PAN AMERICAN HEALTH ORGANIZATION

ACHR 27/89.14
Original: Spanish

XXVII MEETING OF THE ADVISORY
COMMITTEE ON HEALTH RESEARCH

Washington, D.C., United States of America
5-8 September 1989

PROJECT FOR THE ESTABLISHMENT OF A REGIONAL SYSTEM FOR VACCINES IN LATIN AMERICA (SIREVA)

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- SIREVA -

(EXECUTIVE SUMMARY)

30 MAY 1989

PROJECT FOR THE ESTABLISHMENT OF A REGIONAL SYSTEM FOR VACCINES IN LATIN AMERICA (SIREVA)

The Pan American Health Organization (PAHO) has considered it desirable to promote and to sponsor the creation of a Regional System for Vaccines (SIREVA) to be charged with improving and developing biologicals for the control of communicable diseases that affect the population of the Latin American countries.

The demand for biologicals has increased with the size of the population; in 1985 there were already 400 million inhabitants in the Latin American region, of which 54 are children under five; to this is added the exposure of large groups of persons to diseases such as amebiasis, typhoid fever, malaria, dengue, onchocerciasis, Chagas' disease, leishmaniasis, schistosomiasis, meningococcal meningitis, influenza, and diseases produced by rotavirus; however, the large companies in industrialized countries do not develop biologicals for their control because of a lack of commercial incentives.

Vaccines are the most direct, effective, and economic means for improving public health, as the Expanded Program on Immunization (EPI) has demonstrated. The great advances in genetic engineering, fermentation, and molecular biology as well as in microbiology, parasitology, and immunology open broad possibilities for the creation of new vaccines, a list of which has been presented by the Institute of Medicine of the National Academy of Sciences.

A series of studies and work carried out by PAHO with the support of the Rockefeller Foundation have shown the desirability of creating this system for vaccines, based on two units, one in Brazil and another in Mexico, and on member laboratories that carry out works directed toward having more and better biologicals to solve the problems of the Region.

As the first step in the specification of the project, approval has been granted for a feasibility study that would allow determination of the characteristics of the system and the components of the units in Brazil and Mexico, as well as the possibilities for financial and political support. This study will be conducted during the current year, 1989.

Dr. Guillermo Soberón Acevedo, ex-Minister of Health of Mexico and current President of the Mexican Foundation for Health, has accepted PAHO's invitation to serve as the General Coordinator of the project.

It has been established that SIREVA will be regional in character. Its purpose will be "to elevate the capacity in applied biotechnology to develop the vaccines required by the countries of Latin American and the Caribbean."

Its specific objectives will be directed toward public health ends, specifically development of new vaccines and improvement of existing ones, performance of field trials, support of local institutions in acquiring a better understanding of diseases, contribution to the training of personnel, and provision of advisory services and consultations to the countries that require it. The System will develop production only up to pilot scale and will have elements for control of the quality of research, training, and references.

It is considered appropriate that in its first phases SIREVA be framed within the administrative system of PAHO--a situation that may subsequently evolve into other special, legal, and organic circumstances that would accentuate its international character.

SIREVA will not interfere in local programs for production of vaccines, but will support, promote, and contribute to the systematization of the efforts of the investigators and institutions in the Region for the development of inmunobiologicals. It will contribute to the improvement of the understanding of communicable diseases, and can serve as a mechanism for coordination of policies for development of biotechnology and biologicals.

SIREVA will be developed in four phases. The first corresponds to the feasibility study, which will end at the beginning of 1990; the following stage, which comprises the planning, including the specification of individual projects, will be initiated in the last quarter of 1989 and will terminate in 1990; the third will include the construction and integration of the units in Brazil and Mexico and will take from the second half of 1990 until 1992; and the fourth will correspond to the operation of the system, starting in 1993.

For the feasibility study an organization has been established based on the following elements: a) a governing body consisting of the Director and the Assistant Director of PAHO, and the experts of that Organization, b) a General Coordinator, and c) two technical units corresponding to Brazil and Mexico. It will also have the support and facilities provided by the Governments of the headquarters countries, and the local PAHO Country Representative Offices.

The PAHO Adviser on Biologicals will support the project at all levels.

The development of the feasibility study will include the following activities: technical consultation, visits to biotechnology centers, interviews with local investigators, recording of advances in research and development of vaccines, study of needs, promotion in the countries of the Region, and arranging for financial support.

The products of this study will be: a) a work plan, including selection of the possible vaccines to be developed; b) a technological plan, indicating the priority fields in biotechnology; c) the geographical distribution of the countries that would be supported by

SIREVA and the corresponding administrative and operationing structures; d) preliminary technical and architectural plans of the units in Brazil and Mexico; e) personnel requirements; and f) the operating budget.

The feasibility study will cost of US$900,000, to be financed by PAHO, the Rockefeller Foundation, the headquarters countries, and other institutions interested in the project.

It is expected that the construction of the units will be financed by institutional donors and international agencies, the headquarters countries, and the associated countries.

Alternatives for the financing of the operation are being studied. The governments of Brazil and Mexico have manifested their desire to support the project. In the latter case arrangement has been made for the donation of land in the City of Cuernavaca, Morelos, while Brazil has designated the Oswaldo Cruz Foundation as the institution that will house the corresponding unit.

The organization designed for the execution of the feasibility study will provide various forms of participation and institutional benefits to PAHO, to the Ministries of Health of the headquarters countries, and to the associated countries. The creation of SIREVA will provide a resource for appropriate selective utilization of biotechnology, an instrument in the control of communicable diseases, a legacy for the development of personnel, and a systematized contribution toward the achievement of the goal of health for all by the year 2000.

PROJECT FOR THE ESTABLISHMENT OF A REGIONAL SYSTEM FOR VACCINES IN LATIN AMERICA

SIREVA

STATUS, ORGANIZATION AND ACTIVITIES FOR A FEASIBILITY STUDY

In March 1989, a document proposing the bases for the development of the centers for vaccinology was prepared by Dr. Guillermo Soberón Acevedo and Dr. Gregorio Martínez Narváez, with the specialized advisory services of Dr. Jaime Martuscelli Quintana and Dr. José Sosa Martínez; the document was prepared in accordance with agreements with the Director of the Pan American Health Organization.

