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Final Report:

Meeting to Establish a Network of Laboratories for the Surveillance of Emerging Infectious Diseases (EID) in the Amazon Region

(Manaus, Amazonas, Brazil,
9-11 February 1998)

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1. Welcoming Remarks

Dr. Wilson Alecrim, Director of the Institute of Tropical Medicine of Amazonas (IMT-AM), welcomed the participants to the emerging infectious disease surveillance meeting. He emphasized the importance of the meeting as a critical first step toward implementing a system for the rapid identification and timely control of emerging infectious diseases (EID). In this context, he stated that all countries in the region must work together to combat effectively the health threat of emerging infectious diseases. Dr. Alecrim emphasized the enormous challenge presented by EID and wished the participants success in their efforts to achieve their goals of this extremely important meeting.

Dr. Stephen Corber, Director of Disease Prevention and Control, PAHO, welcomed the participants and emphasized the need for member states to cooperate toward developing and implementing strategies to minimize the impact of EID on human health. He indicated that PAHO continued to provide support and that this meeting would play a key role in implementing a regional surveillance program. Surveillance alone, however, would not be sufficient, but must be supplemented with effective control and preventive measures to negate the threat of EID to human health.

The Participants were also welcomed by Dra. Ana Rosa dos Santos, Coordinator of the National System of Health Laboratories, Brazilian Ministry of Health, who stressed the importance of the meeting as an opportunity to work together toward a common goal to improve human health in the region. She noted that most countries already had some types of surveillance but that the outcome of this meeting would eventually lead to strengthening the region's capability to identify and counteract the threat of EID.

2. Objectives of the Meeting

To create a functional network of laboratories within the greater Amazon Region, able to obtain accurate, high-quality laboratory results on new, emerging and reemerging infections found in the Region. The objectives include development of:

- Accurate laboratory results
- Prompt information-sharing
- Strong linkage to epidemiological studies
- Implementation of common protocols to address specific diseases, using identical or comparable laboratory procedures with good quality control to ensure accuracy of results obtained.
- A forum for rapid technology transfer

3. Background

A. Summary of Previous Recommendations

In recent years, considerable attention has been given to the serious threat posed by emerging and re-emerging diseases. Many new pathogens have been identified in the past twenty years and several diseases once thought to be well controlled, such as cholera, dengue and tuberculosis, have re-established themselves as public health problems.

In 1995 the Pan American Health Organization (PAHO) convened a meeting of international experts to discuss strategies for the prevention and control of emerging diseases. The resulting Regional Plan of Action for Combating New, Emerging, and Re-emerging Diseases in the Americas was approved by the Directing Council of PAHO later that year.

This Regional Plan has four goals:

- Strengthen regional surveillance networks for infectious diseases in the Americas.
- Establish national and regional infrastructures for early warning of and rapid response to infectious disease threats through laboratory enhancement and multidisciplinary training programs.
- Promote the further development of applied research in the area of rapid diagnosis, epidemiology, and prevention.
- Strengthen the regional capacity for effective implementation of prevention and control strategies.

Under the goal of strengthening regional surveillance, three objectives were identified:

- Enhance and integrate existing infectious disease surveillance networks in the Americas.
- Establish a regional steering committee for emerging infectious disease surveillance.
- Develop uniform guidelines that link surveillance and reference diagnostic services.

A workshop to define priorities for institutional strengthening held in Goiania, Brazil in March 1996 noted the importance of strengthening regional laboratories and identifed several specific requirements for improved laboratory surveillance.

The regional steering committee met in Toronto, Canada in November 1996 and in Rio de Janeiro, Brazil in November 1997 to identify priorities for regional surveillance. A specific recommendation of the second meeting was “to support the initiative on surveillance for emerging infectious diseases in the Amazon Basin and extend it to other subregions.”

B. Description of Participating Institutions (by country)

Bolivia: The National Center for Tropical Diseases (CENETROP) is an institute of the Bolivian Ministry of Health and Social Security. It is located in Santa Cruz, Bolivia and administratively is part of the National Direction of Epidemiology. CENETROP was founded in 1974 by an agreement between Bolivia and Belgium. Its mission is to train health personnel in the diagnosis and treatment of tropical diseases, to find solutions based on epidemiological studies of local problems, to support the regional laboratories and to care for patients with tropical diseases.

Brazil: The Evandro Chagas Institute (IEC), Belém, Pará, Brazil is a research laboratory under the National Health Foundation that belongs to the Brazilian Ministry of Health. Its mission is research development in the areas of biological sciences, tropical medicine and environmental sciences. It also has operational responsibilities.
The Institute of Tropical Medicine of Amazonas (IMT-AM) is located in Manaus, Amazonas, Brasil. It is a state institution created in 1970 as a tropical disease hospital. Throughout the years, it has expanded its capabilities in research and teaching. The mission of the IMT-AM is to provide health services, to conduct research in tropical diseases and to contribute to the training of personnel in tropical diseases.

Colombia: The National Institute of Health of Colombia (INS-C) was restructured in 1994 and is responsible to the Ministry of Health. Its mission is to promote, guide, execute and coordinate scientific research in health and biomedicine; to develop, apply and transfer science and technology in the corresponding areas; to act as a national reference laboratory; and to develop, produce and to distribute biological reagents, chemicals, biotechnologies and diagnostic materials.

