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Plasmodium falciparum Response to Chloroquine in the Americas

P. falciparum resistance to chloroquine was first observed in 1960-1961 in patients coming from the Lake Maracaibo region in Venezuela, the Magdalena River Valley in Colombia, and the Amazon Basin in Brazil.

Between 1961 and 1964 a number of controlled field studies reinforced those observations, and some carried out in research centers confirmed resistance to the 4-aminoquinolines and to other malaria drugs.

In 1965 a WHO Scientific Group described a standardized procedure for the *in vivo* determination of the effect of the drug administered orally in a standard dose of 25 mg of cloroquine (base) per kg body weight for three days. To observe the immediate and curative effect of the drug, parasite counts are made daily during the first week following treatment and weekly during the following three weeks.

With this procedure different responses to chloroquine have been observed, depending on the proportion of susceptible plasmodia and the immunity level of the patient.

In Central America, Haiti, and Mexico, asexual parasitemia in patients studied in malarious areas is controlled in 48-72 hours and, in the last 20 years, no relapses have been recorded during the four weeks of observation, which indicates that the infections are *susceptible* (WHO, 1973).

In South America, about 40 per cent of the infections have been found susceptible to the standard dose in semi-immune persons living in areas in which transmission occurs in Bolivia, Brazil, Colombia, Ecuador, French Guiana, Guyana, Panama, Paraguay, Peru, Suriname, and Venezuela. Another 40 per cent of the infections in those countries relapse between the second and fourth week following treatment. In addition, recrudescence of infection has been observed in the first seven days or in infections in which the parasitemia is not controlled in the same period (15 per cent) and, finally, there are infections whose parasitemia remains at the same level or increases following treatment, with consequent worsening of the patient's condition (5 per cent). This last-mentioned group is found in particular in land-settlement areas in the basins of the major rivers of Brazil and Colombia.

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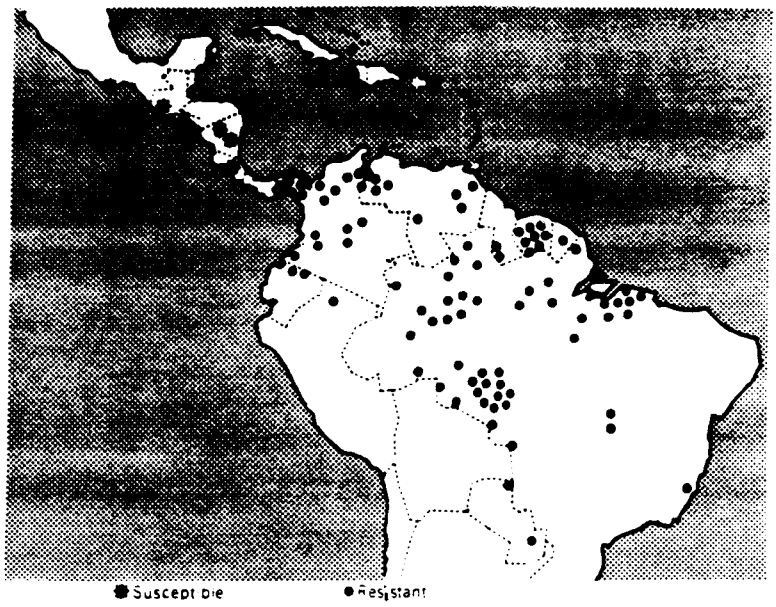
Figure 1. Geographic distribution of the results of susceptibility tests of *P. falciparum* to cloroquine in the Americas, 1961-1980.



To evaluate the inhibition of the maturation of the schizonts to different amounts of cloroquine (the same as or higher than the levels obtained with the recommended doses), a simple *in vitro* method has been used. The advantages of this method are as follows: on the one hand, the patient is not bothered with successive examinations over a period of several weeks; results are obtained within 24 hours and operating costs are reduced; on the other hand, such factors as the absorption and metabolism of the drug or the immunity status of the patient, which may alter the results of the *in vivo* tests, are ruled out.

In Central America, Haiti, and Mexico the inhibition of the schizonts 24 hours following incubation varies from ≤ 0.5 nmol of chloroquine diphosphate per ml of blood in the more susceptible strains of Haiti to 0.75 nmol in Mexico, and 1.25 in Nicaragua. In South America, the inhibition of schizonts was found to be between 1.0 and ≥ 3.0 nmol, but more resistant parasites have been found in Brazil and Colombia.

The malaria programs of the Region of the Americas, in cooperation with national institutions and PAHO, are endeavoring to expand studies of the resistance mechanisms, the genetic and antigenetic characterization of strains of various origins, the distribution factors in the human population, and different treatment schedules.

In addition, the Special Program for Research and Training in Tropical Diseases (WHO World Bank UNDP) has provided assistance in establishing a worldwide epidemiological surveillance system for the purpose of identifying susceptible and resistant strains as well as any changes that may occur.

Figure 1 shows the geographic distribution of *P. falciparum* reactions observed between 1961 and 1980 in the Americas.

(*Source*: Parasitic Diseases and Vector Control, Division of Disease Prevention and Control, PAHO.)

Diseases Subject to the International Health Regulations

Cholera, yellow fever, and plague cases and deaths reported in the Region of the Americas up to 15 April 1981*

Country and administrative subdivision	Cholera Cases	Yellow fever		Plague Cases
		Cases	Deaths	
BOLIVIA	—	75	10	4
Cochabamba	—	3	3	—
La Paz	—	3	1	4
Santa Cruz	—	69	6	—
PERU	—	5	2	7
Cuzco	—	2	—	—
Madre de Dios	—	1	1	—
Piura	—	—	—	7
San Martín	—	2	1	—
UNITED STATES	—	—	—	1
New Mexico	—	—	—	1

*Provisional figures.
—None.

Vectors of Jungle Yellow Fever

The 119 reported cases of yellow fever (Table 1, Fig. 1) and 92 known deaths from the disease in 1980 clearly indicate the role of non-*Aedes aegypti* vectors in the maintenance and spread of yellow fever in the Americas. However, very little is known about the taxonomy, distribution, ecology, and biology of these mosquitoes, let alone their vectorial capacity. It is known that there are several important vectors of jungle yellow fever in the genus *Haemagogus*. The principal taxonomic work in this field is entitled *Mosquito Studies XXII (Contribution of the American Entomological Institute* 10(2):1-74, 1973), which states that the genus *Haemagogus* includes two subgenera and 24 species. Most of the literature cited dates back to 1960 or prior years. The publication *Mosquito Systematics*[1] includes periodical listings that provide additional information on vector distribution and habitats.

