PAN AMERICAN HEALTH ORGANIZATION WORLD HEALTH ORGANIZATION

XXIV PAN AMERICAN SANITARY CONFERENCE

XLVI REGIONAL COMMITTEE MEETING

WASHINGTON, D.C.
SEPTEMBER 1994

Provisional Agenda Item 5.8

CSP24/19 (Eng.)
3 August 1994
ORIGINAL: SPANISH

REGIONAL SYSTEM FOR VACCINES IN LATIN AMERICA AND THE CARIBBEAN (SIREVA)

The achievements of the Expanded Program on Immunization (EPI) of PAHO/WHO, such as the elimination of poliomyelitis and the marked reduction in the incidence of measles, diphtheria, whooping cough, and neonatal tetanus, have generated widespread recognition of the importance of vaccines in public health activities. Moreover, the significant scientific and technical development in basic areas of the biological sciences and biotechnology has opened up new vistas for the improvement and development of new vaccines.

The countries of Latin America and the Caribbean have traditionally sought training for the development and production of vaccines to address their public health problems. However, despite recognition of the importance of developing new vaccines and of the possibilities that have opened up as a result of the new technologies, no country in the Region has succeeded in obtaining the technological capability for autonomously developing the necessary vaccines or for satisfying its own demand for all the vaccines included in the EPI.

This situation suggests the need for a coordinated technical cooperation effort among the countries of the Region to develop and improve vaccines through the use of new technologies. The PAHO/WHO initiative to create the Regional System for Vaccines (SIREVA) seeks to respond to this need.

SIREVA consists of a network of member institutions that coordinate their activities in certain areas to develop and improve vaccines. Thus, an innovative concept has been adopted that integrates all the activities related to vaccine development, such as epidemiological research and surveillance, basic and applied research, technological development, increased production, quality control, and clinical and field testing.

SIREVA has been recognized as a regional initiative for the Children's Vaccine Initiative (CVI) and has received technical and financial support from scientific institutions, as well as from national and international technical cooperation and financial agencies.

The enclosed document (CE113/17), which contains the objectives, strategies, and lines of action of SIREVA, was presented to the 113th Meeting of the Executive Committee, which reviewed it and adopted it in its entirety, recognizing, moreover, that with the SIREVA initiative, PAHO assumes a leadership role in the worldwide effort to implement the Children's Vaccine Initiative. In that same meeting, the Executive Committee decided to recommend to the XXIV Pan American Sanitary Conference that it approve a resolution urging the Member States and asking the Director of PAHO to take the political, technical, and administrative steps necessary to implement SIREVA.

The XXIV Pan American Sanitary Conference is therefore requested to review the attached document and adopt the resolution transcribed below (CE113.R13). This decisive support will express the political commitment indispensable for mobilizing the resources to be invested in SIREVA's activities.

THE 113th MEETING OF THE EXECUTIVE COMMITTEE,

Having seen and examined the report of the Director containing the Regional Plan of Action for organization of the Regional System for Vaccines (SIREVA) (Document CE113/17),

RESOLVES:

To recommend to the XXIV Pan American Sanitary Conference the adoption of a resolution along the following lines:

THE XXIV PAN AMERICAN SANITARY CONFERENCE,

Having seen Document CSP24/19 on the Regional System for Vaccines (SIREVA);

Considering that vaccines are fundamental instruments for the implementation of programs to control and eradicate diseases preventable by immunization;

Bearing in mind that research for the technological development of new vaccines is the responsibility of the scientific community and national institutions;

Convinced that the development of new vaccines can stimulate biotechnology as part of the technologic development process; and

Considering that only through technical cooperation among countries, based on joint efforts that bring together the technical and scientific experience, capacity, and potential of their institutions through a collaborative program for development within the Regional System for Vaccines, will it be feasible to produce the needed new vaccines and to make those that are already available more safe and efficacious,

RESOLVES:

1. To urge the Member States:

(a) To define and give priority to a policy for the development of a regional system covering the development, production, quality control, and evaluation of vaccines of importance for public health;

(b) To revise and adjust the targets, strategies, and principal actions relating to epidemiological research on diseases preventable by vaccination; development, production, and quality control; and evaluation of new and improved vaccines;

(c) To promote policies and legislation that will commit national resources, mobilize investments, and foster technical, scientific, and financial cooperation among the countries of the Region in order to finance the work programmed for SIREVA.

2. To authorize the Director to enter into negotiations and agreements with public and private institutions in order to promote the development, production, and marketing of vaccines in the Region in response to expressions of interest by the Member Governments.