In the technical area the following documents were consulted: "The Future Vaccine Supply for the Developing World" by Anthony Robbins and Phyllis Freeman; "Enhanced Disease Prevention in the Americas" by Dr. M. González Pacheco and the authors of the previous work; the report of the advisory meeting of experts on the topic, held in Rio de Janeiro in April 1988; and the document titled "Regional Center for Vaccinology - MEXICO-BRAZIL, a Proposal for its Creation," by Dr. Martuscelli and co-workers. The book "New Vaccine Development, Establishing Priorities," published by the National Academy Press in 1985, has been used continuously as a reference.

In the design for the consolidation of the project the following were consulted: "The Formulation of Health Policies" by Drs. Carlyle Guerra de Macedo and Juan Carlos Veronelli, "The Process of Health Planning, Bases for a Program for Investments" by Dr. Pablo Isaza, and other PAHO technical documents.

The document also included the observations of Dr. Jesús Kumate, Secretary of Health of Mexico.

At the beginning of April, that document was reviewed by the Director of PAHO, Dr. Carlyle Guerra de Macedo; the Deputy Director, Dr. Robert Knouss; Dr. M. González Pacheco; and Dr. Guillermo Soberón Acevedo.

An exhaustive revision was completed by a group commissioned by PAHO, with Dr. Guillermo Soberón as coordinator and including Drs. Arlindo Fabio Gómez de Souza, Mario González Pacheco, Arming Isibas, Gregorio Martínez Narváez, and Luis Enrique Sánchez Torres.

At the meeting in Washington in May 1989 the following individuals took part in the discussions: C. Guerra de Macedo, G. Soberón, M. González Pacheco, A. Gómez de Souza, A. Isibasi, A. Homma, C. de Quadros, F. de Paula-Pinheiro, G. Schmunis, V. Escutia, P. Freeman, A. Robbins, and S. Halstead.

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INTRODUCTION

The Pan American Health Organization (PAHO) has promoted studies and work for the analysis of the problems of communicable disease control and the alternatives for improving the quality, effectiveness, and availability of current biologicals, as well as research and development of new ones for the campaign against communicable diseases in the Latin American countries.

The foregoing has led to the proposal for creating a system supported by two regional centers for vaccinology, located in Brazil and Mexico, which would function as operational units for scientific and technological development, whose purpose would be the improvement of existing vaccines and the development of new ones, and as specialized instruments for investigators and specialized institutions in the countries of the Region.

PAHO has invited the Executive President of the Mexican Foundation for Health (FMS) to coordinate the work for the consolidation of the regional centers for vaccinology, through the realization, in the first place, of a broad study to determine the feasibility of the project, which would be carried out in 1989. In anticipation of this, the present work has been prepared; it contains a summary of the progress in the development of the regional centers for vaccinology and proposals for the execution of the feasibility study.

The purpose of the document, which has been discussed, reviewed, and adapted in conversations with directors and experts from PAHO, is to propose forms of organization and participation as well as the activities, sequences, and expected results of that study.

In the preparation of the document the valuable contributions of those who have participated in the conceptualization and design of the project have been taken into account; and the proposal has been based on the concept that the regional centers for vaccinology constitute indispensable instruments for the development of biotechnology, for the production of vaccines for disease control, and in general, for the attainment of the goals of "health for all by the year 2000" in the countries of Latin America.

REGIONAL SYSTEM FOR VACCINES

SIREVA

I. CURRENT SITUATION.

1. Communicable Diseases and Vaccination Programs

It is estimated that respiratory and diarrheal diseases caused by bacteria and viruses still kill four million children under one year of age annually in the developing countries.

According to data provided by the Pan American Health Organization, acute intestinal and respiratory diseases appear among the five leading causes of death in 10 of 15 countries of Latin America and are the primary causes of mortality in children under one year of age.

The percentage of deaths from acute respiratory infectious diseases in the entire population is greater in Central America than in other parts of the world, and together, respiratory and intestinal diseases cause more than 50% of the deaths in children under four years of age.

Public health experts agree that certain immediate measures, such as oral rehydration and general medical treatment, can reduce the damage while improvement of economic and environmental conditions can, over the long term, improve health conditions; however, considering cost and ease in achieving direct control of a disease - thanks to broad coverage of the susceptible population, vaccination represents one of the most effective health public weapons.

These factors have determined that the World Health Organization and the Pan American Sanitary Bureau have promoted the Expanded Program of Immunization (EPI) through six basic vaccines. It is estimated that 50% of the susceptible population in the world receives protection against diphtheria, whooping cough, tetanus, poliomyelitis, measles, and tuberculosis, compared with 20% before the 1974 program.

The positive results obtained throughout the world through that vaccination program and the growth of world demand indicate that it is necessary to maintain and increase the availability of vaccines.

In Latin America between 1980 and 1985, the population grew from 354 to 400 million inhabitants, with an annual rate of increase of 2.6%. Approximately 13.5% of this population, or 54 million, are children under five years of age, who are the objects of the vaccination programs; although the growth rate has shown a decline since the 1960s, it continues to have an significant impact on estimates of births in future years and consequently on the existence of a significant number of susceptible individuals.

In addition to the requirements for the six traditional vaccines, the need should also be taken into account for human rabies vaccine for the postexposure protection of 300,000 exposed persons, for tetanus toxoid, and for typhoid and yellow fever vaccines, as well as for tetanus antitoxin and biologicals for passive protection.

2. Need for New Vaccines and Improvement of Existing ones in Developing Countries; Technical Feasibility

The needs for vaccines in the developed countries frequently differ from those in the developing countries; the industrialized countries focus their attention on the enhancement of vaccines that are required in their own markets. For example, the countries of the European Economic Community, the United States of America, and Japan direct efforts toward the improvement of the whooping cough component of DPT vaccine in order to avoid some serious reactions that are occasionally presented. The cell-free vaccine being investigated would avoid them; however, it would increase the cost for the countries needing to acquire it. Another example which illustrates the economic difficulties is that until 1988 the current vaccine against hepatitis B cost 130 dollars for the series of three doses.

Meanwhile, the developing countries are affected by diseases of their own ecological regions, involving on occasion large numbers of people; it is estimated that near half of the world population lives or travels to malarial regions with the inherent risks of contracting that disease; in Latin America alone it is estimated that 257 million people reside in areas originally marshy.

Among the most frequent causes of gastrointestinal morbidity are amebiasis and typhoid fever; in addition, dengue, malaria, onchocerciasis, Chagas' disease (trypanosomiasis), leprosy, leishmaniasis, schistosomiasis, meningococcal meningitis, influenza, and diseases produced by rotavirus constitute regional public health problems. In all these cases experts are studying the technical possibilities for developing new vaccines for their control.

