

**TECHNICAL REPORT:**  
Recommendations for  
Scientific Evidence-Based  
Yellow Fever Risk Assessment  
in the Americas



Pan American  
Health  
Organization

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Health  
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## INTRODUCTION

Yellow fever (YF) is the only disease for which the *International Health Regulations* (IHR [2005]) lay down requirements for travelers to provide proof of vaccination whenever entering certain countries that have specific regulations (see IHR [2005], Annexes 2, 6, and 7). The reemergence of urban YF transmission in Paraguay in early 2008, as well as reports of rare but severe and fatal adverse events associated with the YF vaccine (such as YF vaccine-associated viscerotropic disease), were some of the crucial factors that triggered the need to revisit the current criteria for designating and mapping countries where there is a risk of transmitting the YF virus, as well as for formulating recommendations on YF vaccination for international travel.



Image 1: Panama YF Expert Meeting  
Source: PAHO

In September 2008, WHO convened a *Consultation on Yellow Fever and International Travel*. Its objectives were twofold:

- Review the criteria for inclusion and removal of countries and/or areas from the YF virus transmission list.
- Review the current list of countries and determine any areas of YF virus transmission where vector control disinsecting would be required for conveyances, according to the stipulations laid down in Annex V of the IHR (2005).

The final conclusions of the 2008 consultation included a recommendation to form a subgroup or working group. This subgroup was subsequently called the “Informal Working Group on Geographic Risk of Yellow Fever,” or WG. Starting in 2008, the group held several teleconferences and face-to-face meetings, followed by a meeting in Stockholm, Sweden, in March 2010. There, the WG proposed changes to the 2008 consultation<sup>1</sup>, publishing a consensus report in 2012 that included the revised global YF risk map and the recommendations for vaccination made in 2010.<sup>2</sup>

As a result, several countries from the Region of the Americas (hereafter called “the Region” or simply “the Americas”) approached the Pan American Health Organization, Regional Office of the World Health Organization (PAHO/WHO). They asked PAHO to conduct a detailed review of the current classification of YF risk areas. In response, the PAHO Secretariat met with a group of regional YF experts from different technical areas (Epidemiology, Laboratory, Vector Control, Epizootic Surveillance, and Mapping) at a meeting held in Panama City, Panamá, on 9-13 June 2012.

<sup>1</sup> World Health Organization (WHO). *Background for the Consultation on Yellow Fever and International Travel*, 2010 (update February 2011). Geneva: WHO; 2011. Available at <http://www.who.int/ith/YFrisk.pdf> [Accessed 19 April 2013].

<sup>2</sup> Jentes ES, Pomeroy G, Gershman MD, Hill DR, Lemarchand J, Lewis RF, Staples JE, Tomori O, Wilder-Smith A, Monath TP; Informal WHO Working Group on Geographic Risk for Yellow Fever. The revised global yellow fever risk map and recommendations for vaccination, 2010: consensus of the Informal WHO Working Group on Geographic Risk for Yellow Fever. *Lancet Infect Dis* 2011;11(8):622-632. Available at: <http://www.ncbi.nlm.nih.gov/pubmed?term=Informal%20WHO%20Working%20Group%20on%20Geographic%20Risk%20for%20Yellow%20Fever%5BCorporate%20Author%5D> [Accessed 21 April 2013].

The purpose of this PAHO meeting was to discuss how the countries could make a scientific evidence-based determination of YF risk areas, to ensure the safety of people living or traveling therein. The objectives were as follows:

- Determine best practices for YF surveillance and produce a document with recommendations for the countries.
- Discuss the revised IHR (2005) and the criteria used therein to include or exclude countries at risk of YF transmission in the WHO publication *International Travel and Health* (ITH). Annex 1 of the ITH lists countries at risk of transmitting the YF virus.
- Consider steps to take for potentially revising the status of those countries listed in ITH Annex 1 and for updating the YF risk map for international travelers.
- Analyze the situation of YF risk in Panama with authorities from the Ministry of Health as well as with other actors, such as the Gorgas Memorial Institute for Health Studies and the University of Panama.



Image 2: Panama YF Expert Meeting  
Source: PAHO.

The methodology of the meeting included a two-day workshop with regional experts (see Annex 1, Agenda). Each expert presented a review of current best practices per component, based on strong scientific evidence. The current epidemiological and vaccination conditions for YF in the Region were reviewed. Also, the goals of the revised YF regulations in IHR (2005) were discussed. These were namely to: prevent the international spread of disease by protecting countries from the risk of the importation or spread of the YF virus, and protect individual travelers who might be exposed to the YF virus.

The meeting included a lengthy discussion on best practices for human epidemiological surveillance of febrile icteric and icterohemorrhagic syndromes. The experts examined the need for comprehensive surveillance that would encompass the interface between humans and the surrounding ecosystem. They presented examples of vector surveillance in urban or jungle (sylvatic) scenarios, as well as both active and passive epizootic surveillance in nonhuman primates (in the case of the Americas, monkeys)—all with a view to suggesting what might constitute best practices for successful monitoring. From the perspective of laboratory surveillance, the experts stressed the importance of improved diagnostics in both animal and human cases and of detecting adverse events associated with vaccination. All the countries undergoing analysis face the challenge of distinguishing cases of YF from other hemorrhagic fevers—not to mention infections by other flaviviruses or illness displaying febrile symptoms.

The experts reviewed the methodology and results of YF risk mapping in South America and Panama, analyzing factors examined in risk areas when selecting potential environmental conditions (altitude, characteristics of the ecosystem, and history of infections). These geo-ecological and epidemiological factors can then be used as a starting point for evidence-based risk evaluation and risk classification.

Following all the presentations, two working groups prepared a set of recommendations for evidence-based assessment of YF risk in different contexts: clinical-epidemiological, laboratory, monitoring of epizootic diseases in (nonhuman) primates, vector surveillance, and consideration of environmental factors. Each group presented a summary of recommendations that appears later on in this document.

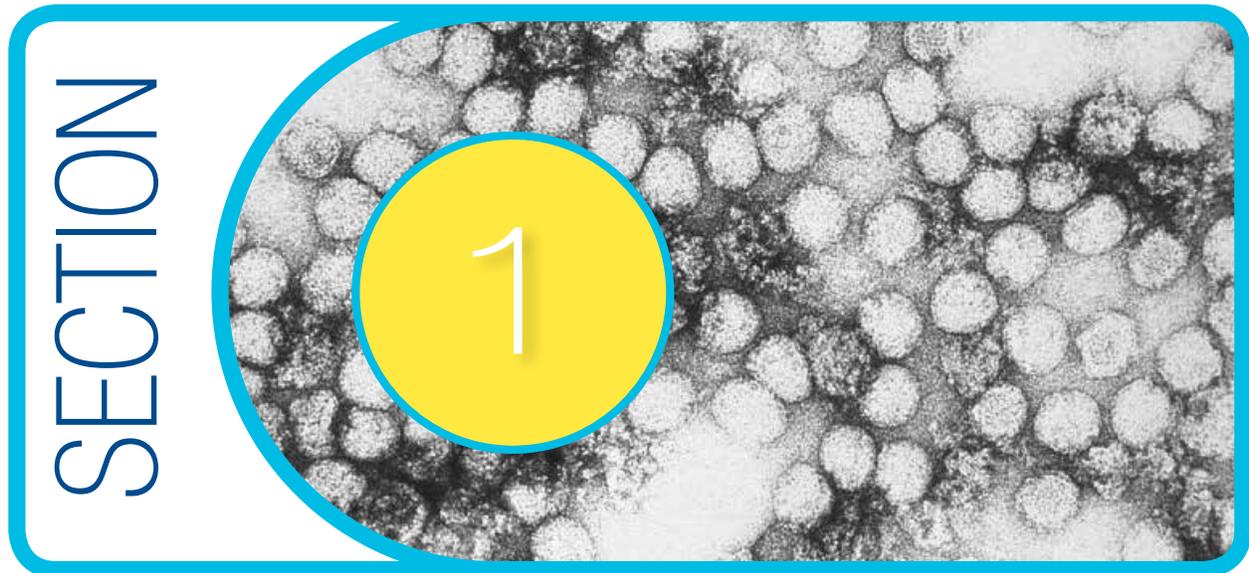
On the last day of the Panama meeting, the experts met with national authorities from the country's Ministry of Health and with scientists from the Gorgas Memorial Institute for Health Studies and the University of Panama. Together, they analyzed the current status of YF risk in Panama and provided recommendations for assessing risk in transitional areas (i.e., the country's western provinces).

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### OBJECTIVES OF THIS DOCUMENT

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1. Respond to a request made by the countries to assess their YF situation, in light of new criteria for adding and removing countries, and update the list of countries currently at risk of YF transmission—while at the same time, considering the possibility of revising risk map and designation criteria.
2. Provide technical recommendations for the countries of the Americas for YF risk assessment in their transitional and low-risk areas, based on scientific evidence (i.e., for evidence-based risk assessment).
3. Provide general support and strengthen implementation of the IHR (2005) in YF-endemic countries.

Image 3: The Yellow Fever Virus.<sup>3</sup>

## I. CURRENT SITUATION OF YELLOW FEVER IN THE AMERICAS

Yellow fever (YF) continues to be an important public health problem in the Americas. Despite improved vaccination coverage in endemic areas, sporadic cases and limited outbreaks still continue to occur. This continued occurrence of cases, coupled with the proliferation of the *Aedes aegypti* mosquito vector throughout the Americas, demonstrate the high risk that still exists of the potential re-urbanization of YF.<sup>4</sup>

### TRANSMISSION CYCLES FOR YF IN THE AMERICAS

- **Sylvatic (jungle) YF:** This is the predominant transmission cycle in the Americas (Figure 1).<sup>5</sup> The cycle involves the circulation of the YF virus between nonhuman primates (various species of monkeys) and tree-dwelling mosquitoes, namely *Haemagogus* spp and *Sabethes* spp, in tropical rainforests. Humans become infected as they enter the forest and come into contact with a mosquito carrying the virus. The majority of jungle YF cases occur among unvaccinated migrant workers, namely young men coming to work in jungle areas. These sporadic cases can occasionally induce small outbreaks in the jungle areas of South America. The risk of YF tends to be higher toward the end of the rainy season and at the beginning of the dry season, due to increased vector density at these times.<sup>6</sup>

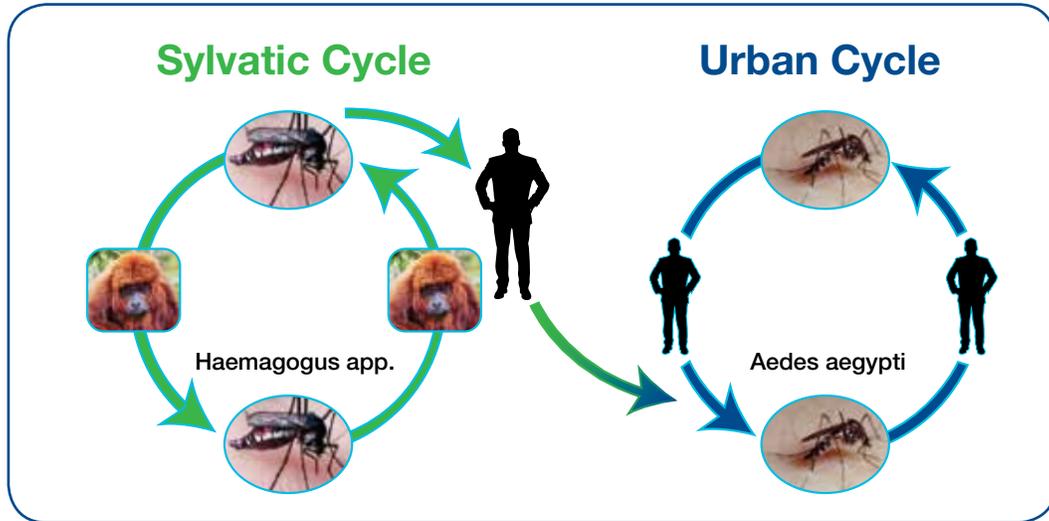
<sup>3</sup> Source: Hardin Library of the Health Sciences, University of Iowa. Available at: <http://hardinmd.lib.uiowa.edu/cdc/2176.html> [Accessed 20 April 2013].

