Pan American Health Organization World Health Organization

XXIX MEETING OF THE ADVISORY COMMITTEE ON HEALTH RESEARCH

Washington, D.C., 2-6 August 1993

ACHR 29/93.9
Original: English

RESEARCH ACTIVITIES OF THE PAHO COMMUNICABLE DISEASES PROGRAM (1989 - 1992)

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Communicable Diseases Program
July 1993

TABLA DE CONTENIDO

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I. INTRODUCTION

At the request of the Advisory Committee on Health Research, a description of the activities of the Program on Communicable Diseases (HCT) for the period 1989-1992 is presented. The Program is concerned with the prevention and control of communicable diseases, particularly vector-borne diseases. Its objective is to strengthen individual countries' capacity to implement technically feasible, economically viable, and socially acceptable prevention and control programs. The main goals of the Program are to integrate disease prevention and control activities within the local health systems, to promote community participation, and to advocate for efficient use of the available resources within local programming.

HCT does not conduct prevention and control activities per se. Rather, it strengthens the infrastructure in both field and laboratory operations, providing under its mandate the tools to assist the national counterparts in initiating or implementing their own prevention and control activities efficiently and effectively. Technical cooperation is provided within the framework of the six projects that make up HCT. Three of these projects are of a general nature: General Communicable Disease Prevention and Control (OCD), Vector Biology and Control (VBC), Parasitic diseases (PDP) and Tropical Disease Research (TDR); and three are concerned with specific diseases: Leprosy (LEP), Malaria (MAL), and Tuberculosis (TUB) (Figure 1).

This document describes the strategic orientations of the technical cooperation and program priorities for research. It provides a summary of the sponsorship, promotion, and coordination of research activities carried out by the Program.

The cooperation in research provided by HCT necessarily reflects the needs and organizational status of individual prevention and control programs at the country level. Despite the fact that techniques to reduce transmission of diseases targeted by the Program are known, the practical methodologies for implementing prevention and control programs at a realistic cost are still inadequate. Use of diagnostic methods and procedures for effective treatment is limited because of lack of experience or economic and operational obstacles. Often, there is a time lag between the availability

of new knowledge and its application for the purpose of improving local prevention and control activities. This is the particular case of the vector-borne diseases. Vertical eradication programs, although effective under certain conditions, cannot be maintained under the socioeconomic conditions that prevail in the Region. Most national governments and/or international financing agencies are no longer willing or able to sponsor expensive vertical programs based on the use of chemical products. The environmental pollution resulting from the use of these products and the resistance of the vectors to insecticides are additional concerns. These factors have prompted the abandonment of control strategies based on a single method (for example, the use of chemicals) in favor of integrated, self-reliant, and community approaches that incorporate the appropriate technologies of environmental management, biological control, health education, and epidemiological stratification in order to make better use of the limited resources available.

PAHO research resources in comparison with those of other agencies are minimal. Therefore, the Organization's research activities promote, sponsor and coordinate research through catalytic input. A comparison of the funding from the Region for malaria research shows the small part that PAHO funds represent in comparison with those of other national or international agencies (Table 1).

The Strategic Orientations and Programs priorities defined by PAHO/WHO Governing Bodies form the foundation for all the research activities done by the HCT Program (Figure 2). Those in which the technical cooperation on research is an essential part of the strategy are listed below.

I. STRATEGIC ORIENTATIONS

1. Reorganization of the Health Sector

HCT's contribution to reorganizing the health sector has focused on promoting decentralization of prevention and control activities, integration with activities of the general health services, and strengthening of local health systems with regard to the diseases targeted by the Program. Decentralization and strengthening of the health services are fundamental elements in combating malaria, vector control, leprosy, and, in general, in preventing and controlling communicable and parasitic diseases. As a consequence of this initiative, several of the national programs are presently in different stages of decentralization and integration into local health systems as a means of extending coverage and achieving a better response to the problems at hand. Integration and rational use of resources are difficult to achieve at the local level. This is due, in part, to the lack of a well-defined national policy for carrying out the

decentralization process and to the lack of technical knowledge at the local level that would permit rational decision-making in the campaign against vector-borne diseases. Research is essential for establishing the problem-solving capability of the health services and their capacity to respond to the demand. Projects of this type have been promoted in Colombia and Mexico.

2. Targeting High-Risk Groups

Review of the strategies for the prevention and control of vector borne diseases has required the promotion and financing of research based on the concept of epidemiological stratification. Epidemiological stratification was recently applied to characterize the current situation of malaria. The working premise of this epidemiological concept is recognition of the existence of various patterns for the transmission of malaria, which are determined by the presence and interaction of various individual, socioeconomic and ecological factors and determinants related to organization of services. Identification and ranking of the principal risk factors at the local level permits the selection of specific intervention measures aimed at both management of disease and control and elimination of the factors determining transmission. The concentration of efforts on high-risk groups makes interventions more effective and efficient. Two prospective epidemiological studies using epidemiological stratification are under way in Rondonia, Brazil, and in Bolívar and Sucre, Venezuela. Another retrospective case-control study is being carried out in Brazil with the aim of determining the demand for malaria interventions and its underlying epidemiological factors.

3. The Use of Mass Communication in Health

Information on the proper use of mass communication as an instrument to enhance prevention and control activities has been provided to the national authorities. Mass communication is considered an essential tool to stimulate community participation, the foundation of integrated control of vector-borne diseases.

Well-informed and committed community participation, which includes individuals, their families, and their communities, continues to be an essential concern of the HCT Program. An attempt is being made to move from the simple--but no less important--practice of information dissemination, to implementation of comprehensive health education. The objective is to achieve a sustained impact, not only on the population but also on the formal educational system. This is a crucial path toward the main objective: changing the attitudes and behaviors of current and future generations. Two research projects combining mass communication, health education,

and integrated biological control of vectors (*B. turingiensis, Cyclops*) in Honduras, and Venezuela are currently under way.

4. Health Promotion

Since healthy and hygienic dwellings and surroundings are essential in preventing and controlling the diseases with which this Program is concerned, HCT's concept of health promotion involves strategic interventions aimed at protecting the environment, improving living conditions (work and housing), and on changing the lifestyles of high-risk population groups. These actions are primary prevention strategies for communicable disease control. It is in this context that activities to promote environmental sanitation focused on dwellings and their surroundings are carried out. For example, dirt floors not only make domestic hygiene difficult, but can also lead to the transmission of helminthiasis through the soil; walls and roofs in poor condition provide excellent environments for infestation by arthropod disease vectors. In addition, unprotected windows and doors allow the entry of insect vectors. In the case of walls and roofs, a typical example is infestation by triatomids, the vectors of American trypanosomiasis; and in the case of windows and doors, entry by the vectors of malaria and/or dengue.

Dwellings and their surroundings can be risk factors in the transmission of communicable diseases. As a result, the promotion of healthy dwellings is part of HCT's operational routine. Strategies for the improvement of housing was a topic to which the Program devoted part of its research efforts in the 1980s with the assistance of a grant provided by the Edna McConnell Clark Foundation. Currently, it is an important component of the Program's Southern Cone initiative to eliminate *T. infestans* which is testing different control strategies. In addition, technical and logistical support were given to the project to modify housing for the prevention of household infestation by *Rodnius prolixus*.[1]

In order to carry out health promotion activities, it is necessary to know better the knowledge, attitude and practices of the population. Two research projects supported by HCT were aimed to improve our knowledge on this topic in relation to malaria and native population from Guatemala and Panama.