It is currently accepted that advances in molecular biology, fermentation engineering, and genetic engineering open possibilities for the creation of new vaccines. For example, new ways to combine antigens can expand the possibilities of immunization and the use of genetically modified viruses allows development of new types of vaccines. It is also considered feasible to code several antigens in the genetic material of existing vaccines and there are possibilities for developing antiparasitic vaccines. New methods of stabilization and shorter times from manufacture to use can eliminate the need for refrigeration and the addition of preservatives in the final presentation of the vaccines.

To the foregoing are added specific needs for research related to the epidemiological patterns of the developing countries. For example, there have been discussions on the proper age for children to be vaccinated against measles and the quantities of antigen necessary for

producing the best results. It has also been mentioned that attenuated viruses 1 and 3 in polio vaccine have occasionally failed to induce immunity, resulting in presentation of cases of paralysis in vaccinated children; for this reason adjustments in the concentration of the antigens in the trivalent vaccine have been suggested. However, these problems can only be resolved through ordered, controlled research processes that impact on the methods of production and packaging of vaccines.

A recent review of the vaccines that would be desirable for the countries of the third world in the next 10 years, carried out by the Institute of Medicine of the National Academy of Science, pointed out that of the 21 priority vaccines, fewer than 10 would generate an economically significant demand in the world markets and therefore be of interest to the commercial laboratories.

3. Commercial Problems Related to the PRoduction and Availability of Vaccines

An example of limiting circumstances in the use of vaccines regarding the costs of production is the new rabies vaccine of "Vero cells" produced by the Merieux Institute of France which is used for only 20% of world consumption, whose production must be increased to at least 7 million doses in order to reduce the cost of production which is approximately 10 dollars per dose. Currently, most of the world has to resort to the less reliable vaccine based on nerve cells.

For the large producers of vaccines economies of scale are important, since industrial production of vaccines for fewer than 40 million children is not considered profitable.

The EPI has the six basic vaccines thanks to the following phenomena: a) the large laboratories of the industrialized countries produce these vaccines for their own markets and can increase their volume at very low cost; b) consolidated purchase by WHO and UNICEF for the Expanded Program of Immunization has promoted production of large quantities and has reduced the price; and c) the governments promote the production through subsidies and distribution that is free or priced under the cost of production.

But the development of new vaccines entails facing the problems of technology and economy of production. The principal obstacle is the need for resources of all kinds in order to translate the results of laboratory research into large-scale production of vaccines.

When the commercial firms carry out their investment and development programs, they do not find sufficient economic stimulus in the countries of the third world to justify the expenditures for installations and personnel. Thus it is necessary to continue developing an international effort, based on philanthropic motives and on the efforts of the developing countries themselves, in order to be able to attend to the diseases of the Region.

Isolated efforts must overcome greater obstacles, since when an investigator develops a new antigen that can produce immunity, much time must pass and expensive stages must be experienced before a vaccine can be used widely and practically. Small-scale scale production of new vaccines can be proportionally very expensive. Complex systems of quality control which represent a constant effort and an additional financial charge must be established; this represents a constant effort and additional financial responsibilities.

It is understood that the most important limitation on the development of new vaccines is the lack of investments for research and for their creation and production. It is estimated that the international market currently is valued at 600 million dollars per year. If 12% of this sum were destined for research and development, there would be 72 million dollars worth of investments of this nature, which if distribution were in accordance with percentages of sales, would give the third world 4 million for development of biologicals necessary for the problems of its countries.

The World Health Organization has taken these circumstances into account and allocates 10 million U.S. dollars from its budget for research on vaccines, with emphasis on stimulation of subsequent investments and programs; however, there is no system that leads from results of research to generalized availability of new biologicals.

4. Alternatives Examined for the Development of Vaccines and Biologicals for the Developing Countries

The experts that have analyzed the problem for PAHO/WHO and in studies financed by the Rockefeller Foundation have considered various alternatives, among which are the following:

a) Support of isolated efforts of investigators.

b) Promotion of the development and production of vaccines by large companies and laboratories through consolidated purchase by international agencies, as in the Expanded Program of Immunization.

c) Creation of an international center for research, development, and production with financing by WHO and international agencies.

d) PAHO has studied the possibility of creating regional centers for development of biologicals in Latin America in order to solve the regional problems.

PAHO's approach has taken into account the advantages and disadvantages of each option. In any case, special thought has been given to the elements that have generated the analysis of the problem, that is to say, the difficulties that exist when a developing country

tries to develop the necessary vaccines by itself, integrate and manage the new biotechnology, or establish the industrial production of biologicals.

The absence of economic incentives for large companies in the markets of the third world and the need for obtaining the support of the international community for the financing of activities geared toward resolution of the health problems of the countries of the third world have also been taken into account .

One of the accepted criteria has been the decentralization of the systems and the units, since the presence of more than one center for development of vaccines, located in the regions where the problems persist, would allow their monitoring and the development of local capacities for their adequate control.

The reasons previously mentioned have given rise to the strategy, proposed by the Pan American Sanitary Bureau, of creating in Latin America a system based on two regional centers for vaccinology that would be located in Mexico and Brazil, taking into account the experience in the production of biologicals in these countries. These centers would promote and support the various efforts that the countries of the region are carrying out concerning biotechnology in health and in particular the development of new vaccines.

5. Progress in the Establishment of the Regional Centers for Vaccinology

The World Health Organization and the Pan American Health Organization have pointed out the desirability of continuing with the programs for vaccination in order to contribute to the attainment of the goal of "health for all by the year 2000," and have underscored the need for having systems that make it possible to have the inputs required for the Expanded Program of Immunization (EPI).

Through continuous analyses of the epidemiological situation PAHO has confirmed that the Latin American countries are affected by infectious diseases prevalent in the Region, while the opinions of the experts indicate that there are possibilities for the development of new means for their eventual control; however, a significant research effort would be required to provide better knowledge of the diseases, their causative agents, and the employment of genetic engineering and biotechnology for the development of new biological instruments of control.

It is important to point out the specific actions carried out under the "Tropical Disease Research Program," sponsored by WHO, the United Nations Development Program, and the World Bank.

The foregoing has made it evident that there is a need for promoting in the Latin American countries the capacity necessary for the development, use, and dissemination of biotechnology, genetic

engineering, and fermentation engineering and incorporation of the scientific advances in microbiology, parasitology, immunology, and field epidemiology - all this applied to comprehensive strategies for control of communicable diseases.

