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MEETING TO ESTABLISH A NETWORK OF LABORATORIES FOR THE SURVEILLANCE OF EMERGING INFECTIOUS DISEASES (EID) IN THE SOUTHERN CONE REGION

Buenos Aires, Argentina
17-19 April 1998

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EXECUTIVE SUMMARY

The goal of the meeting was to create a functional network of laboratories within the greater Southern Cone Region: Argentina, Bolivia, Brazil, Chile, Paraguay and Uruguay, able to obtain accurate, high quality laboratory results on new, emerging and re-emerging infections found in the Region. The specific objectives include to: 1) Enhance capacity for early detection and monitoring of EID in the Southern Cone Region; 2) Begin implementation of common survey protocols to identify specific pathogens of significance; 3) Strength laboratory capacity for surveillance of EID; 4) Begin implementation of common protocols to address specific diseases, using identical or comparable laboratory procedures with good quality control to ensure accuracy of results obtained; 5) Create a forum for rapid technology transfer; 6) Encourage research to develop new methodologies for the identification of pathogens important to the region; 7) Facilitate prompt information sharing; 8) Establish strategies to alert clinicians and epidemiologists for outbreak investigation and identification as well as strengthening linkages between epidemiological and laboratory studies.

A Plan of Action was prepared for surveillance of: 1) Disease syndromes; 2) Specific pathologies and 3) Antimicrobial resistance.

The following syndrome and diseases were selected for **initial surveillance:**

- Influenza
- Antimicrobial resistance, especially for tuberculosis
- Acute diarrhea, especially bloody diarrhea leading to hemolytic uremic syndrome
- Hantavirus pulmonary syndrome and hantaviral disease

Seven disease syndromes were selected for inclusion in the proposed surveillance program. A definition of each syndrome is given below:

1. Undifferentiated febrile syndrome: Fever >38.3 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.

2. Hemorrhagic fever syndrome: An acute febrile hemorrhagic illness.

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

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

5. Unexpected death syndrome: Previously healthy persons, 1-49 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.

6. Infectious neurologic syndrome: Febrile neurologic symptoms with clear CSF in a non-immunodepressed patient.

7. Enteric syndrome: Bloody or non bloody, acute diarrhea, with fever or not, in children or adults.

A list of possible diseases that will be tested for was prepared for each disease syndrome.

In addition to the above syndromes, the participants agreed to include the following specific pathologies to be under surveillance: Hemolytic uremic syndrome, Muco-cutaneous and visceral leishmaniasis and plague.

The Surveillance for Antimicrobial Resistance was agreed for: a) Resistance of *Streptococcus pneumoniae* and *Haemophilus influenzae* to penicillin; b) Resistance of *Salmonella* and *Shigella* to one or more drugs; c) Vancomycin resistant *Enterococcus* and d) Yeast and filamentous fungi.

1. WELCOMING REMARKS

Dr. Dora Vilar de Saráchaga deputy secretary for Health Community Care, Argentine Secretary of Health, welcomed the participants from countries of the Southern Cone and from the Centers for Disease Control and Prevention (CDC) attending the meeting. She stressed the importance of establishing a laboratory network for the surveillance of Emerging Infections Diseases (EID) for effective detection of these agents and appropriate response. She also acknowledged that the Secretary of Health was committed to provide full support to the initiative.

On behalf of Dr. Stephen Corber, Director of Disease Prevention and Control, PAHO, Dr. Francisco Pinheiro welcomed the participants and thanked Dr. Elsa L. Segura and her staff for the support to the organization of the meeting. He also acknowledged the critical role played by the CDC in providing cooperation to this initiative. In addition, he reiterated PAHO's commitment to cooperate with countries of the Southern Cone to strengthen Laboratory Surveillance for EID and to implement appropriate measures to combat the problem.

Dr. Elsa L. Segura, Director de la ANLIS "Dr. Carlos G. Malbrán", welcomed the participants and acknowledged PAHO for conducting and coordinating the initiative for the improvement of the epidemiological surveillance of diseases, particularly the organization of the laboratorial surveillance of emerging infectious diseases in South American countries.

2. OBJECTIVES OF THE MEETING

The goal of the meeting was to create a functinal network of laboratories within the greater Southern Cone Region: Argentina, Bolivia, Brazil, Chile, Paraguay and Uruguay, able to obtain accurate, high quality laboratory results on new, emerging and re-emerging infections found in the Region. The specific objectives include to:

- Enchance capacity for early detection and monitoring of EID in the Southern Cone Region;
- Begin implementation of common survey protocols to identify specific pathogens of significance;
- Strength laboratory capacity for surveillance of EID;
- Begin implementation of common protocols to address specific diseases, using identical or comparable laboratory procedures with good quality control to ensure accuracy of results obtained;
- Create a forum for rapid technology transfer;
- Encourage research to develop new methodologies for the identification of pathogens important to the region.
- Facilitate prompt information sharing;
- Establish strategies to alert clinicians and epidemiologists for outbreak investigation and identification as well as strengthening linkages between epidemiological and laboratory studies.

3. BACKGROUND

Summary of Previous Recommendations

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

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

This Regional Plan has four goals:

- Strengthen regional surveillance networks for infectious diseases in the Americas;
- Establish national and regional infrastructures for early warning of and rapid response to infectious disease threats through laboratory enhancement and multidisciplinary training programs;

- Promote the further development of applied research in the area of rapid diagnosis, epidemiology, and prevention; and
- Strengthen the regional capacity for effective implementation of prevention and control strategies.

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

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

In 1996 a workshop to define priorities for institutional strengthening was held in Goiania, Brazil. At this meeting the importance of strengthening regional laboratories was recognized and several specific requirements for improved laboratory surveillance were identified.

PAHO's regional steering committee for EID met in Toronto, Canada in November 1996 and in Rio de Janeiro, Brazil in November 1997 to identify priorities for regional surveillance. A specific recommendation of the meeting in Rio de Janiero was: "to support the initiative on surveillance for emerging infectious diseases in the Cono Sur Regions and extend it to other subregions."

4. SUMMARY DESCRIPTION OF PARTICIPATING LABORATORIES

4.1. ARGENTINA

In mid-1996, a decision was made to integrate the National Institutes into the "Dr. Carlos G. Malbrán" National Institute of Microbiology, under the Second State Reform Law. This integration gave rise to the establishment of the ANLIS, the "Dr. Carlos G. Malbrán" National Administration of Institutes and Health Laboratories (Decree 1628/96), organized as an "Administration", so that it could be decentralized and independent of the State, from an administrative standpoint. Organized in this manner, all the institutes and centers can: (a) enjoy status and financing as a scientific and technical agency, something that was not possible for the institutes and centers under the previous legal regime; (b) enter into national and foreign agreements with public or private organizations to promote the activities for which they are responsible; and (c) harmonize activities and budgets.

