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

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Executive Summary

The goal of this second meeting was to continue efforts to create a functional network of laboratories in the greater Amazon Region, including Bolivia, Brazil, Colombia, Peru and Venezuela, with the capability to obtain accurate, high quality surveillance results on emerging and re-emerging infections. The specific objectives were to 1) review and/or modify the plans prepared during the first meeting held in Manaus, Brazil, Feb., 1998, 2) describe the current status of emerging infections in the participating countries, 3) review and discuss ongoing surveillance activities, and 4) discuss possibilities for cooperation among participating countries and international reference laboratories.

The original plan of action was modified slightly to include minor changes such as a revision of definitions of disease syndromes and endorsed.

The syndromes selected for initial surveillance were the same recommended previously, with the possibility of subsequently including neurologic and enteric disease syndromes:

- 1) Undifferentiated febrile syndrome - fever, (axillary temperature $\geq 38^{\circ}\text{C}$), that has no obvious etiology and has no more than 7 days evolution in a previously healthy person 5 years of age and older.
- 2) Hemorrhagic fever syndrome - an acute febrile (axillary temperature $\geq 38^{\circ}\text{C}$) hemorrhagic illness with or without evidence of capillary fragility in a person of any age.
- 3) Febrile icteric syndrome - febrile patients ($\geq 38^{\circ}\text{C}$) more than one year of age with acute or insidious onset of icterus in whom there is no detectable cholelithiasis or biliary obstruction or malignancy.
- 4) Acute respiratory distress syndrome - febrile patients ($\geq 38^{\circ}\text{C}$) more than 5 years of age, 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.
- 5) Sudden unexplained death syndrome - previously healthy person, 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.

The list of possible disease pathogens for diagnostic testing for each disease syndrome was revised, including testing algorithms. The participants recommended that testing should emphasize the most common and/or important disease agents in each country, which included the following: **malaria, dengue, viral hepatitis, yellow fever, leptospirosis and influenza.**

Since surveillance programs were already established for anti-malarial and anti-tuberculosis drugs and for antibiotic resistance in the participating countries, these were not included under the Amazon network program

All participants agreed that for the surveillance network to be effective, it must be integrated with existing national and regional health surveillance program, and there must be close interaction among clinicians, and staff of the diagnostic laboratory and the epidemiology programs.

The associated institutions that intend to help support the Amazon network by providing reference services, multilateral agreements, and training and reagents are as follows:

Pan American Health Organization, World Health Organization, Ministry of Health of Brazil, Oswaldo Cruz Foundation, Brazilian Army Institute of Biology, Amazon Center for Investigation and Control of Tropical Diseases "Simon Bolivar", U.S. Naval Medical Research Institute Detachment, Lima, Peru, Centers for Disease Control and Prevention, and the University of Texas Medical Branch, Galveston.

Several potential funding sources were discussed for supporting the surveillance network, including: PAHO (limited), U.S. CDC, U.S. Department of Defense.

The participants recommended that the next meeting be held in Atlanta Georgia just before the International Conference on Emerging Infectious Diseases, July, 2000.

1. Welcoming Remarks

The political authority of the San Martin region of Peru, Ms. Astorgia Tuanama welcomed the participants and stated that she was especially honored for this important meeting to be held in Peru. Dr. Ariel Depetris, PAHO conveyed cordial greetings from Dr. Marie Andrée Diouf, PAHO country representative for Peru. He thanked the staff of INS, Peru and the local San Martin authorities for organizing the meeting and welcomed all of the participants.

Dr. Miguel Vela Lopez, Director of Regional Health, Department of San Martin welcomed the participants on behalf of the Ministry of Health. He indicated that with the rapid changes in our society, it is impossible to handle health problems in an isolated manner. Clearly, this meeting will help to unify both national and international efforts to effectively combat emerging infections through the establishment regional and subregional surveillance networks. He thanked the organizers and all the international agencies for their support of this meeting.

The persons at the Table of Honor are listed on Annex-1.

2. Objectives

The overall objective was to review ongoing efforts to establish a functional network of laboratories within the greater Amazon Region, with the capability to obtain accurate, high quality surveillance results on emerging and re-emerging infections.

The specific aims were to 1) review and/or modify the Manaus action plan, 2) describe the current status of emerging infections in the participating countries, 3) review and discuss ongoing surveillance activities, and 4) discuss possibilities for cooperation among participating countries and international reference laboratories.

In order to achieve these objectives/aims, the surveillance network will need to be integrated into the existing national surveillance programs, and not to be a separate program on its own. In addition, a close link needs to be established between laboratories and epidemiology, and between surveillance and prevention and control actions, bearing in mind three concepts, 1) We used to say that surveillance was information for action, now we say timely information for timely action. Or even better, timely quality information for timely quality action, 2) Practice a type of public health surveillance which integrates the surveillance of syndromes and diseases with the surveillance of agents and the surveillance of risk in order to get there before the epidemic curve or as early as possible, and 3) The bell of emerging diseases rings at local level and it is necessary to strengthen the base of the surveillance, at the level of the technical, operational teams and the community.

Other requirements needed to strengthen and sustain a functional surveillance network are 1) research and collaborative studies, 2) horizontal cooperation between countries in the Amazon Region, 3) actions to link with international reference laboratories, 4) matching actions with those of other projects in search of complementing or improving resources and results, 5) actions to link with other sectors for surveillance, prevention and control actions, especially in high risk and poverty areas, and 6) exchange of epidemiological information and studies for collective appropriation of the knowledge.

3. Background

A. Introduction and Summary of Previous Recommendations

The scenery of emerging infectious diseases has become a story of the fragile balance in the Americas. In spite of some progress, our current reality shows that some historic pre-visions and triumphalistic outlooks have exceeded themselves, views that talked about the ending of the transmissible disease chapter", of the "epidemiological transition", or of an exaggerated trust in the "magic bullets" that contributed to the control or eradication of some disease entities. This sends us to the complexity and dynamics of the biological, ecological, social and cultural phenomena of the genesis of the problematic of the emerging of infectious diseases and to the need to shared efforts to develop national, sub-regional and regional prevention and control programs.

In 1995, the PAHO's Regional Plan of Action was approved by the Directing Council of PAHO for combating new, emerging and re-emerging infectious diseases in the Americas. Two of the four goals addressed the need to 1) strengthen the regional surveillance networks for infectious diseases in the Amazon and 2) establish national and regional infrastructure for early warning of and rapid response to infectious disease threats through laboratory enhancement and multidisciplinary training programs.

Under the goal of strengthening regional surveillance, the objectives were to 1) enhance and integrate existing infectious disease surveillance networks in the Americas, 2) establish a regional steering committee for emerging infectious surveillance, and 3) develop uniform guidelines that link surveillance and reference diagnostic services.

The PAHO's Task Force on Surveillance of Emerging and Reemerging Diseases is comprised of experts from PAHO/WHO and member countries. At the second meeting of the Task Force during 1997 in Rio de Janeiro, a recommendation was made "to support an initiative on surveillance for emerging infectious disease in the Amazon Basin and to extend it to other subregions".

As specified in the goals of the Regional Plan and based on the recommendations of the Task Force, PAHO has supported 1) the preparation and publication of technical documents and guidelines, 2) training on diagnosis, prevention and control, 3) sub-regional meetings to prepare proposals for establishing surveillance systems, based on notification of specific and symptomatic diseases, 4) preparation of manuals to respond to outbreaks, 5) pilot tests for syndromic surveillance (in the context of the Meeting for International Health Regulations), and 6) configuration of Sub-Regional Networks of Public Health Laboratories (Southern Cone, Amazon Region). These activities will be registered under a triple outlook, promoted to confront disease threats, including 1) surveillance of emerging diseases and syndromes, 2) detection and intervention responses to outbreaks, and 3) surveillance and prevention of resistance among selected pathogens to anti-microbial agents.