The conception, need, and possibility of developing the regional centers for vaccinology were solidified in a study carried out in 1987 under the sponsorship of the Pan American Sanitary Bureau and led by Dr. M. Gonzáles Pacheco, with the participation of Phyllis Freeman and J. D. Anthony Robbins, M.D., of the University of Massachusetts and the University of Boston respectively. This work was carried out with the support of the Rockefeller Foundation.

In the study the modes of production and development of vaccines at the world level and their corresponding impact on Latin America were reviewed and the regional epidemiological situation was analyzed. Through field visits assessment was made of the needs for new vaccines to solve the problems of communicable diseases in the Region, the advances in each country, and their current technological availability and the possibilities for their development.

In conclusion, recommendation was made to create two regional centers for vaccinology, with specific technological infrastructure, functions, and modes of operation adapted for the tasks of research, development of new vaccines, and improvement of those that are used currently in the countries of the Region.

The document presented in October 1987 points out the importance that international participation would have for the financing of the creation and operation of the regional centers for vaccinology, taking as background the experience of the Consultative Group for International Agricultural Research (CGIAR) which has more than 25 years of experience in the management of programs and institutions to improve food production in the neediest regions of the world and which currently has 13 centers, mainly in developing countries.

After studying the possibilities that the Latin American countries offer for the creation of the regional centers for vaccinology, particularly Argentina, Chile, Venezuela, Cuba, Costa Rica, Guatemala, Brazil, and Mexico, those responsible for the feasibility study recommended the last two countries for the location of the centers, considering tradition, experience, and the availability of the technology for the production of vaccines.

Continuing with the recommendations proposed for the definition and development of the project, PAHO organized a "Meeting for Consultation on the Regional Centers for Vaccinology," held in Rio de Janeiro on 14 and 15 April 1988 and attended by invited experts from Colombia, Brazil, Cuba, Mexico, Argentina, the United States of America, and the Pan American Sanitary Bureau itself.

At this meeting the conclusions of the feasibility study carried out in 1987 were affirmed, and policies for the development and operation of the centers were issued; the possibilities for developing new vaccines were also reviewed. Subsequently PAHO commissioned Dr. Jaime Martuscelli of Mexico to develop a study directed toward specifying the characteristics of the regional centers for vaccinology, work sponsored by PAHO and the Rockefeller Foundation and whose results were delivered in December 1988.

A fundamental purpose is that all the countries benefit from the activities of both centers for vaccinology, located for strategic reasons in Brazil and Mexico; however, a geographical distribution has been proposed to facilitate the participation of the countries and for involvement in the governing structures of each of the centers.

The descriptive document establishes that the regional centers for vaccinology should have as their objectives contributing to public health care through the improvement of existing vaccines and development of new ones; integrating and coordinating the scientific advances concerning design, production, testing, and evaluation of vaccines; and contributing, in addition, to new techniques for diagnosis of infectious diseases. The centers will promote scientific and technological endeavors, will provide the bases for training the personnel of Member Countries of the Region in the disciplines related to the work of the regional centers for vaccinology, and will strengthen and integrate the efforts that are carried out in each country.

The centers will also have as their mission disseminating the knowledge and scientific and technological advances among the health services of the Region and implementing exchanges of information.

It is necessary for adequate fulfillment of its objectives and functions that each center should have the structural resources of installations, equipment, systems, and human resources, according to the current state of scientific and technical knowledge and its long-term projection.

Thus it is proposed that each center have the following basic areas:

a) Research and development on a pilot scale

b) Pilot-scale production

c) Quality control

d) Human resource training

e) Administration and services

The technical document prepared by Dr. Martuscelli (1988) contains descriptions of the functional characteristics of each area, its

principal objectives, its methods of work, the scientific and technical fields in which it will operate, its interrelationships, and the prospects for its tasks.

In September 1988, the Director of PAHO asked the Ministers of Health of the Region to consider the desirability of developing the project and received the corresponding approval to continue the work.

PAHO has had exchanges with the headquarters countries, Brazil and Mexico, and options for the location of the centers have been studied. In the case of Mexico, arrangements have been made to ensure adequate land (35,000 square meters) in the city of Cuernavaca, Mor., which may be donated by the Federal Government or the Government of the State of Morelos.

In November 1988, in the presence of the President of the Republic, Mr. Miguel de la Madrid, the Director of PAHO, and the Health Secretary of Mexico, an agreement was signed for cooperation between the Federal Government of Mexico and PAHO for the establishment of the regional center for vaccinology in that country.

That agreement established the purposes of the center, its geographical area of influence, the specifications for the scientific, technical, legal, and administrative characteristics of the regional center for vaccinology, the physical installation of the center, and the customs, legal, and administrative facilities that the Government of Mexico will grant for the installation and operation of the center.

In February 1989, the Health Secretary, Dr. Jesús Kumate, obtained the approval of the President of the Republic, Mr. Carlos Salinas de Gortari, for the development of the regional center for vaccinology.

In accordance with the agreement, in addition to the land, the Mexican Government will contribute technological resources and the experience of scientific personnel to collaborate in the design of the project. It would also contribute other kinds of supports. In a recent agreement, the President of the Republic has confirmed to the Executive President of FMS its contributions for the execution of the feasibility study.

In the case of Brazil, the Ministry of Health, having analyzed the possibilities with several research institutions, selected the Oswaldo Cruz Foundation (Fiocruz) in Rio de Janeiro as the most adequate to house the regional center for vaccinology in Brazil.

In addition to physical space, the Brazilian Government, through the Fiocruz, will contribute the technical and scientific experience necessary for achieving the objectives and goals of the project.

II. BASES FOR THE DEVELOPMENT OF THE REGIONAL SYSTEMS FOR VACCINOLOGY

Taking into account the work carried out, the recommendations and points of view of the experts, and the suggestions and contributions of

international agencies, the following framework of policies, objectives, and operating mechanisms for the harmonious development of the regional centers for vaccinology and their contribution to the improvement of public health has been designed.

1. Policies and Objectives of the Regional Systems for Vaccinology

The regional systems for vaccinology constitute an international effort because they emerge from a promotion by PAHO/WHO, and they have a regional approach because the countries of Latin America and the Caribbean participate. They have been conceived as a system to increase the local capacity to develop biologicals through the use of genetic engineering, microbiology, parasitology, immunology, and other disciplines related to biotechnology and to contribute to the solution of health problems that affect the countries of the Region, contributing, in addition, to the improvement of world health.

Although the consolidation of two operational units has been foreseen, the regional centers for vaccinology form part of a concept of technological development, whose purpose is to meet the needs of the countries of the region, combining the experience and capacity of the experts and institutions of the countries interested in the development of immunobiologicals.

