



Control of Yellow Fever

Field Guide

CONTROL OF YELLOW FEVER

FIELD GUIDE



**Pan American
Health
Organization**



Regional Office of the
World Health Organization

Scientific and Technical Publication No. 603

PAN AMERICAN HEALTH ORGANIZATION
Pan American Sanitary Bureau, Regional Office of the
WORLD HEALTH ORGANIZATION
525 Twenty-third Street, N.W.
Washington, D.C. 20037
www.paho.org

2005

Also published in Spanish (2005) with the title:
Control de la fiebre amarilla. Guía práctica.
(ISBN 92 75 31603 1)

PAHO HQ Library Cataloguing-in-Publication Data

Pan American Health Organization
Control of Yellow Fever: Field Guide.
Washington, D.C.: PAHO, © 2005
(Scientific and Technical Publication No. 603)
ISBN 92 75 11603 2
I. Title II. Series
1. YELLOW FEVER - prevention and control
2. YELLOW FEVER VIRUS
3. YELLOW FEVER VACCINE
4. YELLOW FEVER - epidemiology
5. EPIDEMIOLOGICAL SURVEILLANCE
6. GUIDEBOOKS [PUBLICATION TYPE]
NLM WC530

This publication was prepared by the Immunization Unit and the Communicable Diseases Unit of the Pan American Health Organization.

Photo credits (left to right): Luzi Claudio Marigo (Centro Nacional de Primatas, Ministry of Health, Brazil); PAHO; James Gathany (CDC).

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ABOUT THE IMMUNIZATION FIELD GUIDES

The Expanded Program on Immunization is viewed as one of the most successful public health experiences in the Americas because it has played a pivotal role in reducing infant mortality from vaccine-preventable diseases in the Region. In fact, since the program was launched, our countries stopped the transmission of wild poliovirus in the Region in 1991 and interrupted indigenous measles transmission in November 2002; they also are making significant gains in the battle to eliminate rubella and congenital rubella syndrome. In addition, national immunization programs are undertaking extraordinary efforts to identify at-risk populations and overcome inequities in vaccination. To maintain these advances and to cope with new challenges, such as the introduction of new vaccines, partnerships will have to be strengthened among governments, donor agencies, the private sector, scientific associations, and society as a whole.

To this end, PAHO is promoting the best technical quality by issuing these practical field guides that have been prepared by the Immunizations Unit in the Family and Community Health Area. The most recent techniques presented in the field guides, coupled with useful illustrations, will help health workers in their efforts to control, eliminate, or eradicate diseases such as poliomyelitis, neonatal tetanus, yellow fever, diphtheria, pertussis, tetanus, *Haemophilus influenzae* type b infections, hepatitis B, measles, and rubella. The field guides also include standardized methods and procedures for conducting epidemiological surveillance and maintaining an up-to-date information system that makes it possible to take timely and effective decisions.

These field guides are based on the latest scientific information and they bring together the experience of prominent health professionals in the field. As a result, they are particularly suitable for promoting strategies that have already proven to be effective. The strengthening of prevention activities, the reduction of health inequities, and the promotion of technical expertise in vaccination services were the principles that guided the preparation of the guides.

The Expanded Program on Immunization, a joint effort of all the countries of the Americas, effectively contributes to the attainment of the Millennium Development Goals.

Dr. Mirta Roses Periago
Director
Pan American Health Organization

PREFACE

This field guide was designed by the Pan American Health Organization (PAHO) to offer health workers at different levels of the health care system and different programs in the schools of health sciences the tools to control jungle yellow fever and prevent its reurbanization in the Region of the Americas. It emphasizes clinical and epidemiological aspects of the disease, together with prevention and control strategies. It also offers practical exercises on a clinical case and outbreak for use in training health workers, especially local personnel in enzootic areas. The field guide covers prevention, proper case management, and the improvement of epidemiological surveillance.

Yellow fever remains a major public health problem in the Americas. The emergence of cases of the jungle form of the disease and the proliferation of *Aedes aegypti* throughout the Hemisphere denote the high risk of reurbanization of the disease.

The prevention and control measures described in this guide are based on the recommendations of the PAHO Technical Advisory Group on Vaccine-preventable Diseases, which urge the countries to put plans into action to combat yellow fever. The main recommendations include vaccination of all residents of enzootic areas, introduction of the vaccine in the Expanded Program on Immunization (EPI) to maintain high coverage in countries with enzootic areas, and vaccination of all travelers to these areas (migrants, ecotourists, etc.).

Although a great deal of progress has been made in yellow fever prevention and control, the countries must continue to adopt the recommended measures to prevent cases and outbreaks in historically enzootic areas and the reurbanization of the disease.

1. INTRODUCTION

1.1 BACKGROUND

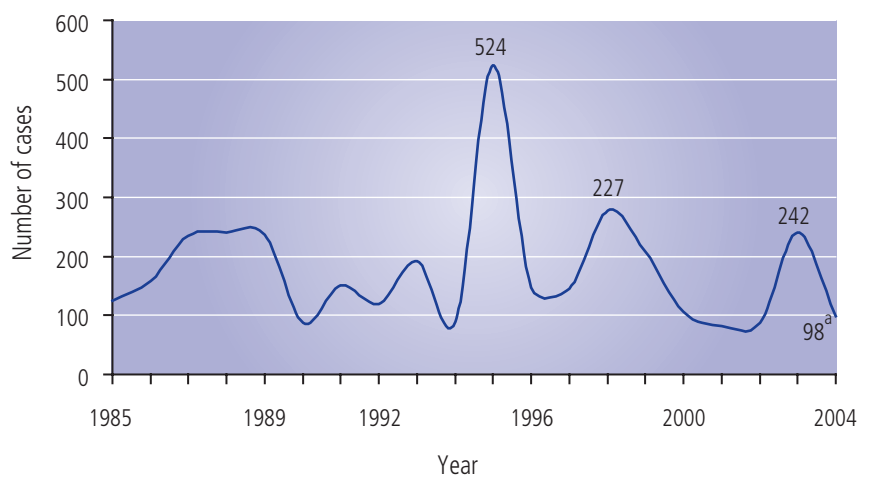
Yellow fever is a zoonosis indigenous to some tropical regions of South America and Africa which has caused numerous epidemics with high mortality rates throughout history. Its etiologic agent is the yellow fever virus, an arbovirus of the genus *Flavivirus* (family *Flaviviridae*).

1.2 STATUS OF YELLOW FEVER IN THE AMERICAS

The area in which cases of jungle yellow fever are observed is confined to northern South America, including Bolivia, the east-central region of Brazil, Colombia, Ecuador, French Guiana, Guyana, Peru, Suriname, and Venezuela, and Trinidad and Tobago in the Caribbean. From 1985 to September 2004, 3,559 cases of jungle yellow fever, resulting in 2,068 deaths, were reported to PAHO.

Peru had the most cases during the period (1,939), followed by Bolivia (684), Brazil (539), Colombia (246), Ecuador (93), Venezuela (57), and French Guiana (1). The disease has cyclical characteristics, and there have been three major epidemic spikes in the past 10 years (Figure 1). The highest number of cases was recorded in 1995, resulting from a major outbreak in the western Andean region of Peru. In 1998, the number of cases again rose, this time as a result of outbreaks in Peru, Bolivia, and Brazil. From 1999 to 2002, the number of cases of jungle yellow fever fell sharply, with only isolated cases and limited outbreaks observed. This can be explained in part by the intensification of yellow fever vaccination in enzootic areas in Brazil and Bolivia. In 2003 a rise in the incidence of this disease was observed, owing to outbreaks in Brazil and Peru and an extensive outbreak along the border between Colombia and Venezuela.

Figure 1. Number of yellow fever cases in the Americas, 1985 to 2004.



^a Provisional data up to week 37

2. EPIDEMIOLOGY

There are two yellow fever transmission cycles: the jungle cycle and the urban cycle.

In the jungle cycle, the virus circulates among nonhuman primates and perhaps among susceptible marsupials. Transmission occurs through the bite of certain jungle species of mosquitoes. In the Americas, the primary vectors are mosquitoes of

the genera *Haemagogus* and *Sabethes*. Transovarian transmission can contribute to the persistence of the infection. In this cycle, humans contract the infection in jungle areas when they are bitten by mosquitoes infected with the yellow fever virus (Table 1).

An **enzootic area** for yellow fever is understood as a geographical location with confirmed circulation of the virus that causes the jungle cycle of the disease and ecological conditions for maintaining transmission (the presence of competent vectors and susceptible vertebrates capable of maintaining the chain of transmission). When an area does not exhibit these conditions, it is considered a **nonenzootic area**.

The urban cycle is characterized by circulation of the virus among susceptible humans. The virus is transmitted through the bite of the *Aedes aegypti* mosquito, a domestic vector. The **urban cycle** begins when someone who has contracted the infection in the jungle moves to an urban center with high *Ae. aegypti* density during the phase in which the virus is circulating in his or her blood (viremia), and once there, is bitten by this vector, which in turn transmits the virus to another susceptible individual, thus establishing the chain of transmission of yellow fever in the urban environment.

Table 1. Epidemiological characteristics of yellow fever

Infectious agent	The yellow fever virus, an arbovirus of the genus <i>Flavivirus</i> , family Flaviviridae.
Reservoirs	In the jungle cycle, mainly monkeys and jungle mosquitoes. In urban areas, humans and the <i>Aedes aegypti</i> mosquito.
Distribution	In the enzootic form, in tropical areas of Africa, South America, and Trinidad and Tobago in the Caribbean.
Transmission	In urban and certain rural areas, the bite of infective <i>Aedes aegypti</i> mosquitoes. In jungle areas of South America, by mosquitoes of the <i>Haemagogus</i> and <i>Sabethes</i> genera.
Incubation period	From three to six days after the mosquito bite.
Communicable period	The mosquito can become infected by biting a patient during the viremia phase, which starts shortly before the onset of fever and can last until the fifth day of the illness. <i>Ae. aegypti</i> can become infective 9 to 12 days after having bitten a viremic person (extrinsic incubation period).
Susceptibility/risk	All non-immune people who enter areas of transmission or risk of transmission of the disease (tourists, farmers, fishermen, truck drivers, and migrants, among others), or who live in these areas without having been vaccinated.
Immunity	By vaccination or natural infection. The immunity produced by the vaccine is probably for life. The <i>International Health Regulations</i> require revaccination every 10 years for travelers in yellow fever endemic areas.
Morbidity and mortality	Between 1993 and 2003, 2,099 cases of jungle yellow fever were reported in the Region with a case-fatality rate of 45% (956 deaths). The countries reporting cases in that period were Bolivia, Brazil, Colombia, Ecuador, French Guiana, Peru, and Venezuela.

Source: Heymann DL. (ed.) *Control of Communicable Diseases Manual*. 18th ed. Washington, D.C.: American Public Health Association; 2004.

The widespread proliferation and high density of *Ae. aegypti* populations, coupled with growing migration to different parts of the Region, constitute risk factors for the reintroduction of yellow fever in urban areas of the Americas. Prevention of jungle yellow fever is possible only with vaccination. To prevent the urban form of the disease, an additional measure is the implementation of vector control programs.

3. CLINICAL ASPECTS

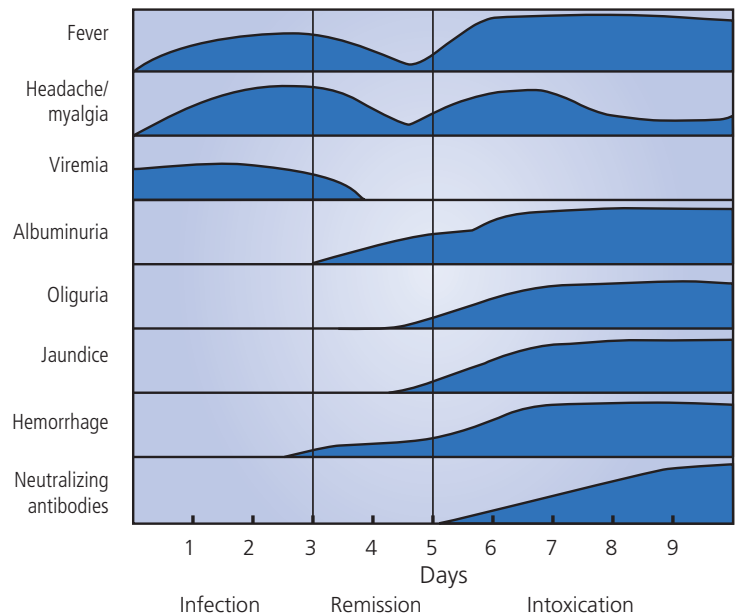
3.1 CLINICAL MANIFESTATIONS

The clinical manifestations of infection with the yellow fever virus vary considerably, ranging from asymptomatic forms to mild cases with nonspecific symptoms, to classic hemorrhagic fever, associated with high case-fatality.

The incubation period is from three to six days after a bite from an infected mosquito. The classic form of yellow fever is a severe systemic disease with a high case-fatality rate, characterized by fever, prostration, compromised liver, kidney, and cardiac function, hemorrhagic manifestations, and shock. The progression of the disease can include three clinically distinct stages: infection, remission, and intoxication.

The **infection stage**, which corresponds to the onset of symptoms and includes the viremia phase, begins abruptly with high fever ($>39^{\circ}\text{C}$), chills, headache, nausea, dizziness, malaise, and muscle pain, especially in the lower back. On physical examination, the patient is febrile, prostrate, with red conjunctiva and flushing. Bradycardia accompanied by fever (Faget's sign) is sometimes observed. The main alterations revealed by the respective laboratory tests during this stage are leukopenia with relative neutropenia, elevated transaminase levels, and albuminuria (Figure 2). The infection stage lasts roughly three to six days and is immediately followed by the remission stage. This can last anywhere from two to forty-eight hours, during which time the symptoms abate and the patient's general condition improves. In mild forms of the disease, the patient enters the **recovery phase**, which takes two to four weeks. Yellow fever cases are generally very difficult to diagnose when the disease has not progressed to the intoxication stage.