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[1] See "La Casa Enferma," [The Sick House] R. Briceño. Caracas, 1990.

5. Management of knowledge

The collection, analysis, dissemination, and production of knowledge is the prerequisite for the selection of technically appropriate, economically feasible, and socially acceptable interventions. For this reason, the promotion of research activities remains a primary concern in HCT. Paramount are efforts which combine the various technical cooperation strategies, mobilize national and/or international resources to support research proposals; direct technical cooperation for the design, follow-up, and review of research proposals and projects; strengthen institutional research; disseminate information on areas of recent development; and train personnel in priority areas such as epidemiology and entomology.

Although the economic crisis that affects the countries has had a negative influence on national research capacity, most of the research activities programmed by HCT were carried out as planned. This was also true with regard to the projects for institutional strengthening financed by TDR. In only 1 of the 10 institutions was the strengthening process delayed relative to the projected time schedule.

In keeping with the aforementioned cooperation strategies, attempts are being made to fill in the gaps in knowledge through the use of Program resources. Once a research topic has been defined, professionals who are capable of developing it are identified. Support is then provided for execution of the protocol by Program personnel and/or consultants, if required. Normally, Program professionals intervene by supporting one or more stages in the research process, for example, identification of the problem, design of the protocol, mobilization of financial and human resources, and/or follow-up or periodic technical review. Sometimes, regional and country personnel in Barbados and Brazil have intervened in all stages of the process, from development of the protocol, through collection and analysis of the data, to the publication of the report.

The Program thus promotes the testing of technologies; the carrying out of research to learn the local determinants of the distribution, prevalence, and incidence of selected communicable diseases; the testing of innovative intervention strategies; the problem-solving capacity of the services; the development and evaluation of simple and practical methods for diagnosis and treatment; and the evaluation of integrated control activities.

During the period, HCT participated in the testing and evaluation of insecticides for malaria control in Mexico; entomological studies in the malarious areas of Guatemala, Mexico, and Venezuela; the testing of curtains impregnated with

insecticide in Guatemala and Mexico;, and biological control of anophelines and *Aedes* in Panama and Venezuela. Testing was also promoted on the various strategies for the control of triatomids, such as the use of smudge pots, paints containing residual insecticides, traditional spraying, and the effect of parasiticidal treatment in children infected with *T. cruzi*.

6. Mobilization of Resources

The Program seeks to join together the efforts and resources of various sectors in carrying out its activities. From promoting the cause of health in various forums to coordinating the search and technical support for obtaining resources, HCT assisted in resource mobilization for both the improvement of infrastructure and/or the operation of programs, including the training of personnel and the carrying out of research.

During this period the Program was successful in mobilizing financial resources for the following research activities: US$2,179,575 from the United States Army for phase test III of a hemorrhagic fever vaccine in Argentina, and from USAID for phase IV test of the same vaccine; $2,120,000 from TDR to support institutional strengthening (for research on malaria, bancroftian filariasis, wuchereriasis, and leishmaniasis in Brazil, Guatemala, Mexico, and Venezuela); $750,000 from TDR for research on Chagas' disease in Argentina, Bolivia, Brazil, and Honduras; $300,000 from the Rockefeller Foundation for research on the control of dengue with community participation and the use of biological control methods in Honduras; and $170,000 from the United States Navy for research on malaria. In addition, HCT was instrumental in managing $225,000 donated by a Brazilian national agency to an institution in Brazil for the purpose of strengthening its capacity to carry out research on malaria and $120,000 for research on risk factors in Rondonia.

II. PROGRAM PRIORITIES

Overall program priorities for each specific program component are shown in figure 3. Those related specifically to research are described below.

1. Eradication/elimination of diseases

The establishment of eradication targets may be extraordinarily useful, not only in mobilizing the Region's resources, but also in order to increase the credibility of the health sector and its capacity to provide concrete responses to real problems through highly visible activities. The Region of the Americas has frequently been in the vanguard in eradicating diseases, and it was the first region to eradicate smallpox.

In 1985, the Region also mobilized to eliminate the transmission of poliomyelitis. Other infectious diseases whose eradication or elimination may be possible when certain conditions are fulfilled are leprosy, onchocerciasis, nonvenereal treponematosis, and transfusional *T. Cruzi* infection. The establishment and fulfillment of the targets is considered important not only for the control of each specific disease but also because of the effect that the achievement of specific targets has on the health infrastructure and public health as a whole.

In order to support these elimination activities, epidemiological studies are being done on non venereal treponematosis and onchocercosis, the former in Colombia, Ecuador and Venezuela and the latter in Brazil, Colombia, Guatemala, Mexico and Venezuela. These studies will serve as a basis for evaluating control measures. In leprosy, research is focused on the problem-solving capacity of health services. In addition, investigations in the Southern Cone countries are aimed at filling gaps in knowledge that will help eliminate domestic *T. infestans* the vector of Chagas disease.

2. Technological Development

The development and evaluation of technologies applicable to communicable disease prevention and control has been an important component of all HCT Projects, not only those supported by the Special Program for Research and Training in Tropical Diseases. The projects which have been promoted and/or supported have employed both sophisticated molecular biology techniques and epidemiological methodologies for testing interventions in field investigations. Thus, projects were promoted in Mexico for the development of the polymerase chain reaction (PCR) and the ligase chain reaction (LCR) for the diagnosis of *P. vivax* malaria; the production in Argentina of hepatitis B antigens in *B. subtilis* through the use of genetic engineering; and testing in Guatemala and Mexico of bed-nets impregnated with insecticide for the prevention of malaria. Between these two extremes, methodologies were also tested in Guatemala and Mexico for the use of insecticides for the control of malaria and for the control of *Aedes* in Honduras and Venezuela. The use of biological methods for the control of mosquitoes was tested in Colombia, Honduras, and Venezuela. New control strategies, (smudge pots, paints containing residual insecticides) for American trypanosomiasis were evaluated in Argentina, Bolivia, Honduras, and Paraguay. Treatment of *T. cruzi* infection was tested in children in Argentina and Brazil with benznidazole and in adults in Argentina, Bolivia and Brazil with allopurinol. Argentine Hemorrhagic Fever (AHF) vaccine was conducted in Argentina.

III. BRIEF DESCRIPTION OF MAIN RESEARCH ACTIVITIES

1. Aedes/Dengue

a. Prevention and control

In order to test ways to improve control programs, an evaluation of the efficacy of vehicle-dispensed ultra low volume (ULV) malathion for the control of *Aedes aegypti* was done in urban areas of Jamaica and Venezuela.