Total personnel is 840 staff members, 300 of whom are professionals in the medical, technical, chemical, biological, and social sciences, as well as other areas. The permanent staff of the Ministry of Health and Social Action numbers 750, and there are 90 investigators, including those with positions at the National Council of Technical and Scientific Investigations (CONICET), as well as scientific investigators, research assistants, and research fellows or contracted personnel.

Coordination with the national institutions of other countries or international institutions with similar objectives led to national and PAHO/WHO recognition of 10 reference laboratories.

Special priorities of the Malbrán ANLIS are: emerging diseases, diseases controllable by the year 2000 (Chagas' disease, leprosy), and pathologies leading to infant morbidity and mortality. They

will cover scientific and technical research, output, quality control of biologicals, and the application of field strategies.

The objectives of the institutes, according to their expertise, are to generate knowledge, carry out their functions as health reference laboratories of the national laboratory network, to train the human resources working in the health services, and to produce biologicals and develop technical standards on procedures for diagnosis and quality control, as well as advisory services within the framework of their role.

4.1.1 Mission of the Malbrán ANLIS is:

To understand the scientific, technical, and implementation policy regarding the allocation of funds, and the promotion, approval, and evaluation of projects of the institutes and centers under its jurisdiction, in cooperation with units of the Ministry or the provinces and with other national or international organizations;

To supervise the work of the National Health Reference Laboratory for the National Laboratory Network for the prevention, diagnosis, and treatment of nutritional, genetic, and microbial diseases, guaranteeing the quality of diagnosis in the country;

To supervise the preparation and quality control of biologicals, research, and action taken with a view to improving these products or generating new ones; and

To coordinate research on etiological agents, on genetic or nutritionally-based diseases, and their social and environmental consequences.

4.1.2 The ANLIS Malbrán this made up by the National Institutes of:

Acute Infectious Diseases, in the city of Buenos Aires (INEI)
Production of Biologicals, in the city of Buenos Aires (INPRO)
“Dr. Juan H. Jara” Epidemiology, in Mar del Plata (INE)
“Dr. Emilio Coni” Respiratory Diseases, in the city of Santa Fe (INER)
“Dr. Mario Fatala Chabén” Parasitology, in the city of Buenos Aires (INP Fatala)
“Dr. Julio Maiztegui” Human Viral Diseases, in Pergamino (INEVH)

and the National Centers of:

Nutritional Research, in the city of Salta (ININ)
Medical Genetics, in the city of Buenos Aires (INGEM)
Quality Control of Biologicals, in the city of Buenos Aires (CENCAL)
Diagnosis and Research of Endemoepidemics, in the city of Buenos Aires (CEDIE)
Argentine Network of Health Laboratories, in the city of Buenos Aires (RELAS)

4.1.3. Description of the laboratories

The institutes and centers that participate in the surveillance of EID have sufficient laboratories to conduct the work, even though in many cases they are obsolete. Only one has facilities at the BSL-3 biosafety level. The others have P2. The five central units that do the work as emerging infectious disease (EID) laboratories are:

UNITS	m^2 laboratory
Inst. Nac. of Infectious Diseases	800
Inst. Nac. de Virosis Humanas “Dr. J. Maiztegui”	800
Inst. Nac. de Enfermedades Respiratorias "E. Coni	300
Inst. Nac. de Epidemiología “J. Jara”	300
Inst. Nac. of Parasitology Dr. M. Fatala Chabén	100

In 1998, BSL-3 biological safety facilities will be constructed in the center of the city of Buenos Aires.

The Malbrán ANLIS has an area of 700 hectares, 150 of which are used for work related to the production of biologicals.

4.1.4. Description of the National Network of Laboratories:

The Center for the National Network of Argentine Health Laboratories (RELAS) has 700 laboratories working in a network, in keeping with the standards of each national reference laboratory, and provides support for epidemiological surveillance and disease prevention and control. There is one central laboratory and approximately 20 departmental laboratories in each province. University and municipal laboratories that carry out epidemiological surveillance activities are also part of this network.

4.1.5. Methodology utilized for epidemiological surveillance

The methodology designed by the Bureau of Epidemiology under the Ministry of Health is being used. This is a public health subsystem that collects data (usually on morbidity), confirms and analyzes that data, and issues recommendations from the local to the national level (**Table 1**).

4.1.6. Laboratory monitoring of the EID in Argentina

Laboratory surveillance of EID is coordinated by the Reference Centers in each institution that specialize in the topics listed in **Table 2**.

The synergy of the joint work of a laboratory network with the case reporting and analysis that constitute epidemiological surveillance had been already demonstrated in Argentina, in the prevention of blood-borne infection transmission, the control of Chagas’ disease, and the

monitoring of tuberculosis. However, it was first AIDS and then the re-emergence of cholera in the Hemisphere in 1991 and in Argentina in 1992 that demonstrated the usefulness of joint work in Argentina between the National Epidemiological Surveillance System and the National Laboratory Network in addressing emerging or re-emerging diseases.

4.1.7. Annex 1 shows the list of principal publications of ANLIS

4.2. BOLIVIA

Emerging Infectious Diseases (EID) in Bolivia represent a concern to the Public Health. Among these diseases, most important are dengue, cholera, yellow fever, malaria and tuberculosis (TB). The Bolivian health structure is formed by health services from the Ministry of Public Health as well as welfare services, self-administered institutions and non-governmental or private organizations. The Instituto Nacional de Laboratorios de Salud (INLASA) is the main institution for health laboratories. Founded in 1908, it is located in La Paz City where 186 employees including physicians, biochemists and technicians develop their activities. As any self-administrated institute, it has its own budget. It has formerly performed guiding tasks on diagnosis of endemic diseases and contributed to the country with products for diagnosis and treatment of bacterial and viral diseases. At present, the INLASA is the central unit of the Laboratory Network with emphasis on clinical diagnosis and the food, drug and beverage quality control. The Institute produces products such as anti-rabies vaccine for human and animal use, antigens for immunologic tests and cultures, and supplies reagents to all laboratories of the networks. It also supports all activities related to epidemiological surveillance, teaching, supervision, evaluation and counseling on technical and administrative organization for different health services departments. One of the important issues is the applied research, which leads to a better knowledge of the relevant pathogens in Bolivia. The laboratory system under INLASA is organized in Laboratories Networks for cholera, TB, HIV, and food and beverages.

4.2.1. National Network of Cholera Laboratories

This network includes 13 departmental laboratories and 3 district laboratories, which provide materials and supplies to facilitate diagnosis activities. The network performs teaching courses, follow-up and research, quality control – internal and external – and the surveillance for bacterial resistance. Strains identified are mainly the *Ogawa* serotype with a very low frequency of the *Inaba* serotype. Antimicrobial resistance has not been found to date.

4.2.2. National Network for Tuberculosis

This network is run by the Reference Laboratory and has manuals containing technical and administrative guidelines. It periodically performs evaluations and follow-up work on the system through information analysis, and it supplies reagents, culture media, and biologicals (PPD) to the Network's entire national laboratory system.