Figure 2. Clinical characteristics and neutralizing antibody response to yellow fever infection.



Patient with hemorrhagic febrile disease

Courtesy of Dr. César Cabezas, National Health Institute, Peru

In some 15% to 25% of cases, the symptoms recur in a more serious form and the **intoxication stage** begins, marked by jaundice, epigastric pain, hemorrhagic manifestations—mainly epistaxis, gingival hemorrhage, hematemesis (black vomit), melena, and oliguresis—followed by anuria, which is indicative of renal failure. Transaminase levels become very elevated. The fatality rate in cases that progress to the intoxication stage is about 50%. In the terminal phase, the patient exhibits hypotension, psychomotor agitation, stupor, and coma. Death generally occurs seven to ten days after the onset of symptoms.

3.2 DIFFERENTIAL DIAGNOSIS

The clinical symptoms of yellow fever can also be seen in other febrile diseases that progress with jaundice, hemorrhagic manifestations, or both (Annex 1). In the Region of the Americas, the principal diseases that should be considered in the differential diagnosis of yellow fever are:

- Leptospirosis;
- Severe malaria;
- Viral hepatitis, especially the fulminating form of hepatitis B and D;
- Dengue hemorrhagic fever;
- Bolivian, Argentine, and Venezuelan hemorrhagic fevers.

Summary of laboratory criteria for diagnosing cases

- Isolation of the yellow fever virus;
- Specific presence of IgM for the yellow fever virus;
- At least a fourfold increase in IgG antibodies against the yellow fever virus (seroconversion) in serum samples taken in the acute and convalescent phases, using hemagglutination inhibition, complement fixation, or neutralization tests;
- Histopathologic lesions compatible with those of yellow fever or the detection of viral antigens in tissue samples through immunohistochemical methods;
- Detection of viral genome sequences in tissue or blood (see Annex 3) through polymerase chain reaction (PCR).

For a thorough examination of aspects related to laboratory diagnosis, see Section 6.

3.3 TREATMENT

In 1986, a committee of PAHO experts recommended a support therapy for the management of severe cases of yellow fever that includes: nutritional maintenance and the prevention of hypoglycemia; nasogastric suction to prevent gastric distention,

and aspiration; treatment of hypotension with fluid replacement and, if necessary, vasoactive drugs; the administration of oxygen; the correction of metabolic acidosis; treatment of hemorrhage with frozen fresh plasma; dialysis, when indicated by renal failure; and the treatment of secondary infections with antibiotics. Early administration of ribavirin has proven beneficial in some cases. These recommendations remain in effect; however, since few yellow fever patients have been treated at tertiary care hospitals, their validity has not been assessed.

In mild cases the symptoms are treated. Salicylates should not be used as they can produce hemorrhage.

4. VACCINES

4.1 IMMUNITY

The yellow fever vaccine contains attenuated live virus, is safe and effective, and has been used for over 60 years to actively immunize children and adults against infection with the yellow fever virus. It confers lasting immunity, perhaps for life.

All current vaccines against yellow fever are based on seed-lots derived from the original attenuated 17D strain, developed in the late 1930s and early 1940s by Max Theiler and others at Rockefeller Foundation laboratories in New York and Rio de Janeiro. Although these seed-lots differ in terms of the number of passages and their biological and genetic properties, they retain the same safety and efficacy, demonstrated in clinical trials and the results of surveillance following their distribution.

They are lyophilized, heat-stable vaccines produced in fertilized chicken eggs free of specific pathogens. Each dose should contain at least 1,000 mouse LD₅₀ (lethal dose 50% in mice), or its equivalent in plaque-forming units (PFU), as determined by each production laboratory.

4.2 VACCINATION SCHEDULE

It is recommended that the yellow fever vaccine be administered at 12 months of age. In the case of outbreaks, it can be administered as early as 6 months of age. The *International Health Regulations* recommend vaccinating travelers to enzootic areas every 10 years for the purpose of validating the International Yellow Fever Vaccination Certificate. However, routine revaccination of residents is not necessary in enzootic areas.

4.3 ADVERSE REACTIONS, CONTRAINDICATIONS, AND PRECAUTIONS

Adverse reactions

The yellow fever vaccine is generally considered one of the safest. Over 400 million people have been vaccinated, with very good results in terms of safety and tolerance. The reactogenicity of the vaccine was monitored in 10 clinical trials between 1953

and 1994.¹ Mild, self-limited reactions, such as pain and reddening at the injection site, and systemic reactions, such as fever, headache, myalgia, and malaise, appear five to seven days after vaccination in a minority of those vaccinated.

Serious adverse reactions allegedly caused by the yellow fever vaccine are very rare. Cases of postvaccinal encephalitis (neurotropic disease) from virus 17D have been described in infants aged less than 4 months (rate of 500–4,000 per million doses administered). **The vaccine is contraindicated for infants aged less than 6 months**, thereby establishing a greater margin of safety.

In recent years, moreover, some cases of serious adverse reactions linked with the vaccine have been reported in apparently healthy people who received the vaccine in the United States (nine cases), Brazil (four cases), and Australia, Colombia, France, the United Kingdom,² and Switzerland (one case each). These involved multisystemic (viscerotropic) disease similar to that caused by natural infection with the wild yellow fever virus. The vaccinal virus has been isolated, but sequencing of the viral genome revealed no mutation capable of explaining this alteration in its biological characteristics. These are very rare cases, determined perhaps by strictly individual factors that are still unknown. People over age 60 seem to be more likely to experience adverse reactions.³

Contraindications

The yellow fever vaccine should not be administered to individuals in the following groups:

- People with acute febrile diseases, whose general health status is compromised;
- People with a history of hypersensitivity to chicken eggs and their derivatives;
- Pregnant women, except in an epidemiological emergency and at the express recommendation of health authorities;
- People with disease-related (for example, cancer, leukemia, AIDS, etc.) or drug-related immunosuppression;
- Infants aged less than 6 months (consult the vaccine's laboratory insert);
- People of any age with a disease involving the thymus.⁴

¹ Monath TP. Yellow fever vaccine. In: Plotkin S, Orenstein WA (eds.) *Vaccines*. 4th ed. Philadelphia: W.B. Saunders; 2004: 1095-1176.

² Barwick RS, Marfin AA, Cetron MS. Yellow fever vaccine-associated disease. In: Scheld WM, Murray BE, Hughes JM, (eds.) *Emerging Infections*, 6th ed. Washington: ASM Press 2004; 25-34.

³ Kitchner S. Viscerotropic and neurotropic disease following vaccination with the yellow fever 17D vaccine ARILVAX. *Vaccine* 2004; 22: 2103-2105.

⁴ WHO, Global Advisory Committee on Vaccine Safety (2-3 December 2004) *Wkly Epidemiol Rec* 2005 Jan 7; 80(1): 3-7.

Precautions

- The yellow fever vaccine can be administered to HIV patients, but only those who are asymptomatic and have not yet developed acquired immunodeficiency syndrome, or as the physician determines.
- Theoretically, administration of the yellow fever vaccine to pregnant women is not recommended; however, there is no proof that it causes fetal anomalies. In deciding whether or not to vaccinate, the epidemiological risk should be weighed against the risk of pregnant women contracting the disease.
- It is recommended that the epidemiological risk of contracting the disease versus the risk of an adverse event be evaluated individually for travelers to enzootic areas who are over age 60.

4.4 DOSE AND ADMINISTRATION OF THE YELLOW FEVER VACCINE AND SIMULTANEOUS USE WITH OTHER VACCINES

The yellow fever vaccine should be administered subcutaneously in the upper arm in a single dose of 0.5 mL. It can be administered simultaneously with any vaccine, including other live-virus injectables, such as measles, MMR (measles, mumps, rubella), MR (measles, rubella), and chickenpox, provided that they are administered at different sites. **The only exception is the cholera vaccine**, which should not be administered at the same time as the yellow fever vaccine. These two vaccines should be administered at least three weeks apart to generate a good immune response.

If the yellow fever vaccine is **not** administered at the same time as other injectable live-virus vaccines (measles, MMR, MR, chickenpox), a minimum of four weeks between vaccinations should be observed.

4.5 COLD CHAIN AND RECONSTITUTION

The manufacturer's instructions included in the package insert should be followed. The vaccine must always be kept under refrigeration at temperatures between 2 °C and 8 °C. Since the product is lyophilized, the bottle containing the freeze-dried vaccine comes with a diluent that should be stored at room temperature. Before using it to reconstitute the vaccine, **the diluent should be at the same temperature as the vaccine** (2 °C to 8 °C). The diluent should, therefore, be refrigerated one hour before the vaccine is reconstituted.

The diluent provided by the manufacturer of the vaccine must be used, since another diluent could damage it, inactivating the vaccinal virus. The amount of diluent used to reconstitute the vaccine will depend on the number of doses in the presentation but generally corresponds to the full amount of diluent supplied by the manufacturer. The diluent should be added slowly; the vial should then be shaken gently to achieve uniform suspension of the vaccine, avoiding the formation of

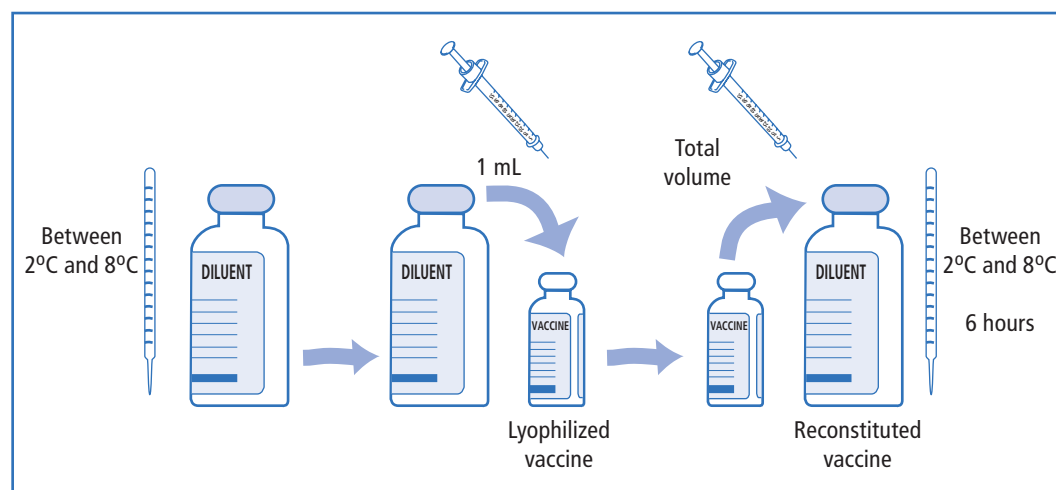
foam. Vaccinators should always pay close attention to the number of doses in the vial that will be used. There are presentations with 5, 10, 20, and 50 doses.

In general, the 50-dose presentation is used in mass campaigns for the control of epidemics. Reconstitution of the 50-dose presentation should be done in two steps: first, reconstitution of the lyophilized vaccine with 1 ml of diluent, and second, its transfer to the vial containing the rest of the solution (Figure 3). It is always essential to read the package insert that comes with the vaccine. After reconstitution, the vaccine should be kept under refrigeration at temperatures between 2°C and 8°C. It is recommended that the vial of reconstituted vaccine be placed in a container with ice or cold packs to ensure its optimal conservation. Under these conditions, it can be used for a maximum of six hours after reconstitution.

Precautions

- After reconstitution, the vaccine should be kept under refrigeration and out of direct light.
- The reconstituted vaccine should be used, at a maximum, until the end of the work session, when that period is no more than six hours.
- The reconstituted vaccine should not be frozen.
- Use of the wrong diluent can damage the vaccine and/or cause serious reactions.
- The vaccine should not be administered intravenously.

Figure 3. Reconstitution of the yellow fever vaccine



4.6 EFFICACY AND POTENCY

Several serologic studies conducted with the viral neutralization test for vaccines correlated with yellow fever immunity have shown that these vaccines have an efficacy

of over 90% in children and adults. As for potency, one dose of the yellow fever vaccine should contain at least 1,000 mouse LD50 or its equivalent in plaque-forming units, according to the basic requirements of WHO.

5. VACCINATION ACTIVITIES

The PAHO Technical Advisory Group on Vaccine-preventable Diseases recommends that countries with enzootic areas vaccinate residents in those areas against yellow fever and gradually introduce yellow fever vaccine into the routine vaccination schedule.

In non-enzootic areas and areas that are not a source of migration, outbreak control measures should be strengthened on a national scale, improving the sensitivity of the epidemiological surveillance system through the adoption of a syndrome approach, intensifying vector control, and conducting mass vaccination in areas where outbreaks occur (Table 2). A national reserve of the vaccine should be maintained to deal with such emergencies.

Table 2. Summary of vaccination activities by area

Areas	Routine vaccination in the EPI	Vaccination of other age groups
Enzootic areas and areas where migrations originate	Introduction of the vaccine in the regular schedule for children at 12 months of age, with minimum coverage of 95%.	Vaccination of 95% of the population residing in the area who are over 1 year of age (urban, rural, or forest areas). Vaccination of travelers entering the area.
Non-enzootic areas	Vaccination of travelers entering enzootic areas. Creation of a national vaccine reserve for the control of outbreaks. Mass vaccination in areas where an outbreak occurs until 95% coverage is attained. The affected area should be reclassified as an enzootic area, and vaccination of new cohorts should be maintained.	

5.1 VACCINATION OF RESIDENTS OF YELLOW FEVER ENZOOTIC AREAS AND AREAS WHERE MIGRATION TO THESE AREAS ORIGINATES

All people over the age of 1 year living in urban, rural, or jungle areas considered enzootic, as well as the residents of areas where migrations to enzootic areas originate, should be immunized against yellow fever, with a minimum coverage of 95%.

5.2 VACCINATION OF TRAVELERS

The vaccine is indicated for anyone traveling to enzootic areas. *International Health Regulations* recommend the revaccination of travelers every 10 years. This recommendation applies to all countries.



Sign announcing yellow fever vaccination campaign in Peru.