Three treatments of Ultra Low Volume (ULV) malathion were made in the areas under study. An untreated area was monitored and used as control. Two methods were used to assess the wild *Aedes aegypti* population on a daily basis: ovitraps "enhanced" with hay infusion and back-pack aspirators. Female mosquitoes were dissected to determine stage of follicular development and parity. Post-treatment results showed a reduction in the number of females and rate of oviposition. Recently fed mosquitoes were less vulnerable to treatments than those that were unfed, and the importance of adjusting discharge rates according to the street layout in the specific areas being treated was clearly demonstrated. Moreover, it was found that the enhanced ovitrap method yielded results similar to aspirator collections, but was much less demanding on manpower and resources, and less prone to subjective influences. This research allowed investigators to estimate the cost of the interventions and also suggested that weekly ULV treatments alone are likely to have a significant impact on the total number of cases during an epidemic of dengue or yellow fever. Computer simulations indicated that they will reduce daily incidence and extend the period of transmission ("flattening the curve"). The principal advantage of this could be to provide extra time for emergency source-reduction operations to take effect. On the other hand, more frequent ULV applications at higher dosages would probably achieve an additional reduction of adult mosquitoes, but would require substantially greater resources.

The general consensus in the Region is that the "government" alone cannot resolve the problems of *A. aegypti* and dengue/DHF. However, a frequent concern in programs counting on community involvement is whether the positive effect of short-term interventions can be sustained. Methods that might increase the sustainability of such programs include a) addressing other health and sanitation problems considered important by the community such as pest mosquitoes, lack of refuse collection, poor conditions of roads and the lack of a functioning sewage system; b) collaborating with other private or municipal organizations working concurrently in the community and c) integrating community activities with routine government disease prevention services. Although only time will determine if these approaches are the right ones, it was considered important to develop and promote studies

generating methodologies for community participation. One of them was carried out in Venezuela.

In the first stage, a base-line study on social, cultural, entomological, and urban aspects of the breeding places of vector mosquitos was prepared. Baseline measurements provide both insight into project design and the opportunity to evaluate the ultimate impact of community participation strategies. In the second stage, a methodology of intervention was established. Its objectives were to achieve active participation by the community in the initiatives to combat *Aedes aegypti* and dengue, as well as the testing of a set of strategies that, managed by the community, allowed for this control. This second stage was divided into two steps: The preparation of the participation program, which meant entering in the community, negotiating community involvement, and the identification and consolidation of a leading group. Next, the execution of the interventions in the community, which included the preparation, testing, and evaluation technological devices and educational strategies.

The study indicated that the poor social condition (water supply, type of dwelling, members of the family, family income) is a determining factor in the existence of positive mosquito breeding places inside houses. Families' knowledge about illness prevention, however, is not correlated with the presence of positive breeding places. The structural cause of the problem of mosquito breeding places around the home is the irregular water supply to 75% of houses, which obliges them to store water in containers. Without rectifying this condition, the only way to produce a change in behavior in relation to mosquito breeding places is to promote the development of "a culture against dengue", where sanitary education plays a major role. The surveys indicated that:

a) Only a third of the population understands the mosquito cycle. The majority do not know what the reproductive stages are;

b) More than 54% of inhabitants believe that in their houses there are not mosquito breeding places and that mosquitoes come from outside;

c) The population expressed a positive link between dengue and the mosquito, but in 75% of answers, the identification of each one of the cycle elements was deficient.

It was concluded that neither the desire to avoid mosquito attacks nor to prevent dengue were sufficient to encourage participation. The efforts of the population, most of which lives in poverty (87%), are devoted exclusively to survival. A strategy of participation would require researchers to be involved, as external agents of change, in one of the community priorities closer to their perceived needs,

so as to gain credibility, educating by means of achievements, and then introducing actions for dengue control. The main problem of the community was the irregular water supply, and it was also the main cause of existence of positive containers with *A. aegypti* larvae.

Another study on how to develop/improve community based Aedes aegypti control programs is being implemented in Honduras. Neighborhoods have been organized in "integrated health groups" which are coordinated by a health facilitator. Later on this facilitator is replaced by a committee elected among the members of the different health groups. The activities promoted in the community include education about breeding sites, elimination/control of positive and potential containers, as well as community development actions such as refuse service improvements, sewage systems installation, reforestation, etc. One year after the project began larval indexes were decreasing in all but one community. Simultaneously, biological control methods were used in other neighborhoods. In one of them, community organization and participation was reached with biological controllers as a key component. An interesting approach of this project has been the use of baby turtles for biological control.

2. Chagas Disease

a. Entomology

A three-year analysis of field populations of *Triatoma infestans*/Hemiptera: Reduviidae) shows that population growth rate is affected by both density-dependent and density-independent mortality. Although an equilibrium exists, apparently as a consequence of a density dependent-mechanisms, population density fluctuates throughout the year because of the effect of monthly mean minimum temperature as a density-independent source of mortality. Simulation studies based on Moran curves shows that high population densities have an approximately constant extinction probability, independently of the season the population starts growing. However, at very low population densities, the extinction probability depends strongly on the season when the population begins to grow. Very low density populations beginning in winter or autumn have the highest extinction probability. The outcome of the simulation studies coincides with results observed in field populations affected by insecticide application at different seasons.

b. Prevention and Control

Characteristics and possible risk factors associated with *Trypanosoma cruzi* infection among blood donors were assessed within a routine blood transfusion screening program in an area endemic for Chagas disease. More than six thousand

voluntary blood donors were interviewed and tested for anti-*T. cruzi* antibodies by hemagglutination and complement fixation tests in six blood banks in Goiania-Central Brazil. An overall prevalence of 2.3% for *T. cruzi* infection was obtained, with 3.3% of first-time blood donors and 1.9% of regular donors being positive. Considering this seropositivity among regular blood donors, selection of candidates relying only on the history of previous donation would obviously be inadequate. The risk of infection decreased with the amount of education and monthly income. There was a 9.2% risk of infection for those who had lived more than 21 years in an endemic area compared to subjects who had never lived in rural settings. It was concluded that in order to improve quality of blood products in endemic areas a review of the criteria of selection of donors must be implemented.

Assessment of the impact of programs for the control of Chagas disease is usually based on entomological monitoring of house infestation and on serological evaluation of selected cohorts of the population. The seroprevalence of *T. cruzi* infection among children is a sensitive indicator of household rates of seropositivity, and for the assessment of the risk of transmission in the community it is more practical and economical than entomological evaluation. In sparsely populated rural areas, where house-to-house surveys are operationally difficult, an alternative approach is the serological screening of schoolchildren. A study of this sort was done utilizing a cross-sectional serological survey carried out among schoolchildren living in a poor rural area in central Brazil. Eluates of blood collected on filter-paper were tested for anti-*T. Cruzi* antibodies using immunofluorescence, hemagglutination, and enzyme-linked immunosorbent assays. The overall seroprevalence of *T. cruzi* infection indicated that a twofold to threefold reduction in prevalence has occurred over the last years. The incidence of new cases was estimated to be 44 per annum in the study region. In rural areas with a scattered population, surveillance of *T. cruzi* transmission by serological screening of children at school entry is more practical and economical than entomological evaluation for assessing both the risk of transmission in the community and the efficacy of vector control measures. A sample size of approximately 100 schoolchildren was sufficient to detect prevalences as low as 2% and such an approach would be practical and applicable to most areas where Chagas disease is endemic. A study designed to establish whether there is vectorial transmission of *T. cruzi* in school age children in Uruguay was also elaborated by the Program.

