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PAN AMERICAN HEALTH ORGANIZATION

SCIENTIFIC ADVISORY COMMITTEE ON DENGUE

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DENGUE IN THE AMERICAS

A REPORT TO THE DIRECTOR

FIRST DRAFT

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Pan American Sanitary Bureau, Regional Office of the
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Washington, D.C.

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INTRODUCTION

The meeting was opened by the Minister of Health of Colombia, Dr. José Maria Salazar Bucheli, who extended the hospitality of his Government and the Instituto Nacional para Programas Especiales de Salud to the invited scientists. Referring to the recent epidemic of dengue suffered by his country, he expressed the hope that the information and international collaboration arising from such meetings would contribute to a new freedom from dengue throughout the Americas.

Dr. Hamlet Eduardo Sarué, the PAHO Country Representative, then officially responded on the part of the Organization, by expressing appreciation for the opportunity to meet in Bogotá. He commended the officials of the Ministry for their excellent preparation for the meeting, and offered the services of his staff for the success of the meeting.

The meeting was then called to order by the Chairman, Dr. Philip K. Russell, in accordance with the agenda adopted for the following two days. Five subgroups prepared the draft of the Committee report which was discussed in plenary session and adopted on the final day.

DENGUE IN THE AMERICAS

I. Current Status and Importance of Dengue in the Americas

Tens of million of people and an undetermined number of tourists are at potential risk of dengue outbreaks in tropical and subtropical regions of the Americas where the vector mosquito, Aedes aegypti, exists. In Southeast Asia transmission of dengue viruses appears to be increasing as human populations grow, and over 34,000 cases of dengue hemorrhagic fever (DHF) with 613 deaths were reported to the World Health Organization from six countries in 1973.

Epidemics of dengue and dengue-like diseases have recurred at frequent intervals in the Western Hemisphere. In this century, major outbreaks occurred in 1904, 1915, 1922, 1934, 1941, 1949-50, 1963-64, 1968-69, and 1971-72. Those since 1960 have been limited to the Caribbean region (See Figure 1 and Table 1). Attack rates were high, sometimes exceeding 70 or 80 percent.

Only serotypes 2 and 3 are currently recognized in the Americas. Serotype 2 virus was first isolated in Trinidad in 1953, and serotype 3 was first recovered in Puerto Rico during the 1963-64 epidemic. Both serotypes caused epidemic disease in the Caribbean region during 1968, and serotype 2 predominated in 1969. The most recent outbreak was the Colombian epidemic of 1971-72, which was caused by serotype 2 and resulted in 450,000 cases (Figure 2). Persistent dengue-2 transmission has been detected in Puerto Rico during 1974 (Figure 3), and sizeable outbreaks have occurred in two communities (Guanica-Ensenada in 1972 and Villalba in 1973), resulting in several thousand cases in each community.

Infection with one serotype does not confer protection against later infection with another, and multiple infections in Asia are associated with dengue hemorrhagic fever (DHF), including the shock syndrome. Classic dengue may have relatively innocuous hemorrhagic

manifestations, but profound shock and life-threatening hemorrhage define the DHF syndrome. It should be appreciated that severe gastrointestinal hemorrhage may be the predominating sign of DHF and that hospitalized patients may first be admitted to surgical services. In Southeast Asia, DHF, including shock syndrome, occurs in areas where all four dengue virus serotypes are endemic. On the Pacific Island of New Caledonia, however, shock syndrome and DHF have been observed in association with an apparent serial infection from dengue 2 following a dengue 3 infection; on Niue, another Pacific island, possible DHF and shock syndrome have been epidemiologically associated with primary dengue 2 infections.

Dengue shock syndrome has not yet been identified in the Caribbean. Although surveillance has not been complete in all areas, there has been enough during the past few years in certain areas such as Puerto Rico and the Dominican Republic and in susceptible regions with A. aegypti such as Cuba and some other Caribbean islands, to detect DHF if it occurred as more than occasional, isolated cases.

Dengue's high attack rate, associated morbidity, and long periods of convalescence lead to absenteeism, impaired efficiency at work, and a burden on health facilities. Yet to be fully explored are the possibilities of congenital abnormalities, abortion, and recrudescence of other underlying diseases. The toll of an outbreak includes both the direct costs of patient treatment and the indirect costs of emergency vector control measures, lowered work productivity, and decreased tourist revenue. The costs of continuing A. aegypti control must also be taken into account.

In regions where the vector has been eradicated, dengue outbreaks may develop if reinfestation of A. aegypti occurs from other areas. Moreover, the geographic extent of the disease may also increase as reinfestation continues into areas once free of A. aegypti. Increasing susceptible human populations and A. aegypti indices indicate that yellow fever could also occur.

2. Implementation of Previous Recommendations

The recommendations of the Second Meeting of the Scientific Advisory Committee on Dengue appear on pages 12-14 of its Report (1972). The following review summarizes the recommendations and progress, if any, in their implementation.

Recommendation A: Assign three PAHO epidemiologists to the dengue program in the Americas.

The Organization hired a virologist/epidemiologist for the Trinidad Regional Virus Laboratory in September 1972. Among his many activities, he has coordinated virologic and epidemiologic studies of dengue and other group B arboviruses on Trinidad, Grenada, and Barbados.

The Organization hired an epidemiologist for the Dominican Republic in June 1973. A portion of his time is allotted to aiding a dengue surveillance program conducted by Dr. Joel N. Ehrenkranz, of the Cedars of Lebanon Hospital group in Miami.

Negotiations between PAHO and the U.S. Peace Corps for the employment of two epidemiologists to work in the Caribbean area have, so far, been inconclusive.

Recommendation B: Establish an effective system for exchanging information on dengue and related diseases.

Five issues of the Dengue Newsletter for the Americas have been published in 1973 and 1974. Dr. Barnett L. Cline, who has served as scientific editor, has collected and compiled the contributions, which were then forwarded to PAHO's Department of Communicable Diseases. The PAHO Central Offices arranged for final editing, translating, and duplicating of the newsletter, which has been distributed to more than 500 health officials, libraries, physicians, administrators, and other interested persons throughout Latin America and the Caribbean area.

Recommendation C: Develop specific technical guidelines for dengue investigations.

The first draft of a technical guide for dengue and dengue hemorrhagic fever surveillance was prepared in the fall of 1972 and distributed to the Committee members for comments and revision. Meanwhile, Dr. William F. Scherer prepared a simple, one-page information sheet on emergency procedures to be followed in any suspected outbreak of dengue. This was reproduced and distributed in the Dengue Newsletter and additional copies were made available for persons requesting them.

A Guide to the Histopathological Diagnosis of Yellow Fever is being prepared by PAHO and the U.S. Armed Forces Institute of Pathology, Washington, D.C. The Guide and accompanying histopathologic slides are in the final stages of preparation and will be available for distribution to all pathologists in the Caribbean and Central and South American areas.

Recommendation D: Provide specific virologic assistance, as member countries request, during a suspected epidemic; designate one central reference laboratory for identification of dengue virus isolates.

Under the general guidance of the Committee, emergency epidemiologic and laboratory assistance was given through PAHO to Colombia to extend the investigation of the large dengue outbreak of 1971-72.

The CDC Regional Arbovirus Reference Center, the WRAIR Virology Section, and the Yale International Arbovirus Reference Center have provided diagnostic services and reagents to Colombia and Puerto Rico during the past 2 years. Three consultants from the Cedars of Lebanon Hospital were hired by PAHO to conduct preliminary investigation of a suspected outbreak of dengue in the Turks and Caicos Islands in early 1974. The Yale International Arbovirus Reference Center received a contract from PAHO in 1972 to prepare and distribute inactivated dengue and yellow fever antigens to all arbovirus laboratories in Latin America and the Caribbean.