Table 1: Reporting Methodology

Pathology	Reports			Monthly notif by age
	By special file card	By Tel/Fax	Laboratory	
Botulism		Yes	Yes	
Brucellosis			Yes	
Anthrax		Yes	Yes	
Chagas	Yes		Yes	
Chan/Blan/Suppuration Genit			Yes	
Cholera		Yes	Yes	
Whooping Cough				Yes
Dengue				
Diarrhea <5 years			Yes	
Diphtheria		Yes	Yes	Yes
Poison Animal Bite	Yes			
Schistosomiasis			Yes	
Yellow fever		Yes		
AHF	Yes			
Rheumatic F./recurr.		Yes		
Typhoid F.				
Hepatitis			Yes	Yes
Hydatidosis			Yes	
Influenza				Yes
Food Poisoning			Yes	Outbreak Investigation
Leishmaniasis		Yes	Yes	
Leprosy	Yes		Yes	
Leptospirosis		Yes	Yes	
Red Tide	Yes	Yes	Yes	
Meningitis TB <5 yrs.	Yes		Yes	
Meningoencephalitis		In Epidemics	Yes	Yes
Deep Mycosis			Yes	
Pneumonia				Yes
Malaria	Yes		Yes	
Mumps				
Plague	Yes	Yes	Yes	Yes
Pesticides			Yes	
Polio-AFP <15 yrs.	Yes	Yes	Yes	
Psittacosis		Yes	Yes	
Rabies H and A		Yes	Yes	
Rubella			Yes	Yes
Measles	Yes	Yes	Yes	
HIV/AIDS	Yes		Yes	
Syphilis 1 and 2			Yes	
Tetanus and Neon.tet.				Yes
TB w/o sputum	Yes		Yes	
Typhus Exant		Yes	Yes	
Trichinosis`		Yes	Yes	Outbreak Investigation

All the pathologies are reported weekely to the epidemiological department by name, age, residence place and diagnosis.

Table 2: Malbrán ANLIS Report: EID surveillance activities being carried out at the Institutes and Centers of the Malbrán ANLIS, and in other laboratories of the National Network of Health Laboratories, Argentina, 1998.

	INEI	INEVH	INE	INPAR	INER	UNDIE	LB, ANLIS	Dir. Epidemio-logía	HIV National Reference Center	IVIRMED Córdoba	SV/MS Santa Fé
a. Malaria				+				+			
a. Antimicrobial Resistance	+										
a. AHF		+									
a. Dengue/YF	+	+				+					
a. Salm/Shig	+										
a. Measles	+										+
a. Cholera	+										
a. Polio	+										
a. Influenza	+		+							+	
a. HPS	+	+		+		+					
a. HIV									+		
a. HUS	+										
a.*Strep.pneu*	+										
a.Tuberculosis	+		+		+						
a. IHI			+			+					
b. Mycosis#	+										
b. Leptospirosis.	+										
b. Brucellosis							+				
b. Meningitis	+										

a. Monitoring already conducted, b. Monitoring underway. #Cross-sectional studies are conducted to monitor resistance to antimicotic for cryptococcosis. **AHF** - Argentine Hemorragic Fever, **HPS** - Hantavirus Pulmonary Syndrome, **HUS** - Haemolitic Uremic Syndrome, **IHI** - Intrahospital Infections, **YF** - Yellow Fever. **INEI** - National Institute of Acute Infectious Diseases; **INE** - IN de Epidemiología "Dr. Juan H. Jara", **INER** - IN Enfermedades Respiratorias "Dr. Emilio Coni", **INPAR** - IN Parasitología "Dr. Mario Fatala Chabén", **INEVH** - IN Enfermedades Virales Humanas "Dr. Julio Maiztegui", **CENDIE** - Centro Nacional de Diagnóstico e Investigación de Endemoepidemias, **LB** - Laboratorio de Burcelosis de la ANLIS Malbrán, **IVERMED** - Instituto de Virología Médica, **SV/MS** Servicio de Virología/Ministerio de Salud Santa Fé.

It has 348 district laboratories that perform bacilloscopies and 11 departmental laboratories that are responsible for running the district laboratories and coordinating activities with the National Reference Laboratory. Cultures are done at four laboratories. Sensitivity and resistance tests are done at the INLASA National Laboratory.

Quality control of the microscopic examination is performed on an ongoing basis, and is available for 95% of the services. Monitoring of antituberculosis drugs is done regularly following WHO protocols. The initial resistance to INH is of 5.8% and SM 4.4%; the acquired rate to INH is 14.7%, to RFP is 12.6%, and to SM is 11.5%.

4.3. BRAZIL

In 1970s, the Brazilian government made a policy decision to organize a National Public Health Laboratory System (SNLSP). In recent years, the coordinating body of the SNLSP, integrated into the National Epidemiology Center (CENEPI) of the National Foundation of Health/Ministry of Health, has been restructuring and reorganizing laboratory diagnostic activities within the Unified Health System (SUS) adopted in the country under Law 8080/90, which advocates the decentralization of activities in a hierarchical and structured manner at different levels of complexity, with responsibility for epidemiological surveillance, sanitary, and population health activities.

With the implementation of the SUS policy, the Coordination of Public Health Laboratories (COLAB) was given responsibility for defining and coordinating the Laboratory networks by disease and health problems, carrying out existing activities within a new framework based on modern management concepts, strengthening the information network, and modernizing the laboratory infrastructure by instituting the appropriate biosafety measures. In order to carry out these activities, resources from the World Bank were sought, together with technical cooperation from the CDC in Atlanta.

Some national laboratories are recognized internationally for their expertise in specific areas. The national coordination of the SNLSP/COLAB carries out national coordination activities, plays an administrative policy role in this national laboratory structure, and has an annual budget of 18,000,000 *reales*. (app USD 15,500,000).

This public health laboratory network system is made up of National Reference Centers (CRN) which deals with specific diseases; state (LACEN) public health laboratories, municipal (local) laboratories (LM), and other components of the system.

4.3.1. Adolfo Lutz Institute

This Adolfo Lutz Institute is the public health laboratory of the State of São Paulo and a component of the National System. Founded in 1892 as the Bacteriological Institute, in 1940 it became the Adolfo Lutz Institute with the incorporation of quality control in health (Food Science and Chemistry). Today, it has 900 staff members and is maintained by the state

government. Its mission is to work jointly in epidemiological and health surveillance for disease prevention and health promotion. It also conducts technological scientific research activities.
It works in the areas of:

Medical biology. - Parasitology, Bacteriology, Virology, Mycology, and Immunology.
Pathology - Biochemistry and immunohystochemicals, histopathology and pathological anatomy.
Training is provided.
Diagnosis of the following emerging diseases: Dengue, Yellow Fever, Hantavirus, Leptospirosis, Arbovirus in general, Influenza, Rickettsiosis, Leishmaniasis, Measles, Rubella, Hepatitis, Typhoid fever, Parvovirus, and Arenavirus (depending on biosafety facilities).

It also acts as a human resource training center and is a PAHO collaborating center for various diseases, a national reference center for meningitis, and a macroregional reference center for the southern part of the country (for the public health laboratories of Paraná, Mato Grosso do Sul, Santa Catarina, and Rio Grande do Sul).