Females of many species of *Haemagogus* can bite man. Many are arboreal and seldom descend to ground level, but as a result of deforestation and new land settlement projects, as well as road construction, man comes into intimate contact with the mosquitoes. However, other species breed both at ground level and in the forest canopy. Breeding places are primarily treeholes, bamboo, and bromeliads, but they have also been collected in ground pools and rockholes.

Haemagogus janthinomys is considered the most important vector of jungle yellow fever; it has extended from the Atlantic coastal regions of Honduras and Nicaragua, through Central America, the South American watersheds flowing into the Caribbean, and Trinidad and Tobago; it has also been found in Argentina, Bolivia, Brazil, Colombia, Ecuador, and Peru. Other involved

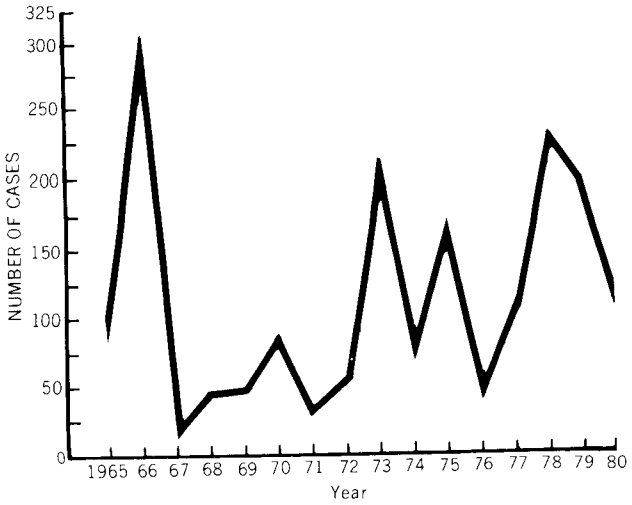
Table 1. Cases of jungle yellow fever notified from 1975 to 1980 in the Americas, by country.[a]

	1975	1976	1977	1978	1979	1980
Bolivia	151	19	2	11	10	46
Brasil	1	1	9	27	12	26
Colombia	12	22	9	105	51	11
Ecuador	3	1	—	1	14	2
Peru	1	1	82	93	97	30
Trinidad and Tobago	—	—	—	—	18	—
Venezuela	—	—	—	3	3	4
Total	168	44	102	240	205	119

[a]Up to 31 December 1980 (provisional figures).
—None

[1]*Mosquito Systematics*. Collection Records of the Project "Mosquitoes of Middle America." Department of Biology, University of California, Los Angeles, California.

Figure 1. Reported cases of jungle yellow fever in the Americas, 1965-1980.*



*Up to 31 December 1980 (provisional data)

species are *H. spegazzini*, *H. leucocelaenus*, and *Sabethes chloropterus*, though *H. capricornii*, *H. mesodentatus*, *H. albomaculatus*, *H. soperi*, *H. equinus*, *H. celeste*, and *H. lucifer* are also suspected of being involved in the transmission cycle. *S. chloropterus* may be important since it lives long enough to explain its survival through the dry season. However, it is not considered a very active vector.

The observation of Tinker (PAHO, Bogotá, Colombia) that epidemics of jungle yellow fever occurred at El Tarra, Sierra Nevada, and Caquetá in the apparent absence of *Haemagogus*, and the finding of yellow fever antibodies in the sera of four porcupines by Méndez (Institute of Public Health, Lima, Peru) indicate a great need for a long-term ecological study of yellow fever in endemic areas. A further observation by Tinker of jungle vectors in urban areas makes it essential to expand distribution studies and to investigate any changes in behavior and habitat of those vectors. In addition, the increasing invasion of man into the natural habitats of *Haemagogus* and *Sabethes* will prolong the jungle yellow fever problem and will create the need to expand epidemiological surveillance into those newly settled areas.

(*Source*: Parasitic Diseases and Vector Control, Division of Disease Prevention and Control, PAHO.)

First Endemic Focus of Onchocerciasis Discovered in Ecuador

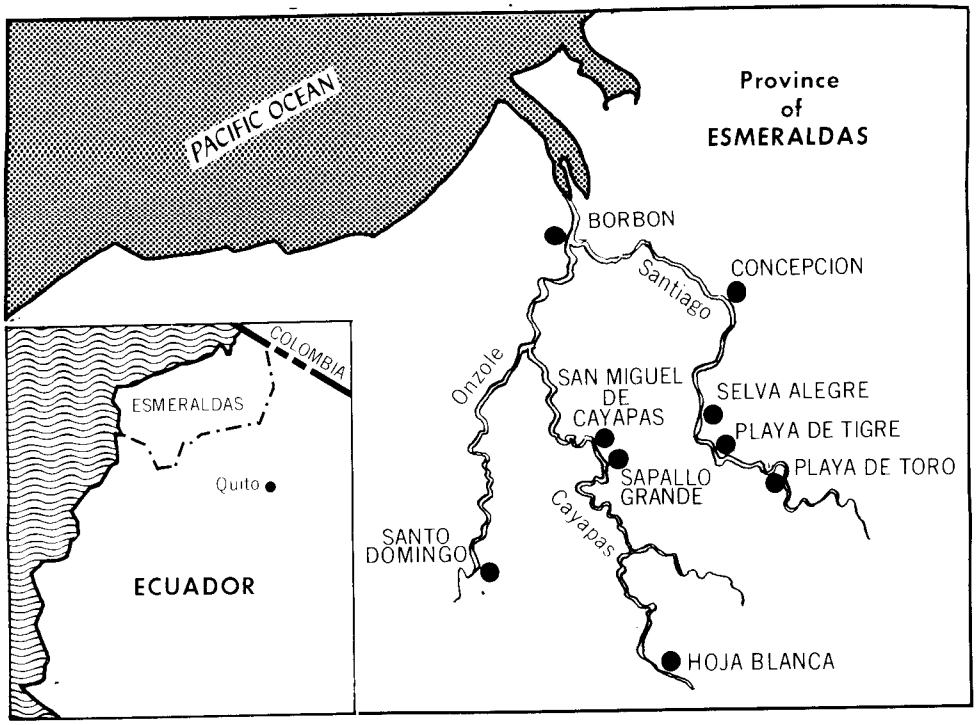
The first case of onchocerciasis in Ecuador was diagnosed in May 1980 by Dr. Luis Carvajal and Dr. Fortunato Zerega in histopathological sections of a subcutaneous nodule and confirmed parasitologically by Dr. M. E. Arzube, Chief, Research Division, "Leopoldo Izquieta Pérez" National Institute of Hygiene, Guayaquil.