A policy that will determine the functionality of the regional centers for vaccinology will be directed toward the improvement of the human resources in the disciplines related to biotechnology in the countries included in the Region, which should be reflected in the work programs and internal structure of the centers.

The programs for the regional systems for vaccinology will be affected by the state of technological development and the availability of human resources within the centers for research in the service of the participating countries; and the respective work programs, structure, and projects of each center will be determined by the records of needs and progress in each and in the countries together.

The centers of the system, in addition to working on technological development and research to find products that help control the diseases of the Region, will provide advisory services to the countries requesting it with respect to the availability of vaccines and the development, follow-up, and evaluation of their vaccination programs.

In accordance with the concept of functional units, the regional centers for vaccinology will operate as centers for scientific and technological development within their installations and as decentralized support mechanisms for the local efforts of investigators and institutions.

It is necessary to underscore that the regional centers for vaccinology in the north (Mexico) and the south (Brazil) have been conceived <u>as a single system</u>, with two operational units that will

complement each other scientifically and technologically by establishing mechanisms for coordination to facilitate mutual exchange and support and avoid duplication of effort. The operational plans will also consider the exchange of technical information with the countries with highly developed technologies and with the countries of other regions of the world for purposes of cooperation and mutual support.

The work of the regional system for vaccinology will be framed within the following objectives:

A. General objective.

To raise the regional capacity in biotechnology for the development of the vaccines that are required in the Region.

B. Specific objectives.

a) To develop the new vaccines required for the public health problems of the Region.

b) To contribute to the improvement of existing vaccines and their proper use in the countries of the Region.

c) To carry out the field trials required for providing the efficacy of the vaccines (Phases I, II and III);

d) To support the activities of the health institutions in acquiring the best understanding of the communicable diseases that prevail in the countries of the Region.

e) To contribute to the training of the personnel required by the countries of the Region in the disciplines related to genetic engineering, biotechnology, microbiology, parasitology, immunology, epidemiology, and administration of the activities of the center.

f) To serve the countries as an organ of advisory services, consultation, and technical support for problems within the competence of the center.

2. Strategies and Modes of Operation

In their first phases, it is considered desirable that the two centers of the system be developed within the administrative framework of the Pan American Health Organization, with subsequent analysis of the organic and legal alternatives so that they operate as international organs.

It is considered necessary that the two operational units, in Brazil and Mexico, be provided with sufficient human resources, equipment, and infrastructure to handle biotechnology in its current

state and its possible development; therefore they will require international financial and technical support for their effective operation.

For their operation as a local support system for the countries of the Region there should be a process for selecting the projects and the corresponding resources for their development. All institutional support to local investigators will have to be given under a specific program approved by the bodies of government; this support for investigators will proceed under agreement specifying the expected results.

In order to obtain international financial and technical resources, the system will be supported by the growing solidarity with respect to health between the industrialized countries and those in the process of development, and by recognition of the epidemiological reality that health problems do not recognize geopolitical borders, which makes world effort for its control appropriate. It should be clear that SIREVA is not to be constituted as a mechanism that monopolizes or in some form interferes with local projects in biotechnology or in other scientific and technological areas conducive to the development of new vaccines or the improvement of those that exist. On the contrary, the centers can establish the means to support them, by amassing resources, either their own or through solicitation of donor agencies, placing at their disposal resources located in the operating units so that they can overcome technological limitations, carry out laboratory-scale projects, or produce at pilot scale, and perform field trials in order to prove their effectiveness (Phases I, II and III). Training of personnel will also be an important mission of the centers.

In each case the feasibility study will determine what is required to promote current projects. There will be situations in which the operating units of SIREVA have the principal role and will receive support from local investigators and institutions and there will be others in which their role will be that of collaborator, with the development carried out primarily in member laboratories.

SIREVA can, in addition, unite scattered, disconnected efforts and lead them toward developing or improving vaccines.

The regional centers for vaccinology will form part of a vast system of research and technological development. On one hand, they will seek exchange with and support of institutions and laboratories in the industrialized countries, and on the other, as has been said, the centers for Brazil and Mexico will establish mechanisms for mutual support and intercommunication and to supplement work of common interest. Each center, in addition, will supplement its work with the efforts to be carried out in each country of the Region and will plan its activities in relation to the progress realized in other regions in the fields of biotechnology and communicable disease control.

The strategic focus of the centers is to be a resource for technological progress in relation to the need for disease control in the

Region and they will not intervene in international marketing mechanisms, but will support the efforts of the international community related to the availability of needed vaccines. The feasibility study will establish a preliminary list of priorities for the vaccines to be developed and improved, based on the needs of the countries according to their epidemiological characteristics and also taking into account the scientific and technological viability of these proposals--whether they can be completed in a reasonable time and at an appropriate cost as has been mentioned in work prepared by the Institute of Medicine of the National Academy of Sciences.

Although it may be necessary for the centers to produce vaccines on a pilot scale and develop a system of quality control, they will not interfere with national work in the production of vaccines, nor will they duplicate the efforts of local laboratories, but they will serve as a mechanism for coordinating a regional policy for development and production of biologicals and disease control that allows the best results with the least cost and effort, with attention to factors such as economy in marketing, technological updating, and large-scale distribution and use of products. With respect to quality control, there are at least three aspects in which the intervention of the units is clearly indicated:

a) Research,
b) Training, and
c) Reference

The strategic focus of the centers will not be just on technological development, but also on seeking the best understanding of the epidemiological situation of Latin America, including the environmental and cultural factors of each subregion and their corresponding impact on the level of public health, along with the responsible agencies in each country.

In their operational aspects the centers should maintain a high level of excellence, which should be reflected in their structure and the level of their personnel. Their research projects, development, education, and advisory services will be subject to standards and quality controls.

Although the two centers or operating units in Brazil and Mexico will be planned jointly in order to ensure their interaction in the end, their complementarity, and the existence of mechanisms so that they work in a coordinated fashion, each of them will enjoy broad operational autonomy.

III. ORGANIZATION

Realization of the feasibility study, with the technical factors, policies, and broad geographical distribution of the elements that will have to be taken into account, will require a significant effort and a specific organization; therefore the following organic and functional

structure is proposed for the organizations providing direction and technical consultation in the implementation of the feasibility study.

1. Governing Body

Taking into account that PAHO will be responsible for the overall conduct of the study at the central level, a group will be organized, consisting of the Director and the Assistant Director of PAHO, the general coordinator of the regional centers for vaccinology, and the PAHO Regional Adviser on Biologicals. This group will have the following functions:

- To approve, if necessary, and follow up on the work of the feasibility study and the specific projects for each center.