An ad hoc subcommittee of the Committee, meeting in June 1973, recommended that one reference laboratory be designated for identification of dengue virus isolates in the Americas. Though recognizing that CDC remains the WHO Regional Arbovirus Reference Center, the Committee

suggested that in the case of dengue virus isolates, the WRAIR Virology Laboratory be designated a collaborating center in the specific typing of dengue virus isolates obtained in the Americas.

Recommendation E: Designate a panel of emergency consultants available to supplement national and full-time PAHO personnel if a request is received for assistance.

PAHO informally appointed 16 emergency consultants for outbreak investigations. This panel was reviewed and approved at the June 1973 meeting of the ad hoc subcommittee.

Recommendation F: Identify sources of chemicals and equipment that could be made available for emergency vector control.

PAHO regularly purchases chemicals and equipment for A. aegypti eradication programs and, through an emergency revolving fund, can make special emergency purchases as recommended. For nonemergency purchases, each country is requested to make a deposit in the PAHO budget before obtaining insecticides, chemicals, and equipment. The emergency fund was used in both Colombia and Panama for the purchase of insecticides during the past 2 years.

Recommendation G: Periodically review the status of A. aegypti infestation in Central America.

PAHO published progress reviews of A. aegypti eradication in issues 2, 3, 16, 17, 21, 32, and 33 of its Weekly Epidemiological Report. A complete summary of the status of A. aegypti eradication in the Americas was published in the fourth edition of the Dengue Newsletter.

Recommendation H: Conduct a training course for laboratory directors in the latest technique for the isolation of dengue viruses.

A demonstration workshop, jointly sponsored by PAHO and CDC, was held in the San Juan Tropical Disease Laboratories, San Juan, Puerto Rico, from August 6 to 8, 1973. Dr. Duane Gubler of the Pacific Research Section, NIAID, and the University of Hawaii demonstrated the technique for intrathoracic inoculation of A. aegypti for the primary isolation and

identification of dengue viruses. Twelve participants representing six countries or laboratories attended the workshop. The method was later published in English and Spanish and distributed by the Organization to all arbovirus laboratories in the Americas.

Recommendation I: Arrange for production of educational films and filmstrips on the diagnosis of dengue and its complications.

A filmstrip on the detection, diagnosis, and reporting of dengue and dengue hemorrhagic fever was prepared by the Department of Communicable Diseases and Audiovisual Aids Section of PAHO. One hundred ninety-six copies in English and 98 in Spanish have been distributed. Attempts to arrange for the production of a film on the clinical diagnosis and management of dengue hemorrhagic fever have been unsuccessful. Both the Army Medical Research and Development Command and the National Audiovisual Center in Atlanta were approached but were unable to assist.

Recommendation J: Prepare and maintain a dengue bibliography for distribution to interested persons.

3. Surveillance Problems

The Committee considered that the following are the principal objectives of any dengue and dengue hemorrhagic fever surveillance program in the Caribbean:

1. Identify and confirm clinical cases of dengue
2. Recognize dengue outbreaks
3. Identify the introduction of new dengue serotypes
4. Detect cases of dengue hemorrhagic fever/shock syndrome
5. Bring together necessary data about both human disease and vectors so that the appropriate control measures may be implemented.

The Committee identified certain problems in meeting these goals. Local and national health care personnel have inadequate information on

the clinical symptoms and course produced by dengue. The type of laboratory specimens required for diagnosis and the appropriate methods for their collection, storage, and transport to a laboratory are not widely known. Especially lacking is the knowledge of the dengue hemorrhagic fever/shock syndrome and the range of clinical symptoms or signs associated with this disease. Furthermore, the experts apparently are not now in agreement on the exact criteria for the diagnosis of dengue hemorrhagic fever. Communication in many countries between pathologists, clinicians, and public health authorities is adequate to ensure the early reporting of suspected DHF cases.

Virologic diagnostic laboratories are not located throughout the area uniformly. Of particular importance are facilities for the isolation and identification of new dengue serotypes. The effectiveness of any such centers in isolating dengue virus depends on the prompt collection, storage, and transport of acute-phase sera. This is not easily done in the multinational Caribbean area, where there are many logistical problems in transporting specimens.

Because of these problems, reports of unusual outbreaks of febrile illness are often delayed. There is also an inherent delay in achieving rapid laboratory diagnosis of the etiology of such cases. Such prolonged intervals may be of limited importance in dengue outbreaks, but in the case of dengue hemorrhagic fever can result in needless deaths and community anxiety.

General recommendations to improve surveillance

By providing assistance, PAHO should encourage member governments to initiate laboratory-based surveillance programs in areas with a high risk of dengue transmission or introduction of new dengue serotypes (e.g., Santo Domingo, Martinique, Guadeloupe, and specific areas of Colombia, Venezuela, and Surinam). Where medical epidemiologists are not available, those programs to detect dengue and yellow fever infections should be conducted with properly trained nurse-epidemiologists or their equivalent, and in cooperation with primary health centers and private physicians.

PAHO should assure the continued development of capabilities for isolating and identifying dengue serotypes in at least four geographically representative laboratories of the Caribbean. Laboratories now eligible for such assistance are the Instituto Nacional Para Programas Especiales de Salud, Bogotá, Colombia; the Institut Pasteur, French Guiana; the Trinidad Regional Virus Laboratory; and the Department of Microbiology at the University of the West Indies, Kingston, Jamaica; and others to be identified in Venezuela and Cuba, if evidence of transmission of dengue is obtained in the latter country.

In each country where dengue is considered a problem, a surveillance officer should be designated to receive monthly reports concerning human, laboratory, and vector information, and should prepare a regular summary with the recommendations for appropriate measures. This report should be sent to the executive health authority for decision. Copies of the report should be forwarded to all information providers and other interested persons.

A. aegypti monitoring should be regularly maintained and up-to-date reports should be prepared and submitted to the designated epidemiologic surveillance officer.

Diagnostic laboratories should be required to submit regular or immediate reports on arbovirus diagnosis to the designated national epidemiologic surveillance officer.

4. Laboratory Support for Surveillance and Epidemiologic Studies

The laboratory's central role in dengue surveillance and diagnosis must be emphasized. It seems certain that meaningful advances in dengue epidemiology will come from the laboratory, since conventional national reporting systems are less than satisfactory for this disease.

Progress has been made in using laboratory tests to identify dengue. The following participating laboratories have shown such competence in

varying degrees. CDC's San Juan Laboratory developed successful and extensive epidemiologic surveillance combined with diagnostic serology in Puerto Rico. The Trinidad Regional Virus Laboratory has undertaken the testing of serologic--hemagglutination-inhibition (HI)--surveys from at least five different countries or islands in the Caribbean region (Trinidad, Dutch Antilles, Barbados). The Institut Pasteur operates a dengue surveillance program for France's Caribbean Departments and French Guiana. The laboratory of the Instituto Nacional Para Programas Especiales de Salud in Bogotá has strengthened its facilities. The Instituto Nacional de Higiene in Cuba plans to make an extensive, systematic serologic survey using antigens procured through the assistance of PAHO and CDC. The Department of Microbiology, University of the West Indies, has continued HI serologic diagnosis. Venezuela is reorganizing its dengue laboratory facilities. The Gorgas Memorial Laboratory in Panama has adequate facilities for dengue research. The Cedars of Lebanon Hospital, Miami, has been conducting dengue surveillance in Hispaniola. The recognized reference centers that have been active include the WHO Collaborating Centers for Arbovirus Reference and Research at CDC and Yale University, and the Walter Reed Army Institute of Research, which has been recommended as the PAHO Central Dengue Reference Laboratory for the identification of virus isolates and the performance of plaque-reduction neutralization tests.