5.3 INTRODUCTION OF THE VACCINE IN THE REGULAR IMMUNIZATION PROGRAM

In order to keep new cohorts protected against yellow fever, countries with enzootic areas should add the vaccine to the routine vaccination schedule for children. Its administration at 12 months is recommended, preferably at the same time as the measles-rubella vaccine, but in the other arm.

Measles mop-up campaigns provide a good opportunity to protect children 1 to 4 years of age in a single intervention.

6. EPIDEMIOLOGICAL SURVEILLANCE

The object of epidemiological surveillance of yellow fever is early detection of the circulation of the virus. This allows for timely adoption of appropriate control measures to keep new cases from appearing, interrupt outbreaks, and prevent the reurbanization of the disease.

Epidemiological surveillance of yellow fever virus circulation should be intensified in enzootic and non-enzootic areas alike.

The primary methods employed in yellow fever surveillance are:

- Surveillance of clinical cases compatible with the classic form of the disease, based on WHO case definitions;
- Surveillance of syndromes characterized by fever and jaundice;
- Epizootic surveillance (appearance of the disease and death in monkeys in jungle areas);
- Keeping *Aedes aegypti* infestation indices below 5% to prevent the reurbanization of yellow fever;
- Monitoring postvaccinal events allegedly attributable to yellow fever vaccination.

6.1 WHO CASE DEFINITIONS

- **Suspected case:** every person with disease characterized by fever of abrupt onset followed by jaundice two weeks after the onset of symptoms, and one of the following symptoms: 1) bleeding from the nose, gums, skin, or digestive tract, or 2) death within three weeks of the onset of symptoms.
- **Confirmed case:** every suspected case that has been laboratory-confirmed or is epidemiologically linked to a laboratory-confirmed case.
- **Outbreak:** a yellow fever outbreak is the presence of at least one confirmed case.

6.2 SURVEILLANCE OF SYNDROMES CHARACTERIZED BY FEVER AND JAUNDICE

This type of surveillance, usually conducted at sentinel sites, uses a more sensitive case definition and rules out cases through laboratory testing. This process allows the identification of yellow fever cases who have developed the less serious, or non-hemorrhagic, forms of the disease.

Surveillance of syndromes characterized by fever and jaundice covers all people who live in enzootic areas or have traveled to them and who develop an illness characterized by fever and jaundice with sudden onset. When blood samples taken from these people prove negative for viral hepatitis, malaria, leptospirosis, or dengue hemorrhagic fever, they should be sent to the reference laboratory for specific serologic tests for yellow fever, accompanied by the respective epidemiological investigation report.

6.3 EPIZOOTIC SURVEILLANCE

Health authorities should encourage the population always to report the death of monkeys from natural causes. Verification of an epizootic can mean circulation of the yellow fever virus, which should trigger the vaccination of residents and travelers entering the area, in addition to intensifying the monitoring of suspected cases and cases of fever and jaundice.

6.4 LABORATORY DIAGNOSIS

Laboratory diagnosis of yellow fever is conducted through serologic tests for IgM antibodies and isolation of the virus in the blood. In fatal cases, the presence of viral antigen in tissues, mainly the liver, is demonstrated through immunohistochemical techniques. Morphological alterations in liver tissue are observed through histopathological tests. Some laboratories use polymerase chain reaction (PCR) to detect genetic material (RNA) of the yellow fever virus in blood and tissues.

Isolation of the microorganism and detection of viral RNA in the blood are only possible when the sample is taken in the acute phase, during the viremia period, which is usually one to five days after the onset of symptoms. The virus is isolated through inoculation in suckling mouse brain, cell cultures, or intrathoracic inoculation in mosquitoes.

Serology is most often used in laboratory diagnosis of yellow fever. IgM detection with the MAC-ELISA method is currently the most commonly and widely used technique, owing to its high sensitivity and specificity and, above all, its simplicity. Moreover, the diagnosis can be made with a single sample obtained after the seventh day of disease onset. Other serologic techniques, such as the hemagglutination inhibition and neutralization tests, are also used. These tests are based on seroconversion;

thus, two serum samples are needed to make the diagnosis, one from the acute phase and one from the convalescent phase.

Procedures for the collection and transport of material for laboratory testing

Viral isolation

- The blood sample should be taken during the first five days of fever.
- The sample should preferably be placed in a sterile bottle with a tightly closed screw top to avoid spillage.
- The sample should be immediately frozen and sent frozen to the reference laboratory.
- The bottle should be marked with the patient's name and the date the sample was taken.
- The material should always be sent to the laboratory with the properly completed epidemiological investigation report.
- This sample is also suitable for antigen detection.

Serology

- To make the diagnosis using the MAC-ELISA technique for specific IgM antibody capture, a serum sample taken at least seven days after the onset of symptoms should be sent. This sample can be used as the acute phase serum for seroconversion tests (hemagglutination inhibition and neutralization tests).
- When a second sample is needed to confirm the seroconversion, it should be taken at least 14 days after the onset of symptoms.
- After the blood is separated, the serum sample should be placed in a tightly closed bottle to avoid spillage; it should preferably be frozen or at least kept under refrigeration and then sent to the laboratory.
- The bottle should be marked with the name of the patient and the date the sample was taken.
- The material should always be sent to the reference laboratory with a properly completed epidemiological investigation report.

Histopathological diagnosis

- In the case of death of a person presumably infected with yellow fever, a liver viscerotomy should be performed. A liver sample of least 1 cc should be harvested.
- The liver sample should be harvested preferably within eight hours of death. The later the sample is harvested, the greater the possibility of tissue autolysis, hindering interpretation by the pathologist.

- The sample should be kept in a 10% formalin solution, in a volume of liquid 10 times the size of the sample.
- The sample should be kept at room temperature. It never should be frozen.

6.5 RESPONSE TO OUTBREAKS OR EPIZOOTICS

Early detection of cases or epizootics will permit the rapid implementation of control activities. An epidemiological alert should also be declared.

In enzootic areas, the presence of a single laboratory-confirmed case is sufficient to launch prevention and control measures. In non-enzootic areas, confirmation of the infection by the reference laboratory is required by repeating the ELISA IgM assay (see the practical exercise on controlling an outbreak, pg. 38).

Immediate actions

The basic intervention unit is the municipality where the case occurred and bordering municipalities (Figure 4).

Implementation of a response plan includes the following activities:

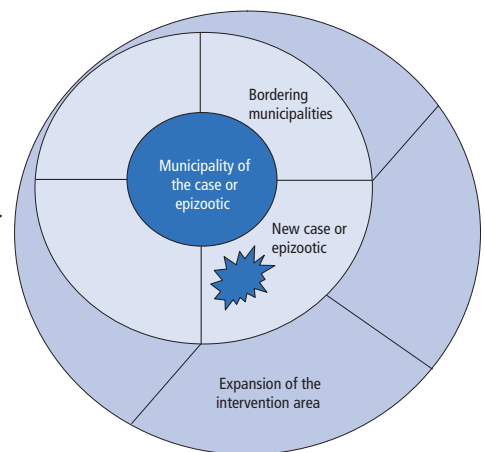
Vaccination activities

- Define the size of the population to vaccinate, as well as supply needs, the type of presentation of the available vaccine, the wastage rate, the cold chain, transportation, the available human resources, and training needs;
- Carry out mass vaccination of the population without a prior vaccination history who live in the affected area and bordering municipalities;
- Promote safe vaccination practices;
- Conduct rapid monitoring of vaccination coverage.

Epidemiological surveillance activities

- Issue an epidemiological alert to municipalities and health services;
- Identify additional cases through an active search for all people with disease compatible with the definition of a suspected case and for people with acute syndromes characterized by fever and jaundice. The active case search takes place in areas where cases have occurred and in bordering municipalities as well as places frequented by the cases in the three to six day period prior to the onset of the disease;
- Collect samples and ensure their shipment to the laboratory;
- Conduct a retrospective study of death certificates to detect cases compatible with the case definition;

Figure 4. Basic intervention unit for controlling a yellow fever outbreak



- Determine the incidence of the disease by geographical area and age group to identify groups at risk and, indirectly, the transmission pattern of the disease;
- Investigate monkey deaths (collection of blood samples from dead monkeys);
- Monitor *Aedes aegypti* infestation indices in urban areas;
- Monitor vaccination coverage.

Clinical diagnosis and management

- Improve clinical management of yellow fever cases.

Vector control measures

- Implement vector control measures in urban areas.

Social communication activities

- Develop and promote educational activities along with community participation in yellow fever prevention and control.

Activities in non-enzootic areas

- Monitor people with disease compatible with the definition of a suspected or confirmed case;
- Investigate the presence of epizootics in monkeys to rule out circulation of the yellow fever virus, and take blood samples from dead monkeys for laboratory diagnosis.

Activities regarding imported cases

Perimeter vaccination among residents of the municipality where the case was reported is necessary, and measures should be taken to prevent exposure to the vector if the detected case was found in the viremia phase (febrile period). The majority of patients enter the jaundice phase or present hemorrhagic symptoms four days into the disease, when they have already passed the viremia phase. In these cases, measures to prevent exposure to the vector are unnecessary.

Intermediate actions

- Maintain 95% coverage of new cohorts of 1 year old children;
- Ensure that the yellow fever vaccine is included in the routine vaccination schedule of immunization programs;
- Guarantee that the epidemiological surveillance system is functioning properly;
- Keep vector infestation indices low, eliminating mosquito breeding sites in urban areas;
- Vaccinate all travelers to enzootic areas;
- Keep the community informed and educated.

6.6 INFORMATION SYSTEMS AND DATA ANALYSIS

Using data analysis and continuous feedback, it is necessary to monitor the yellow fever prevention and control process and prevent the reurbanization of the disease. Monitoring the following aspects of this process is fundamental:

- Early detection;
- Notification of suspected cases;
- Investigation and confirmation of cases;
- Determination of *Ae. aegypti* infestation indices;
- Vaccination coverage;
- Periodic review of differential diagnoses; and
- Changes in trends that may be indicative of an outbreak.

For any suspected case of yellow fever, an epidemiological investigation report should be completed (see Annex 2) and a copy sent to the laboratory.

Epidemiological surveillance consists of a series of activities inherent to all disease prevention and control strategies. Thus, every health worker participates in this process and has a specific role to play, either generating information, analyzing it for decision-making, or carrying out interventions at the different levels of the health system (see Annex 4).

International reporting

Yellow fever is a disease subject to immediate mandatory reporting, under the *International Health Regulations*. Thus, every suspected case of yellow fever must be investigated and, if confirmed, reported immediately to PAHO/WHO.

Monitoring and feedback

The number of units that provide timely reports on the presence or absence of suspected yellow fever cases should be monitored weekly by the epidemiological surveillance system. Feedback consists of informing health workers about the presence of suspected cases, their geographical location, vaccination coverage achieved, and other control activities, as well as specific recommendations for preventing or controlling an outbreak.

Surveillance indicators

To monitor the efficiency of yellow fever surveillance systems, it is recommended that countries use the following indicators:

- 80% of reporting units report weekly;
- 80% of suspected cases are investigated within 48 hours of the report;

- in 80% of cases with serum samples, the samples are sent to the laboratory within 72 hours;
- 80% of laboratory results are obtained within 72 hours;
- 80% of cases are confirmed and appropriate control measures implemented;
- 80% of cases closed within 30 days and 100% closed within 60 days;
- *Ae. aegypti* infestation index (should be less than 5%);
- Dead monkeys in enzootic areas reported;
- Case-fatality rate (should be less than 50%);
- Minimum vaccination coverage of 95% of the resident population in enzootic areas;
- At least one sentinel center per health department or region considered at risk for the surveillance of syndromes characterized by fever and jaundice.

Indicators of the efficiency of yellow fever vaccination

In municipalities in enzootic and bordering areas with *Ae. aegypti* infestation indices of over 5%, the indicators of the efficiency of yellow fever vaccination are:

- 100% of municipalities have introduced the vaccine in their immunization schedule;
- 95% vaccination coverage in the population over 1 year of age.