The data provided by the patient gave rise to a suspicion of the existence of an endemic focus. An epidemiological study was made between 22 June and 2 July to determine whether the patient had acquired the disease in the place in which he lived; to discover the existence of other cases; and to identify possible vector flies (*Simulium*). In October an additional field study was made to obtain more epidemiological information on the focus.

The first patient in whom onchocerciasis was diagnosed had lived for 50 years in a place called "El Tigre," less than a kilometer from the hamlet of San Miguel de Cayapas, on the banks of the Cayapas River, and 80 km from the town of Borbón, in Esmeraldas Province.

In this area the topography is rugged and the rivers make up the Santiago River basin. Because of rains between January and May, the river stage rises by 2 or 3 meters and floods the strips of land between the hills; in the other months, the rains are less intense and frequent and the river flow decreases although in the area it rains 12 months a year. The climate in the area is hot and humid (equatorial tropical climate). The average temperature is 27°C and the humidity ranges between 70 and 90 per cent. The annual rainfall is between 2,500 and 4,200 mm. The vegetation is luxurious and is that of a tropical rain forest.

Figure 1. Distribution of localities found positive to onchocercosis in Ecuador.



The ethnic composition of the population of the area of the hamlets of Sapallo Grande and San Miguel de Cayapas is as follows: 79 per cent negroes, 14.9 per cent indians, and 5.7 per cent whites.

The negro population of the area is sedentary and consists of farmers, fishermen, and hunters; as a rule they do not own any cattle, horses, or goats, but some of them have a few pigs and chickens. Most of the time the men wear shorts and sometimes no shirts or shoes; the women wear knee-length dresses, but when they go into the rivers or streams to do their domestic chores or to wash the sand for gold, they wear short skirts and large hats and are bare to the waist. Their houses, which are built of bamboo (*Guadua angustifolia*) have thatched roofs; they are raised above ground level, and are isolated from the exterior by external walls that have openings that serve as windows.

The Cayapas indians have been nomads, fishermen, and hunters but they are moving toward sedentary agriculture. They do not own any domestic animals nor do they raise any for profit; they wear the same clothes as the negro population. Their houses, which they build with "pambil" (*Catostigma* sp.) and "chonta" (*Bactres* sp.), have thatched roofs, are raised above the ground, are very large, and do not have external walls.

Confirmation of the Focus and Initial Epidemiological Studies

In San Miguel de Cayapas there are seven houses occupied by 40 persons. According to data provided by the National Malaria Eradication Service, in the area between Sapallo Grande, with the river of the same name, and San Miguel de Cayapas and its own river, there is a scattered population of 1,117 persons living in 215 houses.

In the two hamlets, 87 persons were examined: 69 negroes, 13 Cayapas indians, and 5 whites who had lived in the area for many years. Each of these individuals was examined for signs and symptoms of the disease, and an assessment was made of the number and distribution of nodules, the presence or absence of pruritus, severity and distribution of skin manifestations, pigmentary changes and atrophy, lymphedema, lymphadenitis of the ganglia, primarily the inguinal and crural ganglia, as well as of the severity and type of ocular lesions.

Following this physical examination skin biopsies were made in order to confirm and assess the intensity of the infection. Two biopsies per person were made, one on the spine of the scapula and the other just below the crest of the ilium. Microfilia were counted and identified and

found to be *O. volvulus*.

Black flies were captured over a period of two days, in the early morning, using human bait and tubes containing chloroform. Two sites were selected: one house in El Tigre, and the other in San Miguel de Cayapas. The insects captured were divided into two groups, one for taxonomic classification and the other for staining and dissecting in order to discover the larval forms of microfilariae.

Microfilariae infection of the skin was found in 72 (82.8 per cent) of the 87 persons examined: 62 (86.1 per cent) were negroes and 10 (13.8 per cent) Cayapas indians. The examination was negative in the case of the five whites who had lived in the area for many years.

With respect to the distribution by sex, 42 (58.3 per cent) of the persons infected were males and 30 (41.6 per cent) females.

The first cases were found in persons between the age of 5 and 9 years, which demonstrates early exposure and susceptibility to the infection.

The microfilariae density in the skin was greater at the level of the iliac crest in 47 (65.3 per cent) cases, compared with the results obtained on the scapula, which was 25 (34.7 per cent) cases. The degree of infection was classified as slight (with fewer than 50 microfilariae in the two biopsies) in 41 cases (56.9 per cent); average (with 50-100 microfilariae) in 9 cases (12.5 per cent); and serious (with more than 100 microfilariae) in 22 cases (30.5 per cent). In 45 patients (62.5 per cent) subcutaneous nodules of varying sizes were found (between 0.5 cm and 5.0 cm long at their largest diameter); some were flat and others raised above the skin; their consistency also varied.

The distribution of onchocercoma on the body shows that they occur most frequently at the level of the pelvis: in 21 cases (46.7 per cent), with 47 nodules; and on the thorax, in 13 (40 per cent) of the patients, with 35 nodules. The presence of nodules on the head was found in 3 (6.6 per cent) of the cases, with four nodules. The frequency and number of onchocercoma on the upper and lower extremities was not significant.

Skin changes such as dermatitis, atrophy, and pigmentary changes were found in 31 patients (43.1 per cent). There were cases with focal depigmentation and persistence of pigment around the pores and hair follicles; other, with atrophy and sclerosis of the lower layers of the skin and some, with scaling and pigmentary changes.

Most of the corneal opacities were classified as keratitis punctata; there were few cases with keratitis limbica and with lateral pannus.

Among the clinical manifestations an important symptom was pruritus (itch). A total of 49 (68.1 per cent) of the patients stated that it occurred at any hour of the day, intermittently, and intensely. These patients had different manifestations on the skin such as dermatitis, pigmentary changes, atrophy, and lymphedema. No cases of coast erysipelas were found among the patients examined.

Among the black flies captured there were 274 females. According to the information obtained from the inhabitants, black flies and gnats (*Simulium*) are present throughout the year in the area, with a high density toward late March and early April.