It still remains true that laboratory support has not been asked for or provided to many countries. Laboratory investigations directed toward the biologic and antigenic characterization of virus strains represent research developing at major centers. Much remains to be done. An efficient isolation procedure employing mosquito inoculation with dengue virus was developed at NIH's Pacific Research Laboratory in Hawaii, and isolation with specific identification can now be achieved in as little as 8 days. A PAHO-sponsored course on mosquito inoculation techniques was held at the Tropical Disease Laboratory in San Juan. Five national laboratories are now starting to use the technique. Since laboratories in A. aegypti-free areas cannot use this mosquito, there

is a need to explore the use of other locally occurring mosquito species or other insects. The mosquito inoculation technique may potentially be used in field surveillance. The sensitivity of virus detection by mosquito inoculation has been increased by ultracentrifugation of viremic human sera.

Though still experimental, the fluorescent antibody technique offers promise for the rapid identification of group B arbovirus in infected mosquitoes in either laboratory or field.

The plaque-reduction neutralization test is currently used in only a few New World laboratories. Still wider use is recommended. PAHO has not yet made technical guidelines available and should do so because the need for comprehensive and detailed guidelines remains. It would be valuable to many laboratories if detailed procedural guides to current techniques as they specifically pertain to dengue were prepared. Virologic assistance is now available in epidemic situations through the panel of emergency consultants designated by PAHO.

BPL-inactivated HA and CF antigens for dengue 2 and yellow fever have been prepared at YARU in 500-ampoule lots and will be distributed by PAHO. Inactivated dengue 2 antigens for HI and CF testing as well as appropriate immune fluids are available in limited amounts from the CDC San Juan Laboratory. It is anticipated that in the near future this laboratory will routinely provide larger quantities and additional serotypes.

The Committee recommends that all four dengue types be used for diagnosis of dengue in the New World because it is important to know if dengue 1 or dengue 4 is being imported. Since these two dengue types are not known in the New World, only inactivated antigens for them should be used and safety testing should be adequate. Laboratories in areas where A. aegypti occur should take appropriate precautions when using live dengue 1 and dengue 4 viruses.

Since the quantities of PAHO antigens prepared by YARU are limited and they have not been safety-tested in mosquitoes or primates,

the following principles are suggested to guide PAHO in distribution:

1. Dengue antigens should not be sent to areas where the virus is not known to occur.

2. The distribution of antigens should be limited to laboratories where surveillance or research is required and where technical competence is adequate to insure proper use.

3. PAHO officials may make exceptions to these principles under compelling circumstances.

PAHO should arrange for the supply of adequate amounts of safety-tested working antigens for dengues 1, 3, and 4, and continue to ensure a supply for dengue 2. Safety-testing of antigens of viruses not known in the Caribbean region should be conducted in sensitive systems such as mosquitoes and monkeys. Additional funds will be needed to ensure that these safety tests are carried out.

Dengue 2 and dengue 3 hyperimmune ascitic fluids will soon be available from the NIH Research Resources Branch as reference reagents to be distributed to all qualified investigators. Working antibody preparations are needed as control for diagnostic and survey antigens. These are available in limited quantities from the WHO Collaborating Arbovirus Centers for Reference and Research. PAHO should encourage laboratories to obtain high titered secondary-type, dengue-infection human immune sera suitable for fluorescent antibody conjugation and make the necessary arrangements to distribute the antisera.

PAHO should encourage laboratories conducting serosurveys to submit properly collected and documented specimens to WHO Serum Banks for storage. It should also arrange for collection and distribution of coded sera to diagnostic laboratories receiving the PAHO antigens for control and evaluation of serologic tests.

Training will continue to be needed at all levels. A number of institutions, including YARU, WRAIR, CDC, Cornell University Medical College, and Gorgas Memorial Laboratory, are now training laboratory staff individually. PAHO should continue to assist where needed. Should

any advances in laboratory techniques occur, the Organization should arrange a suitable course to disseminate them, as was done for mosquito inoculation techniques.

Collaboration between the laboratories listed above should be encouraged. Developments in technique should be reported in the Dengue Newsletter. The exchange of reagents may be needed for their standardization and where shortages exist. The meetings of the Scientific Advisory Group are invaluable in maintaining contact between laboratories.

5. Research Needs

The reason for the varying clinical consequences of dengue infection in different outbreaks is not now known. Conceivably, such differences could be the result of differences in the virulence of the virus itself, such as is known to occur in the case of the polioviruses. Although laboratory techniques in measuring such hypothetical differences in virulence are not yet adequately developed, it is thought important to begin the collection of virus strains from outbreaks in different geographic areas and in different years so that appropriate material will be available for study when laboratory techniques for biologic characterization of strains are adequately developed. Unpassaged virus in original human sera will be required.

Complement consumption occurs in the dengue shock syndrome and may play an important pathogenetic role. Further information on complement consumption is needed, especially in mild illnesses resulting from both primary and secondary infections. Studies designed to measure serum levels of complement components during the acute phase of dengue should be undertaken in the Americas to provide data comparable to those produced by the 1972 WHO collaborative study on DHF.

In the Americas, it is possible that fatal yellow fever and fatal dengue infections may occur in the same geographic area. Since considerable reliance in diagnosing fatal yellow fever is placed on the histopathologic

changes in the liver, and since similar changes are reported to occur in some cases of fatal dengue, it is desirable that a systematic comparison of liver lesions in the two diseases be carried out. In this way, the degree of confidence that can be placed on a diagnosis based on this type of examination can be evaluated.

The serologic response to a primary dengue infection may be type-specific in a small percentage of cases when measured by HI tests. Therefore, serologic diagnosis of dengue now requires the use of antigens to all four serotypes to avoid missing monospecific serologic rises. A single, highly cross-reactive antigen would be very useful for diagnostic purposes if one could be found. Antigens prepared from other group B arboviruses such as Ilheus, MVE, or zika should be tested against convalescent sera from primary dengue infections to evaluate the extent of cross-reaction and the potential diagnostic value of such antigens.

There is suggestive evidence that dengue type 2 infections which are now occurring in the Caribbean are less likely to cause hemorrhagic manifestations and death than are the dengue type 2 infections in the South Pacific. Since the magnitude of viremia in viral infections may be a reflection of viral virulence, and since it is now possible to measure the level of dengue viremias with precision, a comparison of viremia levels of dengue infections in the two areas would be of considerable scientific interest.

Data already available indicate that A. aegypti from different geographic areas vary in their ability to become infected with dengue viruses in the laboratory. Since vector competence could have considerable bearing on the transmission of dengue in a particular area, it would be desirable to obtain more detailed information on this particular point in order to evaluate the overall importance of variation in vector competence in the epidemiology of the disease. Since new preliminary data about yellow fever are lacking, it would also be highly desirable to carry out similar vector competence studies with that virus.

Continued research in both endemic and epidemic situations remains important for a thorough understanding of the epidemiologic patterns of

dengue in the Americas. Central questions are: Where are the endemic areas? and What serotypes are present or were present in the past?

Three areas now appear to be especially appropriate for epidemiologic research. Puerto Rico, where an endemic situation appears to be developing, is presently the site of intensive epidemiologic studies which should be continued. Hispaniola has been shown to be an endemic area and dengue 2 virus has been found present. The presence of dengue 3 is suspected. Further epidemiologic research to determine which serotypes are endemic on Hispaniola is considered important. Clinical dengue was reported in Venezuela from 1964 through 1969 and endemic transmission is suspected. Epidemiologic research should be instituted to determine if endemic transmission exists and if so, which serotypes are present.

Epidemiologic studies should be carried out to determine the effects of dengue virus on the fetus in utero. Such studies would be feasible in areas where sufficiently large numbers of maternal infections might have occurred in order to detect the expected low incidence of fetal abnormalities, if any.

Dengue Vaccines

The possibility of controlling dengue through A. aegypti control does not appear feasible on a long-term basis in much of the world. Vaccines appear to offer an alternate means of control in areas where vector control cannot be accomplished. Although the potential value of vaccines as a control measure cannot be precisely evaluated from present knowledge, development of experimental vaccines is considered to be very important at this time.