- To review the technical reports and administrative documents that the general coordinator of the regional centers for vaccinology presents to PAHO.

- To approve budgets and financial operations.

- To make recommendations for the advancement of the feasibility study and on the characteristics of each of the regional centers for vaccinology.

- To make arrangements with the donor agencies and the associated countries.

This group will meet in PAHO Headquarters in Washington, D.C.; at the request of the general coordinator of the regional centers for vaccinology, it will invite the coordinators of the units in Brazil and Mexico and others deemed necessary.

2. Specific structures

For the development of the feasibility study the following units will be created:

a) A unit for coordinating the project at the regional level.

b) A technical unit responsible for the development of the project for a regional center for vaccinology in Brazil, responsible for its technical design and local management.

c) A similar technical unit for a regional center for vaccinology in Mexico.

Both the general coordination of projects and the developmental units in Brazil and Mexico would have the technical and administrative support of the personnel in PAHO Headquarters in Washington and of the management resources of its local Country Representatives.

3. Composition and functions of the office of the general coordinator of the regional centers for vaccinology

This office will be composed of the general coordinator, a part-time consultant, and a secretary.

The functions of the general coordinator will be the following:

- To conduct the feasibility study and preparation of the final plans for each regional center for vaccinology, including their respective work programs.

- To promote actions for the financing of the regional centers for vaccinology.

- To propose measures for progress in the development of the regional centers for vaccinology to the Director of PAHO and the group of experts of the Organization, and to present monthly reports.

- To establish and maintain communication with the possible donor agencies, with the support of the Director of PAHO.

- To report periodically to the governments of the countries associated with the regional centers for vaccinology, jointly with the Director of PAHO.

- To supervise and to advise on activities of the directors of the units in Brazil and Mexico.

- To evaluate progress and establish measures for the proper development of the regional centers for vaccinology.

4. Composition and functions of the office of the Director of the technical unit of the regional system of vaccinology

This office will be composed of a unit coordinator, permanent full-time or part-time consultants, and the office personnel required.

Its purposes and functions will be:

- To prepare a work program for the feasibility study.

- To do the technical feasibility study.

- To propose to the general coordinator, within the work of the feasibility study, the operational guidelines for the regional centers for vaccinology, including their priorities and programs, and the vaccines to be developed, field research, and training sessions that are the responsibility of each regional center for vaccinology.

- To support the general coordinator of the regional centers for vaccinology in the actions carried out for the development of the regional centers for vaccinology.

- To compile the technical and administrative reports required by the general coordinator.

The functions of the unit coordinators in Brazil and Mexico will be the following:

- To select the necessary consultants.

- To coordinate the work for the execution of the feasibility study and for the definition of the characteristics of their respective centers.

- To integrate the plans and results of the work of the experts and personnel that participate in the feasibility study and in the definition of the project.

- To coordinate the formulation of the work program.

- To support the general coordinator in the arrangements that are carried out at the subregional and local levels.

- To supervise the work carried out for the establishment of the center physically and functionally.

- To report to the general coordinator.

5. Technical assistance from PAHO

The Pan American Sanitary Bureau will request the Regional Advisory Consultant on Biologicals of the Organization and the experts to consider supporting the work, so that they collaborate directly with the general coordinator in the design and operational development of the feasibility study and in the selection of the consultants; the technical characteristics of each regional center for vaccinology will be specified; PAHO will also participate in the follow-up and monitoring of the work carried out by the units in Brazil and Mexico.

6. Participation of the headquarters countries and the countries of the Region

In accordance with the stages of progress of the work and when consultations are required for the continuous development of the regional center for vaccinology, the general coordinator, with the agreement of the Director of PAHO, will establish advisory groups in which the Ministries of Health of the headquarters countries, Mexico and Brazil, will participate, along with the participating countries and the local

representatives of PAHO; these groups should meet according to areas established by other PAHO programs: Central America, the Andean Pact, the Southern Tier, and the Caribbean. The functions of these groups will be:

- To review and evaluate the plans and programs proposed by the directors of the respective centers.

- To propose measures for the development and consolidation of the regional centers for vaccinology.

- To support the general coordinator of the centers in the actions that develop at the subregional and local levels.

IV. STAGES AND ACTIVITIES FOR THE DEVELOPMENT OF THE REGIONAL CENTERS FOR VACCINOLOGY.

1. Stages

Because of the magnitude, technological significance, impact on public health, and international characteristics of the project, development of actions of varying complexity is required for the establishment of the regional centers for vaccinology. It is expected that this process would have the following phases:

1.1 First, a feasibility study must be carried out; it will make it possible to gather clear, objective information to be be provided to all the participating entities and to analyze the various alternatives for the structure and operation of the regional centers for vaccinology within a system of regional character. These activities could be developed during 1989.

1.2 The second stage, definition of plans and development, will include design and construction, equipment, engineering tests as well as tests of the operation of the physical plant, installations, and equipment, and the integration of the personnel of the center. This would take place from 1990 to 1992.

1.3 The third stage of construction and development will include the work of building, equipping, and performing engineering tests for each technical unit, along with tests of the operation of the physical plants and equipment of the installations, and integration of the personnel of each unit, which can be trained in part thanks to already existing installations in Brazil (FIOCRUZ) and in Mexico (related research institutions of the Autonomous National University of Mexico and the National Polytechnic Institute). It also will include the implementation of supports for member laboratories of SIREVA. This stage will last from 1990 to 1992.

1.4 The fourth stage will extend from the formal beginning of operations to the technical and functional maturity of the units, starting in 1993.

2. Sequence of Operations

The principal activities for the comprehensive development of the regional centers for vaccinology will include the following actions:

2.1 - Request for PAHO collaboration by the Mexican Health Foundation.

2.2 - Appointment of coordinators of the units in Brazil and Mexico.

2.3 - Establishment of the office of the general coordinator.

2.4 - Establishment of the offices of the directors of the units in Brazil and Mexico including the selection of the consultants.

2.5 - Realization of feasibility study. Preparation of the documents necessary for the presentation of requests to donor agencies. Selection of possible donors and preparation of the program for meetings, interviews and visits to possible donors. The study of feasibility should include general subjects such as justification, technical and scientific viability, organization (including participation of donors) and costs of the various stages of development of the project.