<sup>4</sup> Pan American Health Organization / World Health Organization (PAHO/WHO). *Control of Yellow Fever: Field Guide*. Scientific and Technical Publication 203. Washington, DC: PAHO/WHO; 2005. Available at:

<sup>5</sup> Roig C, Miret J, Rojas A, Guillen Y, Aria L, Mendoza L et al. Estudio de Fiebre Amarilla en primates en áreas de brote de los departamentos de San Pedro y Central del Paraguay. *Mem. Inst. Investig. Cienc. Salud* 2009;7(1):40-45. Available at: <http://scielo.iics.una.py/pdf/iics/v7n1/v7n1a07.pdf> [Accessed 21 April 2013].

<sup>6</sup> World Health Organization (WHO). Yellow fever vaccine: WHO Position Paper. *Weekly Epidemiological Review (WER)* 2003;78(40):349-360. Available at: <http://www.who.int/wer/2003/en/wer7840.pdf> [accessed 19 April 2013].

FIGURE 1: TRANSMISSION CYCLE OF THE YELLOW FEVER VIRUS



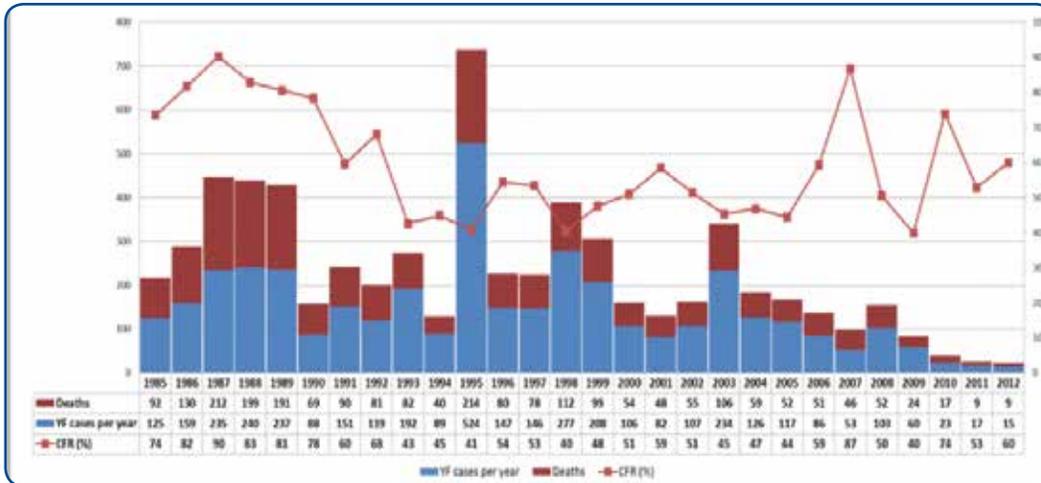
- **Urban YF:** Major epidemics occur when infected people introduce the virus into densely populated areas with a high number of non-immune people and *Aedes aegypti* mosquitoes (Figure 1). *Ae. aegypti* feeds preferentially on humans and breeds predominantly in containers, thus making this vector capable of year-round viral transmission. While urban transmission of YF has fortunately been rare in the Americas, there nonetheless exists the omnipresent threat of urban YF outbreaks in the Region. Urban outbreaks of YF were reported in Santa Cruz, Bolivia, in 1997<sup>7</sup> and more recently in Asunción, Paraguay, in 2008. An additional factor involving epidemic risk to the Region is the widespread occurrence of dengue, a disease also spread by *Ae. aegypti*.

EPIDEMIOLOGY OF YF IN THE AMERICAS

Between 1985 and 2012, a total of 4,066 cases of YF and 2,351 deaths from YF (for a 58% case fatality rate) were reported to PAHO (see Figure 2). During this period, 95% of all cases were reported by four countries; Peru (with 54% of all cases), Bolivia (with 18%), Brazil (with 16%), and Colombia (with 7%). Sporadic outbreaks also occurred in other countries of the South American continent, including Northern Argentina, Ecuador, and Paraguay (see Map 1).

<sup>7</sup> Definition of case fatality rate: The ratio of the number of deaths caused by a specified disease to the number of diagnosed cases of that disease.

**FIGURE 2: TOTAL NUMBER OF YF CASES AND DEATHS AND CASE FATALITY RATE (CFR), AMERICAS, BY YEAR 1985-2012<sup>8</sup>**



Yellow fever in the Americas displays cyclic characteristics, with several large epidemic peaks having been noted to occur (Figure 2).<sup>9</sup> The highest number of cases was recorded in 1995, as the result of an extensive outbreak in the western area of the Peruvian Andes. In 1998, the number of cases increased again, this time as a result of outbreaks in Peru, Bolivia, and Brazil. Between 1999 and 2002, there was an important reduction in the number of cases, with only isolated cases and limited outbreaks being observed—mainly in Brazil. This can partly be explained by the strategy implemented by Brazil and Bolivia for vaccination activities against YF to be intensified in enzootic areas. In 2003, an increase in YF incidence was observed due to outbreaks occurring in Brazil and Peru, coupled with an extensive outbreak on the Colombian-Venezuelan border. In 2008, Brazil, Paraguay, and Argentina all reported outbreaks. However, since then, there has been a sustained downward trend in the number of YF cases reported in the Region.

French Guiana, Guyana, Panama, Suriname, and Trinidad and Tobago—all of them endemic countries for YF—have not reported cases over the past two decades. The last report of YF laboratory-confirmed cases from Venezuela was in 2005. Argentina and Paraguay last reported cases in 2008; and Colombia, in 2009.

<sup>8</sup> Definition of case fatality rate: The ratio of the number of deaths caused by a specified disease to the number of diagnosed cases of that disease.

<sup>9</sup> Source: Reports submitted to PAHO by the Ministries of Health of the affected countries.