In accordance with the classification of Ecuadorian *Simuliidae* of L. León and P. Wygodzinsky, the 274 females captured were provisionally identified as belonging to three species: *S. exiguum*, *S. quadrivittatus*, and *S. dinelli*. The three species have developed anthropophilic habits because of the absence of large animals (cattle, horses, etc.) in the area and endophilic and endophagic habits because of the type of housing construction. Because of the clothing the inhabitants are accustomed to wear and the work they do in the jungle, a close insect/man, man/insect contact has been established, a necessary condition for the endemic disease to become established.

In October a further study was made by a multidisciplinary group. The group included representatives of the Ministry of Public Health, through the National Department of Epidemiology, the National Institutes of Health and the National Malaria Eradication Service, the

Table 1. Results of observations made in localities in the three river basins in Ecuador, 1980.

Basin	Examined			Positive			Positivity Rate (%)
	June	October	Total	June	October	Total	
Santiago River[a]	—	149	149	—	50	50	33.55
Onzole River[b]	—	17	17	—	5	5	29.41
Cayapas River[c]	87	15	102	72	13	85	83.33
Total	87	181	268	72	68	140	52.23

The localities found positive for onchocerciasis were:
[a]Vargas Torres (Playa de Toro), Playa de Tigre, and Selva Alegre.
[b]Santo Domingo.
[c]Sapallo Grande, San Miguel, and Hoja Blanca.

Ministry of Social Welfare, the State University of Guayaquil, and the Technical University of Esmeraldas. The Armed Forces of Ecuador provided logistic support.

Observations were made in localities in three river basins (Santiago, Onzole, and Cayapas) and the results summarized in Table 1 were obtained.

In the 150 patients given clinical examinations during studies designed to delimit the focus, ichthyosis was observed (in 46 per cent of the patients); spots (28 per cent); eczema (4 per cent); lichenification (6 per cent); papules (8 per cent); and nodules (32 per cent). Pruritus was reported by 14 per cent. No cases of hanging groin were observed.

An ophthalmological survey was made in three communities and 68 positive cases of onchocerciasis were found by biopsy; 19 of the patients had benign ocular involvement (punctiform corneal opacity, conjuntivitis and cicatricial choroidoretinitis).

As a result of these observations, the Ministry of Public Health has set up a control program that will carry out reconnaissance, area research, and prevention and treatment activities. In addition, the Ministry of Social Welfare is coordinating social activities with various institutions for the purpose of promoting the comprehensive development of these communities.

(*Sources*: "Oncocercosis en el Ecuador. Primer foco endémico descubierto en el país. Hallazgos clínicos, parasitológicos y entomológicos." Dr. Manuel E. Azube, NIH, Guayaquil, 12 November 1980. "Consideraciones clínicas y epidemiológicas de la oncocercosis en poblaciones predominantemente de color en la Provincia de Esmeraldas, Ecuador." Dr. Juan Runebea and Dr. Ramón F. Lazo, NIH, and Dr. José U. Cedeño, National Department of Epidemiology, Ministry of Public Health, Ecuador.)

Editorial Comment

The number of persons suffering from *Onchocerca volvulus* infection is estimated at between 20 and 40 million throughout the world. Most of the affected population lives in Africa, south of the Sahara, but there are important foci in Yemen and in Latin America.

With the recent discovery of a focus in Ecuador there are now six countries in the Americas in which the disease has been discovered: Guatemala (1915), Mexico (1923), Venezuela (1949), Colombia (1965), Brazil (1974), and Ecuador (1980).

It should be pointed out that the "index" cases, that is, the first cases discovered that subsequently gave rise to field investigations confirming the existence of foci in Colombia, Brazil, and Ecuador, were identified in non-endemic areas (in Buenaventura, São Paulo, and Guayaquil, respectively). This fact underscores the need both for training in tropical diseases, even in those diseases considered exotic in the country or region, to be included in the curriculum of medical schools, and for the authorities responsible for epidemiological surveillance in the countries to remain alert to pathological entities that may exist or may be compatible with the ecology of the various regions.

As a result of the information provided by the patient identified in Guayaquil, field visits were made first to the place where he lived and then to other localities in the region with a similar ecology; seven localities were found positive on the three rivers that unite to form a common river basin. This finding would appear to indicate that additional studies are advisable to define the extent of the focus, the intensity of the infections, and the existence of ocular sequelae and thus to plan the corresponding control measures, as well as entomological studies to identify the vectors, establish the larval cycle and the dispersion or radius of flight of the female flies, and carry out insecticide trials.

The approach of the control measures adopted should be comprehensive and include the provision of primary eye care and the treatment of eye infections and xerophthalmia.

Rabies Control Program in Brazil, 1975–1978

The National Rabies Control Program of Brazil was established in 1973 under an agreement between the Ministries of Health and Agriculture, the Drug Center, and the Pan American Health Organization. The activities carried out include the following:

- preparation of technical standards for rabies control, at present adopted throughout the country;
- support to the production and control of vaccines for

Table 1. Activities of the National Rabies Control Program, Brazil, 1975-1978.

Activity	Year				Total
	1975	1978	1977	1978	
Persons attended	147,393	153,940	183,358	226,117	710,808
Persons treated	84,821	94,297	105,969	132,568	417,655
Ratio of persons treated to persons attended (%)	57.5	61.3	57.8	58.6	58.8
Vaccine doses administered	1,074,548	1,126,022	1,230,229	1,391,821	4,822,620
Average vaccine doses per person treated	12.7	11.9	11.6	10.5	11.5
Human cases of rabies investigated	120	99	141	141	501
Cases of canine and feline rabies[a]	1,380	2,201	2,608	1,875	8,064
Dogs vaccinated	1,888,180	2,503,689	4,163,494	4,646,006	13,201,369
Dogs captured and slaughtered	42,528	46,179	84,845	91,018	264,570

[a]Laboratory diagnosis.

human and animal use;

- supply of vaccines and antirabies serum to the state ministries of health, in accordance with a delivery schedule prepared annually;
- expansion of the network of laboratories for the diagnosis of rabies, training of personnel for those laboratories, and supply of specific antigens;
- establishment of a model schedule for the treatment of persons exposed to the risk of contracting rabies;
- establishment of a system for the epidemiological surveillance of the disease, through a network of notification posts covering the entire country; this makes it possible to obtain regular information on the preventive treatment of human beings, the incidence of animal rabies, and the prophylaxis of canine rabies.

Treatment of Rabies in Man

Since the beginning of the Program, only the Fuenzalida-Palacios vaccine, which is produced in five government laboratories, has been used.