To assess the efficacy of benznidazol among schoolchildren (7-12 years old) seropositive for antibodies to *Trypanosoma cruzi*, randomized controlled field trials are being conducted in rural counties endemic for Chagas disease located in the northeast of Goiás State, central Brazil and in the north of the Province of Salta in northwest Argentina. The trial population was selected by serological screening among village schoolchildren. Those with seropositive tests were recruited for the

trial. It is expected that results of this trial will establish whether children (<12 years) can be cured when treated during the subacute or chronic stage of the infection. Chronically infected adults are not parasitologically cured when treated. If children can be cured, it will be an indication that when *T. infestans* is wiped out from a geographical area, all serologically positive children from that area must be detected and treated.

The testing of different control strategies is being done in selected areas of Argentina, Bolivia, Chile, Honduras, Paraguay and Uruguay. The above-mentioned new control tools are being applied following a common protocol that will permit comparability of epidemiological and entomological efficacy, social acceptability, and assessment of costs. A health education component has also been included in the common protocol. Initial results from Chile, Honduras and Paraguay are very encouraging after the first entomological evaluation at four months post-intervention. The rates of house re-infestation when using the insecticide paints are 2 to 3 times lower than those observed in the group of houses sprayed using traditional insecticides.

3. Leprosy and other dermatological disorders

a. Prevention and Control

As national authorities wished to determine locally the protective efficacy of intradermal BCG against leprosy in a highly endemic area of leprosy in central Brazil, a case-control study was undertaken. Sixty-two cases and 186 controls were included in the study. Cases were all newly diagnosed leprosy patients under 16 years of age attending an outpatient health service, and all of them were schoolchildren. Three controls under 16 years old, matched by sex and age group, were selected from schools geographically located in the area from which the cases came. The presence of BCG was negatively associated with leprosy, indicating a 5.3-fold greater risk of leprosy for those not vaccinated and a protective efficacy of 81%. In addition, paucibacillary patients were more likely to have a BCG scar than multibacillary patients.

Endemic pemphigus foliaceous or Fogo selvagem (FS) is an epidermal organ-specific autoimmune disease mediated by autoantibodies. Individuals at risk are peasants who live and work on farms located in the interior of certain endemic states of Brazil. A case-control study compared a group of 52 FS patients with 52 patients suffering from other dermatoses. In the city of Goiania, Goiás, patients and controls matched 1:1 by age, sex, and occupation were examined by two dermatologists at the time of admission and asked to respond to a prepared questionnaire. This questionnaire concerned current and past (1 and 5 years) exposure to environmental risk factors. The following risk factors were assessed: black fly bites, presence of

rodents at home, exposure to cereal dust, exposure to fumes or dust released by tree and shrub removal, and exposure to insecticides. The only risk factor showing an odds ratio significantly different from one was exposure to *simuliidae* bites. This study reinforces the hypothesis that chronic exposure to black fly antigens may precipitate a specific type of antibody formation in predisposed individuals. These antibodies, in turn, may cross react with epidermal antigens and cause acantholysis and clinical expression of the disease.

In order to implement measures for the elimination of non-venereal treponematosis, epidemiological studies are being done amongst the Indian population of the Amazon area of Colombia, Ecuador and Venezuela. The epidemiological design of the protocol has been completed and data collection has begun in Venezuela.

Brazil is the country with the highest prevalence (260,000 cases) and incidence (26,000 new cases in 1992) of leprosy in the Region. The elimination of leprosy requires the implementation of early diagnosis and multidrug therapy and through the integration of program activities within the general health services. Therefore, a thorough knowledge of how the health services function is needed in order to improve the operational activities of the control program. A study was designed to define the spacial distribution of leprosy cases in urban areas in relation to the coverage provided by local health services, the effect of the rural-urban migration in the utilization of health services in leprosy, how the clientele perceives the health services that provide leprosy treatment in comparison with those nearer to their homes and what are the individual risk factors that could be identified. This study is located in the municipality Goiania and 13 surrounding municipalities in Goiás, Brazil.

4. Malaria

Taking into account the morbidity from malaria in the Region, research on the subject is a priority by the Program. Topics investigated were directed to improve diagnosis, knowledge about malaria vectors, and prevention and control strategies using insecticides and other means.

a. Diagnosis

Although microscopic demonstration of parasites in Giemsa-stained blood smears remains the only widely used method for diagnosis of active malaria, immunodiagnosis plays an important role. In areas where malaria is or has been endemic, serology will provide useful indicators of endemicity, of changes in the degree of transmission, and delineation of malaria areas and foci of transmission. Accordingly, there have been many attempts to develop serodiagnostic tests for use in epidemiological surveys, in the evaluation of control measures or in individual

patients. Tests employing immunofluorescence, immunohemagglutination, immunoprecipitation, and more recently the ELISA, have been used widely for the detection and measurement of antibodies to erythrocytic states of malaria parasites. The most frequently used are the IFAT and the ELISA. Previous work by other authors employed an immunocytochemical peroxidase assay comparable to IFAT to measure antibody to *Plasmodium falciparum*. In the Region, the immunocytochemical peroxidase assay (ICPT) was evaluated for the detection of antibody specific to *P. vivax*. The test proved to be as sensitive as the IFAT and as easy to carry out as light microscopy. This is a tremendous advantage for peripheral laboratories. Although there were cross reactions with sera from patients with malaria by *P. falciparum,* sera from patients with other parasitic diseases did not cross react. Antibody titres as measured by the ICPT showed a positive correlation with past *P. vivax* malarial experiences.

Attempts were also made detect antigens in circulation using monoclonal antibodies as a diagnostic tool. Although monoclonal antibodies either in direct ELISA or in capture reaction were not sensitive enough to consistently detect the antigens in sera, a polyclonal antibody with *P. vivax* specificity did.

Other research was directed to develop and field test in Mexico a PCR and a ligase chain reaction for diagnoses of *P. vivax*.

b. Entomology

The existence of sympatric populations within *Anopheles albimanus* Wiedemann with specific host preferences and the question of whether host selection has a genetic basis or is a learned characteristic were investigated in Mexico. Progeny of wild females collected from corrals or human bait were reared in an insectary. Females were fed on a cow or on a human host, allowed to oviposit, and then were released in an experimental hut divided into three compartments. A fixed proportion of mosquitoes selected either host (64% cow and 35% human), irrespective of their parental origin or source of the first blood meal. The data indicate that the existence of cryptic populations with anthropophilic habits is unlikely and that a "learned" host selection also may be ruled out.

The length of the gonotrophic cycle of *Anopheles albimanus* was also estimated by 12 mark-release-recapture studies conducted in corrals in southern Mexico. The studies indicated that two gonotrophic cycles probably exist, one of 48 hours dominated by parous mosquitoes and one of 4 days by nulliparous, pregravid mosquitoes. Daily survivorship was estimated by regression from the decrease in the daily recapture rate. It was less than that estimated by the parity rates, with no important differences found between wet and dry seasons. Estimates of the

probability of a mosquito living long enough to transmit malaria were 2% taking into account the daily survival rate and the length of the sporogonic cycle.