Peru: The National Institute of Health of Peru (INS-P) is a public, autonomous entity receiving funding from the Ministry of Health. It was created in 1896. Since 1958, its mission has been to act as a center for health research, producing both basic and applied scientific information for the prevention and control of diseases.

Venezuela: The National Institute of Hygiene "Rafael Rangel" (INH-RR) was created in 1938 and is under the auspices of the Venezuelan Ministry of Health and Social Assistance. It is the reference center for surveillance, prevention and control of public health problems within Venezuela. The mission of the INH-RR is to diagnose and investigate both endemic as well as epidemic diseases; to study nutritional problems and water contamination; to provide vaccines for the nation; to guarantee the quality of food; and to maintain programs of sanitary control.

C. Surveillance Activities Already Underway

All of the partner laboratories are already participating in ongoing surveillance systems within their respective countries by providing epidemiologic information on a variety of infectious diseases, including malaria, dengue, rubella, measles, cholera, polio, influenza, pneumonia and HIV infection. Table 1 summarizes these activities.

4. Plan of Action

A. Disease Syndromes

The participants selected five disease syndromes to be included in the proposed surveillance program. A definition of each syndrome is given below:

i. *Undifferentiated febrile syndrome:* Fever ≥ 38.3^{o}C that has no obvious etiology and has no more than 7 days evolution in a previously healthy person 5 years of age or older.

ii. *Hemorrhagic fever syndrome*: An acute febrile hemorrhagic illness with or without evidence of capillary fragility.

iii. *Febrile icteric syndrome*: Febrile patients > 1 year of age with acute or insidious onset of icterus in whom there is no detectable cholelithiasis or biliary obstruction.

iv. *Acute respiratory distress syndrome*: A febrile illness (temp. > 38.3^{o}C) characterized by bilateral diffuse interstitial edema, with respiratory compromise requiring supplemental oxygen, developing within 72 hours of hospitalization, and occurring in a previously healthy person.

v. *Sudden unexplained death syndrome:* Previously healthy persons, 5-49 years of age, who are hospitalized (or admitted to an emergency room) with a life-threatening illness with hallmarks of an infectious disease for which no cause is identified.

Excluded from this study will be patients with preexisting chronic medical conditions such as malignancy; HIV infection; chronic cardiac, pulmonary, renal or rheumatologic disease; diabetes mellitus; immunosuppressive therapy; trauma; toxic ingestion or exposure; or nosocomial infection.

B. Infectious Agents

A list of possible diseases that will be tested for was prepared for each of the first four disease syndromes. Convalescent sera from patients enrolled in the study will be screened for antibodies against the agents causing the diseases listed below. In order to save reagents, money, and time, it was suggested that convalescent sera be screened first (initial screen) against the most common or likely agents to be causing the syndrome locally. If the serum is negative in the initial screen, it then will be tested (in a second or third screen) against other less common agents.

i. *Undifferentiated febrile syndrome*

(a) Initial screen*
malaria (*P. falciparum* and *P. vivax*)
dengue (types 1,2,3, and 4)
Oropouche fever
Mayaro fever
group C virus infection
yellow fever
Venezuelan equine encephalitis (VEE)
leptospirosis
influenza
Q-fever

(b) Second (or third) screen*

ehrlichoses
rickettsioses
parvovirus B-19 infection
measles
rubella
hepatitis A
hepatitis B
hepatitis C
Ilheus virus infection
phlebovirus infection (phlebotomus fever)
vesiculovirus infection
Cache Valley & related bunyavirus infections
typhoid fever
St. Louis encephalitis virus infection

*The order of the agents to be tested may vary from one region (study site) to another.

ii. *Hemorrhagic fever syndrome*

(a) Initial screen: (in order of probability at each site)
dengue
yellow fever
leptospirosis
arenavirus infections (Machupo, Guanarito or others, depending on region)

(b) Second screen:
ehrlichiosis
rickettsioses
hepatitis B
hepatitis C
hantavirus infection (hemorrhagic fever with renal syndrome)

iii. *Febrile icteric syndrome*

(a) Initial Screen: (in order of probability at each site)
leptospirosis
yellow fever
hepatitis A
hepatitis B
hepatitis C

(b) Second Screen:
hepatitis D (only if patient is positive for hepatitis B virus infection)
hepatitis E

iv. *Acute (noncardiogenic) respiratory distress syndrome (ARDS)*
influenza
hantavirus infection (hantavirus pulmonary syndrome)
legionellosis
Q fever
psittacosis

v. *Sudden unexpected death syndrome*

(a) Initial Screen (done locally):
culture
histopathology

(b) Second Screen (done at a reference laboratory):
immunohistopathology
nucleic acid probes with PCR
electron microscopy

C. Specimens

Acute and convalescent serum specimens will be obtained from all patients when possible. To insure that convalescent samples are obtained from most of the people enrolled in the study, home visits are recommended. I cases where specific diseases are suspected (i.e. influenza, leptospirosis, rickettsioses), additional samples (i.e. nasopharyngeal swab, urine or blood clot, respectively) may be collected.