MAP 1: REPORTED YF CASES BY SECOND-LEVEL ADMINISTRATIVE DIVISION, AMERICAS, 2000-2012

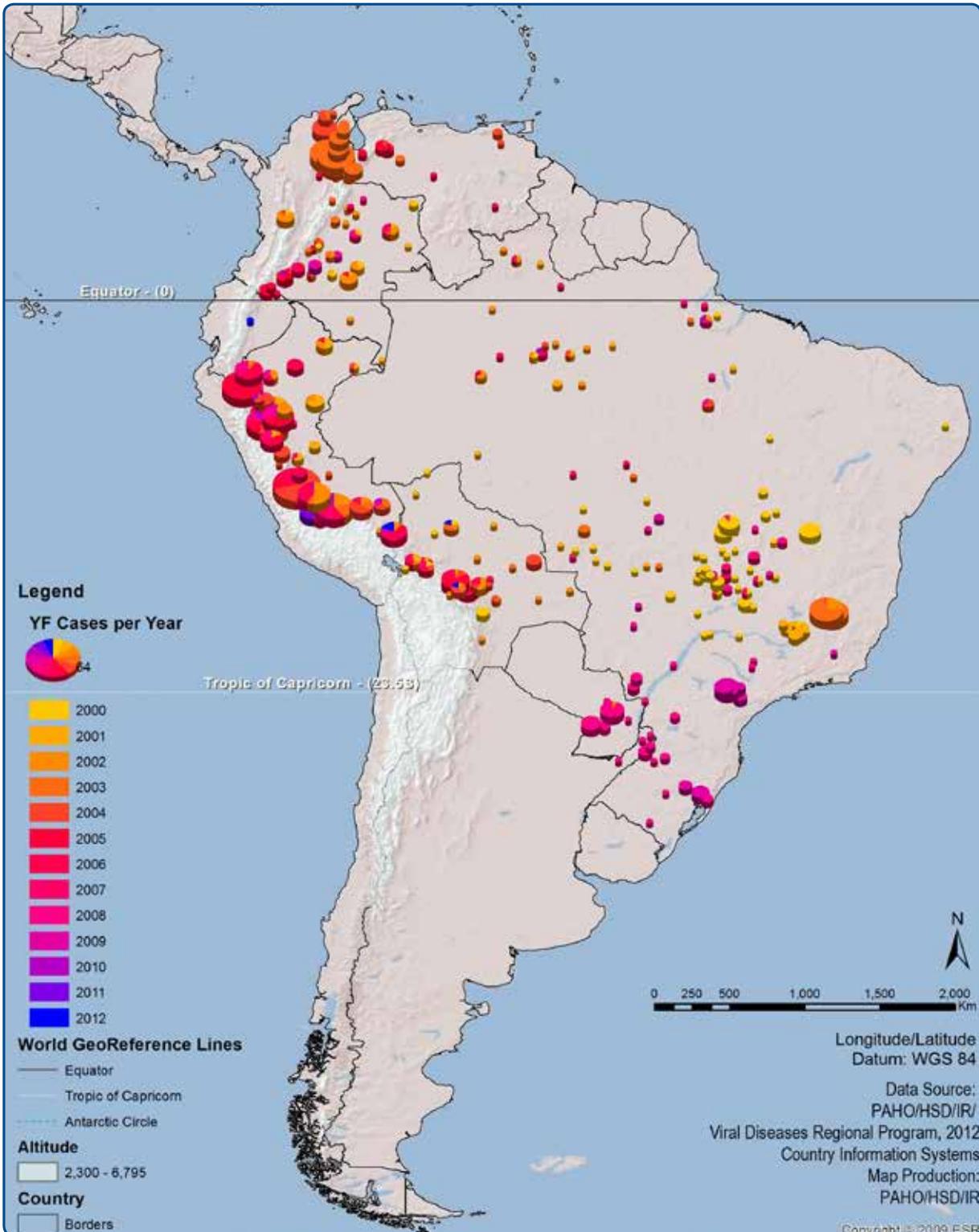




Image 4: A Brazilian nurse prepares for a yellow fever vaccination.<sup>10</sup>

## II. YELLOW FEVER VACCINATION IN THE AMERICAS

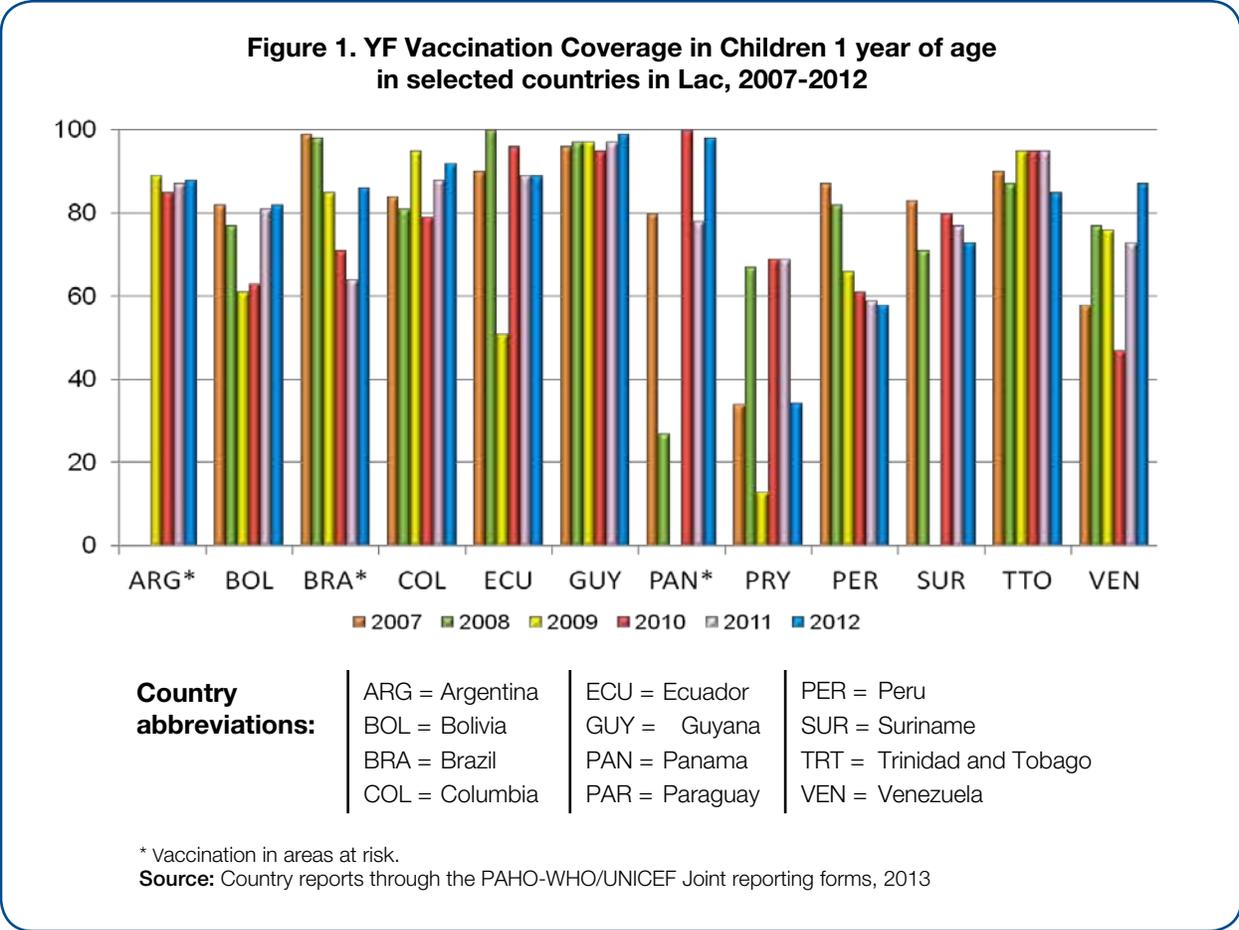
Yellow fever can be prevented through immunization with the live, attenuated YF 17D vaccine. Over 600 million doses have been administered worldwide since its development in 1937. The YF vaccine has been considered to both safe and effective. Recently, however, serious adverse events following immunization with the YF vaccine have highlighted the importance of focusing vaccination efforts exclusively among populations considered at risk of YF.

As of 2011, most countries with enzootic areas have introduced the YF vaccine into their vaccination schedules as part of the Expanded Programme on Immunization (EPI). Brazil, Argentina, and Suriname provide routine YF vaccination in areas considered at risk. Despite the increasing use of the YF vaccine in EPI schedules, however, vaccine coverage in children at 1 year of age has not exceeded a coverage rate of approximately 70% (see Figure 3). Vaccine availability has been the main factor responsible for limiting better coverage rates.

Mass vaccination activities targeting populations in enzootic areas vary from country to country. Some countries have chosen to vaccinate in stages (e.g., campaigns conducted in several phases over a period of several years), while others have chosen short-term campaigns (e.g., intensive efforts conducted over the course of one or two months). For example, Peru vaccinated over 12 million people in the three-year period from 2004 to 2007; Brazil has vaccinated more than 110 million individuals over the past 10 years; and Bolivia conducted a national campaign in 2007, vaccinating approximately 5 million people. All of these efforts have led to an important reduction in YF cases in targeted areas.

<sup>10</sup> Source: Joedson Alves/AFP/Getty Images. Available in: <http://www.guardian.co.uk/world/2008/feb/15/brazil.health>

**FIGURE 3: VACCINATION COVERAGE AMONG 1-YEAR-OLD CHILDREN IN SELECTED COUNTRIES, AMERICAS, 2007-2011**



To lower the risk of YF in the Region, priority must be placed on vaccinating both the local population in enzootic areas and travelers to these areas, using best practices. However, there is a dual need to judiciously use the vaccine and maximize other control efforts, given current supply limitations for the vaccine. The 2008 YF outbreaks in the Southern Cone expanded the area considered at risk to include Paraguay and northern Argentina. This situation highlighted the need for periodic reassessments of YF risk areas, taking into consideration the changing ecological and environmental conditions that favor transmission of this vector-borne disease. This will allow for more accurate definition of the areas and populations to target for vaccination.

## BEST PRACTICES FOR VACCINE ADMINISTRATION

- 1. Introduce the YF vaccine into the national immunization programs of all endemic countries for children at 1 year of age:** In general, in countries with YF risk, resources should concentrate on guaranteeing high coverage for the first vaccine dose, rather than on administering booster doses.
- 2. Conduct mass preventive vaccination campaigns during interepidemic periods.**
- 3. Conduct vaccination campaigns in response to outbreaks or epizootics.**
- 4. Administer the YF vaccine to travelers entering areas at risk of YF virus transmission:** The available scientific data currently show no evidence of the need for a YF booster dose,<sup>11</sup> given that a single dose of YF vaccine appears to confer lifelong protective immunity against the disease. However, at present, the IHR (2005) still require travelers bound for endemic areas to present a YF vaccination certificate valid for a period of 10 years.<sup>12,13</sup>
- 5. Observe contraindications to the YF vaccination before administering it:** The YF vaccine is contraindicated for children less than 6 months of age and is not recommended for those ages 6-8 months, except during epidemics when the risk of transmitting the virus is very high. The vaccine is also contraindicated for individuals with a severe allergy to eggs or with severe immunosuppression. In theory, vaccine 17D is additionally not recommended during pregnancy, despite there being no proof that it causes fetal anomalies. When deciding whether or not to vaccinate persons for whom the vaccine is generally not recommended, due to either their medical conditions or their travel designations, the risk of the disease should be weighed against the risk of an adverse event following immunization.

<sup>11</sup> Summary of the Strategic Advisory Group of Experts (SAGE) April 2013 meeting. Available at: [http://www.who.int/immunization/sage/meetings/2013/april/meeting\\_summary/en/index.html](http://www.who.int/immunization/sage/meetings/2013/april/meeting_summary/en/index.html) [Accessed 14 May 2013].

<sup>12</sup> World Health Organization (WHO). *Background for the Consultation on Yellow Fever and International Travel*, 2010 (update February 2011). Geneva: WHO; 2011. Available at: <http://www.who.int/ith/YFrisk.pdf> [Accessed 20 April 2013].

<sup>13</sup> World Health Organization (WHO). *International Travel and Health* (ITH 2012). Country list, Yellow fever vaccination requirements and recommendations; and malaria situation. Geneva: WHO; 2012. Available at: [http://www.who.int/ith/chapters/ith2012en\\_countrylist.pdf](http://www.who.int/ith/chapters/ith2012en_countrylist.pdf) [Accessed 19 April 2013].

Image 5: International certificate of vaccination.<sup>14</sup>

### III. THE INTERNATIONAL HEALTH REGULATIONS (2005) AND YELLOW FEVER: CATEGORIZATION BY COUNTRY

#### IHR (2005) AND YELLOW FEVER

Yellow Fever is unique among diseases in that the IHR (2005) outlines requirements for proof of vaccination for people who travel to specific countries or enter some countries from an area where YF is endemic (see IHR [2005], Annexes 2, 6, and 7 for specific regulations). As stated by WHO in ITH, there are two main objectives to YF vaccination:

1. Prevent the international spread of the disease by protecting countries from the risk of importing or spreading the YF virus.
2. Protect individual travelers who may be exposed to the YF virus.

#### IHR AND YELLOW FEVER: CATEGORIZATION BY COUNTRY

Global control measures have been very successful in eliminating the risk of YF in many areas. However, many areas have both mosquito vectors and nonhuman primates—both of which act in transmitting the YF virus and thus pose a risk of possible disease outbreaks in those areas. In 2008, the evolving epidemiology of YF—with the reemergence of urban YF disease in Paraguay and continued reports of rare but serious adverse events associated with the YF vaccine—drew attention to the need to

1. revisit criteria for designating at-risk areas for YF virus activity; and
2. revise the vaccination recommendations for international travel.

<sup>14</sup> Source: <http://machupichuenmoto.files.wordpress.com/2011/03/doc-157423.jpg>

As previously stated, in 2008 WHO convened an Informal Working Group on Geographic Risk of Yellow Fever (WG) to discuss factors important for transmission of the virus. Objectives were as follows:

- a. Establish criteria for the addition or removal of countries and geographical regions listed in Annex 1 of the ITH guidelines.
- b. Revise YF risk maps.
- c. Revise recommendations for YF vaccination.

The WG used existing data on the presence of either the YF virus or of YF antibodies in humans, nonhuman primates, or mosquitoes, with a view to categorizing regions into one of the following four risk categories: endemic, transitional, low risk and no risk (see Table 1). Vaccination was then recommended for persons traveling to endemic or transitional areas, generally not recommended for persons traveling to low-risk areas, and not recommended for areas with no risk.

