materials;
  - (b) links between laboratories in developing and developed countries to foster collaborative research and speed application in the field of research results and technological developments;
  - (c) cooperation with other vaccine-related programmes which provide support for research, training or development.
8. To maintain close liaison and interaction with the SC, among other means by having at least one member of SAGE (and/or a designated technical adviser) attend each meeting of the SC, and having Chairmen of SC attend annual meetings of SAGE.
9. To review those applications relating to methodologies relevant to several diseases as well as applications relating to diseases other than those covered by the SC.

10. To advise on the design, management and evaluation of vaccine trials, including assessment of efficacy and safety, in consultation with the relevant WHO programmes.
11. To maintain contact with manufacturers of biological products and to establish an effective interface between the Programme for Vaccine Development and industry.
12. To mobilize funds from international or national sources and private agencies for the Programme.

ANNEX B

TERMS OF REFERENCE FOR THE STEERING COMMITTEES

1. Preparation of a strategic plan of research for the relevant area of the Programme for Vaccine Development.
2. Solicit proposals for research in specific areas and identify scientists and institutions to formulate and carry out specific research and development projects for the Programme.
3. Review proposals submitted for scientific merit and relevance to the Programme and recommend the appropriate level of support. The SC shall solicit opinions from an independent reviewer, and two in the case of applications from Steering Committee members.
4. Preparation of tentative budget for presentation to SAGE.
5. Technical and scientific monitoring of progress of the research activities.
6. Identification of opportunities for new lines of research or of the needs for intensified efforts in existing lines of research.
7. Identification of research training opportunities within the research activities of the Programme.
8. Organization of meetings of the SC (at least one per year) in consultation with SAGE and other scientists to review progress and plans, and the preparation of the reports of these meetings.
9. Preparation of an annual summary report with brief reference to related work outside the SC.

Beyond the elaboration of terms of reference for SAGE and the SCs, the meeting in June 1984 stressed the following points:

- (1) The aim of SAGE is to provide a forum for the development and use of vaccines and to stimulate, catalyze and support such work.
- (2) The Programme should be widely announced and groups who might make particular contributions to the Programme should be encouraged to submit applications for support.
- (3) Scientists with appropriate knowledge who are not working directly on the individual diseases should be added to the SCs to give an added breadth of vision.
- (4) Investigators receiving financial support from the Programme will not be eligible to be members of SAGE.
- (5) Encouragement should be given to work on delivery systems, e.g., fewer administrations and multiple antigens per administration. It was pointed out that the question of antigen presentation in determining the nature of the immune response was being considered by SAGE.

ANNEX C

ALLOCATION OF FUNDS IN 1983-84

The Programme started in late 1983 with an allocation of \$1m by the Director-General of WHO and incorporated the Programme on the immunology of tuberculosis, for which the Government of Norway had already provided \$200,000. They also provided a further \$300,000 for tuberculosis in 1984. As a result, it was possible by June 1984 to approve support for research as follows:

	<u>1983</u>	<u>1984</u>
Tuberculosis	\$273,000	\$506,220
Acute respiratory diseases		\$191,740
Dengue		\$ 55,050
Encapsulated bacteria		\$248,500
Hepatitis A		\$116,400

The SC on Tuberculosis (IMMTUB) met in June 1983 and June 1984 and has dispensed the following funds (which were endorsed by SAGE):

IMMTUB 1983

<u>Title</u>	<u>1st yr award</u> \$	<u>Decision for second year</u> \$
Development and characterization of B-cell hybridoma antibodies and T-cell clones reactive to mycobacterial antigens	25,000	25,000
Genomic analysis of <u>M. tuberculosis</u> BCG, <u>M. bovis</u> and <u>M. leprae</u> by DNA hybridization and cloning	30,000	33,000
Production and characterization of species-specific antibodies to <u>M. tuberculosis</u> H37Rv	12,000	12,000
Identification of antigens involved in cell-mediated immune reactions to tuberculosis	5,000	20,500
Analysis of the efficacy and safety of BCG vaccination <u>via</u> the aerogenic route	33,000	25,000