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ANNEXES

- ANNEX 1. DIFFERENTIAL DIAGNOSIS OF HEMORRHAGIC FEVER AND JAUNDICE DISEASES
- ANNEX 2. EPIDEMIOLOGICAL INVESTIGATION FORM FOR YELLOW FEVER
- ANNEX 3. LABORATORY DIFFERENTIATION OF HEMORRHAGIC FEVER AND JAUNDICE DISEASES
- ANNEX 4. FUNCTION OF EACH LEVEL OF THE HEALTH STRUCTURE

Annex 1. Differential diagnosis of hemorrhagic fever and jaundice diseases

DISEASE	INFECTIOUS AGENT	INCUBATION PERIOD	MODE OF TRANSMISSION	CLINICAL SYMPTOMS	JAUNDICE	HEMORRHAGIC MANIFESTATIONS	LABORATORY	SGOT/SGPT
YELLOW FEVER	Yellow fever virus: <i>Flavivirus</i>	Three to six days	URBAN Urban vector: <i>Aedes aegypti</i> JUNGLE Wild vectors: <i>Haemagogus</i> , <i>Sabethes</i>	Sudden onset with high fever, headache, dehydration, general muscle pain, intense prostration, chills, nausea, vomiting, diarrhea, abdominal pain	Present, early	Between the 3rd and 4th day: hematemesis, melena, puncture sites, ecchymosis hemorrhagic gingivitis, epistaxis	Leukopenia, neutropenia, shift to the left, lymphocytosis, eosinopenia, ESR \uparrow , bilirubins \uparrow (more at the expense of direct-reacting bilirubin)	Very elevated (more than 1,000 IU/L)
LEPTOSPIROSIS	Leptospire: <i>Leptospira interrogans</i> (spirochetes)	4 to 19 days; average of 10 days	Contact of broken skin or mucous membranes with water or food contaminated with the urine of infected animals, mainly rats	Sudden onset, headache, chills, fever, muscle pain (calves, lumbar region), anorexia, nausea, vomiting, and prostration	Present, early Present, late in 15% of cases	Late	Leukocytosis, neutrophilia, shift to the left, eosinopenia, ESR \uparrow , mucoproteins \uparrow , thrombocytopenia, urea \uparrow , creatinine \uparrow	Slightly elevated (not higher than 500 IU/L)
MALARIA caused by <i>Plasmodium falciparum</i>	<i>Plasmodium falciparum</i>	Average of 12 days after the mosquito bite	Bite of the <i>Anopheles</i> mosquito	Clinical triad of intermittent fever, enlarged spleen, and anemia Headache, nausea, vomiting, prostration, intense chills, shakes, sweating, tender spleen Mental confusion may be present.	Present	Minor tendency to hemorrhage: gastric hemorrhage may be present	Early anemia, presence of malaria pigment in leukocytes, leukopenia, monocytosis	Slight increase
HEPATITIS VIRALES	Hepatitis: A virus–HAV (RNA virus–Picornaviridae) B–HBV (DNA virus–Hepadnaviridae) C–HCV (RNA –Flaviviridae) D–HDV (RNA virus) E–HEV (RNA virus, unclassified but similar to the Caliciviridae)	HAV: 15 to 50 days (average: 28 to 30 days) HBV: 45 to 180 days (average: 60 to 90 days) HCV: 14 to 168 days (average: 42 to 63 days) HDV: There is no precise period in man HEV: 15 to 64 days (average: 26 to 42 days)	HAV: fecal-oral transmission HBV: blood transfusion, vertical, injections, and sexual transmission HCV: blood transfusion, injections, and sexual transmission HDV: blood transfusion, injections, and sexual transmission; prior or concomitant infection with hepatitis B virus is required HEV: fecal-oral transmission	Mild or absent fever, anorexia, malaise, abdominal pain, nausea, headache, general myalgia, fatigue	Present	May be present early in the fulminating form, mainly in the gastrointestinal tract	Normal urea, normal creatinine, absence of albuminuria, leukopenia, neutropenia, lymphocytosis, shift to the left	Very elevated; ALT (SGPT) levels usually exceed AST (SGOT) levels

DISEASE	INFECTIOUS AGENT	INCUBATION PERIOD	MODE OF TRANSMISSION	CLINICAL SYMPTOMS	JAUNDICE	HEMORRHAGIC MANIFESTATIONS	LABORATORY	SGOT/SGPT
SEPTICEMIA	Gram-negative bacteria	Three to seven days	Hospital infection; contamination of surgical wounds or scabs, or both	Abrupt onset, high fever, prostration, toxemia, chills, nausea, vomiting, hypotension, shock	May be present	May be present	Leukocytosis or leukopenia with shift to the left	Slight increase
DENGUE HEMORRHAGIC FEVER	Dengue virus (<i>Flavivirus</i>)	3 to 14 days	Bite of the <i>Aedes aegypti</i> mosquito	High fever, headache, joint pain, myalgia, hypovolemia, abdominal pain, enlarged liver, shock	Absent	Positive tourniquet test, petechiae, epistaxis, hemorrhagic gingivitis, ecchymosis; hematemeses, melena	Hemoconcentration, thrombocytopenia, albumin↓	Slightly elevated
BRAZILIAN SPOTTED FEVER	<i>Rickettsia rickettsii</i>	3 to 14 days	Bite of infected ticks	Abrupt onset, high fever, myalgia, headache, anorexia, prostration, nausea, vomiting, abdominal pain, lesions at site of bite, rash after the 3rd day of disease	Present late	Petechiae, ecchymosis	Normal leukocytes, thrombocytopenia, hyponatremia	Normal
ARGENTINE HEMORRHAGIC FEVER (AHF), BOLIVIAN HEMORRHAGIC FEVER (BHF), AND VENEZUELAN HEMORRHAGIC FEVER (VHF)	Tacaribe complex of arenaviruses Junín virus (AHF) Machupo virus (BHF) Guanarito virus (VHF)	7 to 16 days	Inhalation of contaminated aerosolized rodent saliva and excreta Also by ingestion or contact with cuts or skin ulcers	Slow and gradual onset; fever, malaise, headache, general myalgia, nausea, vomiting, palpebral edema, shock	Absent	Petechiae in axillae and thorax, epistaxis, hematemeses, melena	Leukopenia, thrombocytopenia, hemoconcentration, intense azotemia, proteinuria, low albumin	Normal
HANTAVIRUS DISEASE WITH RENAL SYNDROME	<i>Hantavirus</i> , family Bunyaviridae	12 to 16 days; can range from 5 to 42 days	Inhalation of contaminated, aerosolized rodent saliva and excreta	Abrupt onset, high fever (40 °C–41 °C), chills, severe myalgia, frontal headache, flushing, irreversible shock	Absent	Hematemeses, hemoptysis, melena, ocular hemorrhage; petechiae of the soft palate, pharynx, axillae, thorax, scapula, and arms	Significant proteinuria, oliguresis, creatinine↑ (5 to 6 mg/dL), leukocytosis, atypical lymphocytes, thrombocytopenia, hemoconcentration	Normal

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Annex 2. Epidemiological investigation form for yellow fever

Case identification	1. Name of patient:																		
	2. Date of birth: ____ / ____ / ____																		
	3. Age: _____		4. Sex: <input type="checkbox"/> M - Male <input type="checkbox"/> F - Female																
	Street: _____																		
	5. Address: Municipality: _____																		
	District: _____																		
	6. Location: <input type="checkbox"/> 1 - Urban <input type="checkbox"/> 2 - Rural <input type="checkbox"/> 3 - Urban/Rural <input type="checkbox"/> 9 - Unknown																		
	7. Telephone: () - ____ - ____																		
Epidemiological history	Supplementary information for patient:																		
	8. Date of investigation: ____ / ____ / ____		9. Occupation:																
	10. Description of dates and places frequented in the 10-day period prior to the onset of signs and symptoms																		
	<table border="1"> <thead> <tr> <th>Date</th> <th>Municipality</th> <th>State</th> <th>Country</th> </tr> </thead> <tbody> <tr><td> </td><td> </td><td> </td><td> </td></tr> <tr><td> </td><td> </td><td> </td><td> </td></tr> <tr><td> </td><td> </td><td> </td><td> </td></tr> </tbody> </table>				Date	Municipality	State	Country											
Date	Municipality	State	Country																
Clinical information data	11. Vaccinated against yellow fever: <input type="checkbox"/> 1 - Yes <input type="checkbox"/> 2 - No <input type="checkbox"/> 9 - Unknown																		
	12. Date: ____ / ____ / ____																		
Clinical information data	13. Signs and symptoms:																		
	Fever <input type="checkbox"/> 1 - Yes <input type="checkbox"/> 2 - No <input type="checkbox"/> 9 - Unknown		Epigastric pain <input type="checkbox"/> 1 - Yes <input type="checkbox"/> 2 - No <input type="checkbox"/> 9 - Unknown																
	Headache <input type="checkbox"/> 1 - Yes <input type="checkbox"/> 2 - No <input type="checkbox"/> 9 - Unknown		Faget's sign <input type="checkbox"/> 1 - Yes <input type="checkbox"/> 2 - No <input type="checkbox"/> 9 - Unknown																
	Chills <input type="checkbox"/> 1 - Yes <input type="checkbox"/> 2 - No <input type="checkbox"/> 9 - Unknown		Hematuria <input type="checkbox"/> 1 - Yes <input type="checkbox"/> 2 - No <input type="checkbox"/> 9 - Unknown																
	Shock <input type="checkbox"/> 1 - Yes <input type="checkbox"/> 2 - No <input type="checkbox"/> 9 - Unknown		Hematemesis <input type="checkbox"/> 1 - Yes <input type="checkbox"/> 2 - No <input type="checkbox"/> 9 - Unknown																
	Vomiting <input type="checkbox"/> 1 - Yes <input type="checkbox"/> 2 - No <input type="checkbox"/> 9 - Unknown		Oliguria <input type="checkbox"/> 1 - Yes <input type="checkbox"/> 2 - No <input type="checkbox"/> 9 - Unknown																
	Jaundice <input type="checkbox"/> 1 - Yes <input type="checkbox"/> 2 - No <input type="checkbox"/> 9 - Unknown		Anuria <input type="checkbox"/> 1 - Yes <input type="checkbox"/> 2 - No <input type="checkbox"/> 9 - Unknown																
	Melena <input type="checkbox"/> 1 - Yes <input type="checkbox"/> 2 - No <input type="checkbox"/> 9 - Unknown		Bradycardia <input type="checkbox"/> 1 - Yes <input type="checkbox"/> 2 - No <input type="checkbox"/> 9 - Unknown																
			Coma <input type="checkbox"/> 1 - Yes <input type="checkbox"/> 2 - No <input type="checkbox"/> 9 - Unknown																
	Care	14. Hospitalization: <input type="checkbox"/> 1 - Yes <input type="checkbox"/> 2 - No <input type="checkbox"/> 9 - Unknown		15. Date: ____ / ____ / ____															
16. Name of hospital:																			
17. Address:																			
Laboratory data	18. Serological studies:																		
	Bilirubin: _____		AST (SGOT) _____ IU/L																
	Total _____ mg/dl		ALT (SGPT) _____ IU/L																
	Direct (BD) _____ mg/dl		Urea _____ mg/dl																
	Indirect (BI) _____ mg/dl		Creatinine _____ mg/dl																
Albumin:																			
<input type="checkbox"/> 1 - zero																			
<input type="checkbox"/> 2 - +																			
<input type="checkbox"/> 3 - ++																			
<input type="checkbox"/> 4 - +++																			
<input type="checkbox"/> 5 - ++++																			

Laboratory data	19. Specific examinations: Date sample was taken: 1 st ____/____/____ 2 nd ____/____/____ Date sample was taken: 1 st ____/____/____ 2 nd ____/____/____ Date sample was taken: 1 st ____/____/____ 2 nd ____/____/____				Result 1 - Positive 2 - Negative 3 - Inconclusive 4 - Not performed	Titers <input type="checkbox"/> IgM <input type="checkbox"/> IgG S1 _____ 1: _____ S2 _____ 1: _____
	20. Histopathology: <input type="checkbox"/> 1- Compatible <input type="checkbox"/> 2- Negative <input type="checkbox"/> 3- Not performed <input type="checkbox"/> 9- Unknown Immunohistochemical <input type="checkbox"/> 1- Compatible <input type="checkbox"/> 2- Negative <input type="checkbox"/> 3- Not performed <input type="checkbox"/> 9- Unknown					
	21. Viral isolation: Material collected <input type="checkbox"/> 1-Yes <input type="checkbox"/> 2-No <input type="checkbox"/> 9- Unknown Result <input type="checkbox"/> 1- Isolated <input type="checkbox"/> 2- Not isolated If so, which Serum: <input type="checkbox"/> 1-Yes <input type="checkbox"/> 2-No <input type="checkbox"/> 9- Unknown Tissues: <input type="checkbox"/> 1-Yes <input type="checkbox"/> 2-No <input type="checkbox"/> 9- Unknown					
Control measures	22. Control measures carried out: Mass vaccination <input type="checkbox"/> 1-Yes <input type="checkbox"/> 2-No <input type="checkbox"/> 3-Not applicable <input type="checkbox"/> 9- Unknown Vector control <input type="checkbox"/> 1-Yes <input type="checkbox"/> 2-No <input type="checkbox"/> 3-Not applicable <input type="checkbox"/> 9- Unknown					
Conclusions	23. Final classification: <input type="checkbox"/> 1- Urban Yellow Fever <input type="checkbox"/> 2- Jungle Yellow Fever <input type="checkbox"/> 3- Ruled out (specify: _____)			24. Criteria for confirmation/ruling out: <input type="checkbox"/> 1 - Laboratory <input type="checkbox"/> 2 - Epidemiological link <input type="checkbox"/> 3 - Clinical symptoms		
	25. Probable infection site: Country: _____ Municipality: _____ Related disease <input type="checkbox"/> 1-Yes <input type="checkbox"/> 2-No <input type="checkbox"/> 9- Unknown Outcome of the case <input type="checkbox"/> 1-Recovery <input type="checkbox"/> 2- Death <input type="checkbox"/> 9- Unknown Date of death: ____/____/____ Date case closed: ____/____/____					
Remarks	_____ _____ _____					
Investigator	26. State/Municipality _____ Name: _____ Position: _____					Signature: _____

Annex 3. Laboratory differentiation of hemorrhagic fever and jaundice diseases

YELLOW FEVER

Hemogram

- Leukocytosis with neutrophilia and shift to the left (initial).
- Leukopenia with lymphocytosis and shift to the left (3rd to 4th day) + eosinopenia.
- Elevated hematocrit (hemoconcentration).

Transaminases

- AST (SGOT) and ALT (SGPT) 1,000 IU/L.

Urea and creatinine

- Elevated in severe forms of disease. Creatinine can rise to 3-12 mg/dL.

Amylase

- Significant increase.

Urine

- Proteinuria, hematuria, cylindruria, oliguria in severe forms.

Specific tests

Viral isolation

- Serum should be collected within five days of the onset of symptoms.
- Techniques employed: inoculation in suckling mice and cell cultures (C6/36 and VERO).

Serological diagnosis

- MAC-ELISA (IgM capture enzyme-linked immunosorbent assay); the serum should be obtained at least six days after the onset of symptoms.
- Hemagglutination inhibition (paired samples are required: the first in the acute stage, and the second at two weeks, during the convalescent stage).
- Complement fixation (paired samples are required: the first in the acute stage and the second at two weeks during the convalescent stage).
- Neutralization (paired samples are required: the first in the acute stage and the second at two weeks, during the convalescent stage).

Histopathological diagnosis

- Liver: midzonal liver necrosis; steatosis; eosinophilic degeneration of the hepatocytes (Councilman's bodies) and very discrete mononuclear inflammatory reaction.

Immunohistochemical

- Detection of viral antigens in tissues using polyclonal antibodies marked with one enzyme (alkaline phosphatase or peroxidase).

Molecular biology

- Polymerase chain reaction (PCR).
- Permits detection of viral nucleic acid fragments present in tissues.