**TABLE 1: CRITERIA FOR COUNTRY CLASSIFICATION BY YF RISK<sup>15</sup>**

| VACCINATION RECOMMENDED FOR INCOMING TRAVELERS   |  | VACCINATION NOT RECOMMENDED FOR INCOMING TRAVELERS  |   |
|--|--|---|---|
| Endemic areas  | Transitional areas   | Low-risk areas  | No-risk areas   |
| <ul style="list-style-type: none"> <li>✓ <b>Endemic areas</b> show a persistence of enzootic YF virus transmission over long periods of time.</li> </ul>   | <ul style="list-style-type: none"> <li>✓ <b>Transitional areas</b> border on a YF-endemic zone and show periodic evidence of transmission during YF epizootic/epidemic expansions.</li> </ul>      | <ul style="list-style-type: none"> <li>✓ <b>Low-risk areas</b> border on YF-endemic or transitional areas</li> </ul>  | <ul style="list-style-type: none"> <li>✓ <b>No-risk areas</b> have no past or present evidence of YF viral circulation, or where environmental conditions are not conducive to YF virus transmission</li> </ul> |
| <ul style="list-style-type: none"> <li>✓ YF vectors and nonhuman primate hosts are present.</li> </ul>   | <ul style="list-style-type: none"> <li>✓ YF vectors and nonhuman primate hosts are present.</li> </ul>   | <ul style="list-style-type: none"> <li>✓ YF vectors and nonhuman primate hosts are present.</li> </ul>  |   |
| <ul style="list-style-type: none"> <li>✓ Human and/or nonhuman primate YF cases are repeatedly reported.</li> </ul>  | <ul style="list-style-type: none"> <li>✓ Human YF cases (sporadic or epidemic) are reported at long intervals and during YF epizootic/epidemic expansions from bordering endemic areas.</li> </ul> | <ul style="list-style-type: none"> <li>✓ No human or nonhuman primate YF cases have been reported.</li> </ul>   |   |
| <ul style="list-style-type: none"> <li>✓ Human YF cases were regularly reported prior to achieving high YF immunization coverage rates.</li> <li>✓ Serosurveys (prevaccination era) show evidence of a high prevalence of YF infection.</li> </ul> | <ul style="list-style-type: none"> <li>✓ Serosurveys (prevaccination era) show evidence of YF infection in persons born before the last YF expansion.</li> </ul>                                   | <ul style="list-style-type: none"> <li>✓ There may be serological or other evidence of past YF virus transmission, but the evidence is uncertain or indicates a low prevalence of infection.</li> </ul> |   |

<sup>15</sup> ntes ES. et al. The revised global yellow fever risk map and recommendations for vaccination, 2010: consensus of the Informal WHO Working Group on Geographic Risk for Yellow Fever. *Lancet Infect Dis* 2011;8: 622–32;2011. Available at [http://www.thelancet.com/journals/laninf/article/PIIS1473-3099\(11\)70147-5/fulltext](http://www.thelancet.com/journals/laninf/article/PIIS1473-3099(11)70147-5/fulltext) [Accessed 20 April 2013].

EPIDEMIC PREPAREDNESS AND RESPONSE

The IHR (2005) includes a requirement related to national disease surveillance and response systems. Countries have made a commitment to develop and maintain certain core capacities related to surveillance and response, which includes YF.

The topics in Table 2 should be considered as a check list showing how to prepare for, detect, confirm, and respond to YF.

**TABLE 2: STEPS TO TAKE TO PREPARE FOR, DETECT, CONFIRM, AND RESPOND TO YELLOW FEVER OUTBREAKS**

|   |  |
|---|--|
| ✓ | Review National Technical Guidelines for YF surveillance.  |
| ✓ | Agree on strategies for detection and response.  |
| ✓ | Review experiences from past outbreaks.  |
| ✓ | Determine areas and populations at risk.   |
| ✓ | Prepare an action plan for national-level response.  |
| ✓ | Assign responsibilities for early detection and response.  |
| ✓ | Determine roles and responsibilities for the national level.   |
| ✓ | Coordinate and establish clear and reliable communications with other levels (e.g., regional, provincial, district). |
| ✓ | Reserve a stock of essential equipment and supplies.   |
| ✓ | Maintain laboratory testing capacity for YF.   |
| ✓ | Identify a reference laboratory capable of confirming a YF epidemic .  |
| ✓ | Maintain a reserve stock of vaccine (if possible).   |
| ✓ | Determine how much vaccine is to be stockpiled and where it will be held.  |
| ✓ | Establish the mechanism for releasing vaccine.   |

Early outbreak detection, monitoring, and response are all related to the strength of a country’s national and local surveillance and response system. Prompt detection of YF and rapid response through emergency vaccination campaigns are both essential for controlling outbreaks. However, underreporting is a concern. WHO recommends that, in the Americas, every single at-risk country have at least one national reference laboratory capable of carrying out basic YF testing. One confirmed case of YF in an unvaccinated population should be considered to be an outbreak, and any confirmed case in any context must be fully investigated—particularly in an area where most of the population has not been vaccinated.

Investigation teams must assess and respond to the outbreak with both emergency measures and longer-term immunization plans. They must communicate through the IHR National Focal Point.

Image 6: Nurses with YF patients<sup>16</sup>

## IV. BEST PRACTICES FOR EPIDEMIOLOGIC SURVEILLANCE OF ACUTE FEBRILE ICTERIC AND ICTEROHEMORRHAGIC SYNDROMES IN HUMANS

The main goal of YF surveillance is the early detection of viral circulation by identifying cases that are clinically compatible with YF or with other syndromes characterized by acute fever and jaundice or acute febrile illness, and accompanied by icterohemorrhagic diathesis. Early detection of YF viral circulation will allow for taking prompt control measures that will help mitigate the appearance of new cases, interrupt outbreaks, and prevent urbanization of the disease.

There are several ways to determine the risk of humans contracting the YF virus:

1. Conduct serosurveys to detect the presence of antibodies specific to the YF virus.
2. Review reports of human YF cases.
3. Implement syndromic surveillance.
4. Carry out YF surveillance in nonhuman primates.

**Serosurveys** involve taking blood samples from patients to look for the presence of IgM and IgG antibodies against YF. However, antibody testing cannot differentiate between antibodies formed to fight infection and those occurring as a response to vaccination. Furthermore, testing can generate false-positive results due to cross-reactive antibodies against flavivirus (e.g., dengue, West Nile Virus [WNV], St. Louis Encephalitis [SLE], and Ilheus viruses). Therefore, serosurveys have limited utility in highly vaccinated populations and in areas with high levels of circulating flaviviruses—both of which are applicable to many YF-endemic areas in the Americas.

<sup>16</sup> Available at: [http://s254.photobucket.com/user/axelquiroz/media/fiebreamarilla.jpg.html#/user/axelquiroz/media/fiebreamarilla.jpg.html?&\\_suid=136439700178006892565352860123](http://s254.photobucket.com/user/axelquiroz/media/fiebreamarilla.jpg.html#/user/axelquiroz/media/fiebreamarilla.jpg.html?&_suid=136439700178006892565352860123)

**Reviewing reports of human YF cases** using case surveillance definitions can provide information on risk location (see Table 3). However, it will detect only a small proportion of those infected, basically acting as a passive surveillance system. Furthermore, it requires healthcare professionals to suspect YF cases and to have access to appropriate diagnostic testing capacity, and to report the case to public health officials. In areas where YF occurs infrequently, healthcare workers may not readily suspect the disease.

**TABLE 3: UPDATED YELLOW FEVER CASE DEFINITION (2010)**

| TYPE OF CASE     | DEFINITION   |
|------------------|--|
| <b>Suspected</b> | Any person with either acute onset of <b>fever with jaundice</b> or of <b>fever, jaundice, and hemorrhages</b> within 14 days of onset of first symptoms   |
| <b>Probable</b>  | Suspected case AND one of the following: <ul style="list-style-type: none"> <li>• Presence of YF IgM antibodies in the absence of YF immunization, within 30 days before onset of illness</li> <li>• Positive postmortem liver histopathology</li> <li>• Epidemiological link to a confirmed case or outbreak</li> </ul>   |
| <b>Confirmed</b> | Probable case AND one of the following: <ul style="list-style-type: none"> <li>• Detection of YF-specific immunoglobulin M (IgM)</li> <li>• Detection of fourfold increase in YF antibody titers between acute and convalescent serum samples</li> <li>• Detection of YF-specific neutralizing antibodies</li> </ul> OR one of the following: <ul style="list-style-type: none"> <li>• Detection of YF virus genome via polymerase chain reaction (PCR)</li> <li>• Detection of YF antigen via immunohistochemical assay</li> <li>• Isolation of YF virus</li> </ul> AND absence of YF immunization within 14 days before onset of illness |

Finally, **implementation of syndromic surveillance** can make it possible to determine the human risk of YF virus infection. The definition of syndromic surveillance is active surveillance that involves monitoring a group of diseases with similar signs and symptoms, a common physiopathology, and a diverse etiology. It is aimed at rapidly detecting outbreaks of potential harm to public health, considering not only outbreaks of known infectious origin but also those of unknown origin. Syndromic surveillance needs to be longitudinal in order to detect sporadic cases in unvaccinated individuals.

Syndromes that might represent YF include febrile icteric and febrile (ictero)hemorrhagic syndromes (see Tables 4 and 5). However, not all cases of YF will meet the case definitions used in syndromic surveillance. Several other diseases may also be ‘captured’ using syndromic surveillance. Cases that meet the case definitions for syndromic surveillance need to be evaluated based on the frequency of disease occurrence in the area, as well as other clinical and epidemiological features.

**TABLE 4: ACUTE FEBRILE ICTERIC SYNDROME**

| DEFINITION  | DIFFERENTIAL DIAGNOSIS   |
|---|--|
| <ul style="list-style-type: none"> <li>• Acute onset (&lt;3 weeks) of fever and jaundice with severe disease, defined by                             <ul style="list-style-type: none"> <li>⇒ Admission to hospital</li> <li>⇒ Circulatory collapse</li> <li>⇒ Serious organ Insufficiency</li> <li>⇒ Altered state of consciousness</li> <li>⇒ Death</li> </ul> </li> <li>• Absence of predisposing factors in host</li> </ul> | <ul style="list-style-type: none"> <li>➤ YF</li> <li>➤ YF vaccine-associated viscerotropic disease</li> <li>➤ Hepatitis A, B, C, D, and E</li> <li>➤ Malaria</li> <li>➤ Leptospirosis</li> <li>➤ Cytomegalovirus (CMV)</li> <li>➤ Epstein-Barr Virus (EBV)</li> <li>➤ Liver pathology</li> <li>➤ Abscess</li> <li>➤ Cholangitis</li> <li>➤ Dengue</li> </ul> |

**TABLE 5: ACUTE FEBRILE (ICTERO\*) HEMORRHAGIC SYNDROME**

| DEFINITION   | DIFFERENTIAL DIAGNOSIS  |
|--|---|
| <ul style="list-style-type: none"> <li>• Patient with a fever of less than 3 weeks duration and two of any of the following manifestations:                             <ul style="list-style-type: none"> <li>⇒ Hemorrhagic-type skin lesions (ecchymoses, hematomas or purpura)</li> <li>⇒ Hematemesis</li> <li>⇒ Epistaxis</li> <li>⇒ Hemoptysis</li> <li>⇒ Bloody stool (melena)</li> <li>⇒ Other hemorrhagic manifestations</li> </ul> </li> <li>• Absence of predisposing factors in host</li> </ul> | <ul style="list-style-type: none"> <li>➤ YF*</li> <li>➤ YF vaccine-associated viscerotropic disease*</li> <li>➤ Dengue</li> <li>➤ Other viral hemorrhagic fevers                             <ul style="list-style-type: none"> <li>⇒ Argentine hemorrhagic fever</li> <li>⇒ Bolivian hemorrhagic fever</li> <li>⇒ Venezuelan hemorrhagic fever</li> <li>⇒ Hantavirus fever with renal syndrome (HFRS)</li> </ul> </li> <li>➤ Brazilian spotted fever*</li> <li>➤ Rocky Mountain spotted fever</li> <li>➤ Meningococcemia</li> <li>➤ Septicemia (gram-negative bacteria)*</li> <li>➤ Typhoid fever</li> <li>➤ Plague</li> </ul> |