<u>Title</u>	<u>1st yr award</u> \$	<u>Decision for second year</u> \$
1) Identification of the cells in human tuberculoimmunity which make immune lymphokine		
2) The production of human T-cell clones specific for antigens of <u>M. tuberculosis</u>	25,000	25,000
Monoclonal antibodies to myco- bacterial antigens	8,000	8,000
Immunology of tuberculosis	25,000	25,000
Cloning and expression of <u>M.</u> <u>tuberculosis</u> DNA in <u>E. coli</u>	30,000	7,500
Characterization of T cells and antigenic determinants relevant to resistance against tuberculosis	22,000	22,000
Immunodiagnosis and immunogenetics to tuberculosis	4,000	4,000
Experimental studies on mono- clonal antibodies against <u>M.</u> <u>tuberculosis</u> and <u>M. bovis</u> BCG as a model infection/vaccination with <u>M. tuberculosis</u> and BCG in T-cell deficient animals	3,000	3,000
Murine T-cell clones and hybridoma specific for <u>M.</u> <u>tuberculosis</u> antigens	26,000	26,000
Cellular immunology of BCG vaccination	22,000	-
Monoclonal antibodies in monitoring of mycobacterial antigens and specific anti- mycobacterial antibodies in the course of tbc chemo- therapy in human subjects	3,000	3,000
	<hr/> 273,000	<hr/> 329,000

IMMTUB 1984

<u>Title</u>	<u>Amount</u> \$
Immunopathogenesis of tuberculosis Hong Kong	20,000
Characterization of T-cell clones able to induce activation of anti- tuberculosis activity in several types of human macrophage	21,220
Animal models for study of virulence and protective immunity	20,000
Regulation of immunity against tuberculosis by genes and immunocompetent cells	5,000
Expression of mycobacterial genes in foreign hosts	35,000
Isolation and characterization of plasmids of mycobacteria and their possible involvement in virulence	15,000
The development of a new vaccine for tuberculosis by the production of recombinant <u>M. tuberculosis</u> antigens in <u>E. coli</u> using monoclonal antibodies as markers	10,000
	<hr/>
	\$177,220

The other Steering Committees met at the same time as SAGE which endorsed their allocation of funds as follows:

<u>Title of project</u>	<u>Decision</u> \$
<u>Acute respiratory diseases</u>	
The role of T-cell immunity in RSV infection and its induction by vaccination	22,150
Development of an intranasal vaccine for parainfluenza virus	12,100

Title of project	Decision \$
Cloning of human parainfluenza virus 3 glycoprotein genes for vaccine development	30,000
Sendai virus (parainfluenza type I) glycoproteins genes	10,000
A potential subunit vaccine for respiratory syncytial virus.	30,000
The immunobiology of respiratory syncytial (RS) virus.	5,000
Identification of cellular receptors involved in the attachment and penetration of human respiratory syncytial (RS) virus	39,725
Immunogenicity of respiratory syncytial virus glycoprotein for man	7,765
Sequence analysis and expression of the cloned cDNAs of the respiratory syncytial virus glycoprotein genes	25,000
Control of paramyxovirus infection by inhibition of virus proteolytic activation	10,000
	\$191,740
 <u>Dengue</u>	
Identification of dengue-specific peptide(s) for use as sub-unit vaccine	20,000
Molecular characterization of dengue virus genome variation	25,050
The use of crab-eating monkey, <i>Macaca fascicularis</i> , for neurovirulence test in dengue vaccine development	10,000
	\$55,050
 <u>Encapsulated Bacteria</u>	
Analysis of the cell surface of encapsulated meningococci with monoclonal antibodies	22,000
Age-specific development of immunity to <u><i>N. meningitidis</i></u>	45,000
Surface proteins of meningococci	13,000

Title	Decision \$
Characterization of epitopes within meningococcal capsular polysaccharides of serogroups A, B, and C	86,000
Establishment of a serology centre for capsular polysaccharide immunity	48,000
Definition of protection inducing surface antigens of group B meningococci by monoclonal antibodies	20,000
Expression of gonococcal lipooligosaccharides in non-pathogenic microorganisms	14,500
	<hr/>
	\$248,500
<u>Hepatitis A</u>	
Molecular cloning and nucleotide sequencing of Emmortal strain of hepatitis A virus	30,000
Development and use of monoclonal antibodies for the characterization of hepatitis A virus	22,500
Pathogenesis of hepatitis A	18,900
Identification of antigenic sites involved in the neutralization of hepatitis A virus	30,000
Collection and characterization of hepatitis A virus strains of diverse geographical and epidemiological origin	15,000
	<hr/>
	\$116,400

= = =



PROGRAMME FOR VACCINE DEVELOPMENT  
RESEARCH PRIORITIES

The WHO Programme for Vaccine Development is a goal-oriented-programme which funds research only in the following priority areas:

1. Acute viral respiratory diseases of childhood

- (a) Molecular cloning of individual genes of parainfluenza virus type 3 and respiratory syncytial virus.
- (b) Nucleotide sequencing of the genes specifying the immunologically important polypeptides (presumed to be the two surface glycoproteins and the nucleoprotein) and subsequently the other genes and inter-cistronic regions.
- (c) Expression of cloned viral genes in prokaryotic systems (to produce high yields of unprocessed polypeptides) and eukaryotic systems (for modified proteins).
- (d) Production and characterization of monoclonal antibodies for definition of epitopes and for use in affinity chromatography for purification of viral polypeptides.
- (e) Characterization of the function and immunogenic potential of individual virus proteins.
- (f) Study of the protective immune response with emphasis on the role of cell-mediated immunity.
- (g) Support of other initiatives, i.e. development of live attenuated viruses, cell receptors, etc.