i. *Acute serum*: During interepidemic periods, acute blood (serum) samples will be collected from patients within the first five days of their illness. During epidemics, acute blood samples should be taken within the first three days of illness. If appropriate, the acute phase blood clot may also be saved. Acute phase samples will be stored at -70^{o}C.

ii. *Acute phase respiratory samples:* In selected illnesses with respiratory symptoms, it may be appropriate to take nasopharyngeal swabs or pharyngeal washes as well. These samples should be processed immediately or frozen at -70^{o}C.

iii. *Convalescent serum samples*: An attempt will be made to obtain a second (convalescent) serum sample from all surviving patients within 2-3 weeks after the onset of their illness. In cases of hemorrhagic fever, where arenavirus infection is suspected, a third serum sample will be obtained 5 or 6 weeks after onset of illness.

iv. *Autopsy samples*: In fatal cases, an attempt will be made to obtain permission for an autopsy (or viscerotomy) in order to obtain tissue samples. Ideally fresh tissue samples should be saved (untreated and frozen at -70^{o}C) for culture and fixed in 10% buffered formalin for histopathology.

D. Reagents and Diagnostic Tests

i. *Reagents*: All participants emphasized the importance of having available adequate amounts of standardized and high quality diagnostic reagents. After discussing alternative strategies for this goal, it was decided that most reagents would be purchased from commercial vendors or obtained from an international reference laboratory such as CDC. If not available from a commercial or reference source, then one or more of the network laboratories will prepare and share the reagents with the other laboratories. Training of laboratory staff in reagent preparation is another approach for ensuring adequate amounts of reagents.

ii. *Laboratory Tests*: The basic plan will be to begin testing by screening the convalescent serum for antibodies to the probable etiologic agent. In general, the acute sample(s) will be stored at -70C until the serologic results on the convalescent sample(s) are available. Based on these serologic results, the appropriate tests (i.e. culture, PCR) then will be done on the acute sample to confirm the etiologic agent. The group agreed that the same tests and reagents will be used in each of the network laboratories.

A suggested list of specific diagnostic tests and source of reagents is given below. This list could change depending on cost, funds available, and/or the development of newer more sensitive diagnostic techniques.

(a) *Initial serum or convalescent serum*

- Arboviruses and arenaviruses - IgM ELISA (antigens to be prepared in one of the network laboratories or at Univ. of Texas Medical Branch)
- Hantaviruses - IgM ELISA (antigen from CDC)
- Influenza - WHO/CDC kits
- Hepatitis A, B, C, D, & E - commercial kits
- Leptospirosis, Q-fever, typhoid fever and brucellosis-IgM ELISA (commercial kits).
- Rickettsioses and ehrlichioses -IFAT or commercial kits (antigen from UTMB)

- Malaria: Thick smears initially, followed by QBC for confirmation; then commercial tests (Paraslide or OptiMAL) to differentiate *P. vivax* from *P. falciparum*.
- Psittacosis and legionellosis -CF, ELISA or IFAT (antigen from CDC or commercial source).

E. Quality Control

It was recognized by the group that it will be important for all collaborating laboratories within the network to maintain the highest quality of diagnostic tests to ensure that results obtained will be accurate and that all participants will have confidence in the observations made and results obtained. Formal quality control may be difficult since some of the tests to be used are not available commercially and the reagents to be used must be individually prepared. To overcome possible variation in tests results as described above, standardized test protocols and a single source of diagnostic reagents will be used whenever possible. In cases where results of standardized tests are inconclusive or questioned, specimens will be exchanged with other partners in the network for clarification, confirmation or additional testing, or referred to external reference laboratories such as the CDC and UTMB. Finally, whenever possible, a battery of well validated positive and negative control specimens will be distributed under code to all laboratory partners for routine proficiency testing. If significant discrepancies are found through the routine quality control and proficiency testing procedures, specialized training will be implemented to correct the problem.

F. Equipment

Each surveillance site will be supported with a -70^{o}C and a -20^{o}C freezer and an ELISA reader and washer for dedicated specimen storage and testing of samples, respectively. Also, a minimum of at least one liquid nitrogen shipping container (dry shipper) will be provided to each laboratory for temporary storage and transportation of specimens.

G. Project Management

Management of the collaborative project will, by necessity, involve two separate levels. Agreement was reached among all of the laboratories that external sources of funding should be sought to provide resources needed to maintain the network and conduct the proposed investigations. This will require that a single principal investigator with his/her parent organization submitting a specific proposal and assuming responsibility for overall management of funds, including disbursement and accounting. The principal investigator will also be responsible for obtaining progress reports from collaborating laboratories and completing formal progress summaries for the funding agency, as required. At least two potential funding sources were discussed, the United States National Institutes of Health (NIH) and the United States Agency for International Development (USAID). If separate proposals are prepared by different individuals and organizations for these or other

donors, then each principal investigator would have management responsibilities for his/her own grant or contract.