A major constraint on developing vaccine prophylaxis against dengue virus is that severe complement consumption occurs in dengue shock syndrome; this immunopathologic mechanism appears to be due to second dengue infections. Vaccination that does not provide protection against all dengue serotypes could conceivably sensitize vaccinated persons and result in the production of dengue hemorrhagic fever or dengue shock syndrome if vaccinated individuals are infected with a

serotype against which the vaccine does not protect. To preclude this occurrence, it is necessary that a dengue vaccine produce simultaneously effective immunization against all four dengue serotypes.

The development of an inactivated vaccine does not appear economically feasible now, since dengue viruses grow slowly in cell culture and produce low antigen yields. The feasibility of developing attenuated live-virus vaccines has been established with an experimental dengue 1 vaccine. The feasibility of administering four serotypes simultaneously remains to be conclusively established, but experience with other combined vaccines indicates that it can be done.

At present, knowledge of the molecular biology and genetics of dengue viruses and their virulence markers is insufficient to adequately evaluate and characterize candidate vaccine strains by laboratory methods alone.

The availability of acceptable cell culture substrates imposes another major limitation. Only two substrates appear useful and acceptable for vaccine production, primary dog kidney, and diploid fetal rhesus lung cultures.

Another limitation is the apparent genetic instability of some clones of dengue viruses which appear attenuated but which revert to virulence on further cell culture passage.

Three major impediments--inadequate basic knowledge, limited substrates, and genetic instability--combine to make dengue vaccine development difficult and slow.

Dengue 2 strains with reduced virulence have been produced in the laboratory by continuous passage in African green monkey kidney cell culture, by selecting plaque size variants in African green monkey cell culture, and by passage in fetal rhesus lung cell culture. Candidate strains of attenuated dengue 4 virus have been produced in primary dog kidney cell cultures. These strains are now undergoing the extensive laboratory studies required before initial testing in human volunteers.

Attempts to develop candidate vaccine strains from dengue 3 virus have recently begun, but no active research is being conducted with dengue 1 virus.

It seems probable that a multivalent vaccine can be developed. There are major problems to be solved, but none appears insurmountable. The time in which development can be accomplished is very difficult to predict. Additional knowledge relating virulence to in-vitro characteristics must be developed, and candidate strains must be extensively characterized in the laboratory and thoroughly tested in primates before trials in humans. Testing in volunteers will be required to establish safety and immunogenicity for each individual serotype. Later combined vaccines will have to be similarly tested. It appears that initial field trials are several years in the future.

6. Current Status of Aedes aegypti Eradication and Control

The goal of PAHO and its member countries is presumed to be the definitive elimination of serious human disease caused by dengue and yellow fever viruses transmitted by A. aegypti mosquitoes. Eradication of this African insect from the Americas was set as the method to achieve this goal in 1947. Significant progress has been made, but final achievement appears to be remote in part, at least, for reasons outlined in a current PAHO Staff Report (Appendix). In the past 2 years there has been little overall progress in eradication. The island of Bonaire has been cleared and a reinfestation in Belém, Brazil, has been eliminated. Reduction in premise indices has been achieved in several other countries. But in Colombia the campaign against the reinfestation has had only limited success, and Guatemala and Panama City, Panama, have been reinfested. During this same period, dengue transmission has been continuous and sylvan yellow fever activity in the tropical Americas has clearly increased.

The control and eradication of A. aegypti thus continues to present many difficulties. We note that a thorough review of the subject was

made by a study group convened during the Ninth Meeting of the Advisory Committee on Medical Research in 1970. Many recommendations were made at that time which our Committee does not feel competent to review or assess from the standpoint of current implementation. We believe that the Committee as now constituted can do no more than comment in general that measures adopted by PAHO (after a 1973 study group meeting in Guatemala) to increase the efficiency of dealing with the A. aegypti reinfestations appear to represent steps in the right direction.

7. The Current Risk of Epidemic Yellow Fever

The presence of high A. aegypti infestations in susceptible urban communities in the Caribbean always creates the risk of urban yellow fever, because of the existence of permanent enzootic foci in northern South America, and the possibility of introduction of the sylvatic virus into the cities. Such risk probably increases as the distance between the cities and the foci decreases.

If the virus is introduced into a city, it will probably be by viremic humans. viremic monkeys brought into cities for various purposes might play the same role.

At present it is impossible to properly evaluate the risk because information is incomplete regarding the interplay of the different factors that may affect A. aegypti transmission of yellow fever virus. These factors include: vector density; vector density in critical urban areas; magnitude of man-vector contact; transmission competence of local A. aegypti; viremia levels in the possible immigrants from the forest; degree of exposure of probable yellow fever patients to the vector; herd immunity, including that due to vaccination and possibly to previous exposure to other group B agents; and frequency of arrival of viremic humans or monkeys into Aedes-infested cities.

Nevertheless, so long as yellow fever virus persists in the forests of tropical America and so long as A. aegypti are present in significant numbers in urban areas within the region, some risk of urban yellow fever must clearly exist. On the basis of sylvan cases reported to PAHO over the past 20 years (Table 2), Bolivia, Brazil, Colombia, and Peru appear to have the highest chronic risk of such a medical catastrophe. But since A. aegypti is now found only in Colombia, among the countries listed above, that country is clearly the one facing such risk.

Other countries have experienced more isolated sylvan epidemics during the past 20 years, notably Argentina (1966), Venezuela (1972-73), and Panama (1974). Although urban transmission failed to occur in any of these outbreaks, vaccination of 7 and 1 million persons, respectively, in the last two countries testifies to the officially and publicly perceived risk of urban disease.

That the low risk of urban yellow fever is stable and unchanging depends on the assumption that the ecology of the region in the future will not be basically different from the recent past, in which zero transmission occurred. This is demonstrably not the case, but quantification of the degree and rate of important change eludes us. Human travel is an important variable. Increases in international air travel can be documented, but may not be the best kind to measure. How does one determine the increased travel betwen forested rural areas and cities which has certainly occurred in the past decade and which promises to continue increasing as roads, dams, and forest industries are built in the large tropical forests of the Americas? There are specific projects which may be undertaken to illuminate the basic questions and these are mentioned in the specific recommendations of this report.

8. Specific Recommendations

1. The Pan American Health Organization should reconstitute the present Advisory Committee on Dengue into an Advisory Committee on Dengue,

Yellow Fever, and Aedes aegypti. Membership should include persons competent in fields pertinent to both dengue and yellow fever viruses and associated diseases and to problems related to the control of the Aedes vector. This Committee should have no more than 15 members. It should not replace the study groups or other ad hoc committees and ought to stimulate their activities.

2. The Walter Reed Army Institute of Research laboratories should be designated as the PAHO Central Dengue Reference Laboratory for identification of virus isolates and the conduct of plaque neutralization tests.

3. The Organization should encourage laboratories to obtain high titered secondary-type dengue infection human immune sera suitable for fluorescent antibody conjugation and arrange for distribution of the sera.

4. PAHO should assist in the collection and storage (at YARU or other suitable laboratories) of human sera containing dengue virus from various geographic areas and time periods.

5. Comprehensive and detailed guides to the laboratory techniques currently used with dengue viruses should be prepared.

6. A technical guide to clinical recognition and treatment of the dengue hemorrhagic fever/shock syndrome should be prepared and widely distributed. This should include an outline of the necessary steps for establishing surveillance to detect this serious complication of dengue infection.

7. If nurse-epidemiologists or their equivalents are employed in laboratory-based surveillance programs, PAHO should arrange for their training in appropriate centers.

8. It is recommended that a special study by recognized authorities be arranged for the histopathologic comparison of liver lesions in fatal yellow fever and fatal dengue. These comparisons must be carried out only with coded specimens, including suitable control slides.

9. It is recommended that PAHO arrange for the collection of A. aegypti eggs from various parts of the Caribbean for use in vector competence studies.