The strengthening of the public health laboratory networks is a very important step toward the nourishment of all three outlooks detailed above. In this context, the plans prepared to establish an Amazon surveillance network at the Manaus meeting in February 1998 were utilized to produce the 1999-2000 plan of action. The specific aim of this plan is to establish a laboratory network for the surveillance of emerging infectious diseases in the greater Amazon region. The key word for the execution of this plan is cooperation, or the capacity to work together, to consolidate strategic alliances, and to become closer partners for achieving the health goals. This collaborative effort has many dimensions, whose common denominator is the concept of practice in the functional network. In summary, the theme is working together to defend against the possibility of an emerging epidemic through collaboration, solidarity, ethics and health for the communities of the Amazon region.

B. Description of Participating Institutions

The participating Amazon network countries are Brazil, Bolivia, Colombia, Peru and Venezuela. Ecuador is being considered as an additional 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), Belem, Para, 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, Brazil. It is a state institution created in 1970 as a tropical disease hospital. The mission of the IMT-AM is to provide health services, to conduct research in tropical diseases and to train personnel in tropical diseases. (For report, see Annex 3.)

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. (For report, see Annex 3.)

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. Also, the INS provides training in classical and molecular diagnostic techniques for viral, bacterial and parasitic diseases, and the capability to train on outbreak investigations. (For report, see Annex 3.)

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 infectious diseases. 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. (For report, see Annex 3.)

C. Current Status of Emerging Disease Surveillance

As described in the attached country reports (Annex- attached country reports), all of the participating countries are conducting surveillance for infectious diseases. Also, outbreaks investigations, and antibiotic and anti-malaria drug resistance were described in some of the reports. All surveillance activities are integrated with the national program. The approach varied, with some countries beginning to initiate the plans outlined in the Manaus document. Activities aimed at strengthening infrastructure, ranging from diagnostic training to equipping and constructing laboratory are in progress. Support is being received from the national health systems, international associated reference laboratories, and PAHO and the WHO are providing technical assistance and only limited funding.

The following is a summary of ongoing surveillance activities for each participating country:

National Center for Tropical Diseases (CENETROP), Bolivia

CENETROP is responsible for 1) medical services for patients and for laboratory activities, 2) regional reference testing laboratory for AIDS, 3) regional reference testing laboratory for arboviruses and hantaviruses, and for 4) research on selected endemic diseases.

Funding by Belgian sources and WHO/PAHO has helped re-equip the laboratory, train the staff, and develop diagnostic techniques for arboviruses. Collaboration is maintained with several reference laboratories like CDC, NAMRID, IPK and UTMB. Laboratory diagnostic training was provided by NAMRID and diagnostic support was provided by UTMB. With the support of NAMRID, USAMRU-B and PAHO, surveys were recently initiated to determine the cause of febrile illnesses and the cause of diarrhea among children. Surveillance is also in progress for malaria, leptospirosis, and antibiotic sensitivity of selected enteric pathogens.

In 1998, cases of dengue types 1 and 2 were diagnosed, but no DHF cases were reported. The first isolates of dengue virus were made at CENETROP. In 1998 and 1999, the laboratory documented outbreaks of yellow fever, measles, and cases of HIV. The outbreak of Yellow fever in 1999 was confirmed by the isolation of the virus for the first time in Bolivia; 21 of 34 cases were fatal in 1998, and 16 of 38 in 1999 to date.

National Institute of Health Laboratories (INLASA), Bolivia

A laboratory surveillance network for cholera has been established, and will be expanded to implement a nationwide program for bacterial diseases. This will include tests on antibiotic sensitivity for selected organism such as *Salmonella*, *Shigella*, *Campylobacter*, and

tuberculosis. Cell cultures have been established in anticipation of doing influenza surveillance.

National Network of Public Health Laboratories, Brazil

Brazil has a National System of Public Health Laboratories which consists of federal and state laboratories. The laboratories form a national network which comprises five levels, each one with specific functions: Local, Regional, State, Macro-Regional and National Reference Laboratories. There are also networks for specific diseases such as cholera, dengue, HIV, viral hepatitis and others. Brazil plans to construct two biosafety level 4 laboratories.

Institute of Tropical Medicine, Brazil

A surveillance program for emerging infections was established in the Amazonia with the support of the United States Army Medical Research Unit (USAMRU-B) in Rio de Janeiro.

Dengue: A virgin soil outbreak of dengue occurred in Manaus during 1998, with 28,000 confirmed and probable dengue cases caused by dengue 1 and 2 viruses. Cases occurred during the rainy season, and most cases ranged from 15-65 years of age. Dengue spread to 21 other municipalities.

Yellow Fever: Two cases of yellow fever were diagnosed in 1998 and none so far in 1999.

Hepatitis: Hepatitis A, B, and C were diagnosed as the cause of 1,071 cases.

Malaria: A large increase in numbers of malaria cases occurred during the past three years, with 463,000 cases of *vivax* in 1998. The pattern was exactly opposite that of dengue with largest number of cases occurring during the drier season. *Falciparum* malaria is the number one cause of hospitalization in Manaus.

Leptospirosis: Sixteen cases of leptospirosis were diagnosed in 1998 and two cases so far in 1999.

Collaboration has been maintained with the Instituto Evandro Chagas, USAMRU-B, and the University of Texas Medical Branch.

Instituto Evandro Chagas, Brazil

Dengue: The Instituto Evandro Chagas serves as the dengue reference center for Brazil. During 1998, 124 isolates of dengue types 1 and 2 viruses were obtained from patients, and 5377 dengue cases were diagnosed by serology using an IgM antibody ELISA.

Yellow Fever: During 1998, 34 cases of YF were reported, nearly all from the Amazon region. Fifteen were fatal.

Hantavirus: Nine cases consistent with hantavirus pulmonary syndrome occurred in the Amazon region. All cases were negative for hantavirus antibody.

Hepatitis: About 300 patients from rural areas in the Amazon region, who presented with hepatitis consistent with the clinical case definition described in the Manaus report were negative for hepatitis A through E. These samples are being tested for other pathogens, including arboviruses, CMV, and possibly, leptospira.

Parvovirus B19: Of 313 sera obtained from patients with a rash syndrome, 16.3% had IgM antibodies to Parvovirus B19.

Respiratory Viruses: Ongoing surveys showed that influenza, VRS, adenovirus, parainfluenza, and enterovirus were the cause of some of the respiratory diseases. Influenza occurred during all seasons.

Rubella: Between 1989 and 1998, 3,484 cases of rubella were diagnosed by IgM antibody detection.

Measles: The numbers of measles cases have fallen drastically since vaccination was intensified.

National Institute of Health, Colombia

The health sector reforms of 1993 led to a planned framework for disease surveillance in Colombia, including emerging infectious diseases. Laboratory diagnoses through the national laboratory network included mandatory testing for many diseases of interest.

Dengue and Dengue Hemorrhagic Fever: In 1995, there was a >5% rate of *Aedes aegypti* in the Amazonas or Orinoco areas. *Aedes albopictus* was reported for the first time in Leticia during March 1998. The national number of dengue cases was 144.1 per 100,000 inhabitants, with 23.4 cases per 100,000 in Amazonas, and 9.1 cases per 100,000 in Orinoco. There is inaccuracy in reporting common fevers because of the widely held concept that "all warm weather fevers are dengue". The national number of cases of dengue hemorrhagic fever was 12.35 per 100,000 inhabitants, with 20.5 cases per 100,000 in Amazonas, and in 17.3 per 100,000 in Orinoco. Cases occurred mainly in the Departments of El Meta, Villavicencio, Caqueta and Putumayo in the Amazon area.

Malaria: There are three main vectors of malaria: *Anopheles darlingi*, *oswaldoi* and *mediopunctatus* in the Amazon area. The *falciparum* cases were 198.63 per 100,000 inhabitants and the *vivax* cases were 189.5 per 100,000 inhabitants. In the Departments of Amazonas, Caqueta, Putumayo, and Guainerua, the rate was 30 times higher than in other areas. Malaria is the most important febrile disease in these departments.

Yellow Fever: Seventy per cent of the yellow fever cases occurred in Caqueta, Meta and Guaviare. The number of cases has been stationary since 1991, but the number has decreased since the government included yellow fever vaccine within the National Immunization Plan. Most yellow fever cases were limited to the Amazonas and Orinoco areas. Surveillance for yellow fever has been strengthened during the past two years by the use of serological diagnostic tests.