Within each of the collaborating laboratories, a single individual will be identified to serve as the primary point of contact and responsible party to oversee the activities of his/her laboratory in implementing the plans of the network. This individual will also serve as a member of the network executive committee. Responsibilities of the executive committee will include design and agreement upon collaborative studies to be undertaken, management and accounting of funds provided to support these efforts, and timely preparation of semi-annual and annual reports as required by funding agencies. The executive committee will meet at least annually to review progress and define future priorities, and to discuss current and future efforts with the principal investigator(s) of supporting grant(s).

H. Associated Institutions

Several associated institutions have indicated an interest in helping the Amazon Network by providing reference services, multilateral agreements, training and/or reagents. These institutions, as well as their missions and possible areas of collaboration, are described below:

i. *Ministry of Health of Brazil*

The Brazilian Ministry of Health will assist in the coordination of laboratory efforts within Brasil and will facilitate bilateral and multilateral agreements with other nations in the Amazon Region.

ii. *Oswaldo Cruz Institute Foundation (FIOCRUZ)*

This Rio de Janeiro-based foundation is a premier institution in Brazil dedicated to research, training, and infrastructure development. The associated Biomanguinos produces biologicals and diagnostic reagents. FIOCRUZ will be an outstanding resource for quality control and reagents, and as a reference laboratory for the Amazon network for diseases, such as leptospirosis, typhoid fever and viral hepatitis.

iii. *Brazilian Army Institute of Biology*

The Army Institute of Biology (IBEx) is the Health Research Center of the Brazilian Army. It was set up on December 19, 1894, and since then has engaged in research, diagnostic support, and the production of immunobiologicals.

Noteworthy among the studies done by IBEx are a characterization and eradication of glanders in the city of Rio de Janeiro at the beginning of the century; determination of the re-emergence of yellow fever in Rio de Janeiro in 1928 after the disease had been absent for twenty years; production for the first

time in Brazil of gangrene antitoxin in 1932; production of mixed Te-TAB vaccine on the eve of the entry of Brazil into World War II in 1939 for the protection of its troops; and, more recently, clinical and epidemiological studies of malaria, leishmaniasis, dengue and AIDS in the military.

At present the IBEx is pursuing five principal lines of work: laboratory support to clinical diagnosis; the production of immunobiologicals; provision of blood and blood products to military hospitals; instruction in support of the military and civilian sectors by providing advanced training for middle- and high-level personnel, and research in the areas of human and veterinary medicine.

iv. *Amazon Center for Investigation and Control of Tropical Diseases "Simon Bolivar"* (CAICET)

The CAICET was created in 1982. Its objective is to study and control tropical diseases in the State of Amazonas, Venezuela. Since 1995 CAICET has been a part of the Venezuelan Ministry of Health and Social Assistance, co-sponsored by the Government of the State of Amazonas and the Venezuelan Corporation of the Guayanas. The CAICET conducts research on diseases endemic in the State of Amazonas, such as malaria, onchocerchiasis, dengue, viral hepatitis, leptospirosis and tuberculosis that are prevalent among populations of urban areas and Indian communities. The studies performed by the CAICET are interdisciplinary, with regional, national and international cooperation.

v. *U.S. Naval Medical Research Institute Detachment-Peru (NAMRID):* NAMRID was established in 1983 to conduct research on infectious diseases among human populations in South America. The main laboratory is located in Lima, Peru, and a field laboratory and study site are located in Iquitos, Peru. The Lima laboratory is equipped with technology and equipment required to conduct "state of the art" research on infectious diseases, including viral, bacterial and parasitic diseases. The Iquitos laboratory serves primarily as a support base for processing and storage of clinical samples for field studies. All samples are shipped to the Lima laboratory for diagnostic testing. In addition to research, NAMRID also provides training in diagnostic testing and surveillance for emerging and other infectious diseases. NAMRID's diagnostic capability includes classical and molecular testing for sexually transmitted diseases, and for parasitic diseases, including malaria and leishmaniasis.

Since 1994, NAMRID has conducted surveillance for emerging arboviral diseases in Iquitos. Although the emphasis has been on Oropouche and dengue viruses, several other arthropod-borne viruses such as VEE, Mayaro, Guaroa and Group C have been recognized for the first time as causes of human disease in Peru. This program has led to the establishment of an infrastructure and technological capability that will sustain ongoing studies and allow for the surveillance of other emerging pathogens in the Amazon region of Peru.
NAMRID's role in the Amazon surveillance network will be to

(a) Sustain a surveillance project site in Iquitos for emerging infectious diseases in collaboration with the INS-P in Lima.
(b) Train medical research and other health related personnel to perform diagnostic tests and to conduct medical research.
(c) Offer short and long term courses for diagnostic testing and research training, with focus on surveillance and outbreak investigations.
(d) Provide confirmatory diagnostic testing for selective infectious disease pathogens.
(e) Support outbreak investigations, including both field and laboratory activities.

vi. Centers for Disease Control and Prevention (CDC)