4.3.2. Oswaldo Cruz (FIOCRUZ) Foundation

This is a public foundation directly linked to the Ministry of Health of Brazil. Located in Rio de Janeiro, it is comprised of 11 Technical Units that carry out different activities. It also has three Regional Research Centers in Recife/Pernambuco, Belo Horizonte/Minas Gerais, and Salvador/Bahía. Its mission centers on three principal areas: a) biomedical research and education in public health; b) technology development and production in the area of immunobiologicals, drugs and medications, in addition to national quality control work, and; c) two research and services hospitals specializing in maternal and child health and infectious diseases. It has 3,500 full-time employees, more than 500 of whom have doctorates, in addition to 3,500 other part-time employees and graduate students.

In the 11 Technical Units, there are more than 20 reference centers and/or PAHO/WHO Collaborating Centers, the majority of which are concentrated in the Oswaldo Cruz (IOC) Institute, which is the largest technical unit of FIOCRUZ. Through these reference centers it provides specialized advisory and support services for the national epidemiological surveillance system of the Ministry of Health. One of the units–the Institute of Technology of Immunobiologicals/BIOMANGUINHOS develops and produces the reagents for laboratory diagnosis distributed to the state public health laboratories.

4.3.3. Annex 2 shows the diseases and agents for which reporting in Brazil is mandatory, and those recently incorporated in the system. All seven syndromes indicated in the Plan of Action are considered an epidemiological surveillance priority.

4.4. CHILE

4.4.1. Institute of Public Health (ISP)

The predecessor of the ISP is the Bacteriological Institute of Chile. In 1929, the Bacteriological Institute of Chile and its Institutional Regulations were established, with the subsequent creation of reference laboratories, training of bacteriologists, preparation of sera, vaccines, and biologicals,

together with control of the manufacture and sale of these products. In 1947, on land donated by Dr. Suarez, the future Institute of Public Health was constructed, and in 1980, the "Dr. E. Suarez Herreros" Institute of Public Health was established. This Institute, which is directly under the Ministry of Health, is autonomous and financially independent, having its own budget.

4.4.2. Institutional Mission

The mission of the Institute of Public Health is to contribute to an improvement in the health of population as a whole, guaranteeing the quality of the public health products under its purview, becoming a National Reference and Certification Center, and producing products and services with transparency, responsibility, an attitude of service to the user, quality management, technical expertise, and vision in terms of the future.

4.4.3. Department of Health Laboratories

The mission of the Department of Health Laboratories is:

1. Central Coordination of the National Network of Laboratories
2. Laboratory surveillance of infectious diseases (it has a laboratory with BSL-3 biosafety)
3. Research and development of diagnostic techniques and their technological transfer to the country's laboratories
4. Program for External Evaluation of the Quality of Clinical Laboratories
5. To conduct examinations relating to: Clinical Bacteriology, Serology of Syphilis, Mycobacteria, Virology, Immunology, Histocompatibility, Hematology, Parasitology, and Clinical Chemistry
6. To produce guidelines and standards to guide the practice of clinical laboratories in Chile.

4.4.4 Surveillance of Emerging Infectious Diseases is done by National Programs in collaboration with Ministry of Health.

National Program of Tuberculosis:

- Diagnosis and administration of free drugs.
- Quality control of diagnostic laboratories.
- Examinations and maintenance of statistical records of incidence of confirmed cases (clinically and laboratory diagnosed) and of resistance to antimicrobial agents (examinations of susceptibility and typing are only done in ISP) **(Tables 3 and 4).**
- Total incidence: All the cases reported to Ministry of Health.
- All locations are included in the National Program of TB.

Table 3 : Incidence of Tuberculosis in Chile, 1992-96

YEAR	TOTAL INCIDENCE	POSITIVE ZN
1992	39.1	19.4
1993	33.4	14.8
1994	29.6	13.9
1995	29.2	13.0
1996	28.1	12.6

ZN = (Ziehl-Neilsen)

Table 4: Tuberculosis Resistance to Antimicrobial Agents (Mono or Multiple Resistance Included), Chile, 1982-95

YEAR	INITIAL RESISTANCE	ACQUIRED RESISTANCE
1982	8.7%	28.9%
1984	10.2%	-
1985	-	26.5%
1986	10.7%	-
1988	-	25.4%
1989	10.4%	-
1991	-	32.3%
1993	-	31.7%
1994	-	26.3%
1995	10.8%	24.0%

RESISTANCE TO INH + RMP. Constant over the years. Initial: 0% Acquired: 1%

Leptospirosis:

- Leptospirosis is not a reportable disease in Chile, and the diagnosis is not made at ISP.
- Diagnosis in humans is done by test of microscopic agglutination, and culture in EMJH based on blood samples, CSF, and urine analysis carried out in the Austral University, Valdivia, by Dr. Justo Zamora.
- According to its studies published, leptospirosis exists in Southern Chile.
- Diagnosis in animals is done by the Livestock Agricultural Service.

The following seropositivity data in the Southern Area were provided by Dr. J. Zamora:
Animals: Cattle between 59% and 91%; Goats 24.9%; Sheep 7.1%; Horses 48.5%; Pigs 69.9%; and wild rodents 47.2%.

In human populations occupationally exposed: rice-field workers 8%; butchers 20.8%; and rural livestock activity 19.7%.

Cholera

The program is national with training of regional laboratories by the ISP. All cases diagnosed in Chile must be confirmed at ISP, where the bacteriological identification, serotyping and susceptibility is performed. **(Tables 5 and 6)**
All the cases notified in 1998 originated from a small regional outbreak.

Table 5: Strains of *Vibrio cholerae* 01 in Human Samples Confirmed by the Reference Laboratory, Chile

YEAR	REGION	NO. STRAINS	SEROTYPE		TOTAL
			OGAWA	INABA	
1991	II	1			
	IV	2			
	RM	35			
	VII	1			
	X	2	0	41	41
1992	I	26			
	RM	45	48	23	71
1993	I	28			
	II	4			
	RM	1			
	VI	1	32	2	34
1994	RM	1	0	1	1
1995	-	-	0	0	0
1996	I	4	4	0	0
1997	II	1	1	0	1
1998	II	22	22	0	22

TOTAL OF CASES SINCE 1991-1998 (MARCH) =174.
SEROTIPO OGAWA =107.
SEROTYPE INABA =67.
TOTAL OF DEAD = 4.
SENSITIVITY: 1 STRAIN RESISTANT TO `TETRACYCLINE`. CHLORAMPHENICOL. SULFATRIMETOPRIM.