Respiratory Diseases: An outbreak of respiratory disease occurred during March 1997. Among 477 samples tested in 1998, 60 (12.5%) were positive for influenza. This disease is seasonal, from August to December.

A proposal was prepared to establish a sentinel surveillance program to determine the causes of febrile, hemorrhagic fever, icteric and respiratory disease syndromes. The approach is similar to that described in the Manaus document; however, testing for all of the agents will not be possible because of the lack of diagnostic tests.

National Institute of Health (INS), Peru

Emerging and re-emerging diseases are a major concern in Peru. INS has one national reference laboratory, and 14 regional laboratories, which have been mainly funded by the Japanese JAICA, and planning is in progress to establish five new laboratories with funds received from USAID. One of these will be located in Caballococha, near Leticia.

An internal network was established in the Department of Ayacucho with support from Swiss funds. In the San Martin region, the integration of the laboratory, epidemiology and control program will provide the capability to do surveillance for emerging infections. INS will provide the equipment and the local government will provide the infrastructure. Quality control will be provided by INS and collaborating institutions such as CDC, LCDC, Cuba, universities and others.

INS also provides public health services to the General Office of Epidemiology, Department of Health for the People, General Office of Environmental Health, General Office of Medications and to the Regional Health Offices, each of which has an epidemiologist.

Malaria: In 1998, there were 135,534 cases of *vivax* and 77,056 *falciparum* cases, indicating a large increase in the presence of *falciparum* when compared to previous years. The number of cases increased in the coastal area.

Dengue: All regional laboratories perform dengue serodiagnosis with MacElisa and Elisa, and all cases so far have been classic dengue. *Aedes aegypti* was re-introduced into Peru during 1990. Dengue 1 and 2 have been identified, with quality control studies done by international centers.

Yellow Fever: Cases of yellow fever have increased in the last few years. The largest outbreak ever recorded in Peru occurred during 1995 at higher elevation areas, where coca plantations had been replaced by other crops. INS plans to conduct surveillance for icteric and hemorrhagic syndrome. Yellow fever antigen is being prepared and is available for export purposes.

Viral Hepatitis: This disease is hyper-endemic in the high jungle as well as in rural, low jungle and Andean valleys.

Respiratory Diseases: During El Niño, several outbreaks occurred, including a major one in the northwestern coastal region with cases occurring among children under five years of age and the elderly. The cause of this outbreak could not be determined, even though clinical samples were tested for several respiratory pathogens.

Leptospirosis: One case occurred in the Loreto region and was originally diagnosed as dengue hemorrhagic fever, but was later diagnosed as leptospirosis.

Rabies: Since there is rabies in Peru among dogs, cats and wild bats, inclusion of a neurological syndrome in the surveillance network would be of interest to INS.

Antibiotic Resistance: Surveillance for antibacterial resistance showed that of 662 samples tested for bacteria, 69% were resistant to ampicillin.

Anti-Malarial Drug Resistance: Studies in progress in Tumbes showed that the resistance of malaria to cloroquine is higher than 20%, and this information is being used to change the Ministry's therapeutic approach. The resistance to fansidar is acceptable. In the jungle, there is resistance to fansidar and cloroquine.

National Institute of Hygiene, Venezuela

Dengue: Dengue and dengue hemorrhagic fever have been the most serious problem, with rates among the highest in the Americas. Cases are highest in states with the largest populations. Dengue viruses are transmitted throughout the year, but more cases occur during the rainy seasons. There is a continuous circulation of the virus in Caracas, Federal District. There is an increasing incidence, with the risk of the introduction of dengue 3 from the Caribbean, which may later become endemic in Venezuela.

Influenza: There is no unified influenza surveillance in place, the surveillance initiatives are started by interested physicians or clinics.

Yellow Fever: There has been no recent yellow fever with the exception of the imported cases. Every 10 years, there are epizootic waves caused by the migration of monkeys. There was a YF outbreak along the border with the Brazilian state of Roraima, mainly in adults, perhaps infected in Brazil. The University of Texas Medical Branch reported that it was the Amazon strain by phylogenetic analysis.

Venezuelan Equine Encephalitis: This disease was present in 1995, but there were no human cases. With the collaboration of Colombia, Venezuela, and the University of Texas to determine the emerging mechanisms, 4 subtypes/genotypes ID were identified. These subtypes were not pathogenic for equines or humans in Venezuela (but they were in Colombia). The Yumare strain was also circulating; this is not an epidemic pathogen to humans and equines either.

Venezuelan Hemorrhagic Fever: This disease is caused by Guanarito virus and has a case-fatality of 30%. The distribution covers the northwest part of Venezuela. The rodent population has been assessed and well-defined for distribution of Guanarito virus.

Rabies: This disease is a concern for Venezuela, with human cases being associated with the bite of rabid dogs, bats and domestic animals. Although most human cases are due to dog bites, bovine rabies is widely distributed, and there was only one human case associated with vampire bats.

Leptospirosis: This disease was recently integrated in the surveillance system for VEE. All regions have detected cases. No cases were reported from agricultural and cattle-raising communities.

Malaria: There are malaria free areas and areas where the disease is maintained, such as the borders with Brazil and Colombia. There are several vectors, including *Anopheles nunez tovari*, *darlingi*, and *braziliensis*. Seventy-seven per cent of the cases were vivax and 22% *falciparum*, plus 1% mixed infection or *malariae*. Resistance has been reported in 22 to 30% of the cases to cloroquine, less to mefloquine and in vitro to amodiaquine. Many leptospirosis infections are treated as malaria infections and only when they show resistance to drugs, are they tested, and the results are usually positive for leptospira. There is 70-80% serological cross-reactivity between *plasmodium* and leptospira.

Diarrheal Diseases: About one million cases cannot be diagnosed as to the specific etiology. *Vibrio cholerae* started again in 1997, with 2200 cases and 51 deaths. Cases were distributed among all age groups.

Intermediate capability laboratories perform serological testing and have the potential for PCR testing. Low capability laboratories perform microbiological and serological testing. All of the laboratories depend on the National Institute of Hygiene for reference services. Quality control is provided by CDC and the University of Texas Medical Branch.

Regional System for Epidemiological Surveillance

A regional surveillance system of emerging diseases can only exist if local and national systems are available, to share common information. PAHO sees the need for national systems, regional networks, rapid exchange of information and national and international capability to respond to alerts produced in each country. Numerous public health emerging

disease threats have been documented, both in the developing and industrialized countries. Therefore, it is important to understand the definition of emerging and re-emerging diseases as new, emerging or re-emerging infections whose incidence has increased in the last two decades or threatens to increase in the near future.

How much are we prepared to identify emerging and re-emerging disease problems? Our countries have experienced specific examples in the last few years, including outbreaks of cholera, cyclospora, dengue, hantavirus pulmonary syndrome, plague, yellow fever, VEE, dengue and leptospirosis. The PAHO strategy has been to focus on 1) regional surveillance information, 2) regional electronic platform to collect surveillance data, 3) outbreak detection and response and 4) surveillance of antimicrobial resistance.

There are other elements, besides the epidemiological and laboratory diagnostic component, including clinical and laboratory training, information mechanisms, information technology for epidemiological data analysis, management, staffing and information management.

A review was made of the WHO/PAHO efforts to establish an electronic system in the Americas that included surveillance guidelines with a list of the endemic diseases in the countries. More than 13 countries out of all 18 in Latin America have national surveillance systems and their information is published on Web sites.

As for disease notification, this has always been a problem to update. With an epidemiological update system, all countries can publish a notification table weekly. The preferred approach is that disease data be entered from the national system directly through the Internet into a server fed by each collaborating country. This way, no additional document is made but the original file is sent, by province, by district, as a part of the country's information. With a system like this, on the internet, it will be possible to obtain disease data per week, per selected area, at any given time. Thus, information will be released once all countries have fed it into the common Web page.

PAHO has also established a working group on emerging diseases. International Health Regulations guidelines are changing from yellow fever, plague and cholera (disease approach) to a syndromic approach to allow countries to have information on the disease and when to notify. This work involves many members, such as CDC, and others.