2. Dengue

The main aim is to produce second generation vaccines by using the following approaches:

- (a) Biochemical definition of principal neutralizing antibody-inducing epitopes on the virus glycoprotein.
- (b) Definition of epitopes, which induce the formation of neutralizing versus enhancing antibodies by using monoclonal antibodies.
- (c) Viral genome sequencing; cDNA cloning.
- (d) Experimental studies of potential vectors, such as bacteria or viruses other than dengue.
- (e) cDNA cloning of 17D yellow-fever virus to study its possible use as a vector, by substituting gene sequences coding for epitopes capable of inducing dengue neutralizing antibody.
- (f) Generation of non-structural antigens as vaccines.

- 2 -

## 2. Diseases caused by encapsulated bacteria

The Programme will concentrate on developing vaccines against N. meningitides with a principal focus on oligosaccharide (LOS) antigens. The main goal is to develop an infectious replicating vector, engineered to express antigens which induce protective immunity in children. The strategy includes:

- (a) Epidemiological studies of epidemic/endemic disease, with emphasis on immune responses to N. meningitides and other organisms with antigenic determinants shared with virulent Neisseria.
- (b) Development of standardized isotype-specific serological tests for bactericidal (protective) antibody.
- (c) Biochemical and structural analyses of relevant LOS antigens defined by monoclonal antibody and shown to be involved in protective immunity.
- (d) Studies of bacterial genetics to define methods of transferring genes for oligosaccharide expression to potential vector organisms.

## 4. Hepatitis A and Polio

### 4.1 Hepatitis A

The Steering Committee recognizes that hepatitis A continues to be a problem in many parts of the world and that the development of a vaccine is highly desirable. The goal of the hepatitis A programme is to develop a cheap, safe and efficacious vaccine suitable for use in the first year of life in all countries of the world and to be included in the WHO Expanded Programme on Immunization. The strategy includes:

- (a) The collection of well-characterized strains of hepatitis A viruses of diverse geographical and epidemiological origin.
- (b) Studies towards an improved understanding of the pathogenesis and primary sites of replication of the virus.
- (c) Establishment of a panel of monoclonal antibodies against hepatitis A virus strains for use in virus characterization and antigen analysis.
- (d) Identification of critical antigenic sites of the virus relevant to protective immunity using a combination of selection and non-neutralized mutants in the presence of monoclonal antibodies and recombinant DNA technology.
- (e) Molecular cloning and sequencing of the complete genomes of carefully selected hepatitis A strains in order to (i) determine the genetic basis of antigenicity and virulence of the virus and (ii) to rescue infectious virus by transfection to facilitate construction of attenuated strains by strategic modifications of the virus genome.
- (f) Development of experimental vaccines using antigens prepared by controlled gene expression and synthesis of oligopeptides.
- (g) Study of both humoral and cell-mediated immunity to hepatitis A infections.

4.2 Polio

- (a) Determination of the molecular basis of virulence of types 1, 2 and 3 poliovirus with special reference to the Sabin strains and their reversion to virulence.
- (b) Application of information from (a) for the development of safety tests of live vaccines employing molecular methods.
- (c) Evaluation of prospects for the preparation of new attenuated strains of virus by precise genetic modification (e.g. of Sabin strains).
- (d) Evaluation of intratypic recombinant viruses as vaccines or vectors (e.g. for hepatitis A vaccine).
- (e) Collection of further data on the molecular basis of antigenicity of poliovirus and the preparation of new immunogens.

5. Tuberculosis

The strategic plan for research on the immunology of tuberculosis was prepared during an informal consultation held in Boston, USA from 7 to 9 February 1983. It was recommended that research should be conducted on the following subjects:

- 1. Molecular biology
- 2. Monoclonal antibodies
- 3. Immunoregulation in human tuberculosis
- 4. Experimental immunology of tuberculosis
- 5. Cloning of mycobacteria.

Research proposals, prepared on the appropriate application forms, should reach Immunology, WHO, 1211 Geneva 27, Switzerland, before the deadlines, given below:

Tuberculosis	Dengue	Hepatitis A	Encapsulated bacteria	Acute respiratory viruses
<u>Deadlines (1986)</u>				
2 April	26 March	18 April	9 April	25 April
<u>Dates of Steering Committee meetings (1986)</u>				
2-3 June	26-27 May	20-21 June	9-10 June	26-28 June