3. To request the Director:

(a) To support, within the limits of available resources, the basic activities of coordination and technical and scientific cooperation among the countries in the area of research and in the development, production, and evaluation of vaccines of high priority for the control of diseases preventable by immunization;

(b) To assist in implementing research pursuant to the guidelines contained in the master plans formulated and approved by the PAHO/WHO Expert Committee on SIREVA, or for the development of specific immunizing agents;

(c) To promote a system for encouraging participation in research on vaccine development by as many official and private institutions as possible in the countries of the Region;

(d) To provide affiliated laboratories with access to scientific and technical knowledge developed within the Regional System for Vaccines relating to the production of vaccines, as long as the laboratories have facilities and a production infrastructure that meet international requirements, and as long as they assume responsibility for the quality and proper use of the vaccines, pursuant to the guidelines of the PAHO/WHO Expert Committee on SIREVA;

(e) To discuss and come to an agreement on the transfer of technology among the participating parties, for which purpose PAHO/WHO will convene representatives of the Member States and the Expert Committee on SIREVA.

Annex

executive committee of the directing council

PAN AMERICAN HEALTH ORGANIZATION

working party of the regional committee

WORLD HEALTH ORGANIZATION

113th Meeting
Washington, D.C.
27 June-1 July 1994

CSP24/19 (Eng.)
ANNEX

Provisional Agenda Item 4.9

CE113/17 (Eng.)
20 April 1994
ORIGINAL: ENGLISH-SPANISH

REGIONAL SYSTEM FOR VACCINE DEVELOPMENT IN LATIN AMERICA AND THE CARIBBEAN (SIREVA)

The Pan American Health Organization recognizes vaccines as fundamental tools for the implementation of programs aimed at the control, elimination, and eradication of diseases preventable by vaccination. Due to the need of having new and high quality vaccines for the immunization programs in the Region, PAHO has conceived the Regional System for Vaccines (SIREVA) program. This program has been recognized as a regional initiative by Children's Vaccine Initiative (CVI), international agencies (WHO, UNICEF, UNDP, World Bank) and other development agencies, and it has as its principal objective to contribute, through the administration and coordination of the Region's scientific and technological knowledge, to the development and strengthening of research and development, production, quality control and the evaluation capacity of vaccines in Latin America and the Caribbean.

The document defines the strategies that will make the organization and functioning of the system viable and describes the lines of action, as well as the strategic programming and financing that will achieve the objectives. The prospective benefits of the epidemiological, biomedical, technological and operational research activities, coordinated by SIREVA, are also discussed.

As a result of the complexity and demands that vaccine development poses, besides the technical cooperation among different research and development institutions, universities, and public and private vaccine producing laboratories, there is a need for institutional and financial support to this endeavor, as well as the political commitment from the governments of the Region.

The Executive Committee is requested to review the document and assist in the promotion of legal and policy statements to stimulate governments to commit national resources to this effort. A clear, strong position on the part of the Executive Committee and eventually on the part of the Organization, should contribute to generating the political will necessary to mobilize resources for investment in the activities planned under SIREVA.

CONTENTS

1. Introduction

After an analytical review of the magnitude and importance of diseases preventable by vaccination in the world and the Region, as well as the relevant scientific, technological, political, and economic scenarios, this document discusses the background of the initiative developed by the Pan American Health Organization (PAHO/WHO) which is known as the Regional System for Vaccines (SIREVA).

As an innovative solution, this system is designed to improve the immunizing agents that can accelerate control and lead to the possible elimination of a larger number of diseases preventable by vaccination, promoting participation by the existing scientific, technological, human and institutional infrastructures and capacity in the Region.

The objective of the system is to contribute to the development and strengthening of the Region's real and potential capacity for development, production, quality control, producer certification, and evaluation of effective immunizing agents for use by Member States in their immunization programs.

Strategies are outlined for making the system's organization and operation viable, and lines of action are described, along with the strategic programming and financing that will allow the objectives to be achieved. A prospective analysis of the benefits of the epidemiological, biomedical, technological, and operational research coordinated by SIREVA is presented as well.

The development of new vaccines is an extremely complex, costly, and prolonged process requiring the skills of many disciplines. This process therefore relies on the formal commitment as well as the financial support of all the governments in the Region.

2. Background

Vaccines are fundamental tools in programs aimed at the control and eradication of diseases preventable by vaccination, the latter being a public health activity with an undeniably positive cost-benefit ratio.

The Region has made important strides in the elimination of diseases preventable by vaccination thanks to a growing commitment by the governments and agencies who are collaborating with the Expanded Program on Immunization (EPI) of PAHO/WHO. The elimination of poliomyelitis caused by wild poliovirus and the marked reduction in the incidence of measles, diphtheria, whooping cough, and neonatal tetanus are particularly remarkable. Despite these significant advances, however, the quality or effectiveness of certain existing vaccines needs to be improved, while other vaccines

developed recently for some important diseases preventable by vaccination in the Region have costs that are beyond the reach of its immunization programs.

The enormous scientific and technical progress being made in basic biosciences and biotechnology, as well as the scientific and technological knowledge that is being acquired, is also being applied to the improvement and development of vaccines. Industrialized countries already have or are at the brink of producing a large variety of new or improved vaccines which, due to the high costs associated with complex technology and patent protections, will be difficult to introduce and use in developing countries. This could lead to the existence of two types of vaccines: technologically sophisticated vaccines that immunization programs will have difficulty accessing, and traditional vaccines for more general use.