The CDC serves as the national public health reference laboratory for the United States, and as such, maintains technical expertise in virtually all infectious diseases of public health importance. Within the CDC, the National Center for Infectious Diseases (NCID) houses laboratory facilities using state-of-the-art procedures to isolate, cultivate and identify infectious pathogens. Other centers within CDC maintain programs in immunization against vaccine preventable diseases, training in epidemiology, toxicology expertise, and others. Virtually all centers within CDC have an interest in global health and disease prevention or control. The CDC, and especially NCID, are capable and willing to assist the Amazon Region Emerging Diseases Laboratory Network by providing assistance in characterizing isolated agents, helping to resolve difficult clinical diagnoses, providing pathological analysis of clinical specimens, and offering training in specialized laboratory techniques. The CDC also houses several World Health Organization Collaborating Centers, and through the activities of these Centers, assists WHO and PAHO in implementing global and regional activities. For example, the CDC contributes significantly to the global monitoring of influenza viruses, leading to the annual recommendations for influenza virus composition. Finally, the CDC is often called upon by various countries to assist in outbreak investigations.

vii. *University of Texas Medical Branch (UTMB)*

The University of Texas Medical Branch is the site of a World Health Organization (WHO) Collaborating Center for Tropical Diseases and the WHO Arbovirus Reference Collection. The Center for Tropical Diseases currently has collaborative projects in Peru, Venezuela, and Colombia and has historic connections with other laboratories in the Brazilian Amazon. UTMB houses reference collections of rickettsial and fungi in addition to arboviruses, hantaviruses and arenaviruses. Scientists at UTMB will play a leadership role in coordinating funding, training, quality control, and networking. They will also serve a reference function for arboviruses and *rickettsiae*.

viii. *Pan American Health Organization (PAHO)*

PAHO has a mandate to help all countries in this hemisphere to improve their

health structure; it has offices in all five countries involved in this project. PAHO can provide assistance to the network in several ways, such as direct technical cooperation or mobilizing consultants, particularly on epidemiological surveillance. PAHO can also purchase and deliver equipment and reagents, and help transfer funds to the network. Another area of cooperation can be the organization of proficiency programs of teams for external evaluations and technical meetings. Interaction between PAHO task force on surveillance of emerging and re-emerging infectious diseases and the network will also be encouraged.

ix. *World Health Organization (WHO)*

The WHO was directed by the World Health Assembly in 1995 by formal resolution to address emerging infectious diseases. In response to this resolution, the Division of Communicable Diseases was reorganized into a new structure, the Division of Emerging and other Communicable Disease Surveillance and Control (EMC). Among other activities, this division assists region and member states in developing and implementing disease surveillance activities, responding to outbreaks, and developing national capacity through training activities and workshops. WHO/EMC also attempts to provide accurate, timely information on disease outbreaks around the world through both formal publications in the Weekly Epidemiological Record and electronically through a dedicated Web site and various electronic distribution lists. Other divisions within WHO provide regions and member states with technical assistance and training opportunities on specific diseases, conditions or programs. These include the Division for Control of Tropical Diseases (CTD), the program for Tropical Disease Research (TDR), the Global Program for Vaccines (GPV), and others.

I. Study Sites and Populations

Participants from each of the six institutions comprising the surveillance network outlined their proposed study sites and populations to be sampled. The geographic localities of the proposed study sites are shown on the map in Figure 1. It was recognized that uniformity was not practical to achieve, and indeed, not necessarily desirable.

i. *Evandro Chagas Institute (IEC), Belem, Para, Brazil*

In addition to the outpatient divisions at the IEC that care for patients from Belem and nearby counties, other communities will be chosen following prior IEC experience in the state of Para. The other communities include:

- Altamira
- Paragominas
- Abaetetuba
- Santarem

Participants from the IEC indicated that the following populations will have priority for the project:

- Populations involved in large development projects (i.e. roads, dams, etc.)
- Populations migrating into rural areas of the Amazon from large urban areas
- Populations subject to greater exposure and to environmental changes
- Indigenous populations in their natural environments
- Urban, rural and river shore populations

ii. *Institute of Tropical Medicine of Amazonas (IMT), Manaus, Amazonas, Brazil*

(a) *Urban area*: Cases with undifferentiated febrile syndrome, hemorrhagic fever syndrome, acute respiratory distress syndrome, febrile jaundice and sudden death presenting at the IMT Hospital in Manaus will be included in the program. Hospitalized cases from the last three years totaled 518, with a variation of 94 patients from one year to the other. The emergency ward cared for 3,492 patients in the last three years, with a variation of 800, and the outpatient division attended to 14,502 patients with a variation of 4,077. Patients came from throughout the State of Amazonas, but most were from the city of Manaus and nearby counties. They arrived either on their own or were referred to the IMT by other health centers of the area.

(b) *Rural area:* The area preliminarily chosen to start the surveillance includes the communities of Beruri, Anuri and Codajas. The following are reasons for their selection:

- Low malaria incidence
- Lumbering industry
- People constantly entering forested areas for agricultural activities
- Day time and night time fishing
- Abundance of *Culicoides*
- Typical area of the Brazilian Amazon region.

iii. *National Institute of Hygiene "Rafael Rangel", Caracas, Venezuela*

Surveillance activities in Venezuela will be carried out at two regional public health laboratories: the Center for the Investigation of Hemorrhagic Viruses and Other Transmissible Diseases (CIVHET), located in Guanare, Portuguesa State, and the Amazon Center for the Investigation and Control of Tropical Diseases (CAICET), located in Puerto Ayacucho, Amazonas State. The surveillance system in Venezuela will be developed in two stages, depending on currently available infrastructure and resources.