In 1975-1978, a total of 710,808 persons in Brazil received medical care because of the risk of possible exposure to the rabies virus. Of these, 417,655 (58.8 per cent) received specific treatment, the total number of doses administered being 4,822,620, or an average of 11.5 doses per person treated.

In the same period, 501 human cases of rabies were investigated. Only 58 (11.6 per cent) of the cases had received treatment after exposure. Of these, 45 (7.8 per cent) had been seriously bitten. Only 4 were given antirabies serum (in addition to the vaccine).

The results obtained from the antirabies treatment of human cases were not those expected. In this regard, the following is worthy of mention:

1. The high percentage of persons treated as a ratio of those receiving care (58.8 per cent) shows that, in accordance with the standards recommended (in particular that relating to the observation of the biting animals), many treatments could have been avoided.
2. The high average number of vaccine doses per person treated points to excessive administration of complete courses of treatment due to inadequate observation of the biting animal.
3. The high incidence of rabies cases in persons not receiving specific preventive treatment shows that the services available do not cover a large part of the population, especially in localities in the interior of the country and on the periphery of the large cities. In several states there is excessive centralization of services for the treatment of human cases of rabies, which greatly hinders their use by persons that live in places distant from them and do not have means of transportation. This situation and the fact that because of inadequate health education, the population usually has no knowledge of first-aid measures

Table 2. Deaths from rabies by age group, Brazil, 1975-1978.

Age group	1975		1976		1977		1978		Total	
	No.	%	No.	%	No.	%	No.	%	No.	%
0-4	14	12	7	7	14	10	10	7	45	9
5-9	41	34	37	38	37	26	35	25	150	30
10-14	26	21	18	18	26	19	29	20	99	20
15-19	6	5	7	7	11	8	15	11	39	8
20-29	13	11	8	8	10	7	12	8	43	8
30-59	17	14	18	18	37	26	27	19	99	20
60 and more	2	2	3	3	6	4	11	8	22	4
Unknown	1	1	1	1	—	—	2	2	4	1
Total	120	100	99	100	141	100	141	100	501	100

Table 3. Deaths from rabies in persons that received post-exposure treatment by type of treatment, location of wound, and incubation period, Brazil, 1975-1978.

Type of treatment	Location of wound	Incubation period				TOTAL	
		0-30	31-60	61-180	180+	No.	%
Vaccine	Head and neck	18	—	—	—	18	31
	Trunk and upper members	26	1	—	—	27	47
	Lower members	4	1	—	—	5	9
Serum and vaccine	Head and neck	4	—	—	—	4	7
	Trunk and upper members	—	—	—	—	—	—
	Lower members	—	—	—	—	—	—
Serum	Head and neck	—	—	—	—	—	—
	Trunk and upper members	—	—	2	—	2	3
	Lower members	—	—	1	1	2	3
Total		52	2	3	1	58	—

for preventing the disease, are the principal factors that still favor the existence of human rabies in Brazil. Of the cases of human rabies, 59 per cent occur in the age group 0-14 years.

4. In the case of serious bites, the most effective preventive measure is the combined administration of antirabies serum and vaccine; however, this practice has not been routinely followed in the country. Indeed, between 1976 and 1978, only 17,363 persons received serum plus vaccine, which represents just about 5.2 per cent of the total of 332,834 treated in that period. Of these treatments, 80 per cent were given in São Paulo, which means that in the rest of the country combined treatment was given to only 1 per cent of the persons treated.

5. Between 1975 and 1978, of the 417,655 persons that began the vaccination schedule, 43,225 (10.8 per cent) did not complete the treatment. Of the 501 human cases of rabies that occurred in that period, 25 occurred among persons that abandoned treatment.

6. Although the Fuenzalida-Palacios vaccine is believed to entail a low risk of neurological complications, during the period 1975-1978 there were 17 cases of serious post-vaccinal accidents, 11 of which were fatal. Of the 17 cases, 16 received 10 doses or more of the vaccine and one case, five doses. The proportion of serious post-vaccinal accidents in persons treated in 1975-1978 was 1:24,568.

These data indicate that, among other priorities, the number of doses in the official schedule at present in use in Brazil needs to be reduced.

A number of countries have adopted a reduced vaccination schedule and the results have been satisfactory. In Brazil, studies on such a schedule have been made in São Paulo, Minas Gerais, and Belo Horizonte and good results have also been obtained.

Prevention of Canine Rabies

The mass elimination of stray dogs is at present impossible because of the prevailing cultural patterns and the lack of financial resources. Nevertheless, an alternative measure is available—elimination of the incidence of rabies in those animals or its reduction to a minimum level.

Other measures include regular mass vaccination of dogs, the control of rabies foci, the reduction of the number of stray dogs through capture and subsequent elimination of unclaimed animals, and rabies education of the public.

Since it began, the Program has emphasized the rabies vaccination of dogs. This activity was selected as a basic activity because it is well accepted by the population, is relatively cheap, and does not require a complex infrastructure for executing it and, fundamentally, because of its effectiveness in controlling the disease.

Canine vaccination was begun in the capitals of the federal units and later was gradually extended to the metropolitan areas and municipalities in the interior. With the exception of the Federal Territories of Roraima, Fernando de Noronha, and the State of Acre, all the other federal units are conducting rabies vaccination campaigns.

The number of dogs vaccinated rose from approximately 500,000 in 1973 to 4,700,000 in 1978. In the areas in which canine vaccination was correctly carried out—with a minimum coverage of 60 per cent of the existing dogs, in a maximum period of 60 days, on a regular annual basis—good results were obtained in reducing the incidence of human cases of rabies.

The services for the capture and elimination of stray dogs face serious economic, social, and political problems that hinder their operation.

Studies of the dynamics of the dog population show that its annual renewal rate is close to 20 per cent and, therefore, to reduce the present population it would be necessary to eliminate not less than 30 per cent of this population.

In 1975-1978 the number of dogs eliminated was 264,570; of these, 71 per cent were from the municipality of São Paulo and therefore the desired elimination levels were not attained (in 1978 only 9 per cent of the estimated dog population was eliminated). The results obtained in the remaining municipalities of Brazil are difficult to evaluate.

To improve the services for the capture and elimination of stray dogs it would be necessary to prepare new technical standards for their operation and to apply to the government authorities for legal authority to implement them.

Laboratory Diagnosis

When the Program began, laboratory diagnoses of rabies were made in seven states, most of which were located in the southeast and south of the country. This activity was expanded, and at present laboratories capable of making routine examinations are available in 18 states.