In another study in Guatemala, adult *Anopheles* were collected in two localities having distinct ecological systems and known to be endemic for malaria transmission. Of the 19 anopheline species previously reported in the country, five were identified in this study. Capture techniques included intra and peridomicillary human bait collections as well as captures from cattle corrals and natural resting sites. A total of 12,360 mosquitoes were captured of which 82.3% were *An. albimanus*, 11.5% *An vestiipennis*, 3.2% *An. punctimacula*, 2.9% *An neomacutipalpus* and 0.05% *An. pseudopunctipennis*. Observations on transmission dynamics, indicate that the difference in climatic conditions observed in the two localities modulate different transmission patterns for some of the anopheline species. *An. albimanus* and *An. vestitipennis* show an opposite behavior in respect to endophagy or exophagy in the two localities. Mosquitoes were tested for the presence of *Plasmodim falciparum* and *P. vivax* circunsporozoite proteins using ELISA. Combined sporozoite rate was of 30/1000; 14.0 for P. falciparum and 14.8 for *P. vivax*. The highest rate was determined for *An. punctimacula* (27/1000), which previously had not been reported to be an important malaria vector in Guatemala.

Transmission and population dynamics of all anopheline species reported to occur in western Venezuela were reviewed and a longitudinal study was conducted in three villages to assess the malaria risk factors determined by the audience, parous rate, biting activity, sporozoite rate and human blood index of the various potential vector species in relation to weather and human habits.

The collections yielded 14 anopheline species, the most abundant being those belonging to the subgenus *Nyssorhynchus*. Because species identification of adult females with available keys proved to be difficult, linked readings were undertaken. *An. nuneztovari*, comprising over 70% of the total anophelines collected, was the most abundant species, followed by *An. triannulatus, An. albitarsis s.l.* and *An. oswaldoi*. The anopheline populations showed fluctuations which correlated positively with rainfall and humidity.

The four most abundant species showed different diel patterns of biting. The diel peak for *An. nuneztovari* was close to midnight indoors and outdoors, for *An. triannulatus* between 7 and 8 pm outdoors, for *An. albitarsis* mainly before midnight indoors and outdoors and for *An. oswaldoi* 7 pm outdoors, with an additional smaller peak indoors at midnight. Most of the human population uses bed nets, goes to bed before 10 pm and wake up before 7 am; they are therefore most exposed to the bites of those species that bite early in the night outdoors.

Anophelines were assayed by ELISA to detect *P. vivax* circumsporozoite protein. the six specimens confirmed as positive belonged to three species: *nuneztovari, albitarsis s.l.,* and *oswaldoi*. The estimated overall sporozoite rate was 0.0098% and the sporozoite inoculation rate was calculated to be 10.5 positive bites per person per year.

Recommendations for possible improvements in malaria vector control in this area are must be made taking into account the endophagic and exophilic behavior of the incriminated vectors, their diel patterns of biting and some aspects of the behavior of the human population revealed by questionnaires.

c. Prevention and Control

Permethrin-impregnated bed nets were evaluated as a control measure for malaria in northern Guatemala. Twelve hundred forty participants were allocated to one of three experimental groups (impregnated bed nets - IBN, untreated bed nets - UBN, and controls) and followed for a period of 13 months. Malaria infections among the participants were identified by passive and active case detection. Questionnaire surveys and unannounced home visits were used to evaluate the use and acceptance of the bed nets by the participants.

The incidence density of malaria was significantly lower in both IBN and UBN groups compared to controls. No difference in malaria incidence was noted between the IBN and UBN groups. Complaints of fever and chills were less frequent in the IBN group when compared with controls. The participants were enthusiastic about the nets, which they saw as a means for avoiding nuisance insects more than for preventing malaria. A majority wanted to wash their nets every 4 to 12 weeks, a practice known to shorten the duration of residual insecticide action. Larger studies are needed to determine if impregnated bed nets offer an advantage over untreated nets in this setting.

In order to complete this study on bed nets night-bite and pyrethrum spray mosquito collections, capture-release-recapture studies, and inspection of bed-nets for mosquito carcasses were used to measure impact of impregnated bed-nets on mosquito abundance, behavior, and mortality. The duration of residual insecticide effect in the impregnated nets was determined by modified WHO cone field bioassays and laboratory analysis. it was concluded that *Anopheles vestitipennis* abundance decreased following distribution of impregnated bed-nets in one of the communities but no change was detected in abundance of *An. albimanus* species.

It has been hypothesized that different patterns of malaria transmission exist and that they are determined by the presence of individual, social, ecological, and

organizational risk factors which determine the differential risks of becoming sick or dying from malaria[2]. A study testing this premise is under way in Ariquemes, Rondonia. By demonstrating the relative importance of individual risk factors, the different epidemiological patterns of malaria transmission can be isolated. At the local level, this knowledge will permit the selection of specific measures needed to diminish identified risks. The population under study includes different age groups and occupations (from nurses to agricultural workers). Questionnaires for the study have been field tested, the areas of high prevalence of malaria have been identified, and data from two pilot studies in which risk factors were identified are being analyzed.

Another case control study on risk factors is under way in the state of Rondonia. This is a retrospective study of 720,000 histories. Cases were defined as febrile individuals with confirmed malaria. Control subjects were those with fever, who presented with a negative thick blood smear.

d. Treatment

A clinical trial was carried out in Brazil which compared parasitological efficacy, levels of *in vivo* resistance and side effects of oral chloroquine 25mg/kg and 50 mg/kg in 3-day treatment of *Plasmodium falciparum* malaria with an extended followed-up of 30 days. The cure rate in the 50mg/kg group was 89.4% on day 7 and 71.2% on day 14 compared to 44.8% and 24.1% in the 25mg/kg group. 74.1% of the patients in the 25mg/kg group and 48.4% of the patients in the 50mg/kg group had detectable parasitemia at the day 30. However, there was a decrease of the geometric mean parasite density compared with baseline in both groups, especially in the 50mg/kg group. Side effects were found to be minimal in both groups. The present data support the hypotheses that there is a moderate level of resistance to chloroquine in the population and that the high dose regimen only delayed the reappearance of parasitemia and its administration should not be recommended as first choice in malaria *P. falciparum* therapy in Brazil.

e. Vaccine evaluation

The Organization provided support for the analysis of a phase III randomized, double-blind, placebo-controlled, efficacy trial of a *P. falciparum* vaccine done in La Tola, Colombia. 1548 volunteers over one year of age received three doses of either the vaccine or placebo. The results showed that the chemically synthesized SPf66 malaria vaccine is safe, immunogenic, and protective against *P. falciparum* malaria in semi-immune populations subject to natural challenge. The protective efficacy

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[2] Castillo Salgado, S. Mem. Inst. O. Cruz 87 (Suppl III), 1992.

against a first episode was 33.6% against a second episode it was 50.50%. In another field study in Ecuador, support was also provided for data analysis. Five hundred thirty-seven subjects were randomized to receive either SPf66 malaria vaccine against *P. falciparum* or a placebo, in three doses. Subjects completing the three doses vaccination were followed for 12 months. Vaccine efficacy was calculated based on person-time of exposure. The protective effect considering any malaria episode was 66.8% and considering only one episode per individual was 60.2%.

5. Viral diseases

The main thrust of virological research was on vaccine testing for Argentinean hemorrhagic fever. The vaccine prepared with an attenuated strain (candid 1) whose safety and immunogenicity was tested in volunteers in Argentina and USA. In a phase III study, six thousand five hundred individuals were vaccinated. Immunogenicity of the preparation was determined in 5,600 of them. After two years of follow-up, it was established that the efficacy of the vaccine was 95.5%. Further research is now being done in another 50,000 volunteers with the aim of assessing potential side effects (early phase IV).