(a) *First Stage*: A surveillance system for undifferentiated febrile illnesses and febrile hemorrhagic diseases is already established in the area endemic for Venezuelan hemorrhagic fever and a regional laboratory

supporting this surveillance system (CIVHET) is located in the State of Portuguesa.

Using this laboratory as a base, the initial phase of the surveillance system will involve the following communities:

Urban: City of Guanare (est. population ± 200,000)

Rural: Guanarito (est. population 25,000)
Papelon
San Nicolas

Second Stage: The second phase will include the Amazon area because of the potential risk of emergence of new infectious diseases in the region. The program will be established through the reinforcement of the surveillance system for emerging diseases and of the diagnostic capabilities at the regional level (CAICET). The surveillance program in Amazonas State will include the capital city of Puerto Ayacucho (population ± 100,000) and the nearby rural community of El Raton. The residents of these communities are 80% indigenous and fit the criteria established for stable communities, for internally and externally migrating communities and for communities that suffer the impact of important environmental changes. The study populations will be patients seen at selected Health Clinics, who meet with the case definition criteria set forth for this study. Patient follow-up will be performed through follow-up consultations and home visits.

iv. *National Institute of Health, Bogota, Colombia*

The proposed study site in Colombia will be Villavicencio, a city of 300,000 inhabitants and capital of Meta Department. Villavicencio is considered the entry door to the eastern plains of Colombia, which occupy 40% of the national territory. This city has several characteristics which make it ideal for a prospective surveillance study on emerging infectious diseases:

(a) The eastern plains is an area dedicated to cattle raising and farming (including illegal farming); consequently, Villavicencio has a floating population estimated at 30 to 50% of the total stable population. This group is representative of the rest of the country because it comes from all geographic regions including the Central Region (Departments of Cundinamarca, Tolima, Huila), the Western Region (Antioquia and departments of the coffee growing area), Caribbean Coastal Region (Atlantico, Bolivar, Sucre, Cordoba, Guajira), Southern Region (Valle del Cauca, Cauca, Narino) and Amazon Region (Vaupes, Putumayo, Amazonas).

(b) Villavicencio is located near Bogota, just 90 minutes away on a good road; therefore, the organization of the project will be logistically facilitated.

(c) Since 1983, the principal researcher of the surveillance project in Colombia has carried out collaborative research with the Health Service of Meta for surveillance of transmissible viral diseases, including dengue and dengue hemorrhagic fever, yellow fever, AIDS, paralytic poliomyelitis and measles; so he is widely known by local health authorities. He is also a histopathologist at the main private hospital in town (Clinical del Meta, 110 beds) and at the Colombian Social Security Institute for the Meta Region and Eastern Plains (Llanos Orientales). The latter is the main provider of health services in the region.

The study population will be persons attending local health facilities and who meet criteria for the five proposed disease syndromes.

v. *National Center of Tropical Diseases (CENETROP), Santa Cruz, Bolivia*

Surveillance activities in Bolivia will focus in and around the city of Santa Cruz (population 70,000), which is the capital of Andres Ibanez Province (784,700 inhabitants) and is located in the southeastern region of the country. The CENETROP staff is already involved in epidemiologic investigations of measles, dengue, yellow fever, malaria, hospital infections, leishmaniasis, mycoses and other disease outbreaks (i.e. Bolivian hemorrhagic fever) in rural areas of eastern Bolivia. The study population will be mainly persons hospitalized and attending out-patient clinics at CENETROP.

vi. *National Institute of Health, Lima, Peru*

The study site in Peru will be Iquitos, a city of about 300,00 inhabitants, located on the banks of the Amazon River in Loreto Province in the northeastern region of the country. The total human population in the semiurban and rural areas around Iquitos numbers about 600,000 and includes a number of indigenous groups. Primary occupations in the region are agriculture, military, oil and mineral prospecting, small business, tourism and fishing. The Peruvian National Institute of Health has a regional reference laboratory in Iquitos, which is part of the National Laboratory Network. The U.S. Naval Medical Research Institute Detachment (NAMRID) also has a field laboratory located in Iquitos, which works with the National Institute of Health and the Regional Ministry of Health Office under collaborative technical agreements.

Study populations in the Iquitos area will be persons attended at Ministry of Health hospitals and outpatients clinics, Peruvian Army and Navy hospitals, and private hospitals and clinics. These patients come from urban Iquitos and from surrounding rural and jungle communities. More severe cases among military personnel deployed in frontier areas of Peru also are referred to Iquitos for medical care at one of the two military hospitals.

J. Numbers of Subjects

The participants estimated that each laboratory could realistically enroll about 400 subjects during the first year, increasing to 800 subjects in the subsequent four years. These estimates are based on the amount of money expected to be available for reagents and the percentage and numbers of patients on whom convalescent specimens can be secured.

Based on an average estimate of $50 for the reagents needed for testing a single patient and an estimated budget of $20,000 for each laboratory for acquisition of reagents, about 400 patients can be tested in year one at each study site. The participants estimated about 50% success in obtaining the convalescent specimens, meaning that each week, about 16 illnesses meeting the case criteria will need to be identified, bled and followed-up. This number can be doubled in years two through five, anticipating about $40,000 to be available for reagents per year.