Conclusion

Human rabies may be considered under control in most of the more populous cities of Brazil (such as Recife, Brasília, Belo Horizonte, São Paulo, Curitiba, Porto Alegre), in addition to other capitals with a smaller population (São Luís, Maceió, Aracajú, Vitória, Cuiabá, Campo Grande, and Florianópolis).

In the States of Rio Grande do Norte, Paraná, Santa Catarina, Rio Grande do Sul, Mato Grosso, Mato Grosso do Sul, and Espírito Santo, the control of human rabies has attained satisfactory levels. In the State of Acre and the Territories of Roraima and Fernando do Noronha, no human cases of rabies have so far been reported.

These data show that human rabies is ceasing to be a problem in the capital cities, but is still a problem in other areas; efforts to expand and strengthen the Rabies Control Program in the interior of the country therefore need to be continued if control of the disease is to be achieved throughout the national territory.

(*Source*: *Revista da Fundação Serviço Especial de Saúde Pública*, Vol. XXV, No. 1, 1980.)

New IATA Regulations on Restricted Articles

There is an urgent sense of concern among microbiologists, veterinary and public health authorities, transportation and postal industries, and the lay public in many countries about the shipment and transfer of potentially infectious microorganisms. Attention has been drawn to these dangers by recent widely publicized occurrences of individual cases of severe human infectious diseases such as Lassa fever and Marburg disease, and by outbreaks of exotic infectious disease among domestic animals.

The only international regulations pertinent to the shipment of infectious substances are those of the International Air Transport Association (IATA), a nongovernmental international airline organization operating throughout the world. IATA has specified volume limits and stress factors for containers. IATA also requires labels and shipper certificates to be attached to packages containing "etiologic agents." Laboratories and hospitals around the world are often completely unaware of these regulations.

As a result of new technological developments and changing requirements of the air transport industry, IATA introduced many changes and improvements in the *Restricted Articles Regulations*, which became effective on 1 December 1980. The new IATA regulations on the shipment of infectious substances (etiologic agents) include the following:

1. DEFINITION AND CLASSIFICATION

An etiologic agent is defined as any material containing a viable microorganism, or its toxin, which causes or may cause human disease, and is further limited to those agents listed below:

Bacterial Agents

Actinobacillus—all species
Arizona hinshawii—all serotypes
Bacillus anthracis
Bartonella—all species
Bordetella—all species
Borrelia recurrentis, B. vincenti
Brucella—all species
Clostridium—all species
Corynebacterium diphtheriae, C. equi, C. haemolyticum, C. pseudotuberculosis, C. pyogenes, C. renale

Diplococcus (Streptococcus) pneumoniae
Erysipelothrix insidiosa
Escherichia coli, all enteropathogenic serotypes
Francisella (Pasteurella) tularensis
Haemophilus ducreyi, H. influenzae
Herellea vaginicola
Klebsiella—all species and all serotypes
Leptospira interrogans—all serotypes
Listeria—all species
Mina polymorpha
Moraxella—all species
Mycobacterium—all species
Mycoplasma—all species
Neisseria gonorrhoeae, N. meningitidis
Pasteurella—all species
Pseudomonas pseudomallei
Salmonella—all species and all serotypes
Shigella—all species and all serotypes
Sphaerophorus necrophorus
Staphylococcus aureus
Streptobacillus moniliformis
Streptococcus pyogenes
Treponema careteum, T. pallidum, and T. pertenue
Vibrio fetus, V. comma, including biotype El Tor, and V. parahaemolyticus
Yersinia (Pasteurella) pestis

Fungal Agents

Actinomycetes (including Nocardia species, Actinomyces species and Arachnia propionica)
Blastomyces dermatitidis
Coccidioides immitis
Cryptococcus neoformans
Histoplasma capsulatum
Paracoccidioides brasiliensis

Viral, Rickettsial, and Chlamydial Agents

Adenoviruses, human—all types
Arboviruses
Coxiella burnetii
Coxsackie A and B viruses—all types
Cytomegaloviruses
Dengue virus
Echoviruses—all types
Encephalomyocarditis virus
Hemorrhagic fever agents, including Crimean hemorrhagic fever (Congo), Junin, and Machupo viruses, and others as yet undefined
Hepatitis—associated antigen
Herpesvirus—all members
Infectious bronchitis-like virus
Influenza viruses—all types
Lassa virus
Lymphocytic choriomeningitis virus
Marburg virus
Measles virus
Mumps virus
Parainfluenza viruses—all types
Picorna viruses—all types
Polioviruses—all types
Poxviruses—all members
Psittacosis, ornithosis, trachoma, Lymphogranuloma groups of agents
Rabies virus—all strains
Reoviruses—all types
Respiratory syncytial virus
Rhinoviruses—all types
Rickettsia—all species
Rubella virus
Simian viruses—all types
Tick-borne encephalitis virus complex, including Russian spring-summer encephalitis, Kyasanur forest disease, Omsk hemorrhagic fever, and Central European encephalitis viruses
Vaccinia virus
Varicella virus
Variola major and Variola minor viruses
Vesicular stomatis virus
Yellow fever virus

2. PACKING NOTES

2.1 *On Passenger and Cargo Aircraft (IATA Packing No. 695)*: The maximum amount of etiologic agents that can be shipped in one package is 50 milliliters.

Cultures of etiologic agents (infectious substances) and etiologic agents (infectious substances) shall be packed as follows:

(a) They shall be placed in securely closed, watertight primary receptacles (test tubes, vials, etc.) which shall be enclosed in a durable, watertight secondary packaging. Several primary receptacles may be enclosed in a single secondary packaging, providing that the total volume of all the primary receptacles so enclosed does not exceed 50 milliliters. The space at the top, bottom, and sides between the primary receptacles and secondary packagings shall contain sufficient non-particulate absorbent material such as cotton wool, to absorb completely the contents of the primary receptacle(s) in case of breakage or leakage. Each set of primary receptacle and secondary packaging shall then be enclosed in an outer packaging constructed of corrugated fiberboard, wood, or other material of equivalent strength. The maximum amount

of etiologic agents (infectious substances) that may be carried in any one package is 50 milliliters.

(b) If either ice or dry ice need to be used as a refrigerant, it must be placed outside the secondary packaging(s). Interior supports must be provided to hold the secondary packaging(s) in its original position after the ice or dry ice has been dissipated. If normal ice is used, it must be packed in a leakproof outer packaging. If dry ice is used, the outer packaging must permit the release of carbon dioxide gas.