Since the discovery of the Guaranito virus in Venezuela, the etiological agent of another hemorrhagic fever, PAHO has been involved and provided support for epidemiological and ecological studies as well as for the development of a diagnostic test by PCR.

IV. PAHO FUNDS FOR COMMUNICABLE DISEASE RESEARCH

Figure 4 shows that from 1989 to 1992 $3,461,190 was used for research by the Program, not counting staff salaries*3. Sixty-seven percent of that amount was extrabudgetary funds earmarked for specific projects. Table 2 shows how the funds were spent. The majority, 91%, was in direct support of projects at the county level. Table 3 provides the allocation of funds that support research on the different topics of concern of the program. In some of these areas, like Leishmaniasis or Chagas disease, the amount of monies provided by PAHO is minimal. However, they are compensated by the strong funding provided by IDRC for Leishmaniasis and by TDR for Chagas disease.

*Although most HCT staff are involved in research activities, only two staff members provide primarily technical cooperation in research.

V. THE FUTURE

Despite the epidemiological transition related to the aging of the population and other factors, communicable diseases continue to be major health problems. Research, primarily operational, will be needed in order to resolve remaining control problems.

Financial constraints will not permit an increase in program staff devoted to research activities nor the support of research projects with regular budget funds. Therefore, the activities will continue at the same level, except for those efforts supporting individual countries in their pursuit of extrabudgetary funding.

In the current fiscal climate, it is unrealistic to expect PAHO to make a profound contribution to basic biological research. Therefore, the emphasis from the technical view point will continue to be on applied research directed to fill specific gaps in knowledge necessary to improve prevention and control programs, the testing of interventions, and the evaluation of treatments and diagnostic tools.

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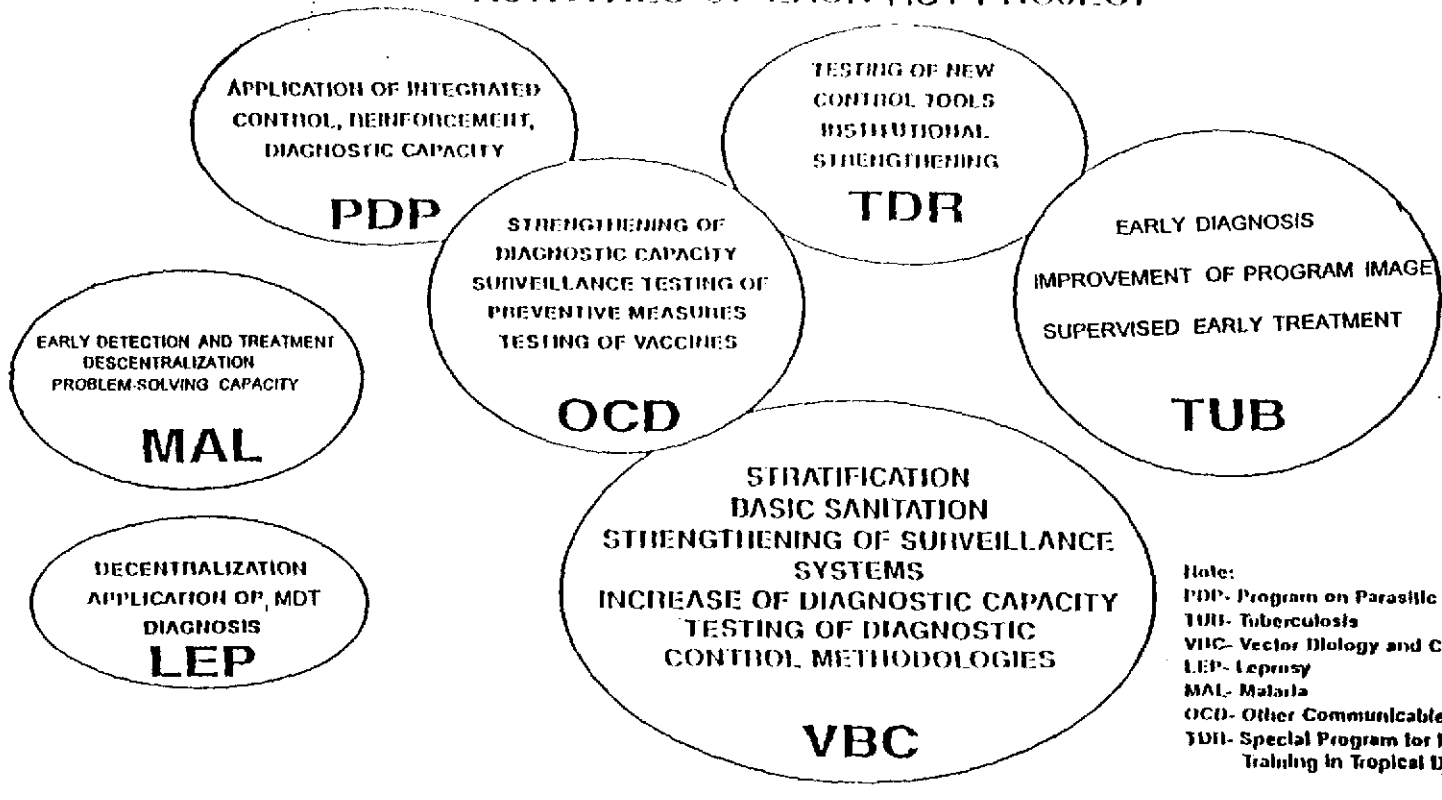
Figure 1

PROGRAM ON COMMUNICABLE DISEASES (HCT)

PROMOTION, COORDINATION, AND SUPPORT ACTIVITIES OF EACH HCT PROJECT



Note:
PDP- Program on Parasitic Diseases
TUB- Tuberculosis
VBC- Vector Biology and Control
LEP- Leprosy
MAL- Malaria
OCD- Other Communicable Diseases
TDR- Special Program for Research and Training in Tropical Diseases