The possible donors have tentatively been classified in the following categories:

a) Foundations and private organizations with a tradition of supporting health projects: Carnegie, Kellogg, Rockefeller, Ford, and Rotary International, among others.

b) International agencies of the United Nations system: WHO, PAHO, UNDP, and UNICEF.

c) Governmental agencies: AID of the United States of America, IDRC of Canada, the Overseas Development Agency of Sweden, DFA of Switzerland, GTZ of Germany, and JICA of Japan, among others.

d) European Economic Community and other governments of industrialized countries.

e) Others.

2.6 - Management of grants.

2.7 - Formalization of the grants, mechanisms for their management, terms of delivery and use, and arrangements for delivery of information to the donors.

2.8 - Preparation of documents to promote, arrange for, and obtain the participation of the Member Countries of each Region; they should include the general benefits for the Region from the point of view of public health, technological development, and training of personnel. They will include the supports that each regional center for vaccinology will provide to each country in particular, including support for investigators, institutes for development of biologicals, and epidemiological research.

2.9 - Promotion of the regional system for vaccinology to the countries of the Region. (For this task the local PAHO Country Representatives can have major responsibility).

2.10 - Formalization of the participation of each country in the respective regional center for vaccinology through general meetings and interviews with representatives of the governments of the Region.

2.11 - Management of the participation of the governments of the headquarters countries of the regional centers for vaccinology in Brazil and Mexico. It has been considered that for adequate development of the centers, the respective governments should contribute: land; immigration, customs, and tax accommodations; institutional support from the public health agencies; arrangements for the infrastructure with regard to the location of the center; and financial support.

2.12 - Specification of plans. The following will result from the feasibility study:

a) Program for technical work, specifying the coordinated actions and the work to be developed by each regional center for vaccinology, in Brazil and Mexico, including priorities in accordance with the epidemiological situation, the need for new vaccines and improvement of the existing ones, and recording of progress in the preparation of vaccines and the personnel that develop them. An inventory of supports needed by investigators for technology, equipment, human resources, information, and other inputs in each country should also be included.

The program should include lists of new vaccines to be developed according to the feasibility, as well as estimates of the time necessary for them to become available. Work to be done in epidemiology and manpower training will be estimated.

In the program, the support that will be provided to investigators, institutions, and countries by each regional center for vaccinology and the expected results of this action will be taken into account.

b) Technological plan. The subregional offices of the regional centers for vaccinology will prepare a document specifying the tasks in the field of biotechnology, fermentation engineering, molecular biology, microbiology, epidemiology, parasitology, immunology, and other disciplines that should be developed in the regional centers for vaccinology for the development of vaccines, specifying the necessary inputs and the exchanges with experts and institutions. In addition, the basic engineering plan for the adequate development of the work will be prepared.

c) Geographical distribution. As a result of the study it is also expected to have a list of countries that will be supported directly by each regional center for vaccinology, in Brazil and Mexico, while conserving the unity of the regional technical approach of the system. With regard to the table that follows it should be noted that: (1) the units in Brazil and Mexico will be established as a program of PAHO, as centers of the Organization; (2) each center should have capacity for research and development utilizing its specialized technology. For example, if a laboratory for culturing cells in microcarriers is available, this unit can be adapted to the development of various viral vaccines produced in that system. This laboratory could be utilized for the development of new vaccines and for improvement of others that utilize similar basic technology; (3) each center could have its own research and development projects. There could also be projects common to both (for example F, in the enclosed table); (4) the research results will be available for all member countries in PAHO. However, of all the member countries, it is possible that only some will subscribe to more active participation in the programs of SIREVA. Each country would be able to participate in more than one project in accordance with its own interest.

d) Preliminary technical architectural proposal. In accordance with the work program, the proposal that will serve in the design of the physical plant and its respective installations will be prepared.

It will consist of the definition of the physical areas according to their function, including basic engineering, pilot-scale production, and quality control. It will include, in addition, a list of the equipment and the

corresponding locations; the utilities needed in the technical areas, the supporting services necessary (isolation, biological containment, safety, traffic, etc.), equipment in support of the operation (boilers, pumps, etc.), and storage and maintenance. The specifications will also include the areas for administration, teaching, feeding, and general services.

The proposal should include the technological equipment and support that will be provided for special on-site projects of investigators and institutions.

e) Personnel requirements. In accordance with results previously mentioned, the units in Brazil and Mexico will prepare lists of professional, technical, administrative, and support personnel required by each regional center for vaccinology, including the corresponding job descriptions.

f) Operating budget. In accordance with the established work program, the physical and functional structure of each center, the necessary inputs, and the personnel plan, the corresponding operating budget proposal will be prepared.

V. FINANCING

Because of the dimensions, structural characteristics, and medium- and long-term projections, the implementation of the project requires considerable investment.

It is recognized that the current economic situation in the Latin American countries is difficult; it is characterized by the excessive weight of the external debt, lowered prices for their raw materials, balance of trade deficits, and reduced availability of foreign exchange. Nevertheless, under these circumstances it is also necessary to take into account that there should be greater appreciation that it is precisely in times of economic pressure that investment must be strengthened in social projects, such as health care, especially with respect to preventive measures that benefit large population groups at reduced cost.

The Director of PAHO has referred on repeated occasions to this social debt and to the need for attending to it in the best possible way.

The cost of creation, development, and operation of the centers for vaccinology could not be covered without supporting resources from the institutional donors and international agencies for health and social development; in this regard, the international community and the countries of the Region should take into account that the regional centers for vaccinology are conceived as instruments for contributing to the solution of public health problems and controlling regional diseases, and that the objectives of these centers are aimed at implementation of greatly effective preventive measures, such as vaccination for communicable disease control.

There should also be appreciation of the fact that the centers are conceived to become the basis of regional development in biotechnology and manpower training in this discipline, which means that the centers can constitute a strategic instrument of great value for the technological improvement of the countries of the third world.

Various types of financing will be required, according to the stage of the project, as follows:

a) Financing for the feasibility study.

b) Financing of the preparation and consolidation of the project.

c) Financing for the construction, equipment, and start-up of the centers.

d) Financing of the operation.

In order to obtain the participation of the countries associated with the regional centers for vaccinology of each one of the subregions, it has been proposed that the documents that are presented as a result of the feasibility study specify the direct benefits that the regional centers for vaccinology will contribute in regard to development of biologicals, technology, equipment, and manpower training.

For the development of the regional system for vaccinology, it would be desirable to explore alternative financing, such as arranging for a loan from the World Bank or the Inter-American Development Bank for the contributions corresponding to each country; this would have the advantage of long-term amortization and "soft" conditions for the borrowing countries. Other formulas could also be explored, such as "SWAPS" exchanges for external debt with the support of international banks, so that grants in the form of equipment can be received.