Table 6: *Vibrio parahaemolyticus*, Chile

HEALTH SERVICE	CITY	NO. OF STRAINS RECEIVED	
		1992 to OCT 1997	NOV 1997-MAR 1998
ARICA	ARICA	12	15
IQUIQUE		0	21
ANTOFAGASTA	ANTOFAGASTA	1	120
	CALAMA	3	13
ATACAMA	COPIAPO	0	25
	HUASCO	0	10
	VALLENAR	0	23
COQUIMBO	LA SERENA	7	
	COQUIMBO	1	22
	LOS VILOS	0	
METROP.ORIENTE	SANTIAGO	4	-
METROP. NORTE	SANTIAGO	0	1
VALDIVIA	LA UNION	1	-

* The number of cases is much greater. These are only the number of strains received at the ISP. Prior to the outbreak, only yellow strains in TB were requested (saccharose +). After the outbreak, green and yellow colonies were requested. Only 10% of the strains were sent if correspondence was 100%. *Vibrio parahaemolyticus* has also been isolated in seafood.

Brucellosis

This is not a reportable disease in Chile. Diagnosis is not made in a centralized manner.
The ISP offers the Huddleson test and cultures. In 1997, the following results were obtained: Serology : 50 patients, 8 positive (titer=1:80); hemocultures: 5 patients, 2 positive.

Salmonella enteritidis

Is not a reportable disease. The reference laboratory is the ISP, which carries out identification up to the serovar level. Laboratories in the country send strains to the ISP, which is the only national statistical data source. In fact, a large and representative number of strains of *Salmonella sp* and *Shigella sp* are referred to the Institute.

Other diseases

In Chile indigenous cases of dengue, yellow fever, hemorrhagic fever due to arenavirus, or rickettsiosis/ehrlichiosis have not been recorded.

4.5. PARAGUAY

4.5.1. Research Institute in Health Sciences (IICS), National University of Asunción

Mission of the Institution: To generate, carry out, and promote scientific research in the Health Sciences, with the contribution of knowledge and solutions to the relevant problems of the country, with the human resource training and development of specialized services to improve the community health. The IICS was established to identify factors in the country that affect health and to apply technology suited to the national situation. Its organic and functional predecessor was the Institute for Human Reproduction, which was established 20 July 1969, through an agreement concluded between the Ministry of Public Health and Social Welfare, the Faculty of Medical of Medical Sciences of the Universidad Nacional de Asuncion, and the Agency for International Development.

4.5.2. The Prevalence (**Table 7**) and Methodology Used for the Surveillance of:

Influenza: No previous serological work has been done. The methodology used to date is the mandatory case notification, which, for influenza, is weekly notification. Laboratory confirmation of clinical cases is done at the central laboratory of the Ministry of Health of Paraguay. In 1997, this group conducted a pilot study of active surveillance of influenza in Paraguay as the first phase of the implementation of influenza surveillance, scheduled to begin in 1998. This study was conducted by providing the technological training for personnel of the Central Laboratory in 1997, when the network of laboratories for influenza and respiratory viruses was established.

Table 7: Surveillance of Diseases Requiring Mandatory Medical Notification in Paraguay. Number of Cases Identified per Year. 1986 to 1997

	Number of Cases											
	1986	**1987**	**1988**	**1989**	**1990**	**1991**	**1992**	**1993**	**1994**	**1995**	**1996**	**1997**
DISEASE												
- AIDS.	6	8	7	11	19	19	28	46	25	20	53	83
- LEPROSY	345	427	362	451	385	412	365	338	376	227	202	419
- HUMAN RABIES	9	5	3	0	2	5	3	3	1	4	6	10
- TUBERCULOSIS	988	1097	1047	2344	2242	2350	1927	1979	1804	898	1168	1105
- MALARIA	4329	3759	29221	5247	2912	2983	1289	436	583	898	680	567
- LEISHMANIASIS	810	412	139	124	180	527	1517	300	733	-	175	102
- DENGUE[1]	0	0	405	40376	0	0	0	0	0	0	0	0
- MEASLES	610	1742	775	352	1396	526	864	2066	142	69	14	185
- NEONATAL TETANUS[2]	59	59	52	31	38	28	18	28	18	16	10	18
- DIPTHERIA	19	19	13	8	10	4	5	5	1	0	0	0
- WHOOPING COUGH	129	251	886	291	115	118	372	272	49	13	40	40

[1]Source: 1992-1996 SENAPA Technical report.
[2]1986, 1987, and 1988 do not include cases in the aboriginal population.

Leptospirosis: No data exists on seroprevalence studies or epidemiological surveillance for this disease.

Brucellosis: No seroprevalence data exists for Brucellosis. Confirmation of clinical cases is done at the National Animal Health Service (SENACSA) through serological analyses involving animals and some cases involving humans referred by the Central Laboratory of the Ministry of Public Health. Four techniques are used, two of which are very sensitive and fairly nonspecific (rapid slide test and the rose bengal test) and two others are more specific and are used as confirmation tests (slow test tube test and the mercaptoethanol-2 test). The antigen used is the 1911-13 strain, provided by the Pan American Institute for Food Protection and Zoonoses (INPPAZ). In 1994, a pilot study was done jointly with the II Health Region, San Pedro, and the data obtained was used at the Microbiology Congress held that same year in Paraguay. Brucellosis is a disease for which immediate and mandatory weekly notification is required.

Dengue: No seroprevalence data exists. Confirmation of clinical cases is done by serological methods at the Central Laboratory of the Ministry of Health. The epidemiological surveillance system used by the Ministry of Health is mandatory and immediate case notification.

Yellow Fever: No data exists on seroprevalence. Like dengue, mandatory and immediate notification is required. The last cases of yellow fever in Paraguay occurred in 1974.

Hantavirus: An outbreak of HPS occurred in the Chaco region of Paraguay in 1995, which was associated with Laguna Negra virus, a new hantavirus. Up to now 34 cases of HPS were reported in the country, all from the Chaco region. Most cases were males 15 to 45 years old. Seroprevalence data obtained from the general population of the Western Region of Paraguay is

available for areas where new cases have been detected. Research reveals that one of the smallest species of rodents, the *Calomys laucha*, is the only reservoir of the Hantavirus in the Western region. Rodents were captured in different places in central Chaco, 12% of which were infected (24/206). No data is available on seroprevalence in other parts of Paraguay. The surveillance system used is immediate and mandatory case notification.

Tuberculosis: A national tuberculosis program exists, which processes data on incidence and per capita death rates from TB in different age groups in Paraguay. The highest prevalence of TB is found in Boquéron, President Hayes and Amambey. There is evidence that only 50% of TB cases are reported.

Sexually transmitted diseases (STD). Surveillance of STD was initiated in 1995. There were 127 cases reported in 1995, 99 ases in 1996, and 313 cases in 1997.

4.5.3. The List of Principal Publications of the IICS are shown in Annex 1.

4.6. URUGUAY

This service began in 1977 at the Public Hygiene Laboratory, whose mission was the centralized diagnosis of syphilis. From there, gradual decentralization of diagnosis began, together with the development of a national reference center with functions related to standardization, supervision of network laboratories, and diagnostic referencing.

In recent years, applied research responsibilities have emerged in priority health areas, such as respiratory viruses, hepatitis, AIDS, resistance to antibiotics, Chagas' disease and others, with the National Reference Centers operating in conjunction with the Service.