Figure 2

STRATEGIC ORIENTATION OF COOPERATION FOR THE PROGRAM ON COMMUNICABLE DISEASES (HPT) 1990 - 1994

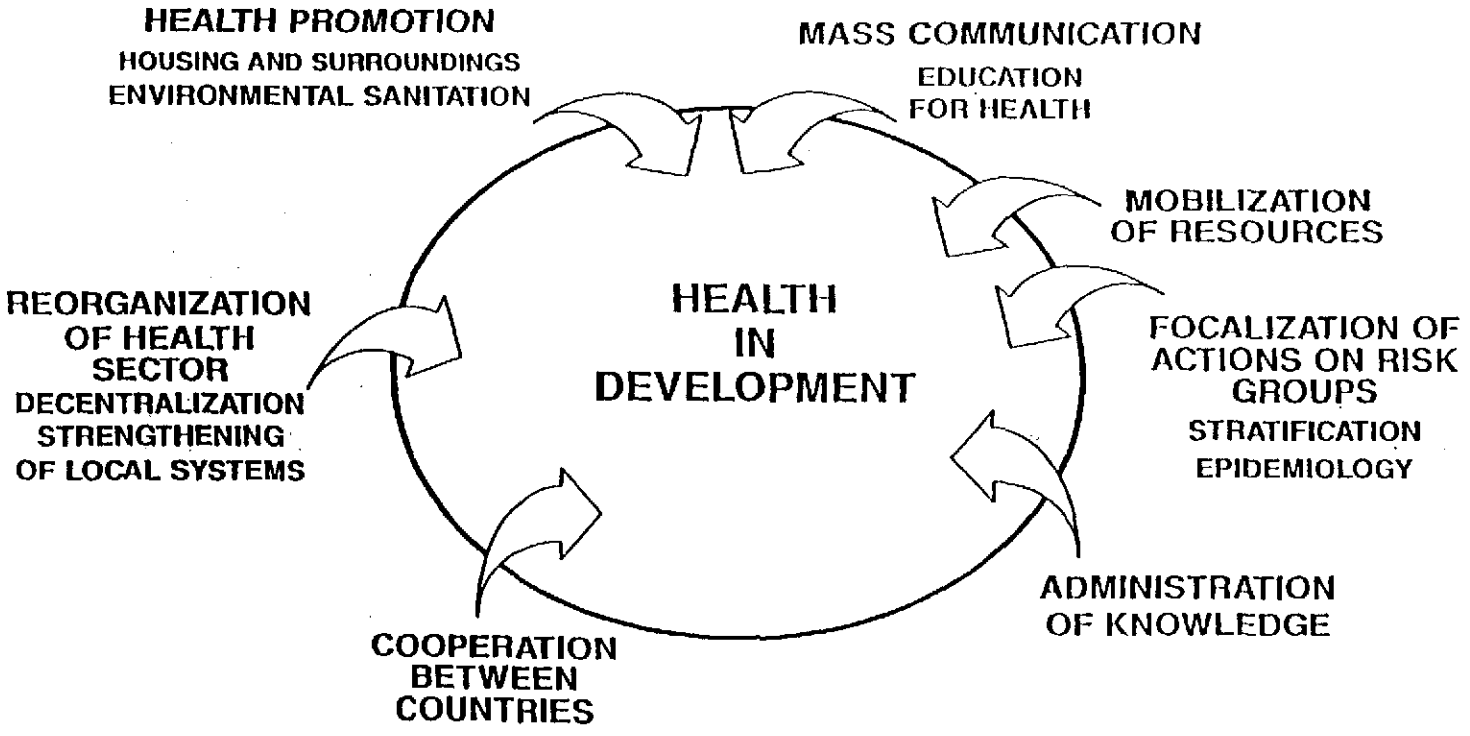


Figure 3

PROGRAM ON COMMUNICABLE DISEASES (HPT)

PROGRAM PRIORITIES

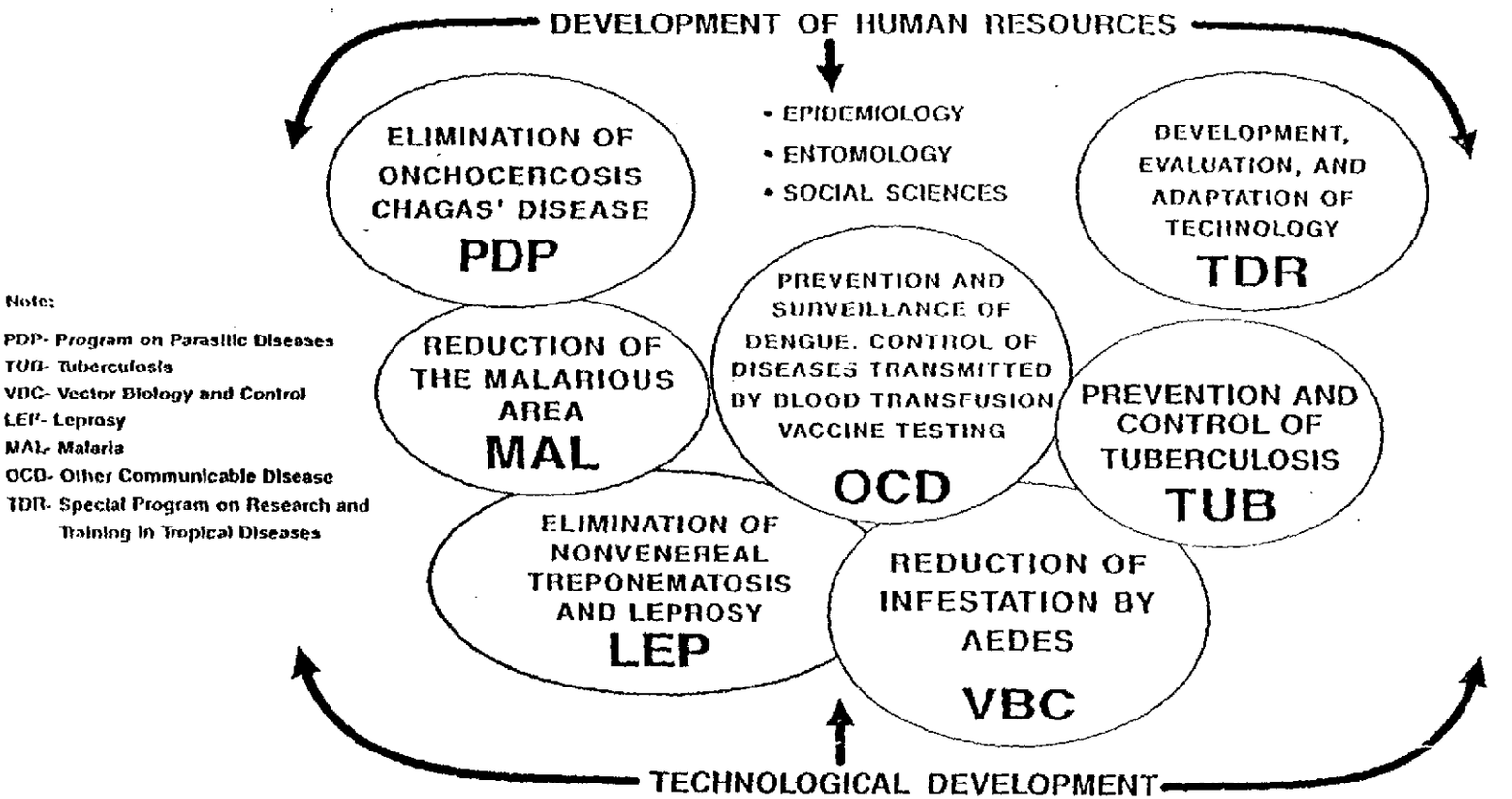


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Table 1

FUNDS FROMCOUNTRY AND INTERNATIONAL AGENCIES FOR MALARIA RESEARCH IN THE AMERICAN REGION, 1985 – 1991 *

	1985	1986	1987	1988	1989	1990	1991
International Development Research Center, Canada x)	38,433	...	...	364,157	53,831	254,264	239,545 a)
Board on Science and Technology for International Development, Institute of Medicine/National Academy of Science, USA, x)	244,176	228,900	187,604	97,012	44,132	28,004	25,000 b)
National Institute Of Allergy and Infectious Disease, National Institute of Health, USA, +), c)	5,708,000	5,993,424	6,122,927	6,803,213	7,842,896	7,783,157	7,376,839
Agency For International Development, USA, +), d)	12,500,000	9,900,000	12,000,000	10,000,000	8,500,339	8,550,000	8,550,000
USA Army and USA Navy +), d)	5,220,000	8,240,000	8,611,000	8,631,000	6,303,000	6,014,000	10,163,000
Pan American Health Organization World Health Organization (PAHO/WHO) x)	334,500	488,125	741,400	99,883	454,000	490,614	400,000
Special Programme for Research and Training in Tropical Disease UNDP/World Bank (TDR) x)+)	1,756,432	1,364,449	1,446,211	1,746,119	2,120,128	2,519,634	2,849,100
Brazil ** x)	...	250,000	759,248	50,000	532,930	30,000	261,072 e)
Colombia ** x)	...	25,000	80,000	...	...	...	...
Mexico ** x)	...	50,000	270,000	339,337	812,528	426,546	583,839

* In USA dollars, except otherwise indicated.
x) Calendar year, 1991. +) Fiscal year, Oct. 1990–Oct.1991.
a) Canadian Dollars, Project in Peru. b) Field Research on mosquitoes, in Venezuela
c) Funds for Institutions in the USA. d) Most of the funds for Institutions in the USA.
e) Funds from CNPq, FAPESP and FNS.
+) Include staff salaries.
** Funds converterd into USA dollars, according to the averge offical exchange rate for the year.