The forms of financing for the development of the centers to be considered, in addition to the monetary contributions, are in-kind supports, such as:

a) Land and infrastructure (water, drainage, electricity, roads and access, communications, etc.).

b) Support for transportation and facilities for field studies.

c) Technological contributions.

d) Participation of locally commissioned experts.

Other supports to be provided by the headquarters country. Agreements with international agencies.

a) Exemptions from taxes for professionals and immigration and transfer facilities.

b) Exemptions of customs taxes for equipment, installations, and materials.

Based on the assessment of feasibility, patent definitions, licenses, and the sale of biologicals should be considered. The centers will strictly follow policies of unconditional support for the improvement of public health; however, if commercial production of a product developed in the regional centers for vaccinology is intended, the corresponding negotiations will be undertaken.

With regard to patents, in this phase the policies and rules established in PAHO will be applied, and when necessary specific decisions required for the case of SIREVA will be made.

SIREVA can, in turn, collect the technological experiences necessary for its development through suitable arrangements adapted to the interests of the countries of the Region.

VI. DEFINITION OF INTERESTS AND FORMS OF PARTICIPATION OF THE ENTITIES INVOLVED IN THE PROJECT.

In accordance with the conditions under which the project would be developed, it is considered appropriate to point out the following:

1. According to the design of the organization of the feasibility study, PAHO may have a special organization for the development of the work.

   The regional coordinating entity will be able to carry out the feasibility study without losing the point of view of comprehensive management for the consolidation of the regional centers for vaccinology to the degree that the local units in Mexico and Brazil can integrate the work with the assent of and close linkage to the headquarters countries and the local investigators of the participating countries. According to the work plan, PAHO will have specific products for the definition of the project, which will determine its viability and practical reality, such as the program for the regional centers for vaccinology, the Technical Plan, the Preliminary Proposal for Technological Development, the Staffing Plan, and the Budget Proposals for Capital Investment and Operations.

   PAHO will be responsible for the general supervision of the project, will ensure the financing for the feasibility study phase (PAHO, Rockefeller Foundation, headquarters countries, others), will support the arrangements through its local representatives to the governments of the countries of the Region, and will arrange for the acquisition of grants to support the general coordinator, as well as the participation of his experts. PAHO also will contribute its experience and knowledge for the adequate selection and contracting of the specialists that can collaborate in the project.

The offices of the local PAHO Country Representative in the headquarters countries of the regional centers for vaccinology will participate in the work of the local groups, will administer the management and control of the resources, will see that the work conforms to policies and standards of the Office, and will do a prior review of the products of the local units in Brazil and Mexico. Those countries that will be visited will make the preparations for the corresponding visits, both technical and political, and will follow up on the concerted actions. The representatives of the countries that are not visited will promote the project directly.

In any case, it is indispensable that reports are made on the arrangements in progress and on the project itself as soon as possible.

b) The Ministries of Health of Mexico and of Brazil will be a local resource and a system of scientific and technical excellence for the development of biotechnology, the training of human resources, and the exchange of information on the subject; they also would have facilities to conduct and operate their research programs with the support of the regional centers for vaccinology, which would work in close collaboration with those who are developing their specialized institutions. In both headquarters countries, if it is deemed desirable the centers will provide the support necessary for a project that leads to local production of vaccines.

In the case of Mexico, the State of Morelos will serve as the seat of the regional center for vaccinology, integrating a broad network of complementary establishments with the units of scientific research which will contribute to its development.

In the case of Brazil, the Oswaldo Cruz Foundation and other research institutions will also have a structure that supplements the existing technical-scientific network.

The competent institutions of the headquarters countries will provide the corresponding legal, immigration, and customs facilities; they will provide technology that can contribute to the best development and operation of the regional centers for vaccinology and, when it is considered desirable, they will commission the consultants and experts that can contribute to the project in accordance with the agreements that are established.

For the execution of the feasibility study the headquarters countries will contribute resources, office facilities, personnel, and other supports and local technical contributions.

c) The associated countries will obtain the same benefits as the headquarters countries with respect to development of biotechnology in health and facilities for training human resources and for research for solution of their public health problems related to the disciplines of the centers. They will

also have access to the scientific and technical information produced in the regional centers for vaccinology, and when they require it they can obtain specialized technical advisory services. They will receive on-site support for the work of their investigators and institutions in the field of biotechnology applied to the development of new vaccines, support that will be provided by the centers in accordance with the forms and regulations determined by the governments for this purpose. The associated countries will contribute political support to the centers and financing for their development and operation according to the criteria - percentages and mechanisms that are agreed upon in each case. Eventually, and if this is considered proper and there is explicit agreement, they can contribute technology and specialized consultants.

d) The Mexican Foundation for Health will be recognized for contributing to the development of a project of international character, of great importance for public health and will obtain the benefits of its linkage to PAHO, which is a specialized agency of recognized capacity, which will permit the Foundation, particularly its consultancy unit, to expand its plans for cooperation with other international agencies.

The Mexican Foundation for Health will contribute the experience and relationships of its executive president and the support of its direct collaborators and the specialists and institutions that develop programs sponsored by the Foundation. Advantage will be taken of the knowledge the Foundation has of institutions and particular companies in obtaining information, and in the development of the local work it can contribute experience in the administration of the project. It will propose specific measures for organization, actions, and products for the execution of the feasibility study.

The Oswaldo Cruz Foundation of Brazil will be a scientific and technological resource closely related to the network of structures and set of projects for the solution of the public health problems; this Foundation can contribute its technical knowledge on the subject and the institutional relationships useful in obtaining a great part of the information that is required for carrying out the feasibility study properly.

ANNEX

REGIONAL SYSTEM FOR VACCINES ESTABLISHED BY DECISION OF THE DIRECTING BODIES(*)

SUPPORT OF COUNTRIES OF THE REGION (1)

GENERAL COORDINATION (2)	CENTERS	EXAMPLES OF PROJECTS	POTENTIAL COUNTRIES PARTICIPATING (4) (**)
PAHO	Brazil	A	1, 5, 7, 9
		B	2, 4, 7, 10
		C	5, 8
	Mexico	M	8
		N	3, 6
		P	8, 4, 9
	Both	F (3)	6, 7, 9, 10

* The numbers in parentheses refer to numbered notes under heading IV, 2.12 (c) of the text.

** Each number in this column corresponds to a different country.