4.6.1. Prevalence and Methodology Used in the Surveillance of Emerging Infections:

Influenza: Studies of observation groups (young adults) have been conducted between March and October of each year since 1981, through MDCK cultures of respiratory secretions. Also included was the surveillance of children who were recruited during research projects supported by BOSTID (USA), SAREC (Sweden), and the European Community for the study of the etiology of acute diseases of the lower respiratory tract.

Hantavirus: Studies are being conducted at the request of physicians treating clinical cases of acute respiratory distress with shock, leukocytosis, and thrombocytopenia. To date, two cases have been identified. So far, no studies have been done on rodents in the foci of the disease that have already been identified. The diagnostic methodology used consists of looking for specific antibodies (IgG and IgM) in conjunction with ANLIS (Malbrán Inst., Buenos Aires), where genomic analysis have also been done.

Dengue: A commercial technique is available for research on antibodies (IgG and IgM) for dengue. The procedure is used in suspected cases from epidemic areas. Seroepidemiological surveys will be conducted in the areas that border Brazil and Argentina, in the north of the country.

Hepatitis C: Although the prevalence of hepatitis C among blood donors in Uruguay is 0.45%, groups at high risk for that infection have been identified (hemophiliacs 60%, drug addicts 71%, hemodialysis patients, 20%). Through diagnostic referencing of hepatitis cases and the study of observation groups (hemodialysis patients and patients who are HIV positive), several aspects of the circulation of the hepatitis C virus were studied. These groups therefore constituted sensitive observation groups for the detection of other viruses that cause hepatitis.

Brucellosis: In 1991, the first human cases were reported with the isolation of *Brucella suis* found in humans and pigs. Since then, periodic surveillance has been done of the serum of workers in cold storage plants and of the registration of new cases involving humans. The prevalence of antibodies was found to be 5.5% (a range of 0 to 14%) using the Huddleson technique.

Salmonellosis: In the past decade, outbreaks of enteritis have been reported, linked largely to the ingestion of foods containing raw eggs. The numbers affected by outbreaks have varied, from families to more than 200 people. In all cases, enteric salmonella was isolated, an enteric subspecies, Ser. enteritidis. Since 1995, the frequency of cases has increased markedly.

Resistance to antibiotics: The principal infectious agents monitored at this institution are: *Streptococcus pneumoniae, Staphylococcus aureus and Staphylococcus* negative coagulase, *Neisseria meningitidis* B and C and *Enterococcus*. Resistance to penicillin was found in 38% of the strains of pneumococcus and also for trimethoprim/sulphametoxaxol. Some 89% of resistant strains belong to the capsular serotype 14, and studies conducted have shown that it involves a clone that was possibly introduced in the 1990s and is responsible for increased resistance. Since type 14 is most frequently found in pneumonia, the problem of resistance to date has focused on this disease and not on meningitis.

Vibrio cholerae: The Laboratories Department is the reference center for *Vibrio cholerae*, and no cases have been detected to date. Active collaboration is under way to identifying isolated vibrios in the environment when tracking the possible spread of *Vibrio cholerae*.

4.6.2. List of Emerging Diseases that can be monitored by the Institution:

Influenza	Leptospirosis
Hepatitis C	Brucellosis
Unclassifiable hepatitis	Antimicrobial resistance
Dengue	Salmonellosis
Hantavirus	Cholera
Cryptosporidiosis	

4.6.3. The List of Publications is shown in Annex 1.

5. SURVEILLANCE AND ACTIVITIES ALREADY UNDERWAY

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

The surveillance of the following Syndromes is considered important for the Region. However, each country will start with the surveillance of any one of these syndromes according to their priorities. **Table 8** summarizes these activities.

6. PLAN OF ACTION

The participants recommended that surveillance should be established for: 1) Disease syndromes; 2) Specific pathologies and 3) Antimicrobial resistance.

6.1. Disease Syndromes

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

6.1.1 Undifferentiated febrile syndrome: Fever >38.3 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. If accompanied by upper respiratory manifestations, non-productive cough or pneumonia prioritizes search for influenza.

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

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

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

6.1.5. Unexpected death syndrome: Previously healthy persons, 1-49 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.

Table 8. Activities for Surveillance of EID and Other Important Diseases in the Region Conducted by the Countries of the Southern Cone: Argentina, Bolivia, Brazil, Chile, Paraguay, Uruguay.

EID	Argentina	Bolivia	Brazil	Chile	Paraguay	Uruguay
Resistance to antibiotics	+a	+a	- b	+	+	+
Nosocomial infections	+a	+a	+b	+	+	+
Argentine hemorrhagic fever	+a	-	-	-	-	-
Dengue/Yellow Fever	+a	+a	+a	-	+/ -	+/ -
Measles	+a	+*b	+a	+	+	+
Poliomyelitis	+a	+*b	+a	+	+ *	+ *
Influenza	+a	+a	+b	+	+	+
HPS	+a	+a	+b	+	+	+
HIV/HTLV	+a	+a	+a	+	+/ -	+
St. Louis Encephalitis, EEE, WEE, VEE	+b	-	+a	-	-	-
Lymphocytic choriomeningitis	+b	-	+a	-	-	-
Hepatitis C, D, E	+b	+a	+a	-	Hepatitis C	+
Viral and bacterial meningo-encephalitis: Herpes, enterovirus, *N. meningitidis*, *S. pneumoniae*, *H. influenzae* #	+b Bacterial meningitis monitored	Herpes, bacter. infections, and meningitis monitored	+a	Bacterial meningitis monitored	Bacterial meningitis monitored	Bacterial meningitis monitored
HUS	+a	-	+a	-	-	+
Salmonella/Shigella	+a	+a	+a	+	+	+
Streptococcus-pneumoniae	+a	+a	+a	+	+	+
Tuberculosis	+a	+a	+a	+	+	+
Cholera	+a	+a	+a	+	+	+
Legionellosis	+b	+b	-	-	-	-
Leptospirosis	+b	+b	+a	-	-	+
Brucellosis	+b	+b	-	-	+	+
Mycosis (cryptococcosis)##	+b	+b	- b	-	-	+
Malaria	+a	+a	+a	-	+	+
Leishmaniasis	+a	+a	+a	-	+	-

Study of outbreaks of meningitis - clear fluids.
Cross-sectional studies are being conducted to monitor resistance to antimycotics for cryptococcosis.
a: Surveillance already conducted. b: Surveillance under way. * Surveillance is taking place and samples are studied at reference laboratories.
HUS: Hemolytic Uremic Syndrome. HPS: Hantavirus Pulmonary Syndrome.