Striking political and economic changes in the world and the Region have promoted the existence of a more global and international economy. At the same time government agreements are creating economic and political blocks. This new world order has redefined the State's role in health systems. These changes include rational and planned use of available financial resources and the attempt to find innovative ways of transforming the concept of spending in health into that of investment in health.

The State's need to rationalize expenditures and redefine its health role makes investment in disease prevention a priority; above all, investment in activities aimed at protecting young groups. Of the six conditions that have the most serious impact on population health (perinatal and maternal causes; respiratory infections; diarrheal diseases; ischemic heart and cerebrovascular disease; childhood cluster: diphtheria, polio, pertussis, measles and tetanus; and tuberculosis), four are diseases preventable by vaccination (*World Development Report*, World Bank, 1993), so that research, development, and production of vaccines is an important aspect of investment in health.

The traditional vaccines in use in the world are produced in both developed and developing countries. However, new technologies and investment in the development of new vaccines are concentrated in developed countries, where production is almost exclusively in the hands of transnational companies. These companies have defined their priorities in line with needs in the developed world. As a result, diseases preventable by vaccination that are of epidemiological importance in the countries of the Region but of low incidence in more developed societies have not succeeded in capturing the attention of vaccine production companies.

There is no country in Latin America or the Caribbean that has the necessary installed technological capacity to meet local demand for all the vaccines included in the EPI (diphtheria, tetanus, whooping cough, BCG, poliomyelitis, measles, hepatitis B, and yellow fever). However, some countries are self-sufficient in their local production of

one or another EPI vaccine, as well as of other vaccines, such as human and canine rabies vaccine, antimeningococcus, serogroup A, C, and B, and antiophidic serum, antivenomous serum, and antitoxins for therapeutic use.

The vast majority of the existing vaccine production laboratories in the Region are either public or indirectly dependent on the government. There is not a single laboratory connected to a transnational corporation in Latin America and the Caribbean devoted to the production of vaccines for human use, and the few private laboratories are very small and have no impact on the market.

Few governments in Latin America and the Caribbean are making large investments in new installations and modern equipment with a view to becoming self-sufficient in the supply of essential vaccines. On the other hand, the governments are organizing themselves to be ready to meet WHO requirements and other international standards regulating the production of vaccines for human use. However, most of Region's existing laboratories do not meet internationally established requirements, nor do all vaccine-producing countries have an adequate national system for quality control. This makes it difficult to guarantee the quality of the vaccines produced in the Region by the laboratories in these countries.

3. Regional Initiative for Vaccine Development

In 1988 a Pan American Health Organization/World Health Organization (PAHO/WHO) experts' group expressed strong support for the idea of establishing a regional system in the Americas to develop new vaccines and improve existing ones.

Another meeting of experts from 15 countries in Rio de Janeiro in 1989 cited the need to conduct a feasibility study of a regional system for vaccine development (SIREVA). The study was launched that same year with the participation of the Government of Mexico, the Rockefeller Foundation, the Inter-American Development Bank (IDB), the International Development Research Center (IDRC, Canada), and PAHO/WHO.

An innovative concept was developed that integrated all important stages of vaccine development: epidemiological research and surveillance, basic applied research, technology development, pilot-scale production, quality control, and clinical and field trials. In addition, it was recommended that every possible effort be made to take advantage of and utilize the real and potential capacity of scientific and technical institutions and their resources; to awaken the interest of and promote participation by the countries of the Region, as well as the international scientific community; to strengthen regional scientific and technological infrastructure; and to obtain political support and economic commitment from the governments of the Region.

Since then, PAHO/WHO has been organizing a series of technical meetings to verify the feasibility of the Regional System for Vaccines. Taking part in these meetings have been international consultants, researchers from scientific institutions, and individuals involved in the production of biologicals from Argentina, Brazil, Canada, Chile, Colombia, Cuba, Ecuador, the United States, Guatemala, Jamaica, Mexico, Panama, Peru, Uruguay, and Venezuela.

In recognition of the fact that millions of children still die every year from diseases that could have been prevented, the Children's Vaccine Initiative (CVI) was launched in September 1990 at the World Summit for Children through the Declaration of New York, with the support of WHO, the Rockefeller Foundation, the United Nations Children's Fund (UNICEF), and the United Nations Development Program (UNDP). This initiative emphasizes the need to expand the spectrum of diseases for which vaccines are available, to simplify the requirements for vaccine supply, and to reduce the costs of vaccine production and vaccination.

This initiative, which grew out of the most important and far-reaching event in the field of children's health care, is a fundamental landmark in the path toward universal prevention and control of diseases preventable by vaccination. Achieving the goals of this initiative will require a substantial investment of time and of human and financial resources, coupled with the efforts of the entire world scientific community. In its 1993 report, the World Bank recognized the development of new vaccines and the improvement of existing vaccines as one of the top six priority areas in health.