Additional Surveillance Activities

Southern Cone Network: Priority syndromes and disease pathogen for surveillance were identified for each country.

Activity assessment of surveillance systems: There is no systematic evaluation, all is done by inertia, but the validity of the system itself is not assessed. Some lists of diseases of mandatory reporting are short, such as Peru's and some others have up to 30 diseases. Does the current list cover enough ground? Does it cover and is it sensitive to outbreaks?

Multidisciplinary team response to outbreaks: There are very important precedents. Field Epidemiology Training Program in Peru, Applied Epidemiology Program in Peru to form teams, during 18 months during which service is provided to the community. Similar programs exist in Colombia, Mexico, Canada, and the U.S.A.

Social communication: Health sectors may find it difficult to communicate with the press without denying or hiding the truth and generating confusion. Therefore, early detection will provide a better understanding of risk factors for these problems, identification and how to decrease the adverse effects of the alarming press.

Outbreak Reporting: There is always concern about reporting outbreaks, especially their international repercussion. The Ministry of Health is one source but there are others, the press, the Web pages, Promed. Before, the only sources for this information were hospitals and clinics, but now NGOs, press, private sector or other groups with direct access to the information have been added. NGOs are increasingly important and must be included as reporters.

E. Antimicrobial Resistance

Although anti-microbial resistance surveillance has not yet been included in the Amazon network program, data on this topic could be gained with surveillance activities similar to those that are being proposed for the Amazon system. As an example, PAHO is supporting a project to standardize techniques and apply quality control in evaluation of antimicrobial sensitivity. A grant of \$415,000 was donated for strengthening the laboratory and epidemiologic capabilities in Argentina, Brazil, Chile, Costa Rica, Mexico, Peru, and Venezuela to execute this project.

Surveillance is used to understand the magnitude and nature of the problem of antimicrobial resistance in each of the participating countries. Emphasis is placed on integrating various institutions in the process of gathering the surveillance information. In the process, capabilities of the participating laboratories will be strengthened. The overall plan is to increase and improve antimicrobial surveillance activities and eventually, implement measures to prevent inappropriate usage of antibiotics in the participating countries.

In this process of improving the surveillance activities, the quality of the data from the hospitals and communities must first be understood. Strengths are identified. In addition, individuals from each laboratory that will perform the sensitivity testing are appointed. These individuals are trained, and tools for performing the testing and quality control are provided. A system such as PHLIS, the Public Health Information System, can then be used for reporting. These measures are designed to 1) improve surveillance activities, 2) improve the quality control measures in the handling of specimens and laboratory data, 3) begin application of a permanent system of evaluation in the participating labs, 4) provide the tools to analyze, interpret, and use the data gathered. Assistance from the responsible Ministry of Health and local epidemiologists should be utilized, and 5) disseminate information of antimicrobial

resistance via the PAHO Web page and via email, and share databases with all countries in the region.

Inappropriate antibiotic usage is also targeted with this program, because this contributes significantly to the emergence of antimicrobial resistance. The results will provide 1) a clear understanding and define the problem of inappropriate antibiotic usage and create a database, 2) a standardized approach to how antimicrobials are prescribed 3) information required to prepare instruction manuals for the rational use of antibiotics, and 4) information needed to obtain support of national authorities for applying the new rules for antibiotic prescription and use, and to work with national and private programs and institutions for implementation.

Several laboratories have successfully implemented this program, leading to updated information for the international community on microbial resistance and implementation of preventive measures for the health of the involved communities.

F. Unexplained Deaths and Critical Illness due to Possible Infectious Causes

As one of the syndromes selected for surveillance under the Amazon network, this topic was presented to share information and to serve as an example for designing and implementing surveys in participating countries.

In the United States, there are a number of unexplained deaths and critical illnesses every year, some of which may be due to as yet unrecognized infectious diseases. A number of new technologies now exist for identifying new infectious agents. This project was initiated in May, 1995, as one of the core activities in the CDC's first four Emerging Infections Program (EIP) surveillance sites, which are located in Oregon, Connecticut, California and Minnesota, in an attempt to better understand and characterize these occurrences.

The specific objectives of the project were: 1) to determine the burden of unexplained deaths and critical illnesses due to possibly infectious causes, 2) To develop a systematic approach and build capacity for early detection of new infectious agents or severe disease due to previously unidentified infectious agents for which currently available diagnostics are inadequate, and 3) to create a population based specimen bank that can be used for future testing for infectious pathogens using novel diagnostic techniques

A pilot study was undertaken first to evaluate the incidence of unexplained deaths utilizing death records. However, this was not the best tool. Ultimately a case was defined as a previously healthy individual, 1-49 years of age, who is hospitalized with a life-threatening illness due to a possibly infectious cause for which no etiology is found on preliminary testing. Cases were found through constant interactions with physicians, intensive care unit managers, other health care providers, such as infection control nurses, medical examiners, medical records reviews and review of death certificates in the study sites. Cases were classified by their presenting clinical syndrome, such as respiratory, neurologic, hepatic, cardiac, and multi-disease syndromes. Clinical and epidemiological information were collected using standardized case reporting forms. Clinical and pathological specimens were requested as

soon as a case was enrolled in the study. Specimens were tested as soon as possible and additional tests were ordered based on the situation. Specimens were archived for future testing.

During May 1995-July 1998, 264 cases were reported and 151 (34%) were enrolled. Reasons for exclusion (n=290) included: underlying illness (36%), residing out of surveillance area (21%), subsequently identified infectious etiology (16%), out of age range (10%), non-infectious cause for illness identified (10%), and non-critical illness (7%). The median age of enrolled cases was 22 years; 84 (56%) were female, 118 (78%) were white and 49 (35%) died of whom 35 (73%) had autopsies. For 1997, the overall incidence was 0.6 per 100,000 persons, and ranged from 0.2 to 2.32 per 100,000 persons by site. The most common clinical syndromes were: neurologic (meningitis, encephalitis) [47 (32%)], respiratory [43 (29%)], and cardiac (myocarditis, pericarditis) [21 (14%)]. The mortality by syndrome was highest for persons with cardiac syndromes, of whom 11 of 21 died (52%). Through March 1998, testing of 45 cases revealed definite etiologies for 9 (20%): *Mycoplasma pneumoniae* (3), *Chlamydia pneumoniae* (2), Lyme disease (1), TSS (1), Group C meningococcal disease (1), and Influenzae A virus (1).

These data show unexplained infectious deaths and critical illnesses to be an important public health problem in young previously healthy persons. Another component of this surveillance infrastructure is to investigate clusters of unexplained illnesses or deaths, including clusters outside of the surveillance areas. Medical examiners are encouraged to submit appropriate cases. Efforts should be intensified to develop and improve syndrome-based laboratory approaches to better diagnose known infectious diseases and to detect emerging infectious diseases earlier.

G. Review of the Manaus Meeting Recommendations

The following disease syndromes, with selected specific diseases, were identified during the Manaus meeting for consideration under the Amazon surveillance network:

- 1) Undifferentiated febrile syndrome
- 2) Hemorrhagic febrile syndrome
- 3) Icteric febrile syndrome
- 4) Acute respiratory insufficiency
- 5) Sudden death without definite cause

Several questions were presented for discussion:

- a) Cooperation: Is there enough sharing between the laboratories and epidemiologists?
- b) Communication: is information required to address problems regionally? Should we create a Web page or a dedicated Intranet site?

c) Staffing: Do we need to add dedicated personnel to our teams? What qualifications are required? We need to identify country leaders and a regional leader.

D) Funding: Some funding is available. How should we spend this money in order to accomplish network goals? We recognize the need for clear-cut objectives so that there will be quantifiable progress to report at the end of the period.