10. The Organization should assist in the performance of vector competence studies using unmodified strains of yellow fever virus and A. aegypti strains found in different countries of the Americas.

11. Because of the possibility of confusing the diagnosis of dengue hemorrhagic fever and yellow fever and also because of the possibility of the occurrence of yellow fever in some areas where dengue virus is active, PAHO should encourage member governments to systematically perform autopsies on febrile cases in the areas concerned as well as to improve and extend current viscerotomy services.

12. The Organization should request the Government of Venezuela to collaborate in a study to determine the actual costs of the recent mass 17-D yellow fever vaccination campaign in Venezuela in order to provide better data for projection of the long-term costs of managing the urban disease threat by such measures.

13. The Committee has identified special research and surveillance needs herein for which substantial additional funds would be needed. For example, there is need for islandwide surveillance of dengue based in the virus laboratory of the University of the West Indies, Kingston, Jamaica. The Committee feels that such programs have international as well as national importance. The increase in communication between territories and islands, the presence of more than one dengue serotype on an island, the proximity of susceptible populations in adjacent territories, and the risk of introduction of yellow fever all illustrate the importance and the international significance of such programs.

The Committee therefore recommends that the Organization use its good offices and facilities to obtain research funds from private or public foundations for projects such as that at the University of the West Indies' Virus Laboratory in Jamaica and similar projects mentioned elsewhere in this report.

APPENDIX

STATUS OF THE CAMPAIGN TO ERADICATE *AEDES AEGYPTI* IN THE AMERICAS

JANUARY 1974

III Meeting of the
Scientific Advisory
Committee on Dengue
PAHO/WHO

Dr. Lelio B. Calheiros
Regional Advisor on
Eradication of
Aedes aegypti

Bogotá, Colombia
May 21-23, 1974

The effort to eradicate Aedes aegypti in the Americas has met with serious difficulties in recent years, chiefly because of the lack of interest in certain countries in achieving the goal set at the First Meeting of the Directing Council in Buenos Aires in 1947. The absence of a serious urban yellow fever problem in the Hemisphere in the last several years appears to be reducing fear of this onetime scourge.

Although the extensive area in which the vector has been eradicated could lead one to conclude that urban yellow fever is virtually under control, it is appropriate to point out that the problem has not been resolved and the danger persists. The existing apathy and neglect in certain still infested countries make the risk all the greater. It is worth recalling the panic that developed and persists in some American countries as a result of the appearance of only two cases of jungle yellow fever in Panama last February. Some countries that had been totally indifferent to the repeated calls of the Organization's Directing Bodies to intensify vector eradication became fearful and panicky.

Greater concern has prevailed in other parts of the Hemisphere, however. This is because dengue in recent years has definitely been the main health problem of the urban population in some countries and territories of the Caribbean area and northern South America still infested by A. aegypti. Almost all such countries and territories are maintaining active eradication campaigns.

Though it is impossible to predict whether or when the hemorrhagic form of dengue will appear in the Hemisphere, we can be certain that for now only those countries free of A. aegypti can assure their populations that they are adequately protected from the diseases transmitted by this vector.

The attached map and table show the A. aegypti eradication situation in the Americas as of December 1973. Of the 11.8 million km^2 in the Americas originally infested by the vector, 8.3 million km^2 are now free and eradication is being maintained in those areas. The remaining 3.5 million km^2 remain infested; active campaigns are under way in 1.9 million km^2, or 54 percent of the infested area.

The following countries and territories are declared free of A. aegypti: Argentina, Bermuda, Bolivia, British Honduras, Cayman Islands, Chile, Ecuador, Nicaragua, Panama Canal Zone, Paraguay, Peru, and Uruguay. Brazil, Costa Rica, and the islands of Bonaire, Saba, and St. Eustatius are negative, with a zero index of A. aegypti. Large areas of Mexico are being kept free of the vector, but part of the country has become seriously infested again.

The situation in the countries that remain infested is as follows:

1. NORTH AMERICA

United States of America. A large area--10 southeastern states, Puerto Rico, and the Virgin Islands--remains infested.

The Government began an eradication campaign in portions of the infested areas in 1964. Because of inadequate coverage, the results obtained by the end of 1968 were very poor. The campaign was interrupted in 1969 in consequence and the Government has so far not decided to reactivate it.

Mexico. The country completed eradication of the vector in 1961 and was declared free in 1963. It maintained an eradication surveillance service, but beginning in 1965 this was not sufficient to eliminate the constant reinfestation of the area along the border with the United States by A. aegypti from the latter country. Today there is rather extensive reinfestation in the states of Coahuila, Nuevo León, and Tamaulipas, and the Government has not concentrated enough resources to meet the problem adequately. The rest of the country, with an active surveillance effort, remains free of the vector.

2. CENTRAL AMERICA

El Salvador. After the vector had been eradicated for more than 8 years, reinfestation in San Salvador and other cities was discovered in 1965. Later surveys showed the country to be almost totally reinfested. Because resources are limited, the eradication campaign reinitiated

in 1965 has so far achieved only limited results, with coverage confined to San Salvador and Ilopango (International Airport).

Guatemala. Guatemala eradicated the vector in 1958 and was declared free in 1959. In late 1972, the eradication surveillance service discovered another focus of reinfestation in the same town near the El Salvador frontier, where a reinfestation had been eliminated in 1967. In 1973, four other localities, all close to infested areas of El Salvador and Honduras, were found to be reinfested. The campaign remains active in an effort to eliminate these foci of reinfestation.

Honduras. This country completed eradication in 1959 and was declared free in the same year. The surveillance service discovered a reinfestation in the northern part of the country (cities of San Pedro Sula and Puerto Cortés) in 1968. Though the campaign was reactivated, a lack of resources made it impossible to act in a prompt or adequate manner. Activities were suspended for lack of funds in 1972. During the aforementioned period, the vector dispersed to various parts of the country, including the entire Sula Valley, the west, and a portion of the south central region. The Government decided to reactivate its campaign in 1973, first in the western part of the country. In 1974, activities were started up again in the Sula Valley area and in the south.

Panama. The country completed eradication of the vector in 1955. In 1969, the city of Colón and three neighboring localities were found to be reinfested. This reinfestation was eliminated in April 1970. An exhaustive nationwide entomologic survey, completed in June 1972, produced negative results. In October 1972, the surveillance service again found A. aegypti in the capital; the vector had been reintroduced in used tires imported from a country that was still infested.

3. SOUTH AMERICA

Colombia. For lack of resources, the reinfestations discovered in the cities of Barranquilla and Cartagena in 1969 were not promptly eliminated. An intensive dissemination of the vector took place throughout most of the

northern coastal region, la Guajira, and a few localities in the department of Norte de Santander. Between 1971 and 1972, the major cities on the northern coast were struck by an epidemic outbreak of dengue, caused by Type 2 virus; the number of cases was estimated at over half a million. The eradication campaign was reactivated in 1972. However, resources permitted treatment of only the major infested cities. These efforts were continued in 1973, reaching 50 percent of all the houses in the area considered infested. The results obtained through 1973 are favorable.

Guyana. The campaign continued to operate in phase I of the Eradication Plan, which embraces the city of Georgetown, the areas east and west of the Demerara River, and part of the eastern region. The infestation index, originally 17 percent to 59 percent has declined to 0.5 percent. The Government has initiated preparatory activities, including environmental sanitation measures (elimination of breeding places), in the phase II area of the Eradication Plan.

Venezuela. The country is highly infested. The Government is conducting a very low-level campaign, with limited results, in the western part of Venezuela.

French Guiana. An active campaign, which is bringing favorable results, is continuing here. Infestation persists only in the city of Cayenne, with a low infestation index.