6.1.6. Infectious neurologic syndrome: Febrile neurologic symptoms with clear CSF in a non-immunodepressed patient

6.1.7. Enteric syndrome: Bloody or non bloody, acute diarrhea, with fever or not, in children or adults.

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

6.2. Infectious Agents for Disease Syndromes

A list of possible diseases that will be tested for was prepared for each of the disease syndromes. Convalescent sera from patients enrolled in the study will be screened for antibodies against the agents causing the diseases listed below. If the serum is negative in the initial screen, it then will be tested (in a second or third screen) against other less common agents**.** Attempts can also be made to culture/isolate infectious agents from samples such as blood, serum, stools, pharyngeal washes, spinal fluid, autopsy tissues. **The order of the agents to be tested may vary from one country/area to the others.**

6.2.1 Undifferentiated febrile syndrome:

(a) Initial screen

Dengue (types 1, 2, 3, and 4)
Brucellosis
Leptospirosis
Influenza
Malaria (*P. falciparum* and *P. vivax*)
Yellow fever
Q-fever

(b) Secondary screen:

Ehrlichoses
Rickettsioses
Parvovirus B-19 infection
Measles
Rubella
Hepatitis A
Hepatitis B
Hepatitis C
Ilheus virus infection
Phlebovirus infection (phelobotomus fever)

Vesiculovirus infection
Cache Valley & related bunyavirus infections
Typhoid fever
St. Louis encephalitis virus infection

6.2.2 Hemorrhagic fever syndrome:

(a) Initial screen: (in order of probability at each site)

Leptospirosis
Arenavirus infections (Junin, Machupo or others, depending on region)
Dengue (types 1, 2, 3, and 4)
Yellow fever

(b) Secondary screen:

Ehrlichiosis
Rickettsioses
Hepatitis B
Hepatitis C
Hantavirus infection (hemorrhagic fever with renal syndrome)

6.2.3 Febrile icteric syndrome:

(a) Initial Screen: (in order of probability at each site)

Leptospirosis
Hepatitis A
Hepatitis B
Hepatitis C
Yellow fever

(b) Secondary Screen:

Hepatitis D (only if patients is positive for hepatitis B virus infection)
Hepatitis E

6.2.4 Acute (noncardiogenic) respiratory distress syndrome (ARDS):

Leptospirosis
Influenza
Hantavirus infection (Hantavirus pulmonary syndrome)
legionellosis
Q fever
Psittacosis

6.2.5 Unexpected death syndrome:

(a) Initial Screen (done locally):

Culture
Histopathology

(b) Secondary Screen (done at a reference laboratory):

immunohistopathology
nucleic acid probes with PCR
electron microscopy

6.2.6 Infectious neurologic syndrome

(a) enterovirus
herpes simplex

6.2.7 Enteric syndrome:

(a) Initial Screen
V. cholerae 01,0139, no-01
V. parahaemolytius and other vibrio
Rotavirus
E. coli 0157 and other Shiga toxin-producing *E. coli*
Salmonella
Shigella
Diarrheigenic *E. Coli*

(b) Secondary Screen
Adenovirus 40 and 41
Norwalk virus

6.3. <u>Specific Pathologies</u>

In addition to the above mentioned syndromes the participants suggested to include the following disease /syndromes to be under surveillance:

6.3.1 Hemolytic uremic syndrome (HUS). Previously healthy children who developed acute renal injury thrombocytopenia and microangiopathic hemolytic anemia, following an acute diarrhoeal prodromal illness.

6.3.2. Muco-cutaneous and visceral leishmaniasis

6.3.3. Plague

6.4 Surveillance for Antimicrobial Resistance

Indiscriminate use of antimicrobial agents in the last decade has generated the appearance of multiresistant strains, thus complicating treatment and, allowing for the re-emergence of some diseases such as tuberculosis that were almost under control. Similar situation is shared with other diseases:

a. Resistance of *Streptococcus pneumoniae* and *Haemophilus influenzae* to penicillin
b. Resistance of *Salmonella* and *Shigella* to one or more drugs.
c. Vancomycin resistant Enterococcus.
d. Yeast and filamentous fungi.

This situation requires urgent implementation of surveillance to establish strategies and control measure.

Pathogen agents proposed to enter under surveillance of antimicrobial resistance

1. *Mycobacterium*
2. *Plasmodium*
3. *Salmonella,*
4. *Shigella*
5. *Vibrio cholerae*
6. *Klebsiella, Enterococcus*
7. *Staphylococcus aureus*
8. *Streptococcus pneumoniae*
9. *Haemophilus influenzae*
10. *Neisseria. gonorrheae*
11. *Candida albicans*
12. *Cryptococcus neoformans*

6.5. Syndromes/Diseases for Initial Surveillance

The following syndrome/diseases were selected for initial surveillance:

- Influenza
- Antimicrobial resistance, including tuberculosis
- Acute diarrhea including *E coli* O157 (HUS)
- HPS/Hantavirus disease

6.6. Specimens

Acute and convalescent serum specimens will be obtained from all patients when possible. To insure that convalescent samples are obtained from most of the people enrolled in the study, home visits are recommended. In cases where specific diseases are suspected (i.e. influenza, leptospirosis, rickettsiosis), additional samples (i.e. nasopharyngeal swab, urine or blood clot, respectively) may be collected. (**See table 9**).

6.6.1. 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.

6.6.2. Acute phase respiratory samples: in illness with respiratory symptoms, nasopharyngeal swabs or pharyngeal washes will be collected. These samples should be processed immediately or frozen at –20 C.

6.6.3. 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.

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

7. REAGENTS AND DIAGNOSTIC TESTS

7.1. 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 proposed to ensure adequate amounts of reagents.

7.2. Laboratory Tests: The basic plan will be to begin testing as soon as possible by screening the convalescent serum for antibodies to the probable etiologic agent, and the acute sample(s) (stored at -70C) by appropriate tests (i.e. culture, PCR). 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).

- Hantaviruses - IgM ELISA (antigen from CDC or from ANLIS)

- 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 CDC).

- 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 Biomanguinhos, Malbran, or commercial source).

- Enterics – *Salmonella, Shigella, Eicoli, V. cholerae;* Serotype identification (INPB/Malbran).

7.3. Provision of Reagents

New reagents will be developed for new pathologies to be shared between laboratories, which will have the added value of their standardization and validation.

7.4 Quality Control

It was recognized by the group that it will be important for all collaborating laboratories within the network to maintain the highest quality of diagnostic tests to ensure that results obtained will be accurate and that all participants will have confidence in the observations made and results obtained. Formal quality control may be difficult since some of the tests to be used are not available commercially and the reagents to be used must be individually prepared. To overcome possible variation in test results, as described above, whenever possible, standardized test protocols and a single source of diagnostic reagents will be used. In cases where results of standardized tests are inconclusive or questioned, specimens will be examined with other partners in the network for clarification, confirmation or additional testing, or referred to external reference laboratories such as the CDC. 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.

The network should have the support of the regional ongoing quality control program in order to assure the good practice in the laboratories, and a team of expert should be formed to develop the program. Topics for consideration may include:

- Callibration of equipment and validation of installation.
- Validation procedures for new methodologies and new reagents.
- To establish the specifications of sensitivity, specificity and stability of diagnostic reagents and
- Laboratory Biosafety

7.5 Equipment

Provided adequate resources become available, each national surveillance site will be supported with a -70^{o}C and a -20^{o}C freezer and an ELISA reader and washer for dedicated specimen storage and testing of samples, respectively. Also, a minimum of at least one liquid nitrogen shipping container (dry shipper) will be provided to each laboratory for temporary storage and transportation of specimens. Biosafety Cabinet Class II and centrifuges with covers cups should also be available.