Nov/4/92

TABLE 2

TOTAL RESEARCH FUNDS 1989-1992

	PURPOSE						
	Staff Travel		Consultant		Proyect support		
YEAR	a	b	a	b	a	b	TOTAL
1989	43,310	3,100	15,050	32,630	42,500	1,496,955	1,633,545
1990	51,298	11,725	11,640	67,982	121,500	636,000	898,920
1991	41,000	0	2,200	0	25,000	574,000	642,200
1992	8,000	*	0	*	77,300	200,000	243,300
Total	143,608	14,825	28,890	100,612	266,300	2,906,955	3,461,190

Legend: * *Data has not been compiled yet*
Numbers in BOLD include $1,225 for Filariasis & $42,000 for Non-venereal Treponematosis
a = Regular Funds
b = Extrabudgetary Funds

Table 3

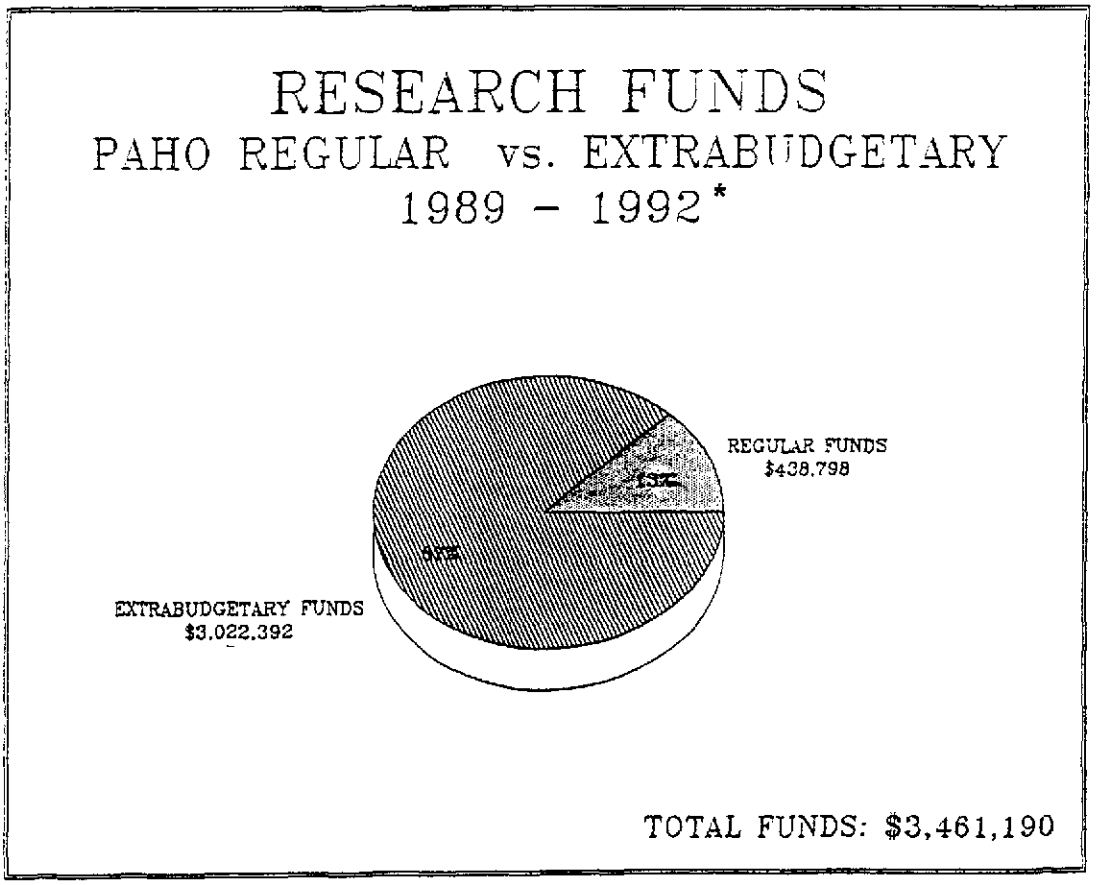
TDRFUNDS

PAHO FUNDS FOR RESEARCH ON COMMUNICABLE DISEASES
1989 - 1992
(Amounts in US Dollars)
Staff time is NOT included

		PURPOSE						
		Staff Travel		Consultant		Proyect support		
SUBJECT	YEAR	a	b	a	b	a	b	TOTAL
Viral Diseases	1989	2,165				24,300	1,233,575	1,260,040
	1990		3,325				596,000	599,325
	1991	3,325					350,000	353,325
	1992	*	*	*	*	18,000	*	18,000
	Total	5,490	3,325	0	0	42,300	2,179,575	2,230,690
Malaria	1989	18,535		3,600	27,005	8,500	245,380	303,020
	1990	18,687		1,965	59,942	106,500	40,000	227,094
	1991	17,500		2,200		13,000	24,000	56,700
	1992	**8,000**	*	*	*	*	100,000	108,000
	Total	62,722	0	7,765	86,947	128,000	409,380	694,814
Aedes/Dengue	1989	4,200		8,400		8,500	18,000	39,100
	1990	6,155		4,100		3,000		13,255
	1991	8,525					200,000	208,525
	1992	*		*		5,300	100,000	105,300
	Total	18,880	0	12,500	0	16,800	318,000	366,180
Leishmaniasis	1989					1,200		1,200
	1990					12,000		12,000
	1991					12,000		12,000
	1992					12,000		12,000
	Total	0	0	0	0	37,200	0	37,200
Chagas	1989	5,100	300					5,400
	1990	2,970						2,970
	1991	8,000						8,000
	1992	*						0
	Total	16,070	300	0	0	0	0	16,370
Institutional Strengthening	1989	13,310	2,800	3,050	5,625			24,785
	1990	22,261	8,400	5,575	8,040			44,276
	1991	3,650						3,650
	1992	*	*	*	*			0
	Total	39,221	11,200	8,625	13,665	0	0	72,711
	TOTAL	142,383	14,825	28,890	100,612	224,300	2,906,955	3,417,965

Legend:	** Data has not been compiled yet*	*a = Regular Fund*
	Numbers in Bold are partial amounts	*b = Extrabudgetary Fund*

FIGURE 4



* Does not include staff salaries.