4. Plan of Action

A. Surveillance Team and Tasks

The emerging disease surveillance plan based on a syndromic diagnosis will be carried out at sentinel sites to be determined by each country. The location should include 1) populations known to be at risk based on previously identified health problems, and 2) existing health structures with the capability to support syndromic surveillance activities

The surveillance team should consist of clinicians, epidemiologists and diagnostic laboratory personnel with clearly defined tasks, to include the following:

- Prepare a work plan and validate it with all of the project coordinators
- Carry-out general and specific training for the detection of cases, recognize syndromes and to perform laboratory techniques
- Design and prepare the tools needed for the collection, analysis and disclosure of clinical, epidemiological and laboratory information
- Prepare standard rules and procedures for the operation of a multi-disciplinary team.
- Review the ethical aspects of each project and submit for review to an ethical committee
- Exchange information with other institutions or groups who are conducting similar surveys in each country.

B. Disease Syndromes

The participants selected five disease syndromes to be included in the initial phase of the proposed surveillance program. A definition of each syndrome is given below. Except for minor changes, these definitions are the same as those described in the Manaus document. *The approach was to begin with five syndromes, and then consider adding others later, such as neurologic and enteric disease syndromes.*

- i. *Undifferentiated febrile syndrome*: Fever, (axillary temperature $\geq 38^{\circ}\text{C}$) 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 (axillary temperature $\geq 38^{\circ}\text{C}$) hemorrhagic illness with or without evidence of capillary fragility in a person of any age.
- iii. *Febrile icteric syndrome*: Febrile patients ($\geq 38^{\circ}\text{C}$) > one year of age with acute or insidious onset of icterus in whom there is no detectable cholelithiasis or biliary obstruction or malignancy.
- iv. *Acute respiratory distress syndrome*: A febrile illness ($> 38^{\circ}\text{C}$) in a patient > 5 years of age, 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 newborns and persons with preexisting chronic medical conditions such as malignancy; HIV infection; chronic cardiac, pulmonary, renal or rheumatologic disease; diabetes mellitus; asthma; chronic alcoholism; immunosuppressive therapy; trauma; toxic ingestion or exposure; or nosocomial infection.

C. Infectious Agents

A list of possible disease agents for diagnostic testing consideration was prepared for each of the first four disease syndromes. Convalescent sera from patients will be screened for antibodies to 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. Each country will decide the algorithm to be used in testing depending upon knowledge of the frequency of the various infectious diseases in the region. If the serum is negative in the initial screen, it 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

Second (or third) screen: *

ehrlichioses
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 will vary from one region (survey 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

D. 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 patients, home visits are recommended. In cases where specific diseases are suspected (i.e. influenza, leptospirosis,

rickettsioses), additional samples (i.e. naso-pharyngeal 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°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°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*: For 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°C) for culture and fixed in 10% buffered formalin for histopathology.

E. 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 Testing Plan*: 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 -70°C 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.

- Arboviruses and arenaviruses - IgM ELISA (antigens to be prepared in one of the network laboratories or at University 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)

F. Quality Control

All collaborating laboratories within the network should maintain the highest quality of diagnostic tests to ensure that results will be accurate. Formal quality control may be difficult since some of the diagnostic tests to be used are not available commercially and the reagents must be individually prepared. To overcome possible variation in tests results, 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.

G. Equipment

Each surveillance site will be supported with a -70°C and a -20°C freezer and an ELISA reader and washer for 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.

H. Project Management

The network of laboratories for the surveillance of emerging diseases in the Amazon Region will be managed by an Executive Council made-up of a representative from each of the participating countries. An advisory group for the Executive Council will consist of individuals from the international reference Laboratories. Responsibilities are as follows:

- Coordinate the operation of the surveillance network
- Officialize the establishment of the network with higher authorities of each country
- Maintain an efficient and sensitive information system
- Monitor progress of the projects and design strategies for the efficient use of resources
- Facilitate the economic functioning and conduct technical advisory of the network
- Facilitate the exchange of laboratory reagents, strains of pathogens, clinical samples, etc. among the laboratories, following biosafety guidelines and health regulations in each country.
- Develop the tools needed to collect clinical-epidemiological-laboratory information under the concept of syndromic surveillance.
 - Surveillance information will be handled by the network members via an Intranet.

I. Financial Support

Funding must be utilized efficiently and surveillance goals must be achieved in a timely manner. Funding is limited and must lead to well defined accomplishments. This will require an action plan with well defined goals and an infrastructure capable of supporting the execution of the plan in a timely manner.

Attempts to obtain funding during 1998 from the NIH to support the Manaus protocol were unsuccessful.

The CDC has provided and will continue to provide support to PAHO to fund the Southern Cone and the Amazon network meetings. USAID (Global Bureau) has provided \$250,000 to CDC to implement the Amazon and South Cone surveillance networks. Also, there is limited funding for laboratory diagnostic and epidemiology training at CDC. Other possible sources of funding are the Rockefeller Foundation, Gates Foundation and the R.J. Williams Foundation.

PAHO is attempting to establish a TCC (Technical Cooperation among Countries) among the five countries presently part of the Amazon network. Each country will receive \$20,000 with the possibility of renewal on an annual basis depending on the progress of the projects (Ecuador, Guyana, and Surinam and French Guiana may be included in the future). A separate TCC) to support Southern Cone is also underway. Also, PAHO has limited funds for diagnostic reagents.

The U.S. Department of Defense (DoD) Emerging Infectious Disease Detection and Response System has funding to increase the capabilities of DoD overseas laboratories over the next 6 years. DoD plans are similar to those of the Amazon Basin and Southern Cone networks, with

interest in surveillance for influenza, antibiotic resistance among enteric pathogens, fever of undetermined etiology, and anti-malaria drug resistance.

The U.S. Naval Medical Research Center Detachment (NMRCDD) is one of the six DoD overseas labs, and is considering joining CDC and PAHO as a funding partner for the Amazon surveillance network. While a definite decision has not yet been made, information on the status of funding possibilities may be obtained by the country network representative from the NAMRID Director.

Another possible source of funding is from the DOD humanitarian assistance program, some of which is targeted for surveillance infrastructure building projects. In the Caribbean, funding was provided to purchase computers to establish a surveillance communication system. A similar project will be carried out in Peru using a new version of the PHLIS system. Humanitarian Funds can be applied for through the local Ministry of Health to the United States Ambassador.

There is also the possibility for industrial funding, large corporations such as MRL in Virginia, work with 100 hospitals in the U.S., downloading information every 24 hours and allow you to search into this database, if you are a subscriber.

The Peru Vigia project has \$24 million for a period of 7 years for emerging disease surveillance. The equipment component is \$1.7 million for some laboratories, including 5 new ones, computers and data management. USAID funds investment projects, not common expenses. A warranty for self-sustainment is required, and each institution must assume its own expenses.

J. Associated Institutions and Supporting Roles

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 Brazil 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 19 December 1894, and since then has engaged in research, diagnostic support, and the production of immunobiologicals.

Noteworthy among the studies done by IBEX was the 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 Guianas. The CAICET conducts research on diseases endemic in the State of Amazonas, such as malaria, onchocerciasis, 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 in Peru and other South American countries. The main laboratory is located in Lima, Peru, and a field laboratory and study site is located in Iquitos, Peru. Since 1994, surveillance has been conducted for emerging arboviral diseases in Iquitos. This program has led to the establishment of an infrastructure and technological capability that offers opportunities for 1) short and long term training on laboratory management and diagnostic techniques for bacterial, parasitic and viral pathogens, 2) training to conduct laboratory and field research, including surveillance and outbreak investigations, and 3) provide confirmatory diagnostic testing for selective infectious disease pathogens. More recent support activities included training of technical and professional staff from Peru, Bolivia and Chile on the diagnosis of emerging viral pathogens.

- 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 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 rickettsiae 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.

More recent UTMB supporting activities included the following: A contract has been awarded by the WHO to UTMB and Evandro Chagas Institute in Belem, Para, Brazil to produce reagents for all 4 dengue serotypes and yellow fever. These reagents can be provided upon request. The UTMB has collaborated with Venezuela in studies on the ecology of Guanarito virus and VEE, with VEE in Colombia under an NIH grant for basic research and epidemiology. Also, support was recently provided to Bolivia during the recent YF outbreak; UTMB has also been working with Peru INS and NAMRID on another NIH Grant to conduct research on emerging infectious diseases. Dr. Pedro Vasconcelos and Dr. Amelia Travassos da Rosa were supported to work at UTMB for 6 and 12 months, respectively. Training was provided for Dr. Cecilia Moreno from INS, Peru on rickettsial diseases, and UTMB sponsored an INS training course two years ago.