Subjects will be chosen to meet the case definition. In each population group and study site, selection of subjects will also be done in a systematic way to ensure an even choice. An example is to choose patients on a specific day each week, or to choose every seventh eligible patient in series.

K. Follow-up

Non-fatal cases will be followed and bled between two and five weeks after the acute phase specimens are collected. A nurse or phlebotomist will be employed to go to the house or place of work to collect the second set of specimens.

L. Disease Questionnaires

A standardized questionnaire will be developed and approved for ethical content by the Human Subjects Committee of each participating institution. Several model questionnaires are available and one of these will be selected and circulated to each participating institution for modification, if necessary.

M. Banking of Specimens

Patient specimens, such as acute phase serum, blood clot, urine, throat swab, or fresh autopsy materials will be archived at -70^{o}C or colder. Convalescent phase sera will be stored at -20^{o}. A -70^{o}C freezer or a liquid nitrogen storage tank, as well as a -20^{o} freezer will be purchased for each laboratory and dedicated to the project. Specimens will be catalogued and records kept in a spread sheet or similar format.

N. Communications/Networking

Participants reported that e-mail was available to all and agreed that this would be used for most communications.

O. Training

It was recognized that training and technology transfer will be important components in the development of the Amazon Region Emerging Disease Network. Although all of the collaborating laboratories are well established and employ highly competent professionals and staff, recent discoveries such as threat of hantavirus pulmonary syndrome and technological advances, such as the widespread diagnostic application of polymerase chain reaction, necessitate the availability of periodic, specialized training opportunities. The Centers for Disease Control and Prevention (CDC) has volunteered to provide training for the appropriate staff of collaborating centers in newly developed techniques to diagnose hantavirus pulmonary syndrome. Likewise, the CDC has recently offered a sub-Regional workshop in Chile for the isolation and characterization of influenza viruses, and future workshops in the Region may be appropriate. The need for hands-on training for the use of specialized diagnostic reagents (primarily antigens) to be prepared and distributed among the collaborating laboratories was discussed and agreed upon. Likewise, a need was expressed for training opportunities in techniques of vector (mosquitoes and culicoides primarily) identification and control, and rodent identification and control. A workshop on emerging infectious diseases was recently held in Lima, Peru, with funding obtained from the Fogarty International Center of the U.S. National Institutes of Health. The possible use of this type of workshop to better educate health professionals regarding emerging infectious diseases was discussed. Finally, all participating laboratories were requested to itemize their anticipated training requirements so that targeted training opportunities will become a significant component of the network.

P. Transfer of Funds

Each member of the participating countries indicated that a mechanism was in place to receive external funds, if available to support the EID surveillance network. After discussing the subject further, the PAHO representatives stated that the funds also could be managed and distributed through their system. But PAHO also indicated that there were no objections on their behalf for the funds to be managed by other agencies.

Q. Evaluations

It was agreed that evaluation is an important component of this project. An evaluation model based on the successful example of the Southern Cone subregional project to eliminate *T. infestans* was chosen.

Participants agreed to meet annually to discuss progress in implementing common projects and protocols, to present results, and to identify strategies to address regional problems. It was noted that the evaluation will be a dynamic process. Early meetings will inevitably focus on implementation issues, while later ones will emphasize results.

Participants also agreed that site visits to the laboratories conducted approximately every two years by other participants and perhaps one or two outside consultants would be useful.

R. Integration of the Network into the National Surveillance Systems

It is anticipated that the proposed network of laboratories for surveillance of EID in the Amazon Basin will be fully integrated into their respective national surveillance systems; thus, they will complement the national surveillance activities, particularly regarding EID. The information generated by the network should be readily available to the local, state and federal health systems for the implementation of appropriate control actions. The network will also contribute to the identification and control of risk factors that can affect the health of populations of the Amazon Region. In addition the epidemiologic studies conducted by the network will improve the knowledge about health problems of national and international importance. The international cooperation between the six laboratories will require governmental coordination, which will involve mainly the Ministries of Health and Foreign Affairs, taking into account presently existing agreements among the five nations and, if necessary, establishing new ones.

In the case of Brazil, the National Center of Epidemiology (CENEPI), Ministry of Health will participate in this initiative through its National System of Public Health Laboratories (COLAB), particularly interacting with the IEC and the IMT-AM. The strengthening of these two institutes will in turn improve the Brazilian network of public health laboratories. A similar approach exists in some of the other countries and should be considered by all countries, involving their national respective laboratory agencies.

5. Conclusions

A. Participants agreed to form a network of laboratories to carry out surveillance and to share information on the incidence and prevalence of emerging infectious disease in the greater Amazon Region, to collaborate in conducing studies to define better the infectious etiology of human disease in the Region, to share laboratory techniques and reagents, and to participate actively in a Regional quality control and proficiency testing program.

B. Participants agreed to create an executive committee that will meet annually to discuss progress in implementing common projects and protocols, to share results and to define strategies to address Regional problems. The next meeting will be held in Lima, Peru, and subsequent annual meetings will rotate among all collaborating laboratories as appropriate. A goal will be to obtain funding for the network including support for the participation of at least two representatives from each collaborating laboratory at each meeting.