May 1991 marked the completion of the SIREVA Feasibility Study which concluded that the development and execution of this system would be scientifically, economically, administratively, and politically feasible. At that time selection criteria were outlined for choosing the vaccines to be developed or improved, and the priorities proposed for the initial phase were vaccines against the diseases caused by *Streptococcus pneumoniae, Salmonella typhi, Neisseria meningitidis* group B, and dengue virus.

During 1992 and 1993 master plans were prepared for the development of those vaccines. These reference documents contain up-to-date information on each disease, including its agents and its epidemiological, pathological, clinical, and immunological characteristics, along with strategies for vaccine development and proposals for lines of research, pilot production, and clinical and field trials.

SIREVA has been recognized as a regional initiative by the CVI, international agencies (WHO, UNICEF, UNDP, World Bank), and other development agencies (Rockefeller Foundation, CIDA, SIDA). In its Strategic Plan for 1993, the CVI expressed the hope that, "as the CVI gathers momentum, additional special regional

priorities with the potential to become regional initiatives for vaccine development will be identified, like the SIREVA initiative in the Americas."

In 1993, at the plenary session of the First Regional Meeting on Improved DTP Vaccines and DTP-Based Combined Vaccines (SIREVA/CVI), which was attended by the directors of all DTP production laboratories in Latin America, there was a discussion of ways to improve the quality of the DTP vaccines currently produced in the Region and to develop new DTP-based polyvalent vaccines. It was recommended to launch the following three programs:

- development of a regional network for quality control of vaccines;
- development of a certification program for DTP laboratories;
- development of a program of consortiums for research and development on improved DTP vaccines and DTP-based combined vaccines.

Thus far, several countries in the Region have participated to a greater or lesser extent in activities within the framework of SIREVA. The Canadian International Development Agency (CIDA) is financing a study of the distribution of *S. pneumoniae* serotypes in eight countries of the Region (Argentina, Brazil, Chile, Colombia, Jamaica, Guatemala, Mexico, and Uruguay). Canada, through the Laboratory Center for Disease Control (LCDC), is providing technical assistance for the execution of this project. With financing from the Swedish International Development Agency (SIDA) field studies for a cholera vaccine are underway in Colombia, Mexico, and Peru. With the support of WHO and regular funds from PAHO, a workshop on *in vitro* techniques for quality control of bacterial and viral vaccines was presented, with the participation of Argentina, Brazil, Chile, Cuba, Mexico, and Venezuela. PAHO regular funds were used for five workshops on Good Manufacturing Practices in Argentina, Brazil, Cuba, Mexico, and Venezuela, with the participation of technicians from other countries in the Region (Chile, Colombia, Dominican Republic, and Uruguay). A meeting was also held between representatives of Brazil, Chile, and Mexico and personnel from the United States Food and Drug Administration (FDA) and the Canadian Bureau of Biologics to discuss the feasibility of a regional network of quality control laboratories.

In 1993, as well as 1990, during the Meeting of the Executive Committee of PAHO, the Director gave a presentation on SIREVA in which he discussed its objectives and strategies, as well as the activities being carried out. The initiative was very well received by the members of the Committee who came out strongly in favor of seeing the activities continue.

Since 1989 at technical meetings Brazil and Mexico have been expressing their willingness to support SIREVA. Since they have been participating through their investment of human and financial resources to promote the system and help bring it into

existence, they were recognized by PAHO/WHO as the sites for two Centers for Vaccines (CENVAC/Cuernavaca in 1992, and CENVAC/Río in 1993), to facilitate the coordination of SIREVA activities throughout the hemisphere.

4. Regional System for Vaccines

SIREVA is an international programming, administrative, and coordination initiative that responds to the need to establish and strengthen scientific and technical cooperation for the development, production, improvement, quality control, and evaluation of vaccines, within the institutional framework of PAHO/WHO.

SIREVA is expected to evolve as an autonomous and permanent system in the countries of the Region of the Americas.

4.1 *Goal of SIREVA*

The goal of SIREVA is to have the necessary knowledge, scientific and technological capacity, and means available in the Region to develop, produce, and maintain quality control of immunizing agents for the prevention and control of diseases preventable by vaccination that are important in Latin America and the Caribbean; and, in particular, to respond to current demands and expand the spectrum of diseases preventable by vaccination that are included in the Region's immunization programs.

4.2 *Objectives of SIREVA*

The objectives of SIREVA are:

- To coordinate the organization and strategic administration (operation, programming, and management) of activities for the development, production, and evaluation of new or improved vaccines in the Region.

- To increase investment in and commitment to the epidemiological study of diseases preventable by vaccination, as well as to research and development on effective vaccines in the countries of the Region.

- To increase and strengthen communication and collaboration between interested groups in the countries of the Region who are working in isolation.

- To increase collaboration with scientific groups in developed countries who are interested in cooperating with national institutions in the Region for vaccine development.

- To increase opportunities for institutional strengthening and human resource development in order to help close the scientific and technological gap between the industrialized and developing countries in the Region.

- To mobilize institutional, human, and financial resources in the countries of the Region for the development, production, and quality control of vaccines in support of immunization programs in the Region.