## BEST PRACTICES FOR EPIDEMIOLOGICAL AND SYNDROMIC SURVEILLANCE

1. **Monitor for clinically compatible cases** of the classical form of YF, according to WHO case definitions.
2. **Conduct a rapid epidemiological field investigation** whenever a suspected case is reported.
3. **Implement syndromic surveillance** at all institutions that provide services to persons residing in and near areas where YF viral circulation is a concern.
  - a. Collect acute and convalescent samples and test samples comprehensively for pathogens causing fever and jaundice and/or hemorrhage.
  - b. Capture thorough exposure histories (e.g., travel, YF vaccination, recent activities).
  - c. Promptly investigate and report potential cases.
4. **Establish surveillance goals.**
  - d. Determine the percentage of notification sites that report on a monthly basis (target: 90%).
  - e. Determine the percentage of all suspected cases with a record of laboratory specimens being collected (target: 80%).
  - f. *For IgM testing:* Ensure that results be sent within 3 days of receipt of an acute blood specimen (target: 80%).
  - g. *For isolating the virus:* Ensure that results be sent within 21 days following the receipt of an acute specimen (target: 80%).
5. **Verify that adequate reporting instruments and channels (e.g., local- to national-level reporting) are in place.**
  - h. Report on both an immediate and weekly basis to the next level, based on the current epidemiological surveillance network.
  - i. File clinical-epidemiological research records and send them to the central/national level.
  - j. Include cases that test negative in the weekly report.
  - k. Provide feedback to the corresponding levels.
6. **Map** and assess the frequency and diagnostic priorities of the main etiologies of febrile icteric syndrome.
7. **Carry out control measures** according to the etiological diagnosis.

See Appendix 2 for more details.

Image 7: Howler monkey<sup>17</sup>

## V. BEST PRACTICES FOR EPIZOOTIC SURVEILLANCE OF YELLOW FEVER IN NONHUMAN PRIMATES

In nature, nonhuman primates act as the primary host for the YF virus. Although YF probably affects all neotropical primates, the *Alouatta* species (howler monkeys) appear to be the most sensitive to the YF virus.<sup>18,19</sup> Species from other genera are easily infected but have lower case fatality rates and often develop immunity to the virus.

In South America, human YF cases and outbreaks have traditionally followed epizootics among nonhuman primates.<sup>20,21</sup> Therefore, epizootic surveillance can be a key component to YF surveillance by allowing for early detection of viral circulation, for determining the human risk of YF virus infection, and subsequently for taking timely prevention and control measures in human populations.

There are two main types of epizootic surveillance, namely passive (on demand) or active:

- **Passive surveillance** relies on reporting dead or sick nonhuman primates. Passive surveillance should be targeted in areas where
  - a. There is presence of YF vectors.

<sup>17</sup> Courtesy of the Ministry of Health of Brazil.

<sup>18</sup> Davis NC. The transmission of Yellow Fever: further experiments with monkeys of the New World. *AJTMN* 1931;s1-11:113-125. Available at: <http://www.ajtmh.org/content/s1-11/2/113.full.pdf+html> [Accessed 21 April 2013].

<sup>19</sup> Holzmann I, Agostini I, Areta JI, Ferreyra H, Beldomenico P, Di Betetti MS. Impact of Yellow Fever outbreaks on two howler monkey species (*Alouatta guariba clamitans* and *A. caraya*) in Misiones, Argentina. *Am J Primatol* 2010;71:1-6. Available at: [http://pinoparana.fundacionazara.org.ar/esp/Publicaciones/22\\_i.pdf](http://pinoparana.fundacionazara.org.ar/esp/Publicaciones/22_i.pdf) [Accessed 21 April 2013].

<sup>20</sup> Soper FL. Febre Amarela Panamericana. 1938 a 1942. *Bol Oficina Sanit Panam* 21(12):1207-1222; 1942

<sup>21</sup> De Almeida MA, Dos Santos E, Cruz Cardoso J, Da Fonseca DF, Noll CA, Silveira DR et al. Yellow Fever outbreak affecting *Alouatta* populations in Southern Brazil (Rio Grande do Sul state), 2008–2009. *Am J Primatol* 2011;74(1):68-76. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22020690> [Accessed 21 April 2013].

- b. There is presence of susceptible humans, i.e., areas with low or non-uniform vaccination coverage rates.
- c. There is insufficient information from the population or from health professionals about potential disease in humans.

Whenever a report of a dead or sick nonhuman primate is received, a field investigation should then be implemented. The investigation should utilize standard case definitions (see Table 6). Control measures, including the potential administration of the YF vaccine to susceptible humans, should be considered as part of the investigation.

- **Active surveillance** consists of sampling and testing nonhuman primates, regardless of death or illness. It can complement passive surveillance by searching for evidence of YF virus circulation during the investigation of a reported epizootic. Active surveillance can also be used to monitor populations of nonhuman primates or areas of epidemiological relevance. Both types of surveillance need to be implemented and maintained longitudinally, in order to optimize the performance and utility of this surveillance system.

**TABLE 6: CASE DEFINITION FOR YELLOW FEVER IN NONHUMAN PRIMATES<sup>22</sup>**

| TYPE OF CASE         | DEFINITION  |
|----------------------|---|
| <b>Suspected</b>     | Nonhuman primate of any species, found dead (including skeletons) or sick, anywhere in the national territory   |
| <b>Confirmed</b>     | Suspected case AND one of the following:<br>Epizootic in any nonhuman primate where the laboratory result was conclusive for YF virus infection in at least one animal from the probable site of infection<br>OR<br>Epizootic in any nonhuman primate, associated with evidence of YF virus circulation in vectors, other primates, or humans in the probable site of infection |
| <b>Discarded</b>     | Epizootic in any nonhuman primate with a conclusive negative laboratory result for YF   |
| <b>Indeterminate</b> | Death or illness of any nonhuman primate where no samples were collected for diagnosis or there was an inconclusive laboratory result for YF  |

**BEST PRACTICES FOR EPIZOOTIC SURVEILLANCE OF YF IN NONHUMAN PRIMATES**

**1. Implement passive epizootic surveillance.**

- a. Utilize partner organizations involved in wildlife and natural areas, as well as the general public, to recognize and report deaths among nonhuman primates to the Ministry of Health (or closest health service).
- b. Encourage training and preparatory activities during periods of low disease occurrence.

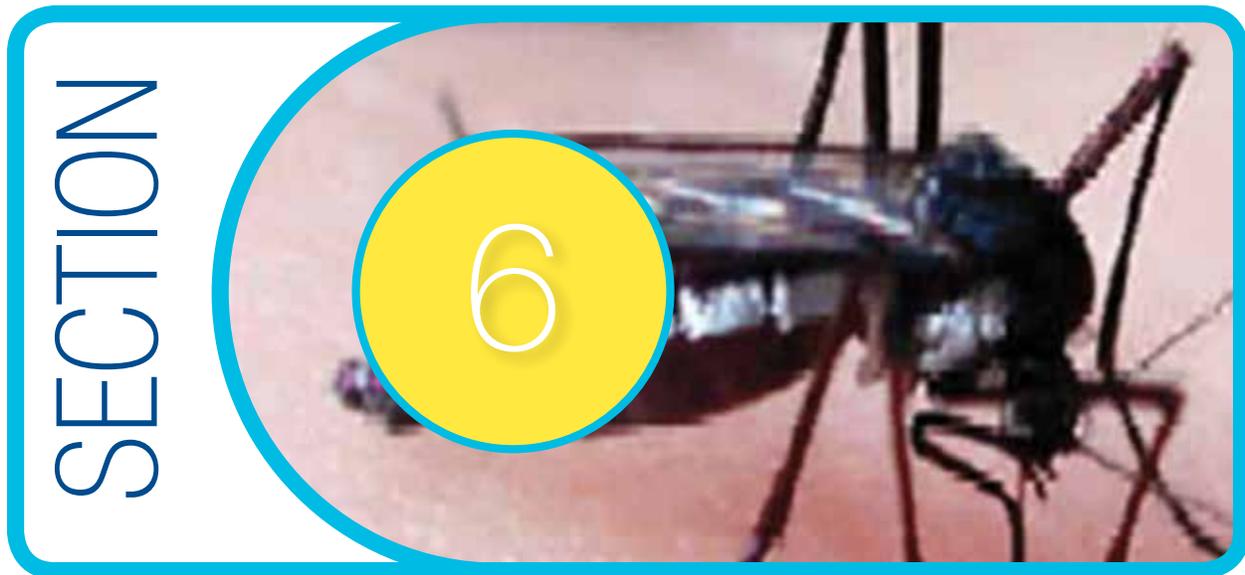
<sup>22</sup> Ministério da Saúde/Secretaria de Vigilância em Saúde (MS/SVS Brazil). *Guia de Vigilância de Epizootias em Primatas Não Humanos e Entomologia aplicada à Vigilância da Febre Amarela*. Brasília: MS/SVS; 2013 (in press).

**2. Investigate any reports of death in a nonhuman primate.**

- a.** Gather information about the event—such as the occurrence of other deaths in the area, the immunization status of the local human population, and the existence of suspected human cases—by consulting medical records in hospital databases.
- b.** Animals that are suspected to be sick should eventually be euthanized, when indicated, by a veterinarian, in accordance with animal welfare policies. An autopsy should be performed to complement clinical findings.
- c.** Samples should be collected for laboratory diagnosis. The type of biological material collected depends on the diagnostic test available in the reference laboratory:
  - i.** *Virus isolation / virus genome detection / serology:* Samples should be taken of blood (3-5ml), sera (at least 1 ml) and viscera (mainly liver; 0.5cm x 2cm fragments of liver, spleen, kidney, brain, lung, and heart)—preferably within 24 hours of death—and preserved in liquid nitrogen or dry ice.
  - ii.** *Histopathology / immunohistochemistry:* Samples should be taken of viscera (0.5cm x 2cm fragments of liver, spleen, kidney, brain, lung, and heart)—preferably within 48 hours of death—and preserved in 10% buffered formalin at ambient temperature.
  - iii.** When transporting the samples to the laboratory, special care should be taken to minimize the risk to researchers and optimize the viability of specimens.
- d.** When samples from sick or dead monkeys are not possible, taking samples from live, seemingly healthy monkeys present in the area can help detect evidence of YF virus circulation. If necessary, the animal should be anesthetized before extracting blood (3-5ml). Primate capture must meet the legal requirements set forth in environmental and animal welfare legislation.
- e.** Vector collection for viral research can also be carried out as a way to establish epidemiological linkage between the presence of the virus and deaths among nonhuman primates

**4. Carry out active surveillance in selected locations, based on reported epizootics, or in areas of epidemiological relevance.****5. Vaccinate unimmunized persons immediately in areas where there is a potential epizootic.****6. Evaluate the need for extra control measures.**

- a.** Professionals should be vaccinated against YF at least 10 days before a field investigation, as well as against hepatitis B and rabies. All procedures require utilization of individual protective equipment. Professionals should adhere to biosafety requirements and receive authorization from the corresponding Ministry of Health to arrange for adequate equipment and the participation of a veterinarian.