DENGUE

Hemogram

- Leukopenia with lymphocytosis (classic dengue).
- Hemoconcentration (hematocrit = 20% and thrombocytopenia = $100,000/\text{mm}^3$) in dengue hemorrhagic fever (DHF).

Transaminases

- AST (SGOT) and ALT (SGPT) normal or slightly elevated.

Specific tests

Viral isolation

- The serum should be obtained within five days of the onset of the symptoms.
- Techniques employed: inoculation in suckling mice and cell cultures (C6/36 and VERO).

Serological diagnosis

- MAC-ELISA (IgM capture enzyme-linked immunosorbent assay). The serum sample should be obtained at least six days after the onset of symptoms.
- Hemagglutination inhibition (paired samples are required: the first in the acute stage and the second at two weeks, during the convalescent stage).
- Complement fixation (paired samples are required: the first in the acute stage and the second at two weeks, during the convalescent stage).
- Neutralization (paired samples are required: the first in the acute phase and the second at two weeks, during the convalescent stage).

Histopathological diagnosis

- Steatosis and necrosis of liver cells associated with areas of hemorrhage, and discrete inflammatory reaction of the portal spaces.

Immunohistochemical

- Detection of viral antigens in tissues using polyclonal antibodies marked with one enzyme (alkaline phosphatase or peroxidase).

Molecular biology

- Polymerase chain reaction (PCR).
- Permits the detection of viral nucleic acid fragments present in the tissues.

LEPTOSPIROSIS

Hemogram

- Leukocytosis with neutrophilia and shift to the left + eosinopenia.

Transaminases

- SGOT and SGPT elevated but < 200 IU/L.

Urea and creatinine

- Elevated.

Bilirubins

- Hyperbilirubinemia due to increase in direct bilirubin.

Urine

- Proteinuria, hematuria, leukocyturia.

Specific tests

Culture

- Week 1: a blood or fluid culture can be performed, with the sample taken within seven days of the onset of symptoms (leptospiremia phase).
- Week 2: a urine culture can be performed, with the sample taken between 7 and 14 days after the onset of symptoms (leptospiuria phase).

Microscopic examination

- Darkfield microscopy.

Serological reactions

- Macroagglutination:
 - Macroscopic seroagglutination (for selection). Antigens of dead strains; not very sensitive.
- Microagglutination:
 - Microscopic seroagglutination; highly sensitive and specific.
 - Live antigen strains.
 - Paired samples are required; a fourfold increase in titers is considered positive.
 - ELISA (IgM and IgG).

Molecular biology: PCR.

MALARIA

Hemogram

- In *Plasmodium falciparum* infections, anemia can occur in 30% of cases, leucopenia in 37%, and thrombocytopenia in 56%.

Transaminases

- AST (SGOT) and ALT (SGPT) slightly elevated.

Bilirubins

- Elevated in patients with jaundice (hemolysis), at the expense of indirect bilirubin.

Specific tests

- Investigation of *Plasmodium*: thick blood film and quantitative test of the leukocyte layer (quantitative buffy coat—QBC).

Immunological tests

- ParaSight-F™ (antigens).
- Immunofluorescence (antibodies).
- Immunoenzyme assay: ELISA.

Molecular biology: PCR.

VIRAL HEPATITIS

Hemogram

- Nonspecific.

Transaminases

- Elevated AST (SGOT) and ALT (SGPT).

Bilirubins

- Hyperbilirubinemia with predominance of direct bilirubin.

Specific tests

Viral markers

- *Hepatitis A*: IgM/IgG anti-HAV.
- *Hepatitis B*:
 - HBsAg: hepatitis B surface antigen; first marker to appear in the serum even prior to the onset of symptoms. In cases that progress toward recovery it ceases to be detected. Its persistence for more than 6 months indicates chronic infection.

Interpretation of hepatitis B results

Test	Results	Interpretation
HBsAg anti-HBc anti-HBs	Negative Negative Negative	Susceptible
HBsAg anti-HBc anti-HBs	Negative Positive Positive	Immune by natural infection
HBsAg anti-HBc anti-HBs	Negative Negative Positive	Immune by hepatitis B vaccine
HBsAg anti-HBc IgM anti-HBc anti-HBs	Positive Positive Positive Negative	Acutely infected
HBsAg anti-HBc IgM anti-HBc anti-HBs	Positive Positive Negative Negative	Chronically infected
HBsAg anti-HBc anti-HBs	Negative Negative Positive	Four possible interpretations ^a

^a 1. May be recovering from an acute infection.

2. May have low immunity and the tests are not sensitive enough to detect very low levels of serum anti-HBs.

3. May be susceptible with a false positive for anti-HBc.

4. May have undetectable levels of serum HBsAg and the person is currently infected.

- IgM anti-HBc: antibody against the hepatitis B core antigen, IgM. Its positivity associated with HBsAg indicates recent acute infection.
- IgG anti-HBc: antibody against the hepatitis B core antigen, IgG. It appears at the initial stages of the disease; it is the marker characteristic of the immunological window. Associated with the antibody against the surface antigen, it indicates the development of immunity against HBV.
- HBeAg: antigen e of hepatitis B. It is a marker for active viral replication and infectiousness.
- Anti-Hbe: antibody against antigen e of hepatitis B. Indicates the absence of viral replication.
- Anti-HBs: antibody against the hepatitis B surface antigen. Antibody associated with the resolution of the disease and the development of immunity. When this marker is alone, it indicates the development of vaccinal immunity.
- *Hepatitis C*: anti-HCV.
- *Hepatitis D*: anti-HDV.
 - PCR (qualitative/quantitative).

Normal laboratory values

Bilirubins:	
Total	up to 1.2 mg/dL
Indirect (IB)	up to 0.7 mg/dL
Direct (BD)	up to 0.5 mg/dL
Creatinine	0.7 to 1.4 mg/dL
SGOT/AST	up to 45 IU/L
SGPT/ALT	up to 50 IU/L
Amylase	up to 195 IU/L
Alkaline phosphatase	up to 320 IU/L (adult)
Urea	15 to 50 mg/dL

ANNEX 4. Function of each level of the health system

In yellow fever prevention and control		
	Routine vaccination against yellow fever	Vaccination and other activities
Local health	Include the vaccine in the regular EPI schedule for children 1 year of age in enzootic areas. Administer at the same time as the measles vaccine, in different arms. Use safe vaccination practices.	Vaccinate 95% of the residents of enzootic areas and the migrant population. Include yellow fever vaccination in measles follow-up campaigns. Use safe vaccination practices.
Municipal or district level	Support routine vaccination activities. Monitor vaccination coverage.	Monitor the surveillance system and ensure that reporting takes place. Conduct ongoing health situation analysis to support decision-making. Monitor <i>Ae. aegypti</i> infestation indices and promote the necessary intervention measures.
Laboratory	Give timely notification of results to the local level for all suspected cases of yellow fever.	
National level	Include yellow fever vaccination in the EPI schedule. Adopt corrective measures based on analysis and monitoring of vaccination coverage.	In enzootic areas, vaccinate the entire population over 1 year of age. Continue vaccination of new cohorts of 1-year-old children.

In yellow fever surveillance		
	Detection and confirmation of suspected cases	Response to a confirmed case
Local health services	Use case definition to identify suspected cases. Immediately notify the next level of the health system. Conduct an immediate investigation. Take laboratory or pathology samples.	When a case is confirmed: Plan and carry out mass vaccination. Work with the municipal level in characterizing the case.
Municipal or district level	Assist the health institution with the investigation, collection of samples, and their shipment. Detect rising trends with respect to cases of fever of unknown etiology or fever and jaundice.	Following the recommendations of the committee formed to control the outbreak, assist health institutions with emergency vaccination, active case search, shipment of samples, and vector control in urban areas. Coordinate activities with the next level of the health system.
Laboratory	Provide containers for collecting samples if necessary, and instructions for collecting and shipping specimens.	Process the samples immediately and send the results to all levels of the health system.
National level	Provide a standard case definition for use at all levels of the health system. Provide feedback about confirmed cases to all levels of the system. Provide laboratory results.	Carry out international notification of the case. Guarantee vaccines and other supplies and resources necessary for controlling the outbreak. Organize the activities in keeping with local needs. Train personnel.

Training Module^a

PRACTICAL EXERCISES FOR A CLINICAL CASE STUDY AND STUDY OF A YELLOW FEVER OUTBREAK

^a Adapted from *Manual de vigilância epidemiológica de febre amarela*, Brasília: Ministério da Saúde, Fundação Nacional da Saúde; 1999.

I. Objectives of the module

At the conclusion of the training, the student should be able to:

1. Conduct an epidemiological investigation of a suspected case of yellow fever.
2. Assess the case and prepare the health services to care for a patient with yellow fever.
3. Perform the epidemiological diagnosis of yellow fever:
 - ✓ Identify a yellow fever epidemic.
 - ✓ Assess vaccination coverage.
 - ✓ Assess the situation of a municipality using a risk map.
 - ✓ Assess the risk of urbanization (infestation by urban vectors).
4. Implement control measures in the event of a yellow fever epidemic.

II. Target audience

Health professionals who work in epidemiological surveillance, immunization, and laboratories in states, departments, districts, and municipalities, and who possess basic skills in epidemiology.

III. Methodology

The training module should be administered to groups of 8 to 20 people, with an instructor for each group and a duration of at least six hours. The module contains two different clinical-epidemiological situations. Nine sheets with related information will be reviewed during the training. The method used is directed study, with group discussions.

Answers to questions for the practice exercises can be found beginning on page 56.

Situation 1. Clinical case study

On 02/10/97, D.L.A., male, married, 39 years of age, employed as a physician, arrived at the emergency service in _____ (*City 1*) presenting with a high fever that had begun on 02/08/97, accompanied by headache, myalgia, nausea, vomiting, and abdominal pain. Fifteen days earlier, he and his wife had traveled to _____ (*Area 1*).

He stayed in _____ (*City 2*), since the rains in the region had caused floods that made the road impassable. He had heard rumors of a dengue outbreak in the city that had affected guests at the hotel where he was staying.

He was only able to reach _____ (*Area 1*) on 02/03 where he and his wife met friends, three couples from _____ (*City 3*). On the 4th, 5th, and 6th of the month they went on excursions to the jungle, and on 02/08 went to _____ (*City 4*).

That same day he developed fever and vomiting. He sought medical care after hearing about indigenous cases of malaria in the region. He was treated for his symptoms at the University Hospital's emergency room and discharged.

As his clinical symptoms showed no improvement, he decided to return home by plane and went to the emergency service at the hospital in _____ (*City 1*), where he worked. He was admitted for observation. He reported that he frequently traveled with friends to _____ (*Area 1*), staying for two to three days.

After a negative blood smear for malaria, the physician from the emergency service suspected that the problem could be dengue, so he requested a blood sample for viral isolation and notified the epidemiological surveillance team from the municipality of _____ (*City 1*).

The epidemiological surveillance team visited the patient in the hospital on 02/12 and obtained the following information:

City 1: Provide the name of a city in an enzootic area with a referral hospital for infectious diseases.

Area 1: Provide the name of an enzootic forest or savannah area that is frequented by tourists.

City 2: Provide the name of a small city located on the road to the tourist area.

City 3: Provide the name of a city located in the nonendemic area.

City 4: Provide the name of the capital of the department/state where the tourist area is located.

LABORATORY TESTS

Hemogram

- Hb: 11 g/dL; Hct: 33%;
- Platelets: 212,000/mm³
- Leukocytes: 4,600/mm³
- Neutrophils: 42%
- Immature neutrophils: 3%
- Segmented neutrophils: 39%
- Eosinophils: 3%
- Basophils: 1%
- Lymphocytes: 49%
- Monocytes: 5%

Biochemistry

- Glucose: 96 mg/dL; K: 3.9 mEq/L; Na: 130 mEq/L
- AST (SGOT): 1,530 IU/L;
- ALT (SGPT): 1,950 IU/L
- Total bilirubin: 4.4 mg/dL;
- DB: 3.4 mg/dL; IB: 1.0 mg/dL
- Urea: 96 mg/dL; Creatinine: 3.2 mg/dL

Other

- Thick blood film for malaria: negative
- Macroagglutination for leptospirosis: negative

Liver function tests:

- AST (SGOT): 12,000 IU/L;
- ALT (SGPT): 9,400 IU/L
- Total bilirubin: 8.8 mg/dL;
- DB: 5.8 mg/dL; IB: 3.0 mg/dL

Histopathology

Macroscopic examination reveals an enlarged, friable yellowish liver. Hepatocytes preserved in the central lobular vein and portal space are observed, with diffuse midzonal necrosis, hyaline necrosis characterized by the presence of Councilman's bodies; hypertrophy and hyperplasia of the Kupffer cells; presence of subcapsular and parenchymatous hemorrhagic foci.

Clinical course

02/12: Patient generally in fair condition, with daily fever and epigastric pain. Physical examination reveals jaundice (++/4+); BP=100/60 mmHg; HR=100 beats/min; liver at 2 cm from the right costal margin.

Question 1 What diagnostic hypotheses could be offered for this case? Engage in a group discussion on Annex 1 (Differential diagnosis of hemorrhagic fever and jaundice diseases).

TRAINING STRATEGIES

- ✓ The students should review Annex 3 (Laboratory differentiation of hemorrhagic fever and jaundice diseases). Discuss the similarities between the clinical symptoms of the diseases analyzed and stress the value of epidemiological data.
- ✓ Students should draw up a list of diagnostic hypotheses compatible with the clinical and epidemiological history presented.
- ✓ Emphasize the need for a syndromic approach in managing diseases with similar clinical manifestations and underscore the importance of epidemiological information.
- ✓ Question the students about other important epidemiological information that might be missing in the assessment of the patient (presence of epizootics in the region, for example).
- ✓ Ask how the epidemiological surveillance system could obtain information on epizootics.
- ✓ Ask about the steps to take if there are indications that an epizootic exists.

Question 2

- (a) What other tests would be essential for obtaining the etiologic diagnosis?
- (b) From a public health standpoint, why is it important to establish the etiologic diagnosis in this case?
- (c) Would you select any test as a priority for epidemiological surveillance?
- (d) Why?