2.2 *On Cargo Only Aircraft (IATA Packing No. 696)*: The maximum amount of etiologic agents that can be shipped in one package is 4 liters.

Each package containing an etiologic agent in volumes exceeding 50 milliliters must be designed and constructed so that, if it were subject to the test conditions prescribed below this Packing Note, there would be no release of the contents to the environment, and the effectiveness of the packaging would not be significantly reduced. In addition, etiologic agents (infectious substances) shall be packed as follows:

(a) They shall be placed in securely closed, watertight primary receptacles (test tubes, vials, etc.) which shall be enclosed in a durable, watertight secondary packaging. Several primary receptacles may be enclosed in a single secondary packaging provided that the total volume of all the primary receptacles so enclosed does not exceed 500 milliliters. The space at the top, bottom, and sides between the primary receptacles and secondary packagings shall contain sufficient non-particulate absorbent material such as cotton wool, to absorb completely the contents of the primary receptacle(s) in case of breakage or leakage. Each set of primary receptacles and secondary packagings shall then be enclosed in an outer packaging constructed of corrugated fiberboard, wood, or other material of equivalent strength. The space at the top, bottom, and sides between the secondary packaging(s) and the outer packaging shall include a shock absorbent material, in volume at least equal to that of the absorbent material between the primary receptacles and secondary packagings. Not more than eight secondary packagings may be packed in a single outer packaging. The maximum gross volume of etiologic agents (infectious substances) that may be carried in any one package is 4 liters.

(b) If either ice or dry ice need to be used as a refrigerant, it must be placed outside the secondary packaging(s). The shock absorbent material shall be so placed that the secondary packaging(s) does not become loose inside the outer packaging after the ice or dry ice has been dissipated. If normal ice is used, it must be packed in a leakproof outer packaging. If dry ice is used, the outer packaging must permit the release of carbon dioxide gas.

3. LABELLING

For the carriage of Restricted Articles, the shipper shall attach to each package containing such articles the appropriate label(s) as shown in this Section. Where space permits, labels shall be adjacent to the consignee's address. Labels may contain other inscriptions if so required in the country of origin, provided that such labels have the same color, size and symbol as shown below. Inscriptions may appear in two languages provided that one language is English and the inscriptions in both languages are given equal prominence.

Infectious Substance. The label may contain Class 6 number, Infectious Substance. The number must be printed in black in the lower corner and be approximately 6.5 millimeters (0.25 inch) high.

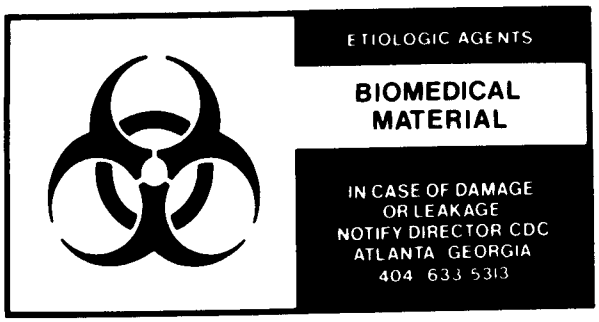
Name	Infectious Substance
Class Number:	6
Cargo Imp Code:	RIS
Dimensions:	10 centimeters by 10 centimeters. For small packages dimensions may be 5 centimeters by 5 centimeters.

Note: The new "Infectious Substance" labels are obligatory. Therefore, the old labels, in force until November 1979, are no longer used.

If the package is to be sent by Cargo Aircraft (because amount exceeds 50 milliliters), it should carry a label indicating: "Cargo Aircraft Only."

Special Restrictions. Special restrictions apply in the United States in cases of shipments within the country as follows:

Packages requiring the "Infectious Substance" label must also be classed as "Etiologic Agents" and in addition bear the "Etiologic Agents" label shown below:



The color of material on which the label is printed must be white and the symbol and printing in red. The label must be 5 centimeters (2 inches) high by 10 centimeters (4 inches) long. The red symbol measuring 3.8 centimeters (1.5 inches) in diameter must be centered in a white square measuring 5 centimeters (2 inches) on each side.

4. SHIPPER'S CERTIFICATE (see p. 14)

For the shipment of etiologic agents, the Shipper's Certificate must be completed as follows:

Article No. 736
Class: Etiologic agent 6
IATA Packing Note No. 695 (Passenger/cargo)
No. 696 (Cargo only)
Correct description of article sent: Etiologic agent followed by name or composition of article in parentheses.
For example: Etiologic agent (virus in liquid medium).

Note: Supplies of Shipper's Certificate forms and labels can be purchased from the following sources:

Bartsch Verlag K. G.,
P.O. Box D-8012,
Ottobrunn-Munich,
Germany
Tel: (089) 601 3031
Telex: 522 128

Labelmaster, 7525 N.
Wolcott Ave., Chicago,
Ill. 60636, U.S.A.
Tel: (312) 973 5100
Telex: 206 170
LBLMSTR

International Aeradio
Limited, Hayes Road,
Southall, Middlesex,
England UB2 5NJ
Tel: (01) 574 2411
Telex: 24114

Caribbean Epidemiology
Center (CAREC)
P.O. Box 164,
Port-of-Spain,
Trinidad and Tobago

Shipper's Certification forms are also available from most air carriers.

5. TRANSPORT

(1) *Cargo Aircraft*

Restricted articles, requiring a "Cargo Aircraft Only" label, should be accessible in flight.

Note: *This is a mandatory requirement in some countries.*

(2) *Passenger Aircraft*

Restricted articles must be located in the aircraft in a place which is inaccessible to persons other than crew members and such restricted articles shall neither be carried in the same compartments occupied by passengers, nor shall they be carried in passengers or crew checked or carry-on baggage.

(*Source*: International Air Transport Association (IATA). *Restricted Articles Regulations*, 23rd edition. Montreal, Canada, 1980.)

Editorial Comment

All vaccines for human and animal use are specifically excluded from the definition of infectious substances. By definition, these do not represent a biological risk, provided they have been authorized by the control agency of the producing country. Such authorization means that the vaccines meet the approved safety requirements and are free of foreign agents.

By the same token, seed strains for the preparation of live vaccines are excluded.

International transport of all vaccines against human and animal diseases require observance of all shipping instructions and restrictions stipulated by the countries of destination or of transit, when applicable.