Image 8: *Haemagogus* spp<sup>23</sup>

## VI. BEST PRACTICES FOR ENTOMOLOGICAL SURVEILLANCE OF YELLOW FEVER: URBAN AND SYLVATIC TRANSMISSION

In the Americas, different vectors are involved with YF virus circulation, depending on the transmission cycle: urban or sylvatic (jungle).

- For **sylvatic transmission**, the vectors for YF in the Americas include *Haemagogus* and *Sabethes* spp mosquitoes. They prefer to live high up in the canopies of the forests, in the crowns of trees—thus making them hard to capture. They deposit their eggs in the moist substrata of natural containers, e.g., orifices in trees or bamboo. *Haemagogus* spp can go to ground to feed on animals or humans, but they predominantly carry out their blood feeding in the high strata of the forest. As for the genus *Sabethes*, its species feed differently, overflying their host before feeding. The circulation of the YF virus is maintained during dry periods through transovarian transmission in mosquitoes, with the eggs resistant to desiccation.
- For **urban transmission**, the main species vector is *Ae. aegypti*. *Ae. aegypti* mosquitoes are also the main vectors for transmitting the dengue virus. These mosquitoes appear throughout the Americas, living in the peridomestic environment and preferring to feed on humans. Since they breed in containers, they are less susceptible to drought or rainfall conditions than are other vectors.

Entomological surveillance of YF vectors provides data that are useful for both research and vector control measures. Historically, vector control campaigns targeting *Ae. aegypti* had successfully eliminated it from most mainland countries of Central and South America. However, this mosquito species has recolonized urban areas in those countries, resulting in a renewed risk of urban YF. Although mosquito control programs targeting wild mosquitoes in forested areas are impractical in terms of preventing jungle (or sylvatic) YF transmission, surveillance nonetheless needs to be carried out, in order to assess the presence and circulation of the virus in these mosquito populations.

<sup>23</sup> Source: Courtesy of a presentation by Dr. J. Boshell.

In some situations, mosquito control is vital until vaccination takes effect. The risk of YF virus transmission in urban areas can be reduced by eliminating potential mosquito breeding sites and applying larvicides to water in places where larvae develop in their earliest stages. Spraying with insecticides to kill adult mosquitoes during urban epidemics, when combined with emergency vaccination campaigns, can reduce or halt transmission of the YF virus. In such a scenario, mosquito control can ‘buy time’ until the vaccinated population builds up protective levels of immunity.

### BEST PRACTICES FOR URBAN ENTOMOLOGICAL SURVEILLANCE AND CONTROL EFFORTS

1. **In the absence of urban cases, focus efforts on determining whether the virus is present in mosquitoes collected in municipalities bordering on endemic areas.**
2. **Following confirmation of a human YF case in an urban setting, *Ae. aegypti* control and elimination methods should be carried out in the localities where the confirmed cases have occurred.**
  - a. **Types of control measures**
    - i. *Physical control*: Protect reservoirs and water storage containers, eliminate breeding sites by reorganizing the environment, and collect trash.
    - ii. *Chemical control*: Apply insecticides and larvicides to control transmission foci.
    - iii. *Biological control*: Carry out focal efforts for larva control.
  - b. **Types of surveillance**
    - iv. Utilize the Breteau Index (BI) and the Container Index (CI), which measure mosquito infestation, to help guide control efforts. In addition, there are new indices—such as the Pupae per Person (PPP) Index,<sup>24,25</sup> currently being used in Brazil,<sup>26</sup> which has been very effective in determining levels of *Ae. aegypti* infestation in a municipality, county, or district.
    - v. Where the BI and CI indices are higher than 5% and 3%, respectively, selective integrated control measures should be implemented until these indices fall below 2%.
  - c. **Strengthen vector control measures in neighboring municipalities.**

### BEST PRACTICES FOR SYLVATIC ENTOMOLOGICAL SURVEILLANCE AND CONTROL EFFORTS

1. **Establish longitudinal entomological surveillance posts** to provide data on annual fluctuation of YF vectors and any changes in viral presence.
  - a. Areas transitional for YF should be targeted. Target areas should include localities reporting epizootics events, with ecological, climatological, and geographical characteristics that correspond to YF and that are, at the same time, operationally accessible during most of the year.
  - b. Information gathered at these posts should be archived and made readily available onsite to field entomologists.

<sup>24</sup> Definition of pupae per person (PPP): Number of pupae collected over the total number of inhabitants in the households inspected and pupae per hectare.

<sup>25</sup> Focks DA, Chadee D. Pupal survey: an epidemiologically significant surveillance method for *Aedes aegypti*: an example using data from Trinidad. *Am J Trop Med Hyg* 1997;56:159-167. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/9080874> [Accessed 21 April 2013].

<sup>26</sup> De Freitas RF, Marques WA, Peres RC, Cunha SP, De Oliveira RL. Variation in *Aedes aegypti* (Diptera: Culicidae) container productivity in a slum and a suburban district of Rio de Janeiro during dry and wet seasons. *Mem. Inst. Oswaldo Cruz* 2007;102(4):489-496. Available at: <http://www.scielo.br/pdf/mioc/v102n4/5733.pdf> [Accessed 21 April 2013].

**2. Establish standard methodologies for sampling.**

- a.** For adult mosquitoes, follow the Human Landing Catch (HLC) method (without repellent), using an aspirator or entomological net.
- b.** For *Haemagogus* and *Sabethes* spp mosquito larvae, report their presence and the number of larvae found in each type of breeding site under consideration, and then register their location.
- c.** Collect data on the following:
  - i.** Mosquito vectors present in the area under study.
  - ii.** Environmental indicators (geographical location, altitude, bodies of water, flora, fauna).
  - iii.** Nearby activities among the human population and nonhuman primates, in order to identify risk areas.
- d.** Any insects collected should be clearly labeled and placed in vials or small boxes for transport.
- e.** Determine the YF index at least once a year, at a time when vectors are the most abundant (during the rainy season) or at least every two months, i.e., six times a year.
  - i.** Optimize the search for adult mosquitoes.
  - ii.** Preserve vectors for RNA testing or for attempts to isolate the virus, by placing them in vials in dry ice or liquid nitrogen, and maintaining them at a laboratory temperature of -70 degrees Celsius.
  - iii.** Avoid contaminating samples with other biological materials.
  - iv.** Utilize reverse transcription-polymerase chain reaction (RT-PCR) in an established laboratory to detect viral RNA.

Image 9: MAC-ELISA plate.<sup>27</sup>

## VII. LABORATORY SURVEILLANCE OF YELLOW FEVER

### YF LABORATORY DIAGNOSIS

It is not easy to differentiate between individual cases of YF and such other viral hemorrhagic fevers as arenavirus, hantavirus, or dengue—or from such diseases as malaria, influenza, Brazilian spotted fever, and typhoid fever (see Chapter 4 for differential diagnosis of fever accompanied by jaundice or hemorrhaging). Useful tools in determining a clinical diagnosis frequently include clinical history, epidemiology, and laboratory testing. Having established testing algorithms for samples that meet a syndromic case definition can also help (see Figure 4).

Rapid and accurate diagnosis of YF infection is critical to understanding the distribution of the virus, determining which areas are at risk of the disease, and implementing and strengthening control measures. Thus, it is critical to have developed laboratory testing capacity for YF in areas at risk of the disease. The three main ways to establish a diagnosis for YF using laboratory techniques include the following:

1. **Virological diagnosis:** Attempts to isolate the virus should be made using cultures or suckling mice, both of which represent the ‘gold standard’ in terms of virological methods to follow. Detecting viral ribonucleic acid (RNA) can also be done via reverse transcription-polymerase chain reaction (RT-PCR) or quantitative real-time polymerase chain reaction (qRT-PCR), either in tissues or in blood. There are several protocols available for molecular diagnosis of YF. As demonstrated in a recent article, qRT-PCR is sensitive and specific.<sup>28</sup>

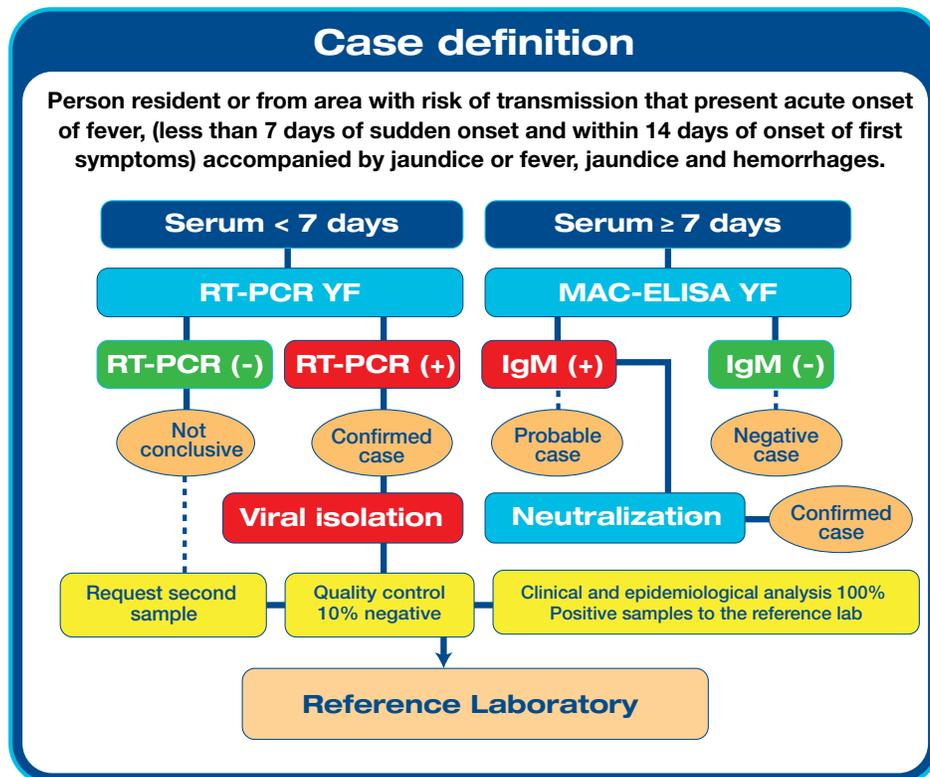
<sup>27</sup> Source: Microbislurve Blogspot. Available at: <http://microbislurve.blogspot.com/>

<sup>28</sup> Nunes MR, Palacios G, Nunes KN, Casib SM, Martins LC, Cuaresma JA et al. Evaluation of two molecular methods for the detection of Yellow fever virus genome. *J Virol Methods* 2011; 174(1-2):29-34. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21419803> [Accessed 20 April 2013].