Clinical course

- 02/15:** The patient showed modest improvement in his symptoms: his temperature returned to normal and his vital signs stabilized.
- 02/16:** The patient symptoms intensified, presenting with the appearance of epistaxis, “black” vomit, and bleeding at venous puncture points. He developed hepatorenal syndrome and was transferred to intensive care. Blood was taken for yellow fever serology and liver function tests.
- 02/17:** Death of the patient. The epidemiological surveillance team requested an autopsy, with the family’s consent.
- 02/21:** The epidemiological surveillance team received the results of nonspecific (liver function) and specific (dengue and yellow fever) tests, and the histopathological autopsy results. Furthermore, it specifically guided the epidemiological investigation to obtain additional information.

Question 3 Discuss the laboratory results comparing liver function test values with the initial values. Discuss the serology results.

OTHER INFORMATION

- The investigation showed that the patient had been vaccinated against hepatitis B but not yellow fever. His wife and three children, according to their respective vaccination cards, had been vaccinated against yellow fever two years earlier.
- The *Aedes aegypti* house infestation rate in _____ (City 3) ranged from 0.5% to 9%, with an average value of 4.8%. In _____ (City 1) it was approximately 3%.

Question 4 How is the house infestation rate calculated?

- The Epidemiological Surveillance Center in _____ (City 3) reported that one of the women who had been traveling with D.L.A. had not been vaccinated against yellow fever and that her husband had experienced fever and malaise during the trip. Serum samples were collected from both individuals for testing, and the samples were positive for yellow fever.
- The Ministry of Health of the State/Department of _____ (Area 1) reported that fishermen from the region stated that they had encountered monkey skeletons about a month earlier in the region of _____

LABORATORY TESTS (continuation)

Isolation of the dengue virus

This was being completed.

Serology

- MAC-ELISA (IgM) for dengue: positive
- Viral markers for hepatitis A and B: IgM anti-HAV: negative; IgM anti-HBc: negative; anti-HBs: positive
- MAC-ELISA (IgM) for yellow fever: positive

(*Area 1*). However, no suspected cases of yellow fever were found among local inhabitants. In late 1996, a door-to-door yellow fever vaccination campaign was conducted in response to a widespread epizootic in the municipality.

- On 02/25 the reference laboratory reported that it had isolated the virus in the blood sample taken from patient D.L.A.: it was negative for dengue and positive for yellow fever.

Question 5 What actions should have triggered epidemiological surveillance after the team's first visit to the patient on 02/12, considering all the diagnostic hypotheses generated?

EPIDEMIOLOGICAL SURVEILLANCE OBJECTIVES

Regardless of the disease under surveillance, epidemiological surveillance involves the following four basic activities:

- *Detection of cases* (this also implies actions geared to making a correct diagnosis);
- *Reporting/notification*;
- *Identification* of the population at risk;
- *Orientation/implementation* of control measures.

TRAINING STRATEGIES

- ✓ Ask the students what they think about the objective of epidemiological surveillance; write their suggestions on the board.
- ✓ After all the suggestions have been made, classify them under each of the four main activities listed above.
- ✓ Complete the responses.

FINAL CONSIDERATIONS

- Yellow fever belongs to a group of diseases that share similar clinical manifestations. It is essential to underscore the importance of a syndromic approach to the diagnosis of these diseases.
- Due to the potential for yellow fever epidemics, it is important to institute control measures as soon as possible, even without diagnostic confirmation.
- It is advisable to explain that other cases have not occurred because this is an example of an epidemiological investigation of one case that appeared in an endemic area.
- It is necessary to alert class participants about the management of seriously ill patients with sudden-onset hemorrhagic fever and jaundice. Treating hospi-

tals should immediately report such cases to the municipal epidemiological surveillance system, which in turn should inform the regional surveillance system. The case should be followed and an epidemiological investigation conducted as soon as possible to obtain as much information as possible to support the diagnosis. In the case of undiagnosed deaths, tissue specimens should be obtained, adhering to the protocol for anatomicopathological examinations.

- Information on vaccination status is key to evaluating a suspected case of yellow fever. If the patient was vaccinated against yellow fever more than 10 days before presentation of symptoms, he/she will have protection against the disease, and the diagnosis will probably be something else. If he was vaccinated less than 10 days before presentation of symptoms, immediately contact the regional level → state/departmental level → national level. **This may indicate an adverse event.** Samples should be taken from such patients. Comment that the National Immunization Program has a special protocol for assessing and monitoring such cases.

In a yellow fever outbreak, the epidemiological questions below can be used to guide the diagnosis of the health situation by identifying the problem, determining its magnitude and distribution, analyzing it, and taking prevention and control measures.

A. Detection of the main health problems

1. What disease or event is impacting your community?

B. Magnitude and distribution

2. How many cases were detected? How many deaths resulted?
3. When did they usually occur (what time of the year/month/week)?
4. Where did they occur? Were they confined to a particular area? Locate them on maps or diagrams.
5. Which people have been affected (children, adults, the elderly, individuals or families, indigenous populations, people of the same socioeconomic status)? Where do they live?

C. Analysis

6. Why did the disease appear? Had the population been vaccinated? What was the level of local vaccination coverage? What happened to the contacts? What are the main factors involved? Did the cases occur among residents or migrants?

D. Steps taken

7. What steps have been taken in the community?
8. What are the results? What difficulties were encountered in attempting to solve the problem?
9. What more could be done? What type of assistance or help is needed?

Situation 2. Study of a yellow fever outbreak

The Ministry of Health of the municipality of San Francisco de Asís received a report on 01/23/2001 from a city hospital about the death of a patient suspected to have contracted yellow fever. An epidemiological investigation was quickly launched and it was determined that the case was indigenous, since the patient had not traveled outside the municipality in the past 15 days, a period during which he was clearing land to be used for growing corn on the outskirts of the city. Subsequent confirmation of the case led the hospital's medical team to suspect yellow fever in two more patients who had died in the hospital of hemorrhagic disease of unknown origin during the same month as the suspected case. Other suspected cases were reported in the municipalities of Villa Pera and Corales.

These three municipalities are located in the central region of Asís in an area where human cases of yellow fever or epizootics had never been detected. They are some 20 km from an area in which epizootics have occasionally been reported. Agriculture is the primary economic activity of these municipalities. According to the Regional Secretariat of Health, yellow fever vaccination coverage in these municipalities is 12% in the rural zone and 35% in the urban zone (administrative data which consider coverage as doses administered/resident population). The *Aedes aegypti* house infestation rate ranges from 7% to 13%.

The mission of the coordinator of the investigative team is to assist the health system in dealing with this situation.

- ✓ Hand out Sheet 1 (pg. 45) (map of the region of Asís, with the location of the affected municipalities and their relation to the enzootic yellow fever transmission area) and evaluate it.

Question 1

- (a) What is the current yellow fever situation in the region of San Francisco de Asís? Are we experiencing an epidemic?
- (b) For the purpose of mounting epidemiological surveillance in the event of a yellow fever epidemic, conduct a situational epidemiological diagnosis that explores the magnitude of the problem, the institutional capacity to manage it, the need to create a committee, and the role that this committee would play.

Question 2 Using rapid data collection, you obtained the information presented in the table on Sheet 2 (pg. 46) (Table of suspected yellow fever cases).

- (a) What is the observed case-fatality rate?
- (b) What does this rate mean?

Question 3 Participants should review Sheet 3 (pg. 47) (Pyramid of clinical forms of yellow fever).

- (a) What comments would you make?

- ✓ Show the clinical characterization of a yellow fever outbreak in Goiás, Brazil, 1972.
- ✓ Consult Sheet 4 (pg. 48) (Percentage distribution of yellow fever symptoms in an outbreak in Goiás, Brazil, 1972).

It is essential to detect all cases, including subclinical cases.

Question 4

- (a) Would what you do to detect other cases of yellow fever in the region?
 - (b) What does “sensitive surveillance system” mean?
 - (c) Do you believe that syndromic surveillance should be implemented?
 - (d) What case definition should be used in this situation?
- ✓ Using the pyramid, assist students in understanding the concept of sensitivity (the closer to the base, the greater the sensitivity).

It is important to verify and record the vaccination status of the suspected case (vaccinated with card, vaccinated without card, and unvaccinated).

Question 5

- (a) Where should the active case search be done?
- (b) What is “zero-case” reporting?
- (c) Should zero-case reporting be implemented at this time?

Question 6

Considering the high potential for a yellow fever epidemic and the capacity for its spread in a susceptible population:

- (a) What does the “timeliness” of reporting mean?
 - (b) At what time and to whom should cases be reported?
 - (c) In this situation, should there be international notification to WHO?
- ✓ Consult Sheet 5 (pg. 49) (Epidemic curve) and Sheet 7 (pg. 51) (Map of the region in Asís with yellow fever).
 - ✓ Ask students to draw a map or diagram of the area to analyze the spatial distribution of cases and to examine the path of the outbreak.
 - ✓ Ask the students to draw an epidemic curve for the cases on Sheet 5 (use the date of the onset of symptoms and trace the curve by epidemiological week).
 - ✓ Consult Sheet 8 (pg. 52) (Epidemiological calendar for 2001).

Question 7 Why is it important to organize the data by time?

Question 8 Why is it important to organize the data by individual?

Question 9 Calculate the *mean* and the *median* age of suspected cases, and incidence rates by age group and sex.

Question 10

- (a) Based on the data presented in Sheets 2 (number of cases) and 6 (Table 1: Population distribution) calculate the incidence rate per 1,000 inhabitants, by age group and sex, and complete the data for Table 2.
- (b) Which age group and sex had the highest incidence rate?
- (c) Why? Analyze the possible reasons and the control strategies targeting these groups.

Question 11

- (a) Why is it important to organize the data spatially? The participants should mark the cases on the map, by date of the onset of symptoms and by place of infection (use Sheet 2: Table of suspected yellow fever cases, pg. 46, and Sheet 7: Map of the region in Asís with yellow fever, pg. 51).
- (b) What other information can be included in the map?

Question 12

How would you organize vaccination efforts to ensure adequate coverage to halt the spread of the epidemic?

Mean = sum of the age of all cases divided by the total number of cases.

Median = value that divides the sample into two equal halves (50th percentile). To calculate the median, participants should arrange the age values in ascending order.

Incidence rate (per 1,000 inhabitants) = number of cases in the age group per 1,000, divided by the total of individuals in the age group. Incidence rates can also be calculated with different population bases in the denominator (100, 1,000, 10,000, 100,000 inhabitants, etc.). The same formula is used to calculate the sex-specific incidence rate.

Question 13 What measures would you recommend in addition to vaccination?

Question 14 Four months after the outbreak in San Francisco de Asís, how would you assess the impact of the control measures implemented? Consider the following:

- Need for detection of all clinical forms of the disease.
- Minimum time needed to implement control measures.
- Clinical manifestations of the disease.
- Targets that should be met to control the disease.

(The Ministry of Health issued a report on this; see Sheet 9, pg. 53: Report of the Ministry of Health Commission on the Yellow Fever Epidemic in Asís.)

Question 15 What indicators could be used to evaluate system operations?

To answer this, consider the following key questions:

- How often should the surveillance system report cases in this situation?
- How is it possible to ensure that a unit reporting no cases did not actually have some?
- How soon after a suspected case is reported should the investigation be launched?
- How soon should the laboratory receive samples taken from the suspected case?
- How soon should the results be issued by the laboratory?
- In which cases should control measures be instituted?
- What vaccination goals should be met to control yellow fever in the country?

Discuss the importance and feasibility of setting up at least one sentinel site with a laboratory per region for the surveillance of syndromes characterized by fever and jaundice (all serum samples from jaundiced patients sent to the Public Health Laboratory for diagnosis of viral hepatitis, leptospirosis, septicemia, typhoid fever, amebic liver abscess, etc., should be tested for yellow fever, once the initial diagnosis is ruled out).

For the next 30 minutes, students should evaluate the training module, attempting to answer whether the objectives outlined at the beginning of the module have been met. It would be advisable to review the objectives before the students complete the evaluation.

- ✓ Hand out Sheet 10: Evaluation of the training module.