As for the shipment of diagnostic samples, if these contain no etiologic agents they are not considered restricted articles according to the IATA Regulations.

Persons or institutions wishing to obtain information on procedures and regulations in effect covering international shipment of biological material should contact the International Air Transport Association, 1000 Sherbrooke Street West, Montreal, Quebec, Canada H3A 2R4.

The following material on the subject is also recommended.

△ SHIPPER'S CERTIFICATION FOR RESTRICTED ARTICLES
(excluding radioactive materials)

Two completed and signed copies of this certification shall be handed to the carrier. (Use block letters)

WARNING: Failure to comply in all respects with the IATA Restricted Articles Regulations may be a breach of the applicable law, subject to legal penalties. This Certification shall in no circumstances be signed by a consolidator, a forwarder, or an IATA Cargo Agent.

This consignment is within the limitations prescribed for: *(mark one)*

☐ both passenger and cargo aircraft ☐ only cargo aircraft

Number of Packages	Article Number (See Section IV RAR)	Proper Shipping Name of Article as shown in Section IV of the IATA Restricted Articles Regulations (RAR). Specify each article separately.	Class	IATA Packing Note no. Applied	Net Quantity of each Package	Flash Point (closed cup) For Flammable Liquids	
						°C.	°F.

Special Handling Information:

I hereby certify that the contents of this consignment are fully and accurately described above by Proper Shipping Name and are classified, packed, marked, labelled and in proper condition for carriage by air according to the current Edition of the IATA Restricted Articles Regulations and all applicable carrier and governmental regulations. I acknowledge that I may be liable for damages resulting from any misstatement or omission and I further agree that any air carrier involved in the shipment of this consignment may rely upon this Certification.

Name and full address of Shipper	Name and title of person signing Certification
Date	Signature of the Shipper (see **WARNING** above)

Air Waybill No.*	Airport of Departure*	Airport of Destination*

* This box is optional for completion by issuing carrier.

• Report of Consultations on International Transfer of Potentially Hazardous Materials. *Bulletin of PAHO*, Vol. XII, No. 1, 62-73, 1978.

• Madeley, C. R. *Guide to the Collection and Transport of Virological Specimens (including Chlamidial and Rickettsial Specimens)*. Geneva, World Health Organization, 1977.

• Pan American Health Organization. *Obtención y manejo de muestras para exámenes microbiológicos*, by M. Kourany. Scientific Publication 326. Washington, D.C., 1976.

New Hepatitis Vaccine

It is estimated that 200 million persons throughout the world suffer from chronic infection due to hepatitis virus B and that the prevalence rate is as high as 20 per cent in some areas. A vaccine that provides protection against this disease is now available. It was developed by a group headed by Dr. Maurice Hilleman of the Merck Institute for Therapeutic Research (West Point, Pennsylvania) and consists of a virus suspension separated from human plasma and then inactivated by an appropriate method. The first clinical trial, which was conducted in 1975 in a group of Merck employees, was rapidly followed by larger-scale trials; these led to the study designed and conducted by Dr. Wolf Szmuness, Director of the Epidemiological Laboratory of the New York Blood Bank.[1]

The report of the Blood Bank[2] on the first large-scale trial in 1,000 volunteer homosexuals in the metropolitan area of New York showed that the vaccine was effective in 92 per cent of the cases as protection in high-risk subjects against hepatitis B and 96 per cent effective in inducing antibodies in vaccinees.

Other clinical trials on the efficacy of the vaccine are being conducted by the same group in high-risk populations such as health personnel and technical personnel responsible for or patients undergoing renal dialysis. These studies are expected to be completed by late 1981.

(*Source*: Program for the Control of the Production and Quality of Biological Products, Division of Disease Prevention and Control, PAHO.)

Editorial Comment

Hepatitis is a major public health problem for most of the world's population. In developed countries the antigen carrier rate is 1 per 1,000 to 1 per 2,000 population. In developing countries the average is 5-10 per cent, but as high as 75 per cent has been reported in some areas. The role of this virus in the etiology of hepatic cell carcinoma is becoming clearer.

The development of a very effective vaccine opens the door to prevention of this disease. At present, the vaccine cost (approximately US$20-50 per dose) makes it impractical for large-scale use in most developing countries. However, new technology, together with more information on the local epidemiology of hepatitis B, will eventually lead to more widespread use of the vaccine and prevention of the disease.

[1] Szmuness, W. *et al.* Hepatitis B vaccine: Demonstration of efficacy in a controlled clinical trial in high-risk population in the United States. *N Engl J Med* 303 (15), October 9, 1980.

[2] The Schechter Report on Blood Banks and Clinical Laboratories, Vol. 6, No. 20, October 10, 1980.

Courses

Courses at the Centers for Disease Control (CDCs). United States, 1981

The courses described below have been prepared especially for professional health workers who are either from, or working in, countries other than the United States.

Applied epidemiology in disease control (The duration and date of this course will be determined according to needs of the sponsoring agency and of CDC.) This course is also for physicians and other professional health practitioners who either investigate or administer investigative programs concerned with disease outbreaks. It covers epidemiological, laboratory, and control aspects of some of the communicable diseases that cause either severe illness or long periods of debility or that have significantly high incidence.

The course will include panel discussions and exercises. The public health departments of the State of Georgia and of other states are collaborating with CDCs in order to provide practice in applying epidemiological and other principles to situations in the field.

The purpose of the course is to present several aspects of disease control peculiar to the areas of origin of the participants, particularly from the epidemiological standpoint.

Communicable disease control for public health officers and nurses (the information on duration and date of the preceding course also applies here). The course is for professional health practitioners (or persons who expect to be involved in professional-level health work) in countries other than the United States. It is desirable, but not required, that participants have knowledge of, and experience in, delivery of health services.

It has been planned to satisfy individual needs of each participant. In general, the course deals with several aspects of disease control as practiced in the CDCs.

The role of a center for disease control in international health (the previous information on dates and duration also applies here). This course is for senior physicians, veterinarians, medical officers, and other professional health practitioners who are responsible for disease control. It covers the epidemiological, laboratory, and control aspects of communicable diseases that cause either severe illness or long periods of debility, or that have significantly high incidence. It explains the role the CDCs play (or could play—multilaterally and bilaterally or on the basis of participation agreements with other agencies—in international efforts to control disease.

The specific disease entities used as examples are selected to meet the special needs of participants and the situations they encounter in their work locations. The course also includes training methods and aids used to teach disease control.

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