2. **Serological diagnosis:** In the acute and convalescent phases of the diseases, diagnosis can be carried out by taking serum samples to detect either the presence of YF-specific immunoglobulin M (IgM) antibodies, or a fourfold or greater rise in serum immunoglobulin G (IgG) antibody levels against the YF virus (seroconversion). Serological testing procedures include the IgM antibody capture ELISA (MAC-ELISA) test, hemagglutination inhibition, the plaque reduction neutralization test (PRNT), and complement fixation—with PRNT most commonly seen as the ‘gold standard’ in this regard.
3. **Histopathological diagnosis:** This involves analyzing tissue samples that show histopathological injuries compatible with those caused by the YF virus in the liver, or that detect viral antigens, following the immunohistochemical method—mostly in samples of hepatic tissue.

Although YF laboratory testing is a critical component of disease recognition and surveillance, there are challenges related to testing. These include a lack of standardization and quality control measures in terms of the laboratory techniques used by different laboratories, as well as problems regarding cross-reactivity in serological assays. Members of the *Flaviviridae* family have similar epitopes that allow them to be categorized as flaviviruses, but this characteristic also causes cross-reactivity in many of the serological assays currently available. One study found that the Dengue-ELISA test showed IgM reactivity in 46% of all YF patients and in 42% of all persons vaccinated against YF. In addition, 16 out of every 20 dengue patients (80%) had high YF virus neutralization titers.<sup>29</sup> Thus, the existence of cross-reactivity may pose a real challenge for seroepidemiological studies and routine case confirmation of both diseases.

**FIGURE 4: LABORATORY ALGORITHM FOR DIAGNOSING AND REPORTING YELLOW FEVER CASES**



<sup>29</sup> Houghton-Triviño N et al. Dengue-yellow fever sera cross-reactivity; challenges for diagnosis *Rev Panam Salud Publica* 2008;10(2):299-307.

## BEST PRACTICES FOR LABORATORY SURVEILLANCE OF YELLOW FEVER

**1. Build regional or national laboratory testing capacity for YF.**

- a.** Perform virological, serological, and histopathological tests for YF.
  - i.** Viral isolation and detection of viral RNA are possible when a blood sample is obtained during the acute phase, usually between 1-5 days after onset of symptoms.
  - ii.** To detect IgM antibodies, the MAC-ELISA test can be used for samples taken later than 7 days after onset of symptoms.
  - iii.** Antibody seroconversion requires two samples, one taken during the acute phase (usually less than 7 days after onset of symptoms) and a second taken during the convalescent phase, usually 14 days after onset of symptoms.
- b.** Build laboratory capacity to ensure adequate testing of samples taken from humans, nonhuman primates, and mosquitoes.
- c.** Identify reference laboratories in the Region that can be used to facilitate confirmatory testing, if necessary.

**2. Optimize sample collection and shipping to facilitate testing for YF and other pathogens in differential diagnosis.**

- a.** Establish transportation procedures (e.g., delivery routes for cold chain shipments) to ensure proper shipment of samples to regional or national laboratories for testing.
- b.** If possible, utilize filter paper for collecting blood samples in remote areas, as per WHO recommendations. This improves safety and simplifies both the acquisition and transportation of samples. Dry blood from filter paper can be analyzed for detecting both viral RNA and YF-specific IgM antibodies. However, it cannot be used for attempting to isolate the virus.

**3. Maintain laboratory performance and efficiency.**

- a.** Participate in and support laboratory quality control programs.
- b.** Standardize YF testing practices with other regional laboratories.

Image 10: Central and South America<sup>30</sup>

## VIII. RISK MAPPING FOR YELLOW FEVER— METHODOLOGY AND RESULTS IN THE AMERICAS

In the Americas, a number of countries have carried out comprehensive and highly detailed YF risk mapping. In addition, there have been broader but less detailed global mapping efforts aimed at defining areas facing a potential endemic and requiring vaccination.<sup>31</sup> Nevertheless, there is still a need for a uniform, in-depth, comprehensive regional assessment of YF distribution throughout the Americas and of the risk of the disease becoming more widespread. One of the challenges to producing a unified, Americas-wide digital YF risk map has consisted of the Region's very diversity, with each country having its own national cartographic projections, coding systems, and distinctive methods used to represent its territory in the best possible way.

In order to develop a YF risk map representing all of the Americas, PAHO carried out a study aimed at the following:

1. Transforming individual country maps into a uniform continental digital cartographic database, integrating environmental digital cartography and satellite images currently available for second-level administrative divisions.<sup>32</sup>
2. Producing a detailed map of YF risk areas for South America and Panama, based on the associated environmental conditions.

<sup>30</sup> Source: shutterstock\_7343107.jpg

<sup>31</sup> entes ES, Pomeroy G, Gershman MD, Hill DR, Lemarchand D, Lewis RF et al. The revised global yellow fever risk map and recommendations for vaccination, 2010: consensus of the Informal WHO Working Group on Geographic Risk for Yellow Fever. *The Lancet Infectious Diseases* 2011;11(8):622-632. Available at: [http://www.thelancet.com/journals/laninf/article/PIIS1473-3099\(11\)70147-5/fulltext](http://www.thelancet.com/journals/laninf/article/PIIS1473-3099(11)70147-5/fulltext) [Accessed 21 April 2013].

<sup>32</sup> United States Aeronautics and Space Administration (NASA), United States Geological Survey (USGS), World Wildlife Fund (WWF), Food and Agriculture Organization of the United Nations (FAO), *WorldClim* Global Climate Database, International Union for Conservation of Nature (IUCN).

Meeting the study objectives involved performing the following tasks:

- Compile digital cartographic data from various national cartography agencies (e.g., national or military geographic census offices), down to the main unit of analysis, namely second-level administrative divisions (municipalities, cantons, provinces, or districts).
- Obtain standardized, updated, geocoded data following the coding procedure laid down by the United Nations Second Administrative Level Boundaries data set project (SALB).<sup>33</sup>
- Determine ecological conditions suitable for YF endemicity by using environmental factors classified according to a climatic scheme.
  - Factors to be assessed included the following: altitude, slope orientation, latitude, and variation of such elements as temperature and rain.
- Transfer data from geoprocessed and georeferenced images and maps showing assessment factors and ecological conditions, to the attribute table of the second-level administrative divisions (using the ArcGIS/Editor spatial analysis tool, with zonal statistics as a table) to perform environmental spatial analysis
- Review the history of previous YF outbreaks. Such a review was carried out by experts from the PAHO Regional Program on Viral Diseases, using the geocoded regional database compiled from each country's information system.
- Geocode 12 years of YF cases.
- Obtain information on areas where there is evidence of both known hosts (*Alouatta* and spider monkeys) as well as suitable vectors (*Haemagogus* and *Sabethes* mosquitoes for jungle YF), and map this information regardless of occasional vague boundaries.

From this process, a total of 8,457 second-level administrative divisions (including municipalities, cantons, provinces, or districts) from 13 countries were classified and mapped according to their YF risk potential (see Map 2). Of these, 58% (4,944) were classified as **endemic**; 3.2%, as **transitional**; 4.6%, as **low potential** for exposure; and 34%, as **no risk**. The classification procedure followed updated IHR (2005) YF risk mapping criteria. Endemic areas were located primarily in Brazil (71%), followed by Colombia (18%), Venezuela (4.5%), and Peru (1.6%). The vast majority of transitional areas were located in Paraguay (80%). **See Map 2: Classification of Second-Level Administrative Divisions from 13 Countries, by YF Risk Potential, South America and Panama.**

Analysis of the different factors felt to be associated with YF risk potential showed the following:

- **Altitude:** In most of the second-level administrative divisions (98%) in the area under consideration, portions of their territory lie in areas with altitudes lower than 2,300 meters above sea level. Of these, 5,565 are located in Brazil, 1,035 in Colombia, and 511 in Argentina. Average altitude does not show consistent differences related to YF risk potential; 432 meters above sea level in endemic areas shows a potential risk; 75 meters shows a transitional risk; 504 meters shows a low potential risk; and 415 meters shows no risk. **See Map 3: Classification of Second-Level Administrative Divisions from 13 Countries, by YF Risk Potential and Altitude, South America and Panama.**

<sup>33</sup> PAHO/SALB cartography. Available at <http://www.unsalb.org> [Accessed 19 April 2013].

- **Latitude:** Latitudes for the area under study lie between 10.5 degrees north and -12.7 degrees south; these are consistent with the literature on the distribution of tropical areas. **See Map 4: Classification of Second-Level Administrative Divisions from 13 Countries, by YF Risk Potential and Latitude, South America and Panama.**
- **Ecosystems and land use:** Major habitat types designated by the World Wildlife Fund (WWF) were a key factor in refining the limits of endemic areas, with 55% of the areas under consideration covered by tropical and subtropical moist broadleaf forests; 17%, by tropical and subtropical grasslands, savannas, and shrub lands; and 5.3%, by tropical and subtropical dry broadleaf forests. Analysis was done by country. This meant adding up the surfaces covered by tropical habitats, mangroves, or flooded grasslands in Guyana, French Guiana, Suriname, Trinidad and Tobago, Panama, and Paraguay—which are 100% covered by these sets of ecosystems. Colombia followed, with 91%; and Brazil, with 82%. When analyzing by YF risk potential, endemic and transitional zones have 95% and 97% of their territory, respectively, covered by a sort of tropical forest or grassland. However, in endemic areas, the broadleaf tropical forest predominates (at 65%)—while in transitional divisions, tropical grasslands predominate (at 50%). (See Map 5.)
  - **Temperature:** Maximum average temperature showed no difference in terms of YF risk potential by second-level administrative division. However, it did vary by country and endemic area, with temperatures being consistently lower in the Andean countries.
  - **Rainfall:** In the case of pluvial precipitation, this was higher in endemic areas (with 1,831 mm) and in areas with a low potential for exposure (with 1,980mm) than in transitional (with 1,682mm) or in no-risk areas (with 1,270mm).
  - **Nonhuman primate and vector distribution:** Analysis of the presence of hosts and vectors in the tropical ecosystems is ongoing. PAHO has practically finished a map and dataset on nonhuman primate hosts: *Alouatta*, *Ateles*, and *Brachyteles* monkeys. It has also digitalized maps from the International Union for Conservation of Nature (IUCN) Red List of Threatened Species, showing locations of the species and subspecies of these primates. Efforts are still underway to refine the western boundaries, which appear to be a bit unclear. While there are also some maps of South America that show the locations of *Haemagogus* and *Sabethes* mosquitoes, primary vectors for the YF jungle cycle on that continent, PAHO is still searching for more reliable sources. **See Map 5: Classification of Second-Level Administrative Divisions from 13 Countries, by YF Risk Potential and Major Ecosystems, South America and Panama.**
- **YF human cases:** A total of 1,070 human cases of YF were reported between 2000 and 2012. After geocoding and exploring their distribution by YF risk potential, the study found 1,030 of them to be located in endemic areas (96%), with 37 cases in transitional areas (3.5%). When examining reported cases by country, it found 35% reported by Peru; 29%, by Brazil; 19%, by Colombia; 8%, by Bolivia; 5%, by Venezuela; 2.6%, by Paraguay; 0.8%, by Argentina; and 0.1%, by Ecuador. Using the second-level administrative divisions as a reference, the study found that **only 276** of them have reported cases over the past 12 years. This represents a mere 3.2% of the area studied. **See Map 6: Classification of Second-Level Administrative Divisions from 13 Countries, by YF Risk Potential and Case Distribution, Major Ecosystem, and Hydrographic Condition, South America and Panama.**

Classifying and comparing the environmental conditions of second-level administrative divisions **with** and **without** YF cases produced the following findings:

- Second-level administrative divisions **with YF cases** show the following characteristics:
  - They are closer to the Equator (4 degrees latitude north or south).
  - They have an average altitude of around 100 meters lower than do areas with no cases.
  - Their slope angle is steeper by 1 degree.
  - The maximum average rainfall is 514mm more abundant.
- In second-level administrative divisions **with no YF cases**, the highest average temperature is 1 degree Celsius above the average temperature.