- 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.
- x. *United States Department of Defense (DoD)*: As a potential associated institution, a variety of training opportunities is available in the DoD laboratories, including those available at the NAMRID laboratory. On a broader scale, there are more resources. Like CDC, the United States Army Medical Research Institute of Infectious Diseases has supported many countries during outbreaks, sending on-site experts, providing reference laboratory services, and sharing reagents.

K. Study Sites and Populations

Participants from each of the six institutions comprising the surveillance network outlined their proposed survey sites and survey populations. 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 and Santarem.

Participants from the IEC indicated that the following population will have priority for the project: 1) Populations involved in large development projects (i.e. roads, dams, etc.), 2) Populations migrating into rural areas of the Amazon from large urban areas, 3) Populations subject to greater exposure and to environmental changes, 4) Indigenous populations in their natural environments, and 5) 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. 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

- (b) *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 the Department of Meta. 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, surveillance project in collaboration with the Health Service of Meta have been conducted for surveillance on viral diseases, including dengue and dengue hemorrhagic fever, yellow fever, AIDS, paralytic poliomyelitis and measles.

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 outpatient clinics at CENETROP.

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

The study site in Peru will be Iquitos, a city of about 300,000 inhabitants, located on the banks of the Amazon River in the Loreto Province in the northeastern region of the country. The total 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 (NMRCD) 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 who present at Ministry of Health hospitals and out-patient 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.

L. Number of Subjects

The participants agreed 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.

M. 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.

N. 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.

O. Banking of Specimens

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

P. Communications/Networking

Participants agreed that email will be used for most communications.

Q. Training

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 the threat of hantavirus pulmonary syndrome and technological advances, such as the widespread diagnostic application of the polymerase chain reaction, need 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.

R. 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.

S. 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.

T. Integration of the Network to 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.

U. Research

Research activities are beyond the scope of the project. Nonetheless, participants are encouraged to conduct or to enter into collaborative research activities that may contribute to the understanding of events associated with the emergence/re-emergence of infectious diseases. Similarly, studies on new approaches toward their control are desirable.

V. Drug Resistance

There are existing programs in the Amazon Region to monitor resistance to anti-tuberculosis drugs, anti-malarial and antibiotic resistance among entero-pathogenic bacteria. The group considers that these surveillance/monitoring studies are very important and should be strengthened, but they are not included in this proposal.

5. Recommendations

A. Uniform protocols

The participants recommended that common protocols including laboratory tests and reagents should be used in carrying out the surveillance program. It was proposed that there should be a workshop in one of the participating laboratories to develop and teach the common protocols and laboratory tests.

B. Disease syndromes and disease agents

The group recommended that the disease syndromes and disease agents to be included in the surveillance network were those described in the Manaus protocol, and included the modifications made in the case definitions described in this report.

C. Algorithm for testing clinical samples

Each country will decide the appropriate algorithm to be used in testing, depending upon the knowledge of the frequency of the various infectious diseases in their region and the more important disease agents common to each country.

D. Priority diagnostic testing approach for disease agents

The group considered that the most frequent and/or important diseases, which are common to the participating countries and are included in the five syndromes to be studied are:

- Malaria
- Dengue
- Viral hepatitis
- Yellow fever
- Leptospirosis
- Influenza.

E. Future Meeting: The next meeting will be held in Atlanta Georgia just before the International Conference on Emerging Infectious Diseases, July, 2000

Annex 1:
Members of the Table of Honor

Members of the Table of Honor

- General Jose Williamz Zapata, Military Head for the Huallaga Area, San Martin, Peru
- Ms. Astorgia Tuanama L., Acting Political Head for the Province of San Martin, Peru
- Dr. Miguel Vela Lopez, Regional Health Director of San Martin, Peru
- Dr. Juana Antigoni, Representative of the Director of the National Institute of Health, Lima, Peru
- Dr. Ariel Depetris, Representative of PAHO, Lima, Peru
- Dr. Jaime Chang, Representative of USAID, Lima, Peru
- Dr. Victor Zamora, National Director of the Vigia Project, Lima, Peru

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Annex 3: Country Reports

Brazil

Dr. Ana Rosa Dos Santos

National System of Public Health Laboratories. The political decision of organizing a national network of public health laboratories was taken after the 3rd Special Meeting of Health Ministers for the Americas in 1972 in Chile. The status of the existing laboratory services in the region was analyzed at that meeting, for Brazil, only 27 laboratory units were available, 17 of which were in Sao Paulo.

Considering the importance of developing a program for the organization of the National Network of Laboratories, a work group was formed (by Resolución Ministerial N1 118, 30 Mar 76) reporting directly to the Minister of Health, to be responsible for the elaboration and implantation of the above mentioned program.

Originally, the program determined that the National Network would be made up by laboratories belong to the Union and to the States, with a total of 509 units, 420 local ones, 65 regional ones and 24 central ones, to be installed or re-sized. According to the strategy adopted for the development, the Ministry of Health would be responsible for the necessary financial support for physical infrastructure, adapting or building of units, acquisition of equipment and basic supplies, and training of human resources, through the Adolfo Lutz Institute in Sao Paulo. The States had to hire their personnel and administer the corresponding execution of the program. During the network implantation period (1976-1979), the Adolfo Lutz Institute trained technicians from all federal units in the areas of Medical Biology, Bromatology and Chemistry.

Activities carried out by the Work Group were transferred in 1977 to the Secretaría Nacional de Acciones Básicas de Salud (SNABS) and more specifically, to the National Division of Public Health Laboratories, according to Resolución Ministerial N1 425, dated 26 Dec 77, which approved the internal estatuto for that Secretariat.

The organization and functioning of the National System of Public Health Laboratories were guided by Resolución Ministerial N1 280, July 77. Besides this entity, the above mentioned Resolución assigned the extinct SNABS responsibility over the coordination and approved the basic guidelines for its characterization, organization and operation of the System.

In 1981 and as per Resolución Ministerial N1 280/77, through Resolución N1 217, dated 17 Sept., the functions of National Public Health Laboratories were defined. The following were acknowledged as such: Instituto Evandro Chagas (Para); Laboratorio Central de la Fundación de Salud Amaury Medeiros (Pernambuco); Fundación Oswaldo Cruz (Rio de Janeiro), and the Instituto de Investigaciones Biológicas (Rio Grande do Sul). The

corresponding jurisdiction of these National Laboratories were specified in the above mentioned Resolution.

With the extinction of SNABS, as the result of the 1990 administrative reform, activities carried out by SNABS were transferred to the Fundación Nacional de Salud (FNS), among which those related to the Sistema de Laboratorios de Salud Pública (SNLSP) (Resolución Ministerial 1331, dated 5 November 1990).

Therefore, and in spite of other political, technical or administrative events in the Health Sector, the SNLSP has for the last 20 years- carried out actions to comply with the objectives, with efficient, efficacious and effective response to the demand. Some of its integrating units are internationally well known, participating in projects of interest in Brazil. The Law N1 8080, dated 19 Sep 90 ratifies in Art. 16, the responsibility of defining and coordinating the Public Health Laboratory Network on the Dirección Nacional del Sistema Unificado de Salud (SUS).

This Law N1 8080 determines the conditions for the promotion, protection and recovery of health, organization and functioning of the corresponding services and others. It also regulates, throughout Brazil, health actions and services, carried out isolatedly and jointly, permanently or temporarily, by individuals or entities, public or private.

With the advent of this Law came the need to review the organization and operation guidelines of the network integrating the System, in order to comply with the principles and regulations of the SUS. Thus, technical criteria were set forth for providing credential to the laboratories, particularly regional and national. The legal definition of the Fundación Nacional de Salud was needed, as the coordinator of SNLSP, within the Ministry of Health, in spite of having inherited the activities of former SNABS (Resolución Ministerial N1 1331, dated 5 Nov 1990). All prior existing laboratory units were also integrated into the System. Thus, Resolución Ministerial N1 699, 24 June 93 ratifies the responsibility of the Fundación Nacional de Salud, in coordination with the mentioned system and determines a review of all existing legal instruments for its organization and functioning, in order to comply with SUS guidelines.