- To help ensure that the countries of the Region have access to the guaranteed quality vaccines they need to solve their priority public health problems.

4.3 *Justification for SIREVA*

Only a few countries in the Region have the scientific and technological capacity to develop new vaccines, as well as large production capacity and adequate quality control.

SIREVA provides mechanisms for accelerating the processes of research, development, production, and quality control of vaccines so that vaccines of guaranteed quality can be provided more quickly and at a lower cost. At the same time, SIREVA creates the opportunity for all the countries in the Region to participate in and benefit from these processes.

Technical cooperation among the countries--in which they combine their efforts, experience, capacity, and technical and scientific potential--will make it possible to produce the new vaccines needed in the Region, as well as to improve existing ones. In this way, SIREVA will help to ensure the effectiveness and efficiency of the various immunization programs carried out in the Region.

Thus SIREVA would appear to be the best option for integrating the efforts of governments, research centers, public and private production laboratories, development and evaluation activities, national control authorities, and national control laboratories, with a view to ensuring the availability of guaranteed quality vaccines produced in the Region.

4.4 *Strategy of SIREVA*

SIREVA implements a global approach to vaccine development that involves systematic execution of all the required phases in this process: epidemiological research and surveillance, basic research, technological development, pilot-scale production, quality control, and clinical and field trials. A Master Plan for each selected vaccine, developed by a technical advisory group specifically designated for this task, serves as

the basis for the coordination and implementation of the several phases related to vaccine development. With regard to production activity, the strategy is supported by the certification program for production laboratories, which will provide technical advisory services on how to adopt procedures and meet other technical requirements in order to guarantee the quality of the vaccine produced. The activities outlined will be carried out through collaborative projects, joint action networks, or consortiums of scientific and technological institutions formed through agreements, alliances, and arrangements.

Likewise, SIREVA will promote joint efforts in vaccine development by strengthening scientific and technical infrastructure with the goal of maximizing existing structures in the Region.

5. Lines of Action

The implementation of SIREVA's conceptual framework will require programmed execution of the following lines of immediate action:

- Organization of a programming, coordination, and administrative infrastructure at PAHO/WHO in Washington, D.C., together with two Regional coordinating units, heretofore called CENVACs and now referred to as Regional Vaccine Coordinations (RVCs).

- Promotion of activities to identify and define priorities for joint technological development, production, and quality control of vaccines in the countries of the Region. In addition, determination of real and potential capacity in areas of common interest for vaccine development in public and private scientific and technological institutions inside and outside the Region.

- Coordination and integration of efforts in the area of basic and applied research and vaccine development carried out by institutions and groups inside and outside the Region, utilizing the structures and capabilities of PAHO/WHO and the health systems in the Member States to the fullest extent possible.

- Contribution to the training, updating, and improvement of the specialized human, scientific, and technical resources needed for research, training, and development in immunization programs and projects in the countries of the American hemisphere.

- Promotion of activities to identify laboratories and research groups in the field of vaccines, and to assess and evaluate the capabilities of quality control laboratories and production laboratories with a view to organizing and implementing the

programs on research laboratory consortiums, the quality control laboratory network, and certification of production laboratories.

- Promotion of appropriate technology transfer between research groups, technology development, and the manufacturing sector in the Latino American and Caribbean countries, and laboratories for research and production of biologicals in industrialized countries.

- Mobilization of scientific, technological, and financial resources in order to strengthen activities in the areas of information, coordination, management, and technology transfer that accelerate the process of developing the priority vaccines.

6. Beneficiaries and Benefits

The principal beneficiaries and benefits of the SIREVA programs are as follows:

- The entire population--particularly children and the more economically disadvantaged social groups--who will have access to safer immunizing agents of guaranteed and effective quality to fight a broader spectrum of diseases.

- Immunization programs under the ministries of health, which will be able to include more effective immunizing agents without any significant increase in operating costs.

- The health systems, which will experience a reduced burden due to increased prevention and control of a greater number of diseases preventable by vaccination and the direct impact that this will have on the cost of medical care.

- National quality control systems, which will become part of a Regional network that will provide them with a continuous flow of information and technical and scientific updating. This network will promote exchanges with other quality control laboratories inside and outside the Region, complementing, rationalizing, and maximizing control methods and facilitating harmonization of regulatory procedures.

- Public and private vaccine production institutions, which will have access to new vaccine development technologies that will open the door to technological innovation and the improvement and enhancement of production procedures, thus making it possible to reduce costs and ensure the production of higher quality vaccines. These institutions will also benefit from the exchange of information with other members of the interinstitutional network. The production of high quality vaccines will open up new markets in other countries and regions, which

will produce economic benefits. In addition, the demand created by the scientific institutions and regional vaccine production will strengthen the industry that produces essential raw materials and thus be a source of new jobs.