C. Participants agreed to joint presentation and publication of findings resulting from collaborations undertaken by laboratories of the network in appropriate scientific journals and meetings. All formal publications will share authorship. This agreement is not meant to exclude publication of their own results separately by workers in individual laboratories.

Figure 1. Location of proposed study sites for surveillance of emerging infectious diseases in the Amazon Region.

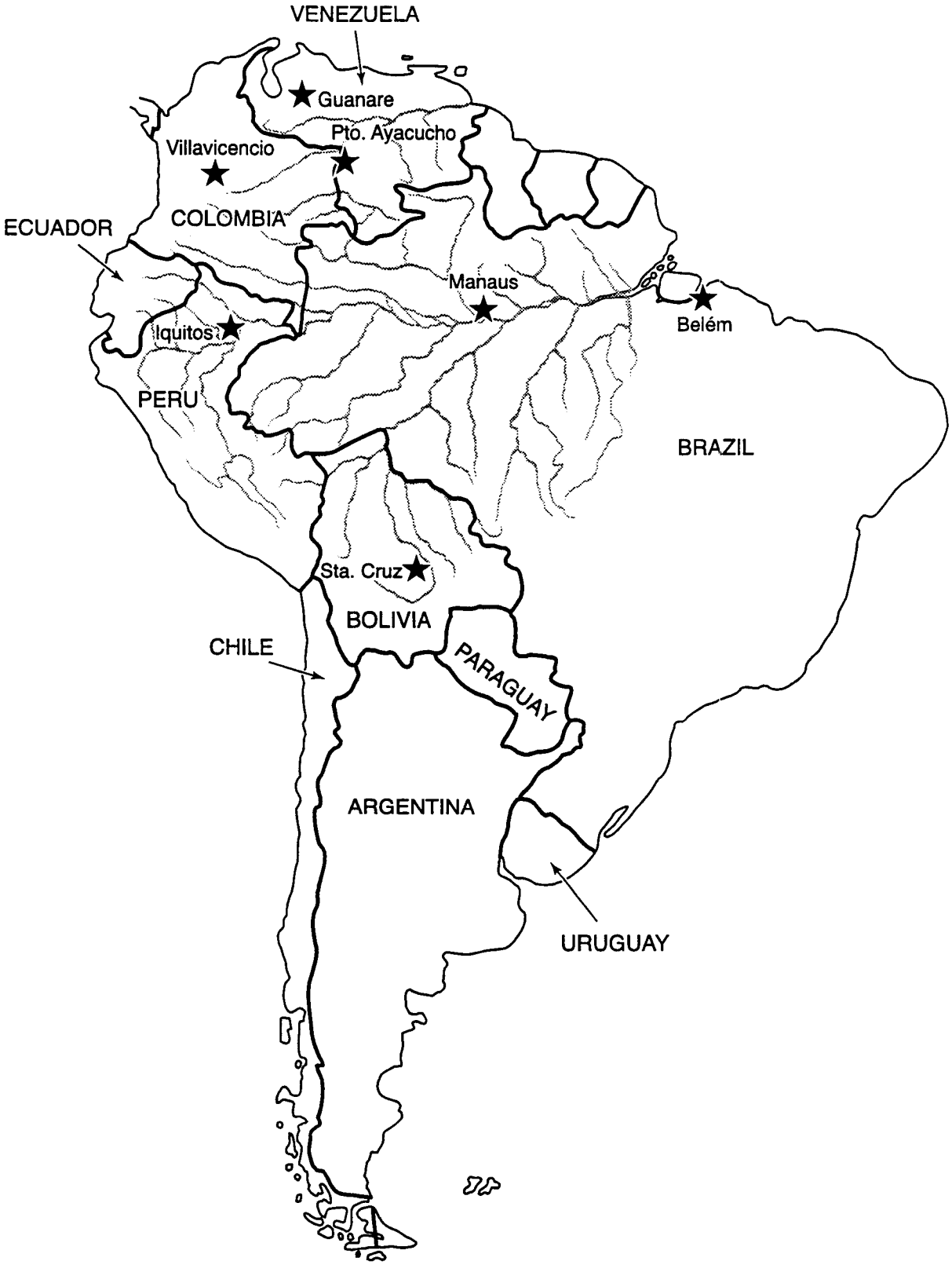

Table 1: Surveillance activities already underway by partner laboratories of the Amazon Region Emerging Diseases Network

	Diseases under Surveillance							
Laboratory	Malaria	Dengue-Rubella	Measles	Cholera	Polio	Influenza	Strep pneumoniae	HIV
Brazil								
IEC	+	+	+	+	+	+	+	+
IMT	+	- **	+	+	+	-	-	+
Bolivia	+	+	+	+	+	-	-	+
Colombia	+	+	+	+	+	+	+	+
Peru	+	+	+	+	+	+	+	+
Venezuela	+*	+	+	+	+	+	+	+

* Conducted in a laboratory separate from INH-RR

** Dengue has not been recognized in Manaus as of the meeting date; however, dengue surveillance is being developed.

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