EXERCISE SHEETS

SHEET 1. Map of the region of Asís with the location of the affected municipalities and their relation to the enzootic yellow fever transmission area

SHEET 2. Table of suspected yellow fever cases

SHEET 3. Pyramid of clinical forms of yellow fever

SHEET 4. Percentage distribution of yellow fever symptoms in an outbreak in Goiás, Brazil (1972)

SHEET 5. Yellow fever epidemic curve in affected municipalities

SHEET 6. Calculation of age- and sex-specific incidence rates

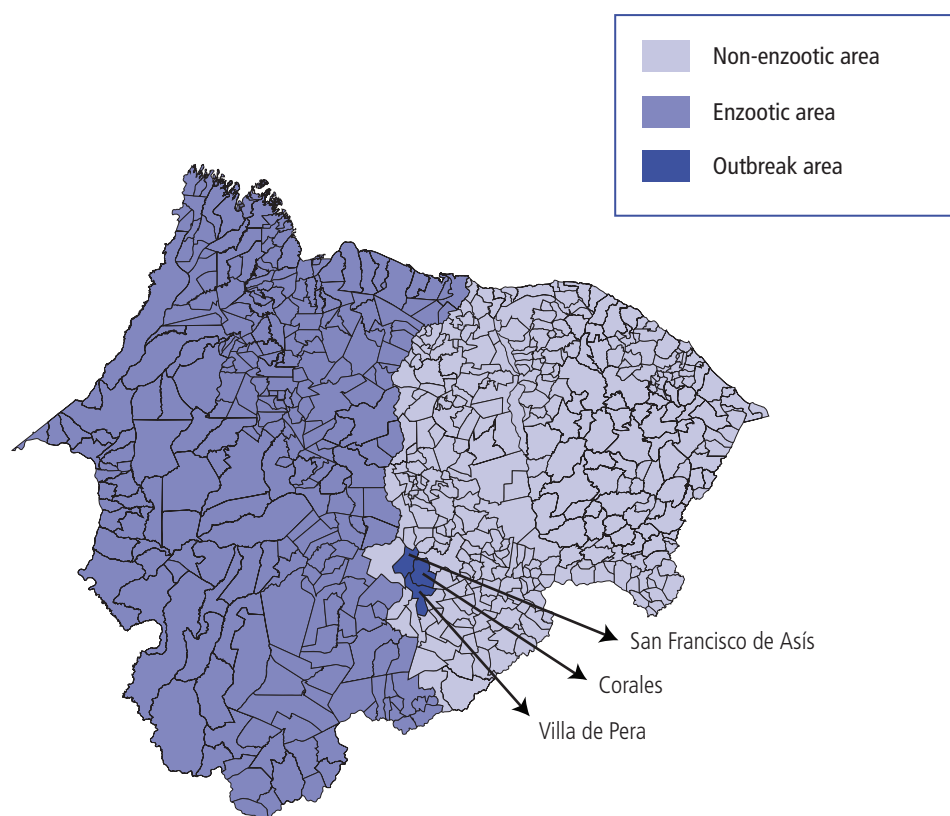
SHEET 7. Map of the region in Asís affected by yellow fever

SHEET 8. Epidemiological calendar for 2001

SHEET 9. Report of the Ministry of Health on the yellow fever epidemic in Asís

SHEET 10. Evaluation of the training module

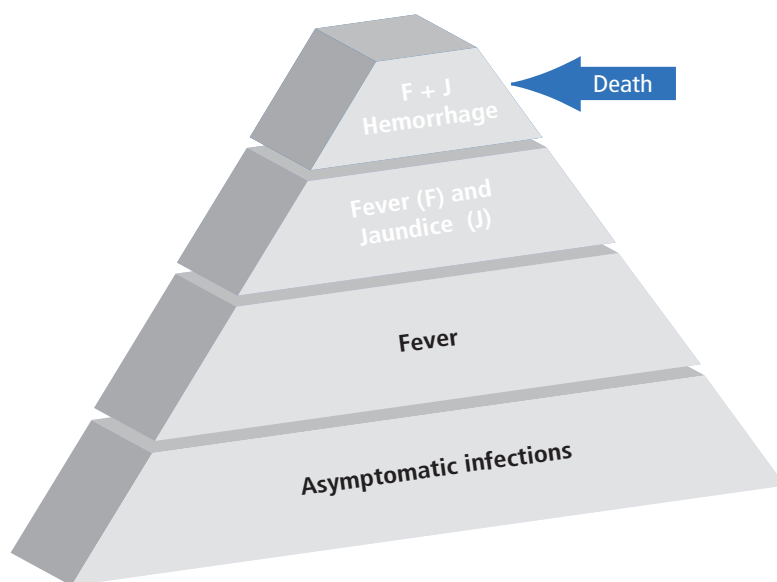
SHEET 1. Map of the region of Asís with the location of the affected municipalities and their relation to the enzootic yellow fever transmission area.



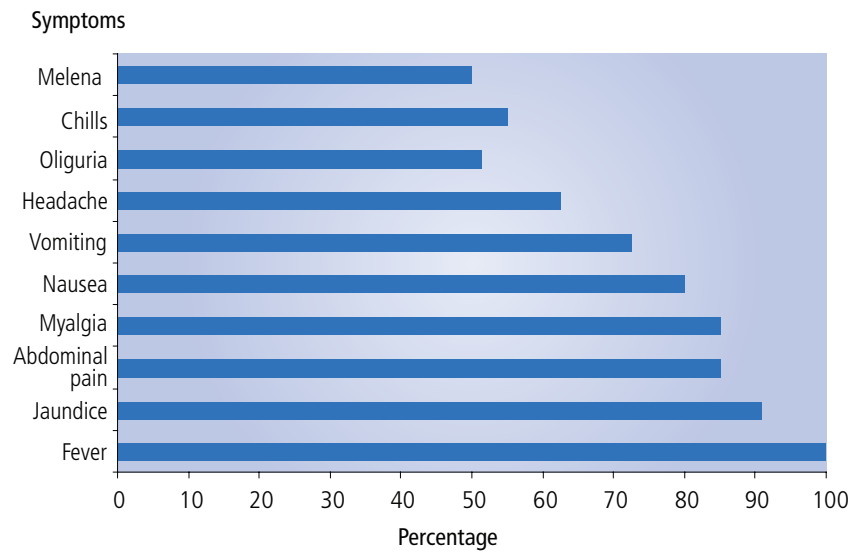
SHEET 2. Table of suspected yellow fever cases

Initials	Sex	Age	Date of symptom onset (day/month/year)	Probable location of infection	Municipality	Outcome
1. A.B.L.	M	23	01/15/2001	Village of Galicia	San Francisco de Asís	Died
2. D.S.B.	M	29	01/19/2001	Village of Galicia	San Francisco de Asís	Died
3. V.M.S.A.	F	32	01/29/2001	Hacienda Grande	San Francisco de Asís	Died
4. M.S.	M	25	02/04/2001	Hacienda Potrero	San Francisco de Asís	Died
5. A.H.R.	M	18	02/05/2001	Hacienda Guayabera	San Francisco de Asís	Recovered
6. M.A.L.	F	23	02/05/2001	Hacienda Onza	San Francisco de Asís	Died
7. S.M.	M	35	02/06/2001	Hacienda Castaño	San Francisco de Asís	Died
8. R.T.M.	F	13	02/09/2001	Village of Juana de Arco	Corales	Recovered
9. J.A.R.	M	30	02/09/2001	Hacienda Monte Bello	Corales	Died
10. A.F.S.	M	16	02/11/2001	Hacienda Monte Bello	Corales	Recovered
11. J.R.C.	F	42	02/12/2001	Village of Carnival	Corales	Died
12. L.A.C.	M	31	02/12/2001	Hacienda Yacaré [I]	Corales	Recovered
13. M.S.S.A.	M	33	02/15/2001	Village of Clavado	Corales	Died
14. A.F.M.	M	24	02/15/2001	Hacienda Yacaré [II]	Corales	Died
15. J.R.D.	M	45	02/16/2001	Hacienda Floresta	Villa de Pera	Died
16. J.L.L.	M	12	02/16/2001	Hacienda Extrema	Villa de Pera	Recovered
17. K.A.S.	F	30	02/18/2001	Hacienda Extrema	Villa de Pera	Recovered
18. L.H.C.M.	M	26	02/19/2001	Village of Vaqueano	Villa de Pera	Died
19. T.C.M.	M	32	02/19/2001	Hacienda Tablero	Villa de Pera	Died
20. H.M.E.	M	33	02/24/2001	Village of Río de Miedo	Villa de Pera	Died

SHEET 3. Pyramid of clinical forms of yellow fever



SHEET 4. Percentage distribution of yellow fever symptoms in an outbreak in Goiás, Brazil (1972)



SHEET 6. Calculation of age- and sex-specific incidence rates

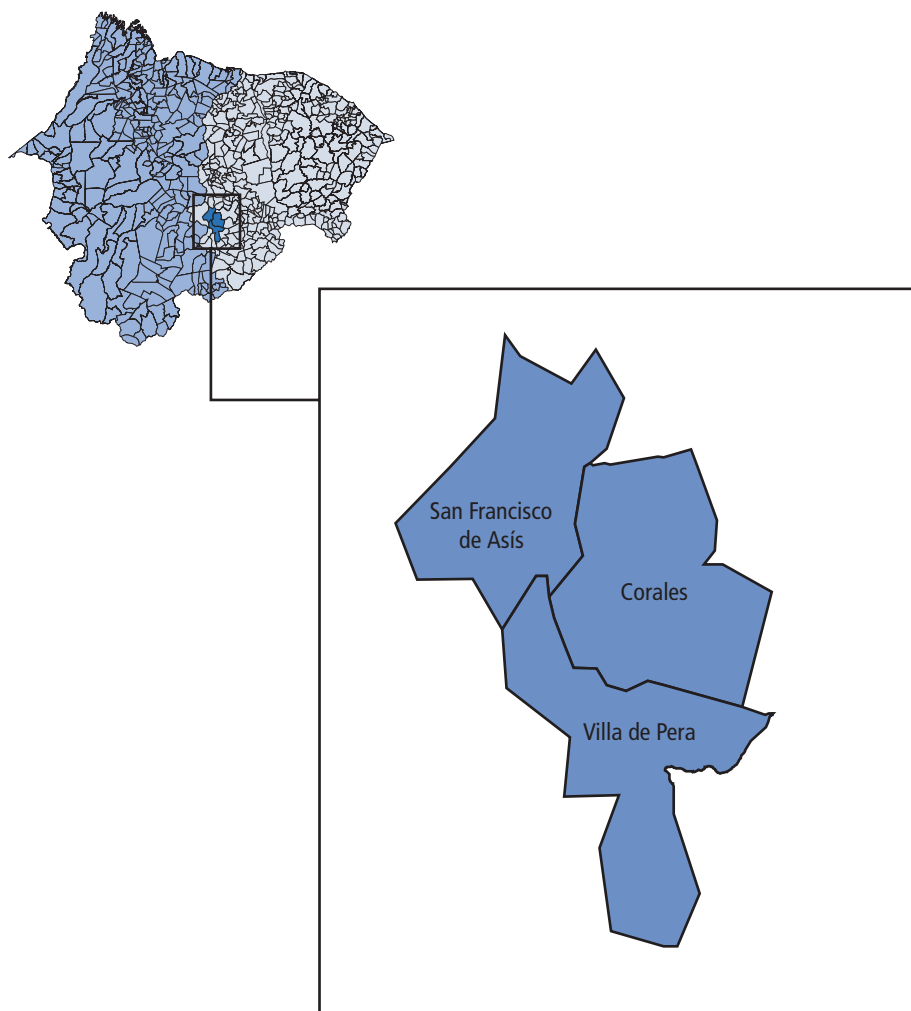
Table 1. Population distribution of San Francisco de Asís, Corales, and Villa Pera, by age group and sex

Age group	Male	Female	Total
0 to 4 years	1,375	1,681	3,056
5 to 14 years	2,265	2,768	5,033
15 to 29 years	2,268	2,752	5,030
30 to 44 years	1,033	1,663	2,696
45 years or more	970	1,187	2,157
Total	7,911	10,051	17,972

Table 2. Incidence rate (IR) by age group and sex

Age group	IR in men	IR in women	General IR
0 to 4 years			
5 to 14 years			
15 to 29 years			
30 to 44 years			
45 years or more			
Total			

SHEET 7. Map of the region in Asís affected by yellow fever



SHEET 8. Epidemiological calendar for 2001

The World Health Organization establishes the epidemiological calendar and sets an international reference standard for receiving epidemiological information from its Member Governments, which is used primarily for mandatory disease notification.

Note: By international convention, weeks are counted from Sunday to Saturday. The first epidemiological week of the year is the week in January with the most days, and the last week of the year is the week in December with the most days.

Week 01	12/31/2001 to 1/06/2002	Week 27	07/01 to 07/07
Week 02	01/07 to 01/13	Week 28	07/08 to 07/14
Week 03	01/14 to 01/20	Week 29	07/15 to 07/21
Week 04	01/21 to 01/27	Week 30	07/22 to 07/28
Week 05	01/28 to 02/03	Week 31	07/29 to 08/04
Week 06	02/04 to 02/10	Week 32	08/05 to 08/11
Week 07	02/11 to 02/17	Week 33	08/12 to 08/18
Week 08	02/18 to 02/24	Week 34	08/19 to 08/25
Week 09	02/25 to 03/03	Week 35	08/26 to 09/01
Week 10	03/04 to 03/10	Week 36	09/02 to 09/08
Week 11	03/11 to 03/17	Week 37	09/09 to 09/15
Week 12	03/18 to 03/24	Week 38	09/16 to 09/22
Week 13	03/25 to 03/31	Week 39	09/23 to 09/29
Week 14	04/01 to 04/07	Week 40	09/30 to 10/06
Week 15	04/08 to 04/14	Week 41	10/07 to 10/13
Week 16	04/15 to 04/21	Week 42	10/14 to 10/20
Week 17	04/22 to 04/28	Week 43	10/21 to 10/27
Week 18	04/29 to 05/05	Week 44	10/28 to 11/03
Week 19	05/06 to 05/12	Week 45	11/04 to 11/10
Week 20	05/13 to 05/19	Week 46	11/11 to 11/17
Week 21	05/20 to 05/26	Week 47	11/18 to 11/24
Week 22	05/27 to 06/02	Week 48	11/25 to 12/01
Week 23	06/03 to 06/09	Week 49	12/02 to 12/08
Week 24	06/10 to 06/16	Week 50	12/09 to 12/15
Week 25	06/17 to 06/23	Week 51	12/16 to 12/22
Week 26	06/24/ to 06/30	Week 52	12/23 to 12/29

SHEET 9: Report of the Ministry of Health Commission on the yellow fever epidemic in Asís

On 05/15/2001 a commission made up of four technical officers from the Ministry of Health traveled to Asís to assess the yellow fever epidemic and reported the following:

- Since March 2001 no additional suspected cases of yellow fever had been reported in the municipalities of Asís.
- From 01/23/2001 to 05/14/2001:
 - Of the region's 13 health units, 8 reported suspected cases and 5 did not report any case.
 - Of the 68 suspected cases, 26 were confirmed, 16 were discarded, and 26 remain open (incomplete investigation or no laboratory results).
 - The Asís Laboratory performed 260 serological tests for yellow fever and to date had sent 89 results. Among them were 39 suspected cases; the rest were samples from suspected cases identified by active case search and the contacts of suspected cases.
 - During that same period the number of suspected hepatitis cases (without diagnostic confirmation) reported by the National Surveillance System increased over the number in previous years.
 - Vaccination coverage in the rural population of Villa Pera was 60%.