- The academic sector, which will benefit by virtue of SIREVA's creation of specific demand in basic and applied areas of research, training, and integration of highly qualified human resources. An additional benefit will be the presence of these professionals in the Region. The Regional technical and scientific community in the technological field will have more stable institutions that are better equipped to incorporate future technological developments in vaccine production. This scientific and technological development will raise the level of the academic community, helping to narrow the gap between the local academic community and that of industrialized countries and allowing that community to play a stronger role in the development of modern immunizing agents.

- Production laboratories, since the certification program will ensure modernization of their installations and operations for all phases of production, and accordingly will also guarantee the quality of raw materials and of intermediate and finished products. The availability of certified intermediate products will benefit laboratories with a smaller production capacity, making possible and encouraging shared production. This will result in a sizeable increase in the supply of guaranteed quality vaccines and ensure that the demands of immunization programs in the Region can be met.

- All the countries in the Region, which will benefit from the availability of vaccines. Countries with institutions that participate in some of the stages of vaccine development--epidemiological research and surveillance, basic research, technology development, pilot production, quality control, and clinical and field trials--will also reap the scientific, technological, and economic benefits of this participation.

7. Organization of SIREVA

The central activity of SIREVA is the scientific and technical cooperation between the participating countries and their institutions for the purpose of vaccine development and production. This requires continuous articulation, coordination, support, follow-up of activities, monitoring, and evaluation. In addition, there needs to be continuous administration and management, as well as adequate financing.

7.1 *Organization of SIREVA Management*

As an international organization, PAHO/WHO provides institutional protection for the initiation of systematic activities that make it possible to integrate centers for research and development; establish a network of participating institutions and laboratories; mobilize scientific, technological, and financial resources; and put the Organization's management experience in this field to use.

The SIREVA/PAHO program has a coordinator and a central organizational and administrative structure located in Washington, D.C. This structure includes regional advisors, technical officers, and an executive secretariat. In addition, it is expected that short-term consultants and temporary advisors will be hired, and technical services contracted from local personnel. The functions of the central structure include general coordination, administration, and management of SIREVA activities. Support is provided by the Regional Vaccine Coordinations (RVCs) and the participating laboratories, as well as the scientific and technical committees.

7.2 *Network of Participating Laboratories and Epidemiology Units*

The broad range of lines of action listed below is coordinated by SIREVA and will give most of the countries in the Region the opportunity to participate in one or more activities, including:

- epidemiological studies;
- basic research in immunology, immunochemistry, biochemistry, molecular biology, bacteriology, and virology;
- applied research and technological development of immunizing agents;
- development of animal facilities;
- pre-clinical studies in animal models;
- clinical studies in humans;
- tests of immunogenicity and reactogenicity of vaccines;
- tests of effectiveness by means of field trials;
- quality control of vaccines;
- production of vaccines;
- marketing techniques;
- studies of cost-benefits and cost-efficacy.

SIREVA proposes to establish consortiums of laboratories and institutions with a common interest in research and development of one or more vaccines so that they can maximize their efforts and share the knowledge gained.

With respect to the production laboratories that are part of SIREVA, the certification program will be implemented through activities to analyze and evaluate

conditions and vaccine production capacity, as well as administrative and economic factors. It will also address international requirements and technical standards and how they should be met in installations, equipment, and human resources capacity. It also proposes the improvements, interventions, and investments that would be needed in order to produce high quality vaccine. During its initial phase the program is focusing on DTP production, and its goal is to evolve to the point of being able to certify all vaccines in the immunization programs. Certification of laboratories and their products will assure the quality of the processes and procedures used in production and quality control, making it possible to obtain intermediate products and bulk supplies. At the same time, this process will guarantee the availability of finished products, i.e., the highest quality vaccines for immunization programs.

7.3 *Committees*

The Technical and Scientific Advisory Committees of SIREVA will be composed of Regional or outside experts who will meet in accordance with the needs and progress of the different projects. These committees will have the following functions, among others: to examine scientific and technological alternatives for the development of each vaccine in the Region in order to identify those with the best prospects for development; to determine the epidemiological studies of each disease that need to be carried out; to recommend members for the networks of participating laboratories and epidemiology units; to guide and review the specific projects for each vaccine; and to evaluate the progress of each project.

8. Budget

The operating costs of SIREVA are estimated at approximately US$14,810,000 for a period of five years and $3,340,000 for the first year (see Annex 1). Some of the financial resources will come from PAHO/WHO regular funds, some of which are already allocated, and some from CVI, supplemented by voluntary contributions from the countries and other sources, so that implementation of the basic activities is ensured.

The operating costs proposed will implement the core activities for the planning and initial execution of the specific projects, as well as for the preparation of projects for the strengthening of the institutions in the Region (see Annex 2). Notwithstanding, the proposal will promote the commitment and participation of the countries in order to assure the higher investments required for research, development, modernization of production capacity, improvement of quality control, formation of critical scientific human resources, and other aspects. These will be the major investments for assuring the availability of high quality vaccines in the Region.