Surinam. The campaign continues to operate in the city of Paramaribo and the northern coastal area, with treatment cycles at irregular intervals. The results have not been favorable, for the infestation index remains stable. This is due to a special problem-- the development of Aedes aegypti foci in the rainwater conduits of the houses (40 percent of all houses). In 1973, the state of the program was reviewed, and a change of strategy and methods of attack, aiming at a short-term solution of the problem, was suggested to the Government. The plan that was submitted is undergoing a budget feasibility study.

4. INSULAR AMERICA (CARIBBEAN)

Barbados. The campaign has made steady progress, with 42 of the country's 61 localities now negative. The overall infestation index for the 19 localities that remain infested is 0.2 percent.

Cuba. The progress of the campaign, which was reactivated in 1971, has been very limited. A general evaluation was carried out in September 1973. The principal obstacles of the campaign's progress were identified, and the program of work was reoriented.

Bahamas. Limited eradication efforts continued in 1973.

Haiti. It remains infested, and no activities are going on.

Jamaica. The Government initiated eradication activities in Spanish Town in 1970, but it has so far not managed to expand activities to the rest of the country.

Dominican Republic. It remains infested, and no activities are going on.

Trinidad and Tobago. The island of Tobago remains free of Aedes aegypti and has a surveillance service. The island of Trinidad remains in the attack phase, seeking to eliminate several foci of reinfestation in the outskirts of Port of Spain. The infestation index is low.

French Territories. Guadeloup and Martinique are still conducting active campaigns, but with limited results.

Dutch Territories. The island of Bonaire is negative and in a consolidation phase. Infestation has been practically overcome in Aruba, where there are only two positive houses.

The islands of Saba and St. Eustatius are negative and in the consolidation phase.

St. Maarten (Dutch part) remains infested and in the attack phase, with an infestation index of 10 percent.

Curaçao is in the preparatory phase, and funds have been approved to begin the attack phase.

Territories of the United Kingdom. The Cayman Islands are negative. The campaign is in a very advanced phase in St. Lucia. There is only one positive locality, with an infestation index of 0.1 percent.

In Montserrat, the infestation index has declined from 22.5 percent to 1.3 percent, and work continues satisfactorily. In St. Vicent and Dominica, work continues to progress favorably, and the infestation indices have fallen from 18 percent to 2 percent and 2.7 percent, respectively. Grenada remains in the attack phase, and the index has declined from 27 percent to 1.4 percent.

Progress has not been satisfactory in Antigua, Anguilla, or the British Virgin Islands. The infestation indices have fallen, but remain above 5 percent.

The Turks and Caicos Islands, St. Kitts, and Nevis remain infested and are trying to organize campaigns.

In order to encourage the Governments, and in fulfillment of resolutions of the Directing Bodies, the Organization has promoted a number of scientific meetings and work groups in recent years to study the situation and problems relating to prevention of the diseases transmitted by Aedes aegypti, including eradication of the vector. It has also brought about a technical meeting of various countries and special ministerial-level meetings of countries to discuss eradication of the vector.

The reinfestation problem was studied in depth in April 1973 in Guatemala at a meeting of the countries of Central America and Panama on eradication of Aedes aegypti. As a result, the standards for eradication surveillance were broadened, and an increase of the funds to be used for this purpose was recommended. Thus, when a surveillance service discovers a reinfestation, it will be able to eliminate it rapidly, using its own resources rather than depending on the lengthy approval process required for additional funding. With the same end in mind, PAHO is assisting by maintaining a reasonable stock of insecticides and equipment to meet the needs of any situation promptly.

The Organization is continuing its cooperation in matters relating to entomological studies of Aedes aegypti in the Region, including routine

measurement of the susceptibility of different strains to insecticides. It is also cooperating in research on new methods of combating the vector; research on two new insecticides--fenitrothion and methyl dursban--is now under way. Besides testing the insecticides by already approved methods, the trials will include new methods, such as ultra-low volume spraying (ULV).

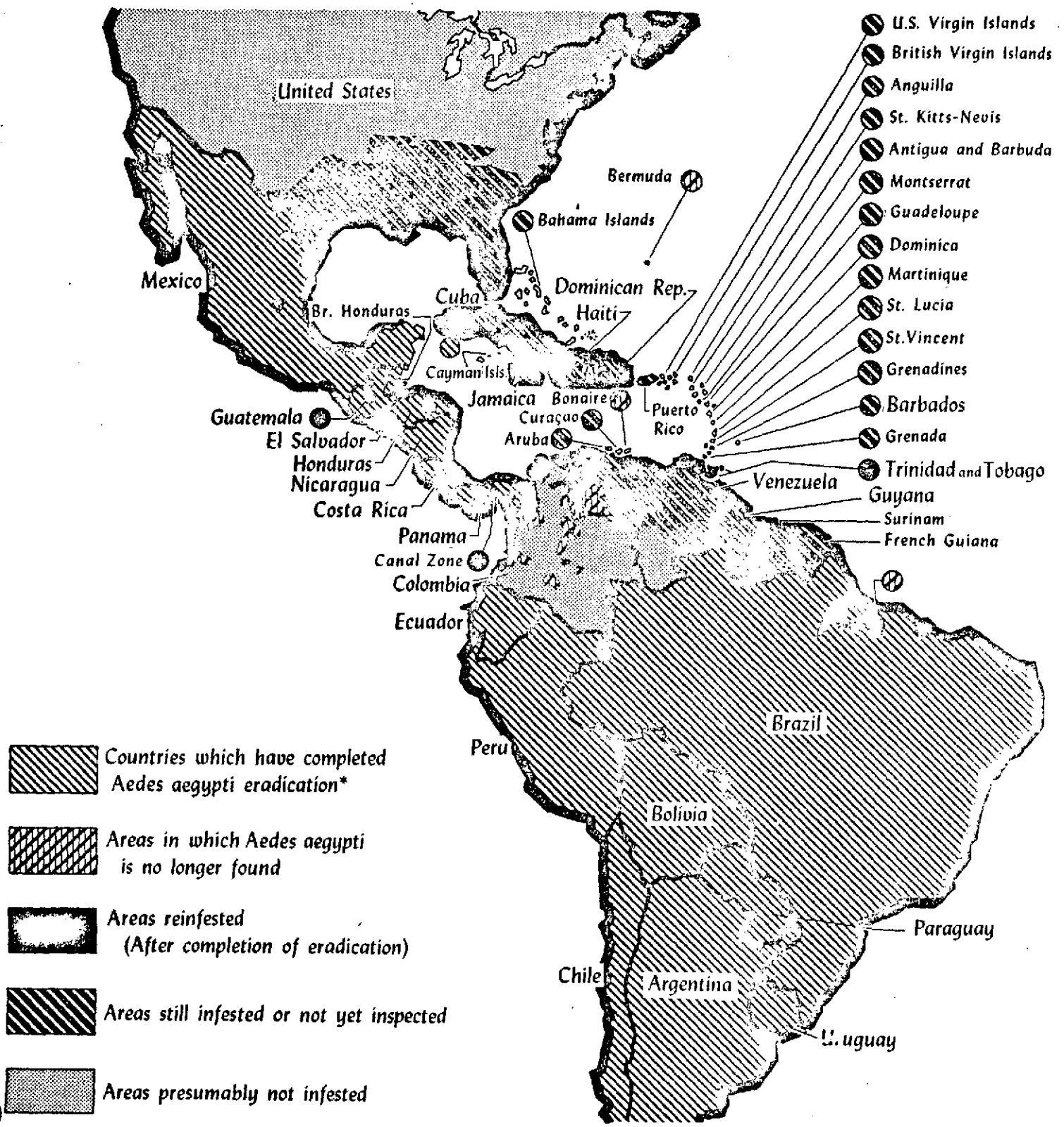
While efforts to eradicate Aedes aegypti in the Americas continue to be relatively free of technical problems, they face serious financial and administrative difficulties.