Sistema Nacional B Red Nacional de Laboratorios de Salud Pública (RLSP)(National System B National Network of Public Health Laboratories)

Five operational levels are established for the public health laboratories in the assistance model:

Local Level: laboratory integrated to the local service network, to respond to the most common needs of the populations, looking for solutions at this level of competence.

Regional Level: laboratory responsible for conducting more complex actions, requested at local level. It's organized based on needs identified within its field of action and must

support local level, including personnel training, transference of techniques and regulations.

State Level: laboratory participates in the definition of health policies at SUS level, and coordinates laboratory activities within the corresponding State. Its main functions are the development, capturing, incorporation and transference of technologies to the State network, standardization of new techniques and quality control, with efficiency, efficacy and effectiveness of the System as goals.

Macro-Regional Level: level for regional administration, within SNLSP, coordinates its own area of action and may conduct activities related to specific requests in emergency situations. Its basic functions are the development, incorporation and transference of technology, as well as the standardization of techniques, regulations and quality control in search of efficiency and effectiveness.

National Level: represented by laboratories considered of technical excellence for problems or specific damage, previously credentialed according to established criteria. Its functions are to support the System in the technical and scientific aspect, when requested, as well as technological transference and quality control at the national level.

Colombia

Based on the recommendations proposed during the first meeting in Manaus, Brazil in February 1998, we are presenting the progress attained in Colombia.

The Health Sector Reform in Colombia started in 1993 for the development and implementation of a Social Security System for the Health Services has implied a permanent adjustment of technical and operational proposals to guide the development of Public Health actions and services in each one of the public and private institutions and organizations which, in an integrated manner, make its execution possible.

Public health surveillance is part of a group of collective actions that the reform guidelines included in a plan of benefits called the Plan of Basic Medical Care, which additionally offers shares for health promotion, disease prevention and control of risk factors, which are under the responsibility of the Colombian government, and for which, a special funding source was allocated.

This plan is in the hands of the municipal governments where these actions are oriented and delivered to the population, in accordance to their health status and under the orientation of national policies and departmental coordination.

In this framework, the Surveillance System for Public Health is being adapted and built and the national network of public health laboratories and the ruling entity the Instituto Nacional de Salud, is being re-oriented.

The behavior of emerging and re-emerging diseases in Colombia is surveyed through this system and network, with a total of 2500 reporting units. Each reporting unit notifies its corresponding department (33) and these, in turn to the Ministry of Health who is the head of the surveillance system.

In the case of laboratory diagnosis of diseases of public health importance, this is done through the national laboratory network. In each department, the clinical laboratories at hospitals and clinics perform the diagnosis, send samples and/or information of results to each Departmental Public Health Laboratory, who, depending on its capability, will confirm, make the diagnosis, and/or send samples or results for confirmation and quality control to the National Reference Laboratory at INS. In many cases, this National Reference Laboratory is still the one who provides diagnosis for these diseases, due to the scarce developments achieved in some parts of the country. However, for the last twenty years, work has been carried out through the network in laboratory diagnosis and it currently provides diagnosis for the main public health problems in all the departments of the country.

To date, two regulations have been issued defining the public health laboratories and the mandatory testing to be carried out by these laboratories, to allow for the guidance and development of the public health laboratories in the new context of the reform. There are an important number of laboratory tests there for the diagnosis of emerging and re-emerging diseases.

The road ahead is to strengthen this network over and over, through the strengthening of the public health laboratories in the departments to carry out quality diagnosis, closer and closer to the population, on a more timely basis, and that contribute to the public health surveillance.

Emerging Diseases in the Colombian Amazon and Orinoquia Regions, 1998

The following is presented based on the agreements set forth by the Manaus meeting in February 1998:

1. Undifferentiated & Hemorrhagic Febrile Syndrome

In 1995, there was a >5% rate of *Aedes aegypti* in the Amazonas or Orinoco areas. The introduction of *Aedes albopictus* was reported for the first time in Leticia in March 1998. She presented a slide showing the map of *Aedes aegypti* distribution in Colombia, on the Atlantic Coast, west central part, where the capital cities are located at 1200 meters above sea level.

- National number of clinical dengue cases was 144,1 x 100,000 inhabitants.
- In Amazonas, the number of dengue cases was 23,4 x 100,000 inhabitants.
- In Orinoco, the number of dengue cases was 9,1 x 100,000 inhabitants.

They have experienced great difficulty in notifying common fevers because of the common concept that “all warm weather fevers are dengue”.

As for **Hemorrhagic Dengue**,

- National number of cases was 12,35 x 100,000 inhabitants
- In Amazonas, the number of cases was 20,5 x 100,000 inhabitants
- In Orinoco, the number of cases was 17,3 x 100,000 inhabitants.
- Cases occurred mainly in the department of El Meta, Villavicencio and then Caqueta and Putumayo in the Amazon area.

Mayaro and Oropouche have been circulating in Colombia. A total of 189 samples that were IgM negative were sent to NMRCB for dengue testing, 12% were positive. 58% of these were positive to Mayaro and 42% to Oropouche. As for Mayaro, 7 out of 100 cases were positive for IgG. These samples were obtained from patients in the Amazonas, Guanare and Casanare areas, and the rate was higher for males (87%). For Oropouche, 3 out of 100 samples were IgM positive and they came from the central eastern area (where a great deal of migration from farmers from one area to another takes place). The rate was 66.7% males, in the 31,5 year-old group, and two thirds of all the cases presented with clinical bleeding. These cases mainly took place in Guaviare. As for Oropouche IgG, 3 out of 100 were positive and it occurred mainly in males.

Malaria: there are three main vectors: *Anopheles darlingi*, *oswaldoi* and *mediopunctatus* in the Amazon area. The falciparum cases were 198,63 per 100,000 inhabitants and the *vivax* cases were 189,5 per 100,000 inhabitants. In the departments of Amazonas, Caqueta, Putumayo, and Guainerua, the rate is 30 times higher than in other areas. This is the most important febrile disease for them.

Yellow Fever: 70% of the cases come from Caqueta, Meta and Guaviare. It has been stationary since 1991, even showing a downward trend. The government had included the YF vaccine within the National Immunization Plan. Yellow Fever is in a downward pattern, with most cases limited to the Amazonas and Orinoco areas. Surveillance for YF has been strengthened. Starting 2 years ago, other type of testing was put into practice, until then all testing was done through viscerotomy.

The Colombian Proposal for a Sentinel Surveillance Febrile Syndrome include the following: Early detection of DEN, YF, *Plasmodium*.

The methodology was as follows:

- Inclusion criteria: fever of less than 15 days duration, residing in the area for over 30 days.
- They obtained one sample a day from the first 5 febrile patients presenting at the study site.

At local laboratory level, a thick smear test was performed, if negative, it would then be tested for dengue, and if still negative, for Yellow Fever. If still negative, then it would be forwarded to an Intermediate Level Lab for further testing.

The second screening would take place at INS, testing for YF, ORO, Leptospira, Rubella, VEE, Mayaro, Measles. The Oropouche and Mayaro capability is still under implementation.

The third screening, which the INS Colombia has no capability to do included a list of diseases, some of which are Erythema, Rickettsial, Parvovirus.

For Hemorrhagic fever, the local screening for malaria would still be applied, if negative, it would be tested at an Intermediate laboratory for hepatitis, dengue, and. If still negative, it would be tested at a Third level lab, no capability yet, for Hantavirus.

Colombia is currently evaluating the efficacy of a Hepatitis B vaccine in children in the Amazon area. The immunization took place five years ago, and now, they aim at determining the coverage and the seroprevalence of infection.

A total of 2500 samples have been tested, with a coverage of 85% after three doses. The prevalence of AHBsAg is three times higher.

2. *Icteric Syndrome*

- Cases of Hepatitis B, C
- Local laboratory: icteric diagnosis and at INS all screening tests.