SHEET 10. Evaluation of the training module

TRAINING IN EPIDEMIOLOGICAL SURVEILLANCE OF YELLOW FEVER

Place:

Date:

Number of hours: 24

Evaluation factors	Mark the appropriate box with an X			
	Excellent	Good	Fair	Poor
1. Program contents				
2. Time requirements				
3. Work methodology				
4. Speakers				
5. Monitors				
6. Educational material				
7. Organization of the event				
8. Location				

Self-evaluation	Mark the appropriate box with an X		
	Yes	No	Could have participated more
1. Did you participate in all aspects of the event?			
2. Did you assimilate the material reviewed?			
3. Were you motivated by the training?			
4. Did the training increase your knowledge?			
5. Will the knowledge acquired be useful in your daily work?			

CONCLUSION (MARK IN THE PARENTHESES)

1. How would you rate the event?

() Excellent () Good () Fair () Poor

Why?

2. Would you recommend it to your colleagues?

() Yes () No

Why?

3. What suggestions would you make to improve the training module?

4. Do you feel that the objectives were met?

Self-Evaluation Responses

RESPONSES TO QUESTIONS FOR SITUATION I PRACTICE EXERCISES

1

Possible hypotheses: malaria, viral hepatitis, leptospirosis, yellow fever, other arbovirus disease, sepsis, etc.

2

(a)

- Viral markers for hepatitis A and B.
- Second sample for leptospirosis (macroagglutination: take the sample at least seven days after the onset of symptoms; the microagglutination should be performed with two paired samples: take the first sample seven days following the onset of symptoms and the second between the 3rd and 4th weeks following the onset of symptoms). A sample obtained before day seven following the onset of symptoms does not rule out a suspected case of leptospirosis. The peak immune response occurs after the 14th day of the onset of symptoms.
- Serology for yellow fever and dengue (at least six days after the onset of symptoms).
- Investigation of *Plasmodium* (thick blood film) for malaria during the febrile peak.
- Viral isolation of dengue, yellow fever, and other arboviruses (up to day five after the onset of the symptoms).

(b) In the context of an individual's health, the etiologic diagnosis is important to orient treatment; nevertheless, in this case, the clinical management will not depend entirely on diagnostic confirmation given the time it takes to perform the tests. With a public health approach, in contrast, it is a priority to establish the etiologic diagnosis of certain diseases with a high epidemiological impact and epidemic potential, as is the case with yellow fever and dengue in certain circumstances.

(c) All the tests listed in (a) to diagnose diseases with high epidemiological impact.

- (d) To determine the necessary control measures.

3

Regarding a positive MAC-ELISA (IgM) for dengue, it is necessary to consider the possibility of a recent mild or subclinical dengue infection, for up to 60 days. (Remember that this study was requested during the first consultation, before the patient presented with jaundice.)

The negative results for IgM anti-HAV and IgM anti-HBc, and positive results for anti-HBs indicate the absence of acute disease. It should be noted that the IgM anti-HAV antibody is specific for hepatitis A, appears early in the acute phase of the disease, and begins to wane after the second week, disappearing in 3 months. IgM Anti-HBc is the first antibody detected after infection with the hepatitis B virus and is the most important serologic marker for the characterization of acute HBV infection. Positive anti-HBs indicates that the patient was immunized against hepatitis B.

4

The house infestation rate is calculated by dividing the number of houses positive for *Aedes aegypti* breeding sites by the number of houses investigated and multiplying by 100.

5

(a) **Detect the cases**

- Intensify the investigation (to obtain information on contacts with rats/mice during the flood, mosquito bites, etc.).
- Investigate the patient's vaccination history (yellow fever and hepatitis B).
- Inquire about a history of blood transfusion (hepatitis B and C).
- Inquire about the type of food consumed during the trip (hepatitis A).
- Find out whether there had been contact with floodwaters, sewage, or garbage in areas where rodents are present (leptospirosis).
- Inquire about contacts with sick people (disease transmitted by person-to-person contact).
- Find out whether there had been accounts of recent epizootics in the area.

- Evaluate *Ae. aegypti* infestation indices in the locality and area (yellow fever, dengue).
- Determine whether there has been an increase in cases of acute febrile syndrome, jaundice, or both, of undefined etiology in the area by searching medical records in the health services and directly questioning people in the community.
- If no samples were obtained, ensure their proper collection for laboratory confirmation.
- If the samples were already obtained, facilitate confirmation of the diagnosis.

(b) Notification and reporting

- Report the strongest suspicion (use the epidemiological investigation form in Annex 2: Epidemiological investigation form for yellow fever, pg. 22). Fill out the investigation form using the current available data. Emphasize the importance of supplying data beginning with the onset of symptoms, as well as information on the history of travel to forest areas, resolution of the case, etc.
- In the case of yellow fever, as it is a disease subject to the *International Health Regulations*, the central level should be notified within 24 hours. Use the fastest means (telephone, fax, e-mail) to communicate the presence of cases to the upper levels of the public health structure.
- Ensure continuous communication between those responsible for surveillance and the Expanded Program on Immunization.
- Continue to educate the at-risk population about how the disease is transmitted, the symptoms, and prevention and control measures (for leptospirosis, dengue, hepatitis, yellow fever).

(c) Identify the population at risk

- Assess vaccination coverage in all the localities frequented by every suspected case and neighboring municipalities (yellow fever).
- Draw a map of the risk area and detect at-risk populations based on the presence of: recent epizootics, human cases, low vaccination coverage, high vector infestation indices, etc. (yellow fever).
- Ascertain basic sanitation status in the area (leptospirosis, hepatitis A).
- Investigate the contacts of the suspected case; obtain adequate laboratory samples, as indicated.

(d) Guide/implement control measures

- Conduct perimeter vaccination of unimmunized persons in locations where the infection was probably contracted to achieve 100% vaccination coverage (yellow fever).
- If the suspected case frequented urban centers during the viremia period (three to four days after the onset of the symptoms), investigate the *Aedes aegypti* infestation indices in each place. If the house infestation rate exceeds 5%, conduct perimeter vaccination in an 800 m radius and intensify activities to reduce the vector population (dengue, yellow fever).
- Intensify vector control measures in areas bordering the location of the suspected case.
- Identify contacts and administer immunoprophylaxis to susceptible people (hepatitis A and B).
- Take steps to improve sanitation (proper waste collection and disposal; water supply network; clean-up of ravines, uncultivated land, and open sewage channels); conduct rodent elimination in the area (leptospirosis).

ANSWERS TO QUESTIONS FOR SITUATION 2 PRACTICE EXERCISE**1**

- (a) This is indeed a yellow fever epidemic in an area free of the circulation of the yellow fever virus.
- (b) In order to mount epidemiological surveillance for situation analysis and decision-making, the problem must be identified and its magnitude and distribution known. Furthermore, all suspected cases should be detected and confirmed, and the number of cases, the number of deaths (mortality), the time of year the cases occurred and where (maps, diagram), what people were most affected, where they live, etc., should be determined. The analysis should cover the principal risk factors implicated— for example, vaccination coverage, whether migrant populations are involved, the measures adopted, the health services' response capacity, and the referral and counter-referral systems. It is important to analyze the results obtained and the problems encountered, and to consider what more can be done and what type of assistance is needed.

The best way of organizing the response to an outbreak is to form a committee that will meet daily to make decisions and evaluate the data, the documentation, and the technical dissemination of the information on the epidemic to the health team. The committee should ensure that there are adequate supplies and equipment (vaccines, laboratory materials, vehicles, etc.). It should establish flowcharts (regarding medical care, biological specimen samples, etc.). It is the committee's responsibility to prepare daily updates for the media and to name an official spokesperson (the Secretary of Health or another authority from the health team). The committee will be comprised of:

- The Secretary of Health;
- Other local political authorities;
- The epidemiological surveillance coordinator;
- The immunization program coordinator;
- Environmental surveillance personnel;
- Health surveillance personnel;
- Laboratory staff;
- Communication and education personnel.

Other potential actors should be identified and invited to sit on the committee; ask them to compare vaccination coverage and *Aedes aegypti* infestation rates.

2

- (a) Case-fatality rate (number of deaths/total cases X 100) = 70%.
- (b) This elevated case-fatality rate (the expected case-fatality is 5% to 10%) indicates that milder cases are not being diagnosed.

3

- (a) All cases (clinical and subclinical) must be detected given the epidemiological importance of all forms of the disease and the high case-fatality of the severe forms.

4

- (a) A syndromic surveillance approach would make it possible to detect other cases.

- (b) The sensitivity of a surveillance system is its ability to detect cases of a particular disease. The more cases it detects, the greater the sensitivity of a surveillance system.
- (c) Syndromic surveillance makes it possible to increase the sensitivity of health systems by detecting the presence of diseases with an epidemiological impact.
- (d) The case definition that should be used is: a patient with an acute febrile condition (less than seven days) from an area with viral circulation (epizootics, a confirmed human case, or viral isolation in vectors).

5

- (a) Active case search should be conducted in the locations where the infection was probably contracted, with a serum sample taken from all people who do not have a history of vaccination against yellow fever. An active search for suspected cases should be conducted in all health services in the locality and its vicinity or in referral services (search for other diagnoses: hepatitis, leptospirosis, etc.).
- (b) Zero-case reporting should be instituted; that is, the health services must report daily to the coordinator, even though there is no suspected case.
- (c) Since yellow fever is a disease subject to the *International Health Regulations*, which require the immediate adoption of individual and collective protective measures, all suspected cases should be reported immediately and confirmed or ruled out as they are investigated, making sure that the cases in the system are closed. Article 3 §1 of the *International Health Regulations* makes immediate international reporting mandatory: “Each health administration shall notify the [World Health] Organization by telegram or telex within twenty-four hours of its being informed that the first case of a disease subject to the Regulations ... has occurred in its territory, and, within the subsequent twenty-four hours, notify the infected area.”

6

- (a) The concept of timeliness refers to reporting the disease as soon as possible to ensure that the necessary prevention and control measures are adopted without delay.

- (b) The flow of notification should be the same as that already established for other reportable diseases (for example, local health unit → State/departamental unit → Ministry of Health → PAHO/WHO).
- (c) Cases should be reported to the international level in a timely fashion, as stated in the *International Health Regulations*.

7

Organization of the data by time makes it possible to determine whether the epidemic is spreading and the impact of the control measures.

8

Organization of the data by individual is used to identify groups in which the vaccination efforts should be intensified, the most affected groups, etc.

9

- The average age of the sample is 27.6 years (552 divided by 20).
- When there are 20 observations, the median age is between the 10th and 11th observation $(29 + 30)/2 = 29.5$ years (12-13-16-18-23-23-24-25-26-**29-30**-30-31-32-32-33-33-35-42-45).
- It is important to calculate measures of central tendency (mean, mode, and median) and determine the best option to use in different situations. That is, in normal distributions (the Gauss, or bell-shaped curve) the best measure is the mean, while in distributions in which extreme values are observed, the median is more appropriate. The purpose of calculating the two measures in this exercise is to refresh participants' knowledge of basic concepts in biostatistics.

10

(a)

Calculation of the incidence rate (IR) by age group and sex			
Age group	IR in men	IR in women	Overall IR
0 to 4 years	—	—	—
5 to 14 years	0.44	0.36	0.40
15 to 29 years	3.09	0.36	1.59
30 to 44 years	5.81	1.80	3.34
45 years or more	1.03	—	0.46

- (b) The highest incidence rate corresponded to adult males (ages 30 to 44 years).
- (c) This is due, in part, to the work that they do. Yellow fever can also be considered an occupational disease, given the large number of cases reported in the population that migrates toward agricultural and mining areas, with the resulting increased exposure in this population group.

11

- (a) Spatial arrangement of the data makes it possible to understand viral dispersion patterns and facilitate the designation of priority areas for vaccination.
- (b) Other information that can be included in the map: epizootics, health services, vaccination coverage, waterways, etc.

12

- Initiate door-to-door vaccination in rural areas of the region where the cases appear.
- Develop specific measures for males aged 15 to 44 years (at greatest risk).
- Establish an immunization safety perimeter, based on the direction in which new cases are appearing.
- The Immunization Program should activate the surveillance system for adverse events associated with the vaccine.

13

- Implement urban vector control measures. Conduct entomological research in urban areas of the municipalities involved (to determine *Aedes aegypti* house infestation rates) and intensify the vector control measures when the parasitic index (PI) is greater than 5%.
- Investigate monkey deaths.
- Ensure that the committee meets on a daily basis.
- Prepare daily reports on the status of the outbreak.
- Provide ongoing information to the higher authorities.
- Widely disseminate the recommendations for handling suspected cases and treating serious cases to health professionals.
- Develop other forms of health education (pamphlets, posters at toll booths or checkpoints, etc.).
- Issue press releases daily (or as needed).

14

The steps taken to control the outbreak were only partial. According to the Report of the Ministry of Health Commission, syndromic surveillance to detect all clinical forms of the disease did not function properly. Although it increased the reporting of suspected cases of hepatitis B, these cases were not confirmed in the laboratory, and other differential diagnoses have not been reported.

Indicators from the epidemiological surveillance system showed deficiencies: only 61% of the region's reporting units sent notification of suspected cases, and weekly "zero-case" reporting was not included. Some 38% of the cases were not fully investigated or lacked laboratory results. The laboratory response was not on time. Vaccination coverage for the area should be a minimum of 95%, but only 60% of the population was vaccinated.

The situation reveals the need for periodic monitoring by the upper levels of the health system given the presence of a yellow fever outbreak. In this case, the Ministry of Health sent an investigative commission four months later so corrective steps were taken very late.

15

With a view to confirming the efficiency of yellow fever surveillance systems, the Pan American Health Organization recommends use of the following indicators and targets:

- 80% of reporting units report weekly (during epidemics);
- 80% of suspected cases are investigated within 48 hours of the report;
- In 80% of cases with serum samples, the samples are sent to the laboratory within 72 hours of taking the sample;
- 80% of the laboratory results (serology) are obtained within 72 hours of the sample's receipt by the laboratory;
- 80% of suspected cases confirmed and appropriate control measures implemented;
- 80% of suspected cases are closed within 30 days and 100% of cases are closed within 60 days;
- Minimum vaccination coverage of 95% of residents and travelers to enzootic areas.



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ISBN 92 75 11603 2