Table 1 STATUS OF AEDES AEGYPTI ERADICATION IN THE AMERICAS

DECEMBER 1973

Country or other political unit	Area in Km2			Stage of campaign	Activities
	Total	Area Initially infested	Percentage total area		
Argentina	4,024,458	1,000,000	24.8	Eradication completed	Vigilance
Barbados	430	171	39.8	Infested	Attack phase
Bolivia	1,098,581	100,000	9.1	Eradication completed	Vigilance
Brazil	8,511,965	5,358,822	63.0	Negative	Consolidation phase
Chile	756,945	100,000	13.2	Eradication completed	Vigilance
Colombia	1,138,338	280,000	24.6	Reinfested	Attack phase
Costa Rica	50,700	20,000	39.4	Reinfested	Attack phase
Cuba	114,524	100,000	87.3	Infested	Attack phase
Dominican Republic	46,734	42,020	86.2	Infested	None
Ecuador	283,561	69,454	24.5	Eradication completed	Vigilance
El Salvador	21,393	18,675	87.3	Reinfested	Attack phase (limited)
Guatemala	108,889	36,423	33.4	Reinfested	Attack phase
Guyana	214,969	4,662	2.2	Infested	Attack phase
Haiti	27,750	27,750	100.0	Infested	None
Honduras	112,088	69,929	62.4	Reinfested	Attack phase (limited)
Jamaica	11,424	11,424	100.0	Infested	Attack phase (limited)
Mexico	1,972,546	1,000,000	50.7	Reinfested	Attack and vigilance
Nicaragua	130,000	65,263	50.2	Eradication completed	Vigilance
Panama	75,650	56,246	74.3	Reinfested	Attack and vigilance
Paraguay	406,752	200,000	49.2	Eradication completed	Vigilance
Peru	1,285,215	638,000	49.6	Eradication completed	Vigilance
Trinidad and Tobago	5,128	3,108	60.6	Reinfested	Attack and vigilance
United States of America	9,359,781	1,536,819	16.4	Infested	Campaign interrupted
Uruguay	186,926	186,926	100.0	Eradication completed	Vigilance
Venezuela	912,050	710,000	77.8	Infested	Attack phase (limited)
Antigua (Barbuda and Redonda)	442	280	63.3	Infested	Attack phase
Aruba	190	174	91.6	Infested	Attack phase
Bahamas	11,405	11,405	100.0	Infested	Attack phase (limited)
Bermuda	53	53	100.0	Eradication completed	Vigilance
Bonaire	281	246	87.5	Negative	Consolidation phase
British Honduras	22,965	22,965	100.0	Eradication completed	Vigilance
Canal Zone	1,432	1,432	100.0	Eradication completed	Vigilance
Cayman Islands	259	259	100.0	Eradication completed	Vigilance
Curacao	472	448	94.9	Infested	Preparatory phase
Dominica	789	789	100.0	Infested	Attack phase
French Guiana	91,000	91,000	100.0	Infested	Attack phase
Grenada-Grenadines (Carriacou, Petit Martinique, and Union)	344	344	100.0	Infested	Attack phase
Guadeloupe (and part of St. Martin)	1,779	1,619	91.0	Infested	Attack phase
Martinique	1,102	1,000	90.7	Infested	Attack phase
Montserrat	103	103	100.0	Infested	Attack pahse
Puerto Rico	8,896	8,896	100.0	Infested	Campaign interrupted
Saba, St. Eustatius (and part of St. Martin)	89	89	100.0	Negative	Consolidation phase
St. Kitts, Nevis, Anguilla	396	396	100.0	Infested	Attack phase
St. Lucia	616	259	42.0	Infested	Attack phase
St. Vincent	388	332	85.6	Infested	Attack phase
Surinam	142,822	48,000	33.6	Infested	Attack phase
Turks and Caicos Islands	430	430	100.0	Infested	Preparatory phase
Virgin Islands (U.K.)	153	153	100.0	Infested	Attack phase
Virgin Islands (U.S.A.)	344	344	100.0	Infested	Campaign interrupted

Status of the Aedes aegypti eradication campaign in the Americas, December 1973



*Eradication carried out according to the standards established by the Pan American Health Organization

TABLE 2. Reported cases or suspected outbreaks of dengue in the Caribbean area, 1960-1973

	1960	1961	1962	1963	1964	1965	1966	1967	1968	1969	1970	1971	1972	1973
Barbados	...	...	...	...	...	...	...	...	(p)	...	-	-	-	-
Colombia	-	-	-	-	-	-	-	-	-	-	-	(p)	(p)	...
Dominican Republic	494	821	822	350	407	527	...	...	-	16	-	3	-	...
Haiti	...	...	...	...	...	...	...	...	(p)	...	...	...	3	49
Jamaica	-	-	-	1,578	156	36	6	6	367	545	31	14	4	3
Venezuela (a)	56	-	-	-	18,306	4,040	7,750	1,330	383	3,917	405	5	25	-
Antigua	-	-	-	-	264	8	-	-	179	...	...	-	-	-
Bahamas	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Dominica	...	...	-	2	43	-	...	-	41	-	-	-	-	-
French Guiana	...	...	...	...	...	...	...	...	...	...	(p)	(p)	...	...
Grenada	...	...	...	...	...	...	...	...	...	81	15	27		
Guadeloupe	...	...	...	...	...	...	...	...	...	...	(p)	-	...	...
Martinique	...	...	...	(p)	...	...	...	...	...	...	(p)	-	-	...
Montserrat	-	-	-	-	-	-	-	-	(p)	...	...	...	...	...
Netherlands Antilles	...	...	...	(p)	...	...	...	...	...	...	...	...	...	...
Puerto Rico	-	-	-	25,737	2,440	93	2	1	-	16,665	136	15	85	658
St. Kitts - Nevis and Anguilla	-	-	-	-	721	-	-	-	(p)	-	-	-	-	-
St. Lucia	-	...	...	...	...	...	...	-	(p)	...	...	-	-	-
St. Vincent	-	-	-	-	-	-	-	...	(p)	-	-	-	-	-
Virgin Islands (UK)	-	-	-	-	-	-	-	-	-	-	...	2	2	...

- No cases.
... No data available.
(a) Reporting area.
(p) Outbreak or presence of dengue-like illness reported.