Annexes

ANNEX 1

BUDGET FOR SIREVA: TOTAL OPERATING COSTS FOR THE FIRST YEAR AND FOR FIVE YEARS

	FIRST YEAR	TOTAL FIVE YEARS
REGIONAL VACCINE QUALITY CONTROL NETWORK		
(A) ADMINISTRATION AND COORDINATION	120,000	540,000
(B) CONSULTANTS	270,000	1,170,000
(C) SUPPLIES AND EQUIPMENTS	250,000	800,000
(D) TRAINING	160,000	740,000
SUBTOTAL	**800,000**	**3,250,000**
CERTIFICATION OF PRODUCERS OF DTP IN THE REGION		
(A) ADMINISTRATION AND COORDINATION	100,000	500,000
(B) CONSULTANTS	300,000	1,330,000
(C) SUPPLIES AND EQUIPMENTS	120,000	600,000
(D) TRAINING	120,000	600,000
SUBTOTAL	**640,000**	**3,030,000**
CONSORTIUMS OF RESEARCH AND DEVELOPMENT OF NEW DTP VACCINES		
(A) ADMINISTRATION AND COORDINATION	90,000	390,000
(B) CONSULTANTS	260,000	1,120,000
(C) SUPPLIES AND EQUIPMENTS	400,000	1,480,000
(D) TRAINING	150,000	540,000
SUBTOTAL	**900,000**	**3,530,000**
VACCINE DEVELOPMENT PROJECTS: *S.pneumoniae, S.typhi, N.meningitidis* GROUP B, AND DENGUE		
(A) ADMINISTRATION AND COORDINATION	240,000	1,180,000
(B) CONSULTANTS	470,000	2,090,000
(C) SUPPLIES AND EQUIPMENTS	150,000	890,000
(D) TRAINING	140,000	840,000
SUBTOTAL	**1,000,000**	**5,000,000**
TOTAL	**3,340,000**	**14,810,000**

(A) ADMINISTRATION AND COORDINATION — Includes the activities of administration, organization and technical coordination.

(B) CONSULTANTS — Consultants, meetings of the technical advisory and expert committee, monitoring and auditing of the project and the programs.

(C) SUPPLIES AND EQUIPMENTS — Includes computer systems, the programs, and maintenance of the system. Development, production, and distribution of reference reagents, standards, and vaccines. Other small equipment and complementary accessories.

(D) TRAINING — Includes workshops, courses, and exchange fellowships between countries inside and outside the Region.

ANNEX 2

PLAN OF ACTION AND ACHIEVEMENTS

In addition to the criteria adopted for selecting priorities in SIREVA, as described below, the choice of projects for the development as well as the production and improvement of vaccines was based on the various stages of development of the different vaccines in the Region. This approach made it possible to simultaneously assess different intrinsic situations.

The criteria for vaccine selection are:

- Epidemiological situation (mortality, morbidity, incidence, prevalence) and social impact of the disease, in terms of unnecessary child deaths and years of potential life lost.

- Scientific and technological feasibility: cumulative knowledge, available technology, potential and real market, potential incorporation of the new vaccines into the EPI, possible generalization of the knowledge obtained for future application in similar projects.

- Local and regional importance of the disease and existence of groups with real or potential capacity in vaccine research, development, production and/or evaluation.

- Costs/benefits of development and production.

The plan of action includes all the activities necessary to achieve the objectives of this system. These activities are related to the production of epidemiological knowledge about diseases preventable by vaccination, basic research, pilot production, optimization of production processes, quality control, and evaluation of immunizing agents in countries of Latin America and the Caribbean, and they are part of the projects listed below.

1. Epidemiological Research: Development of a Vaccine Against *Streptococcus pneumoniae*

As the initial phase in the development of a vaccine against *Streptococcus pneumoniae*, and in line with the recommendation of the master plan, for the last two years a study of serotype distribution has been being implemented in the Region, with financing and support from the Government of Canada through the Canadian International Development Agency (CIDA) and the Laboratory Center for Disease Control (LCDC). This study of the distribution of *Streptococcus pneumoniae* serotypes in Latin America and the Caribbean will make it possible to define the formulation of a multivalent vaccine according to the epidemiological characteristics of the Region. The study was initiated in the population of children under 5 in Argentina,

Brazil, Chile, Colombia, Mexico, and Uruguay, with financial support from the Canadian Government (CIDA and LCDC).

2. New Vaccine Development

The Master Plan prepared for each vaccine will serve as the reference document for the implementation of research, technological development, and related matters.

2.1 *Development of an Improved Vaccine for* Salmonella typhi

In November 1993 a protocol was prepared for joint development of a vaccine against typhoid fever by institutions in Brazil, Chile, and Mexico. It encompasses the development of three vaccines against typhoid fever: Vi polysaccharide antigen; Vi polysaccharide antigen conjugated with porins; and Vi polysaccharide antigen conjugated with tetanus toxoid. The work of developing a vaccine conjugate against typhoid fever is being carried out on a multi-institutional and multicountry basis. The Immunochemistry Unit of the Mexican Social Security Institute, in conjunction with the National Institute of Hygiene, is in the process of pilot production and purification of porins, and Bio-Manguinhos/FIOCRUZ has experimentally produced polysaccharide Vi antigen. Recently scientists from the University of Santiago, Chile, have been incorporated into the process of developing appropriate conjugation techniques.