3. *Respiratory Virus and Influenza Surveillance*

There was an outbreak in March 1997. One notifying unit out of 10 is in Leticia. Direct determination of A and B for influenza 1, 2 and 3 was performed. INS received 477 samples in 1998, 60 (12.5%) were positive for influenza. This disease is seasonal, from August to December. It is in the Amazon area. The following tests are performed at local laboratory level: influenza, para influenza, sincicial respiratory and adenovirus. The second screening involves hantavirus, legionella, Q fever, psittacosis.

Peru

I'd like to apologize for Dr. E. Falconi, he's been unavoidably detained in Lima, he might be able to join us tomorrow.

In spite of the goals set forth in Manaus, which was the development of an Amazon area laboratory network, I believe that if each country's development is not up to this challenge, then we must consider the development of an internal network.

INS agrees with the proposal but there are changes they would like to make.

Even before Manaus, Peru has been working in setting up a laboratory network with the goal of decentralizing diagnosis and making it available to each site where infection actually occurs.

The presence of emerging and re-emerging diseases is a concern. INS currently has 1 national reference laboratory, 14 regional laboratories which have been mainly funded by the Japanese GIKA, and 5 new laboratories are in route to implementation with funding from USAID, one of these will be a lab in Cabalcocha, near Leticia.

Ayacucho, as an example, established an internal network within their region, with the support from Swiss funds. San Martin, by means of the integration of the laboratory and the epidemiology component, epidemiology and control, have achieved a good number of goals. INS will provide the equipment and the local government will provide the infrastructure. As for quality control, INS has standing agreements with CDC, LCDC, Cuba, Universities and other countries. INS also provides public health services to: The General Office of Epidemiology, the Department of Health for the People, the General Office of Environmental Health, General Office of Medications and with the Regional Health Offices, each one of them with a trained epidemiologist.

Malaria. In 1998, *vivax* cases were 135,534 and *falciparum* cases were 77,056, indicating a large increase in the presence of *falciparum* when compared to previous years. The number of cases increased in the coastal area.

Dengue. All regional laboratories are performing dengue serodiagnosis with MacElisa and Elisa, all cases so far have been classic dengue. *Aedes aegypti* re-entered Peru in 1990. Dengue 1 and 2 have been reported with quality control studies done by international centers.

Yellow Fever. The presence of yellow fever has increased in the last few years, in 1995 the most critical outbreak reported occurred in higher elevation areas, where coca plantations had been replaced by other crops. INS is proposing a surveillance of icteric and hemorrhagic syndrome now. Sylvatic yellow fever has been detected. INS is making yellow fever antigen, which is available for export purposes. The question INS still asks is why hasn't yellow fever become urban.

Hepatitis: occurs in hyper endemic manner in high jungle as well as in rural, low jungle and Andean valleys. Laboratories cannot be ignored in the surveillance for this disease.

Respiratory Diseases: during El Niño, several occurred. Talara is a typical case, with infections attacking children under 5 and the elderly. A total of 23 samples were tested and no laboratory diagnosis was ever made, so INS concluded it was heat shock. Several other viruses were detected among these samples, but they concluded these were secondary infections.

Leptospirosis: one case occurred in Loreto and was originally diagnosed as hemorrhagic dengue but turned out to be Leptospirosis.

Rabies is the suggestion INS would like to include in the Manaus proposal, since there is rabies in Peru in dogs, cats and wild bats. So, the inclusion of a neurological syndrome would be of interest.

Surveillance of resistance to antiparasitic and antibacterial agents, by a laboratory network reported the following: a total of 662 samples for bacteria, 69% were resistant to ampicillin.

A typical example of country to country cooperation was given. The cost of each Western blot is US\$7.00 and with the collaboration of INS Chile and Argentina, Peru now produces immunofluorescence slides and can now be used by the regional laboratories. INS has also standardized the technique for differential diagnosis of whooping cough through an immunofluorescent technique. Also, a protocol to test the resistance of *Plasmodium falciparum* to antimalarial drugs has just been published and the study is in progress in several areas. A copy will be distributed among the participants. Resistance studies in progress in Tumbes have shown that the resistance to cloroquine is higher than 20%, and this information is changing the Ministry's therapeutic approach. The resistance to fansidar is ok. In the jungle, there is resistance to fansidar and cloroquine. The region of San Martin will start testing resistance locally. The investigators of the region will be the principal investigators. The disclosure of information obtained from these studies is needed among countries participating in this network.

The Vigia Project and its four components have strengthened the international cooperation: Surveillance, Research, Laboratory and Prevention.

Here are some suggestions to the Manaus proposal:

- Unified surveillance protocols
- Quality assurance for laboratory diagnosis
- Production of standard biological products, available for all the participating countries in the network
- Unified information system (PHLIS)
- Strategic plan for financing
- Coordinating country to monitor actions
- Information network among Amazon countries

Venezuela

Dengue has been the most serious problem, with the highest rates of DEN and Hemorrhagic Dengue in the region. There might be some over-reporting, but the laboratory findings indicate a high endemicity. The infections take place in the states where the largest population concentrates, there are a large number of cases during the rainy season, but the infection goes regularly throughout the year. There is a continuous circulation of the virus in Caracas, Federal District. There is an increasing trend with the alarm of the presence of Dengue 3 in the Caribbean, which may later become endemic in Venezuela.

There is no unified influenza surveillance in place, the surveillance initiatives are started by interested physicians or clinics.

Yellow Fever: no cases with the exception of the imported cases. Every 10 years, there are epizootic waves caused by the migration of monkeys. There was a YF outbreak along the border with the Brazilian State of Roraima, mainly on adults, perhaps infected in Brazil. The University of Texas reported that it was the Amazon strain by phylogenetic analysis.

VEE: EEE was present in 1995, but no human cases. With the collaboration of Colombia, Venezuela, Texas to determine the emerging mechanisms, 4 subtypes/genotypes of ID were reported, these subtypes were not pathogenic for equines or humans in Venezuela (but they were in Colombia). The Yumare strain was also circulating, this is not a pathogen to humans and equines either.

Venezuelan Hemorrhagic Fever: it is responsible for 30% of the deaths. The distribution of Guanarito virus covers the northwest part of Venezuela. The rodent population has been assessed and well-defined for virus distribution.

Rabies: a concern for Venezuela, controlled except for two foci. 94 cases of canine rabies were reported, there has been no human rabies since 1996. The rate of dogs is 1/5 humans. The elimination of dogs is difficult. Bovine rabies has been widely distributed, there has only been one human case, originated in vampire bats.

As for the Original Manaus Proposal: The sentinel site (since most emerging and re-emerging infections are zoonosis):

Leptospirosis: recently integrated in the surveillance system for VEE, all regions have detected positive cases, agricultural and cattle-raising communities are the areas where no cases were reported, which is a source of concern. This disease has been included in the public health mandatory reporting system.

Malaria: there are malaria-free areas and areas where the disease is maintained, such as the borders with Brazil and Colombia. There are several vectors: *nunez tovari*, *darlingi*, and *braziliensis*. 77% of the cases are *vivax* and 22% *falciparum*, plus 1% of mixed infection or malariae. Resistance has been reported in 22 to 30% to cloroquine, less to mefloquine and in vitro to aniduaquine. Many leptospirosis infections are treated as malaria infections and only when they show resistance to drugs, they are tested and results are positive to Leptospirosis. There is a 70-80% seroprevalence (thermal resistant antigen) or cross reactive cases between malaria and leptospirosis. Also reported is tuberculosis resistant to traditional drugs.

Diarrhea: is a problem with one million unresearched cases. *Vibrio cholerae* started again in 1997, with 2200 cases and 51 deaths, cases are distributed in all age groups. There has been a large increase in the number of strains received at INS for identification and resistance testing.

Intermediate Capability Laboratories: serological testing and the potential for PCR type of studies. Low Capability Laboratories: microbiological and serological testing. All the

laboratories depend on the Instituto Nacional de Higiene, so that they can establish a more reliable network. Quality control: CDC, CDC Puerto Rico, University of Texas.

Manaus network: training on laboratory and clinical diagnosis, highlighting surveillance onsite, and immunologic studies (case-control) to determine special characteristics of the study populations, generate populations, complement it with entomological and environmental studies.