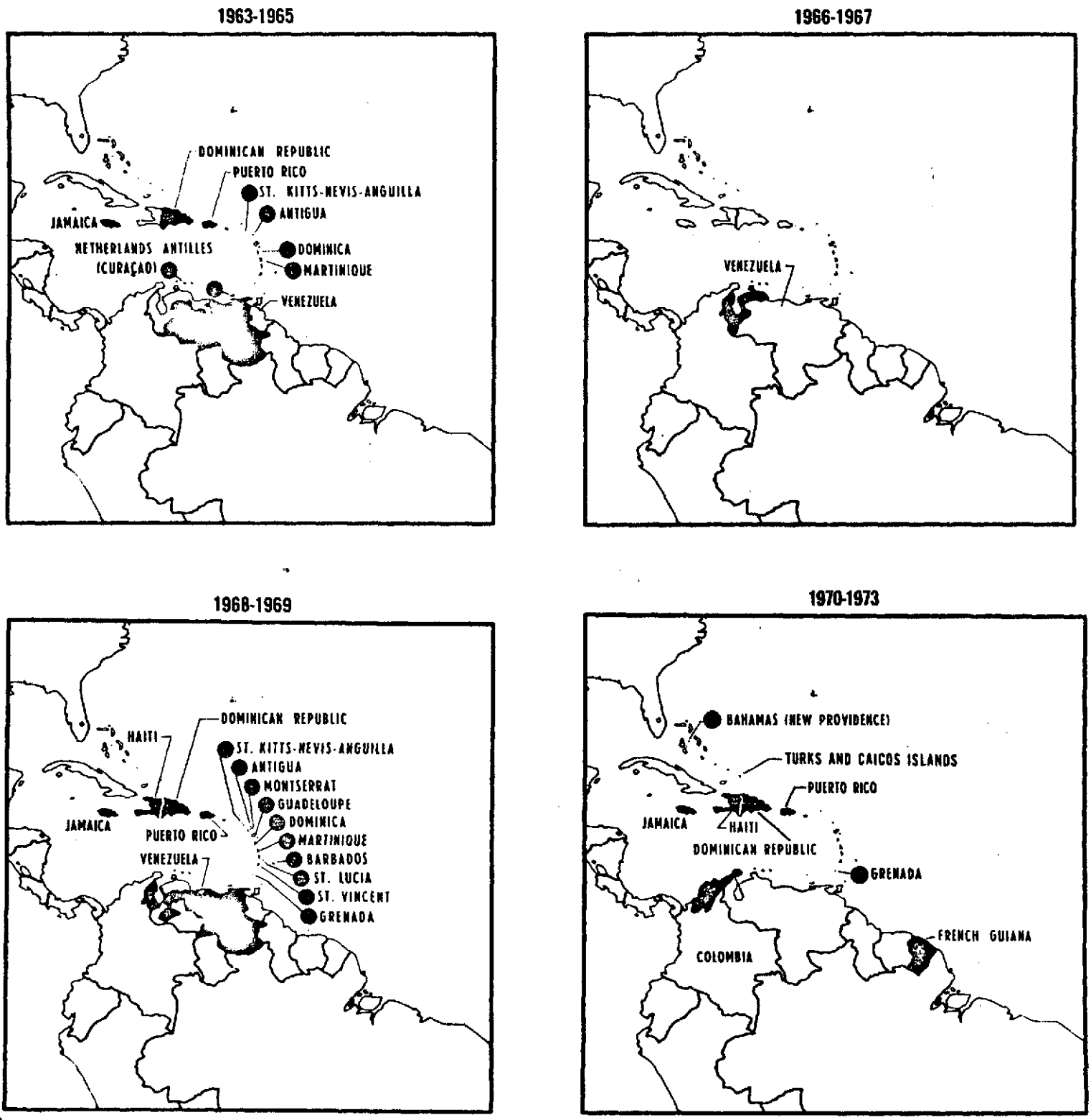
TABLE 3. Yellow fever cases reported to the Pan American Health Organization, 1954-1973.*

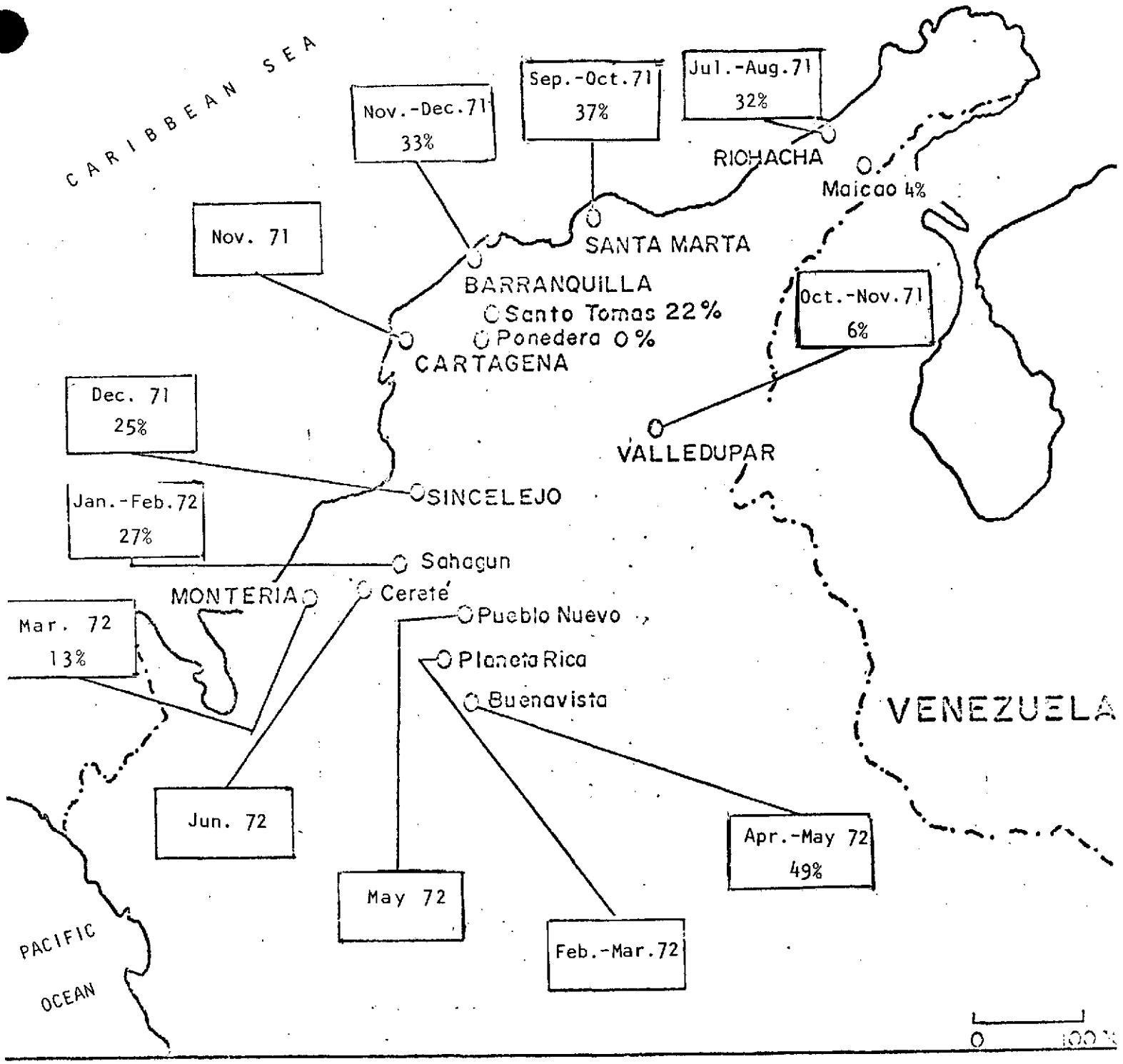
Country or Territory	1954	1955	1956	1957	1958	1959	1960	1961	1962	1963	1964	1965	1966	1967	1968	1969	1970	1971	1972	1973
Argentina	-	-	-	-	-	-	-	-	-	-	-	2	51	1	-	-	2	-	-	-
Bolivia	2	7	6	19	2	2	30	2	-	81	13	19	69	-	27	8	2	8	9	76
Brazil	9	8	2	10	26	3	1	2	1	-	13	14	167	2	2	4	2	11	12	41
Colombia	12	22	16	35	21	21	11	9	30	10	10	2	3	5	11	7	7	9	3	14
Costa Rica	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Ecuador	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Guatemala	-	-	-	3	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Guyana	-	-	-	-	-	-	-	2	-	-	-	-	-	-	1	-	-	-	-	-
Honduras	1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Panama	-	-	1	2	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Peru	26	-	-	3	6	1	4	53	20	49	60	45	9	3	5	26	75	-	7	33
Surinam	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1	1	-	-	1	-
Trinidad	18	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Venezuela	29	5	3	6	9	2	2	14	1	1	2	5	5	-	-	-	-	-	22	6
TOTAL	97	42	28	78	64	30	48	82	52	141	98	87	304	12	47	46	86	28	54	170

*All sylvatic except five urban cases in Trinidad, 1954.

FIGURE 1

OCCURRENCE OF DENGUE IN THE CARIBBEAN





Colombia: Months with maximum incidence of epidemic fever in various localities. Also shown are percentage of sera positive to dengue antigens by CF test in the respective localities.

Figure 3

TOWNS WITH CONFIRMED DENGUE 2 IN PUERTO RICO
1970 THROUGH FEBRUARY 1974