2.2 *Development of an Improved Vaccine for* Neisseria menigitidis *Serogroup B*

Three institutions in Brazil (Instituto Adolfo Lutz, Instituto Butantan, and Bio-Manguinhos/FIOCRUZ), with technical cooperation from the Center of Biological Evaluation and Research of the United States Food and Drug Administration, are working on a vaccine with iron-regulated outer membrane proteins, outer membrane proteins (OMP) formulated through the incorporation of different subtypes, with meningococcus C polysaccharides and lipopolysaccharides. The studies of immunogenicity in laboratory animals have progressed rapidly and studies of pilot production in 100 liter fermentors have been initiated to determine yield and expression capacity of iron-regulated proteins in large volume cultures.

2.3 *Development of a Dengue Vaccine*

Several meetings have been held to discuss proposed joint efforts to develop a dengue vaccine. Based on the recommendations of these meetings, it has been proposed to utilize strains of attenuated live virus developed at the University of Mahidol in Thailand, and to take advantage of the experience with industrial-scale production of cell cultures, development of thermostabilizers for viral vaccines, large volume lyophilization, and utilization of Good Manufacturing Practices in Latin America. In conjunction with the Rockefeller Foundation and the Walter Reed Army Institute of Research of the United States, other alternatives for joint work have been developed, including the use of recombinant DNA technology.

2.4 *Development of a Program of Consortiums for Research and Development of Improved DTP Vaccines and DTP-Based Combined Vaccines*

Establishment of a program to set up consortiums of institutions to conduct applied research and development for the production of new vaccines. The present project proposes to promote research with a view to ensuring that, by the year 2000, the Region has its own improved DTP vaccines and DTP-based combined vaccines.

The consortiums for vaccine research and development will be multidisciplinary and will include scientists and technicians at various institutions, preferably from different countries. They will cover all aspects of basic research, directed and applied to the development, production, and quality control of the new vaccines. The current state of research and the development of new DTP vaccines in the Region makes it possible to predict that interest will be focused on the following areas of research and development:

- toxoids of greater purity (diphtheria and tetanus);
- cellular pertussis vaccine;
- acellular pertussis vaccine;
- DTP-based combined vaccines.

3. Field Trials of Vaccines

3.1 *Field Trial of the Vaccine Against* Vibrio cholerae *(WC/rBS)*

When the seventh cholera pandemic reached Latin America, an experts' meeting convened by PAHO/WHO at the end of 1991 included field trials of cholera vaccines as part of SIREVA activities. These trials are being financed by the Swedish International Development Agency (SIDA). Because of the outbreak of the cholera pandemic in the Region, field trials were programmed in Colombia and Mexico (Phase II) to determine the immunogenicity, antigenicity, and reactogenicity in Mexico and Colombia of the Swedish WC/B vaccine containing dead cells supplemented with recombinant sub-unit B of the *Vibrio cholerae* toxin. Phase III trials are being organized in Peru. These trials are also being financed by SIDA.

4. Development of a Regional Network for Quality Control of Vaccines

This project aims to provide the Region with a framework for action to help in implementing a system that guarantees the quality of the vaccines that are utilized in the Region, and, in particular, seeks to eliminate the use of vaccines in the Region that do not undergo adequate quality control independent of the control carried out at the production laboratory.

The Regional Network for Vaccine Control, made up of the national control authorities and laboratories connected through the information network, will have the following

responsibilities: to harmonize protocols and methodologies; to harmonize registries and licenses; to develop and produce standard reagents and reference vaccines; to organize collaborative studies on new quality control techniques; to validate laboratory methodologies; to develop certification programs for production laboratories; to evaluate production protocols; to develop programs for scientific and technical exchange and training; to implement a Regional post-marketing surveillance system; to control all vaccines (traditional, new or improved) used in clinical research carried out in the Region; and to maintain active ties with USFDA, NIBSC/United Kingdom; Bureau of Biologics/Canada; and other international bodies that regulate biologicals.

5. Certification Program for Vaccine Production: Development of a Certification Program for Laboratories that Produce DTP Vaccine

The project proposes to certify the plants, equipment, and processes of all laboratories producing DTP vaccine in order to ensure that there will be the capacity and consistency necessary for Regional self-sufficiency in DTP vaccine. The project includes a stage of initial assessment of the production laboratories and governmental authorities in order to determine the political and financial commitment and current state of production in each case. For each production laboratory a certification scheme will be carried out that includes a visit for technical, administrative, and economic evaluation which will make it possible to determine needs in the areas of installations, equipment, human resources, and technical and organizational capacity, in addition to costs and the measures that need to be taken in order to meet certification standards. A strategic plan will be developed to improve the competitiveness and capacity of the production laboratory which will include improvements in the plant and/or production procedures. During the plan's implementation, PAHO and WHO will provide advisory services and technical assistance. This scheme will culminate with the certification of the new installations and processes.