Table 9: Syndrome study: specimen and laboratory methodologies

Syndrome	Specimens	Serology	Culture or Isolation	Molecular techniques	Histopathology
Undifferentiated Febril and Influenza	1. Sera 2. Nasopharyngeal swab	+	+ +		
Hemorrhagic Fever	Sera	+	+	+	
Febrile Icteric	Sera	+	+	+	
Acute Respiratory Distress	1. Sera 2. Blood clot 3. Nasopharyngeal swab	+	 +	+ 	
Unexpected death syndrome	1. Blood 2. Autopsy tissues	+	+ +	+ +	 +
Infectious Neurologic	1. Sera 2. Cerebrospinal Fluid	+ +	+ +	+ +	
Enteric	3. Sera 4. Stool	+	 +	 +	
HUS	1. Sera 2. Stool	+	 +	 +	

7.6 Project Management

Management of the collaborative project will, by necessity, involve two separate levels. Agreement was reached among all of the laboratories that external sources of funding should be sought to provide resources needed to maintain the network and conduct the proposed investigations. This will require that a single principal investigator with his/her parent organization submitting a specific proposal and assuming responsibility for overall management of funds, including disbursement and accounting. The principal investigator will also be responsible

for obtaining progress reports from national laboratories participating in the network and completing formal progress summaries for the funding agency, as required. At least two potential funding sources were discussed, the United States National Institutes of Health (NIH) and the United States Agency for International Development (USAID). If different individuals and organizations prepare separate proposals for these or other donors, then each principal investigator would have management responsibilities for his/her own grant or contract.

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

7.7 Associated Institution

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 Southern Cone 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, various countries to assist in outbreak investigations often call upon the CDC.

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 six 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.

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 Diseases Research (TDR), the Global Program for Vaccines (GPV), and others.

7.8 Study Sites and Populations

Individual countries will develop specific plans for the surveillance network, taking into consideration the following factors:

1. Areas of disease risk
2. Existing laboratory capacity
3. Existing epidemiological capacity
4. Diversity of environment (climate and/or socioeconomic)

Every effort should be made to strengthen broadly the capacity of existing laboratories. In defining areas at risk, the participating sites should consider not only areas where a disease is known to occur, but also the surrounding areas to which the disease might spread, including areas in neighboring countries.

7.9 Number of Subjects

The ideal number of subjects will vary depending on the specificity of the syndrome, how widely the syndrome occurs with respect to geography and time, and other special circumstance, such as a need to monitor for antimicrobial resistance. Countries will develop testing quotas based on the preceived prevalence of the syndrome and the availability of resources.

7.10 Follow-up of Patients

Countries will collectively develop a plan for follow-up based on the needs for individual diseases and syndromes. The group felt that testing of the acute specimen would be adequate for most diseases, although attempts should be made to obtain follow-up specimens whenever possible.

7.11 Outbreak Investigations

The capacity for conducting outbreak investigations must be an integral part of the surveillance system. To assist in the identification of outbreaks, sentinel sites should tally weekly the number of cases of each syndrome and, if an excess is noted, report that information to the epidemiology unit. Outbreak investigations should involve a task force that includes laboratory, epidemiology and local personnel. Network countries agree to provide advice to one another as needed to respond to outbreaks.

7.12 Questionnaire

Countries will develop questionnaires based on their individual needs. Summary information to be shared among countries includes the following core data: patient age and sex, rural or urban setting, clinical syndrome, date of illness onset, final diagnosis, basis of final diagnosis (clinical vs. laboratory confirmed), clinical outcome, geographic region of case.

7.13 Specimen Banking

Banking of all specimens will be impractical for most countries. Depending on the available resources in each country, specimens for which demographic and clinical data are available will be banked with the priority:

1. Specimens that are part of an outbreak
2. Specimens for which both acute and convalescent serum are available.
3. Sera without diagnosis.

7.14 Communications/Networking

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

7.15 Training

It was recognized that training and technology transfer will be important components in the development of the Southern Cone Region Emerging Disease Network. Although all of the collaborating laboratories are well established and employ highly competent professionals and staff, recent discoveries such as hantavirus pulmonary syndrome and technological advances, such as the widespread diagnostic application of polymerase chain reaction, necessitate the availability

of periodic, specialized training opportunities. 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. 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.

7.16 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 *Triatoma 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.

7.17 Integration of the network to the national surveillance systems

It is anticipated that the proposed network of laboratories for surveillance of EID in the Southern Cone Region 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 Southern Cone 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 regional laboratories will require governmental coordination, which will involve mainly the Ministries of Health and Foreign Affairs, taking into account presently existing agreements among the 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 FIOCRUZ and the Instituto Adolfo Lutz. 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.

7.18 National Technical Committee

A National Technical Committee should be established in countries that do not have one, in order to organize, strengthen, define, and execute policies related to activities aimed at the creation and maintenance of a EID surveillance network.

8. CONCLUSIONS

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

8.2 Participants agreed that initially the surveillance activities should focus in the following health problems:

- Influenza
- Antimicrobial resistance, including tuberculosis
- Acute diarrhea, including *E. Coli* 0157 (HUS).
- HPS/Hantavirus disease

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

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

ANNEX 1

List of Principal Publications

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M.Rivas; N.Binsztein; G.Basanta; et. al. Antibody responses against Escherichia coli heat-labile toxin and Colonization Factor Antigens l and ll in Argentinian children. **J Infect Dis**, 171: 1045-1049; 1995

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Paraguay

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ANNEX 2

Diseases and agents for which reporting in Brazil is mandatory:

1. - AIDS
2. - `Mumps`
3. - Dengue
4. - Diphtheria
5. - Typhoid Fever
6. - Visceral leishmaniasis
7. - Cutaneous leishmaniasis
8. - Leptospirosis
9. - Hepatitis A
10. - Hepatitis B
11. - Hepatitis C
12. - Unspecified hepatitis
13. - Meningococcal disease
14. - Tuberculous meningitis
15. - Other etiology meningitis
16. - Unspecified meningitis
17. - Hanseniasis
18. - Bacilliferous pulmonary tuberculosis
19. - Others tuberculosis
20. - Human rabies
21. - Malaria falciparum
22. - Malaria vivax
23. - Malaria malarie
24. - Falciparum vivax.
25. - Congenital syphilis
26. - Acute flaccid paralysis
27. - Accidental tetanus
28. - Neonatal tetanus
29. - Yellow fever
30.--Cholera
31. - Measles

Diseases and agents recently incorporated in the system:

1- Hantavirus
2- Influenza
3- Strepto pneumoniae
4- Haemophillus influenzae
5- Foodborne diseases

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