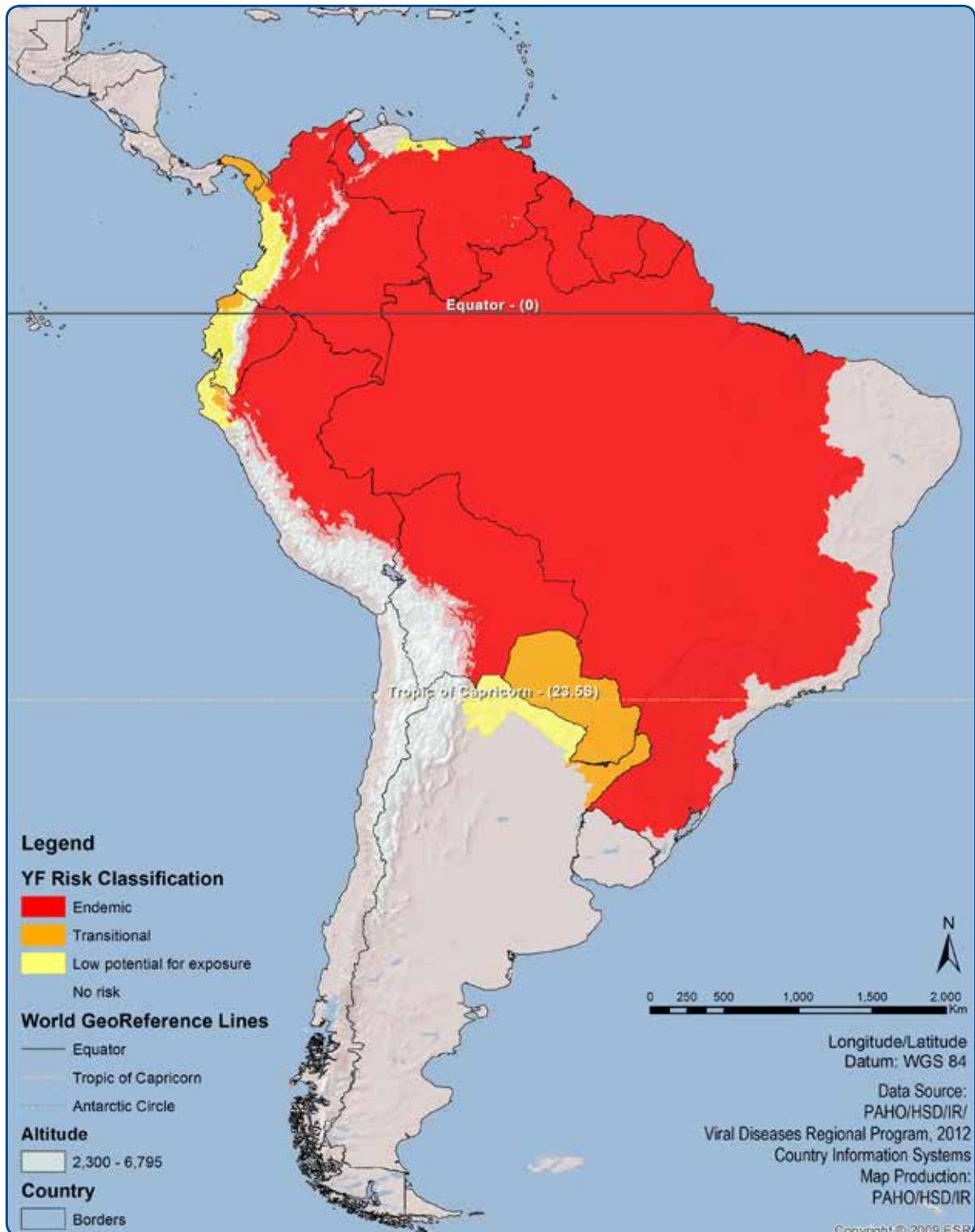
Geographically processing and standardizing multiple cartographic sources and epidemiological records allowed for creating a uniform, detailed digital database useful for overlaying and comparing environmental and health data. The main intention was to have the aforementioned database available and ready, so that epidemiologists and health authorities could have a more comprehensive set of elements to use as a foundation for evaluating, delineating, and focusing efforts targeted at YF-endemic, at-risk areas.

## BEST PRACTICES FOR YF RISK MAPPING

- 1. Record as much detail as possible on the location and timing of YF human cases and epizootics.**
  - a. Besides the usual information provided to characterize cases, obtain the geographic coordinates for the location of the infection, using both latitude (north-south) and longitude (east-west) in decimal degrees (e.g., -3.8575657 degrees south for latitude and -98.7598475 degrees west for longitude), as well as the World Geodetic System 1984 (WGS84) datum.
  - b. If georeferencing or geocoding is not possible, we recommend noting the community, town, locality, municipality, canton, district, department, or province, in hierarchical order. This will enable better identification of the location of each case.
  - c. Record the date of each disease event, in order to correlate them with seasonality factors.
- 2. Collect data on the distribution of nonhuman primates and mosquito vectors involved in YF transmission.**
  - a. Georeference and geocode the data if at all possible, or record as much detail on the location using the different administrative divisions at the different levels to assist in defining location.
  - b. Correlate the data with available environmental data (e.g., land cover use, rainfall, temperature, elevation) to potentially determine the geographic limits of primate or mosquito populations.
  - c. Record the date of each disease event, in order to correlate them with seasonality factors.
- 3. Exchange information with PAHO and other entities to allow for further definition of potential environmental indicators of YF risk.**

## MAP 2

### CLASSIFICATION OF SECOND-LEVEL ADMINISTRATIVE DIVISIONS FROM 13 COUNTRIES, BY YF RISK POTENTIAL, SOUTH AMERICA AND PANAMA



\* includes municipalities/cantons/provinces/districts

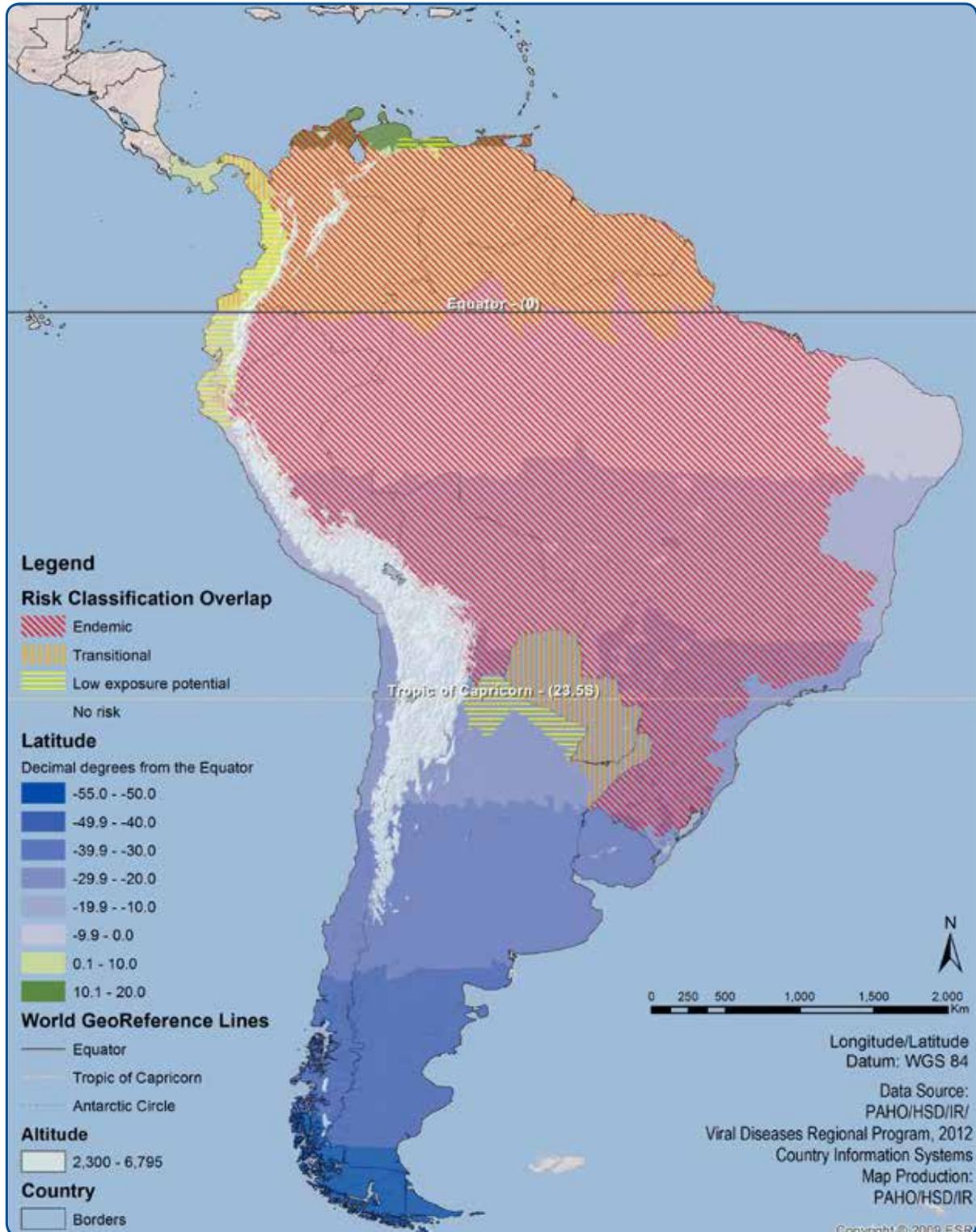
## MAP 3

### CLASSIFICATION OF SECOND-LEVEL ADMINISTRATIVE DIVISIONS FROM 13 COUNTRIES, BY YF RISK POTENTIAL AND ALTITUDE, SOUTH AMERICA AND PANAMA



## MAP 4

### CLASSIFICATION OF SECOND-LEVEL ADMINISTRATIVE DIVISIONS FROM 13 COUNTRIES, BY YF RISK POTENTIAL AND LATITUDE, SOUTH AMERICA AND PANAMA



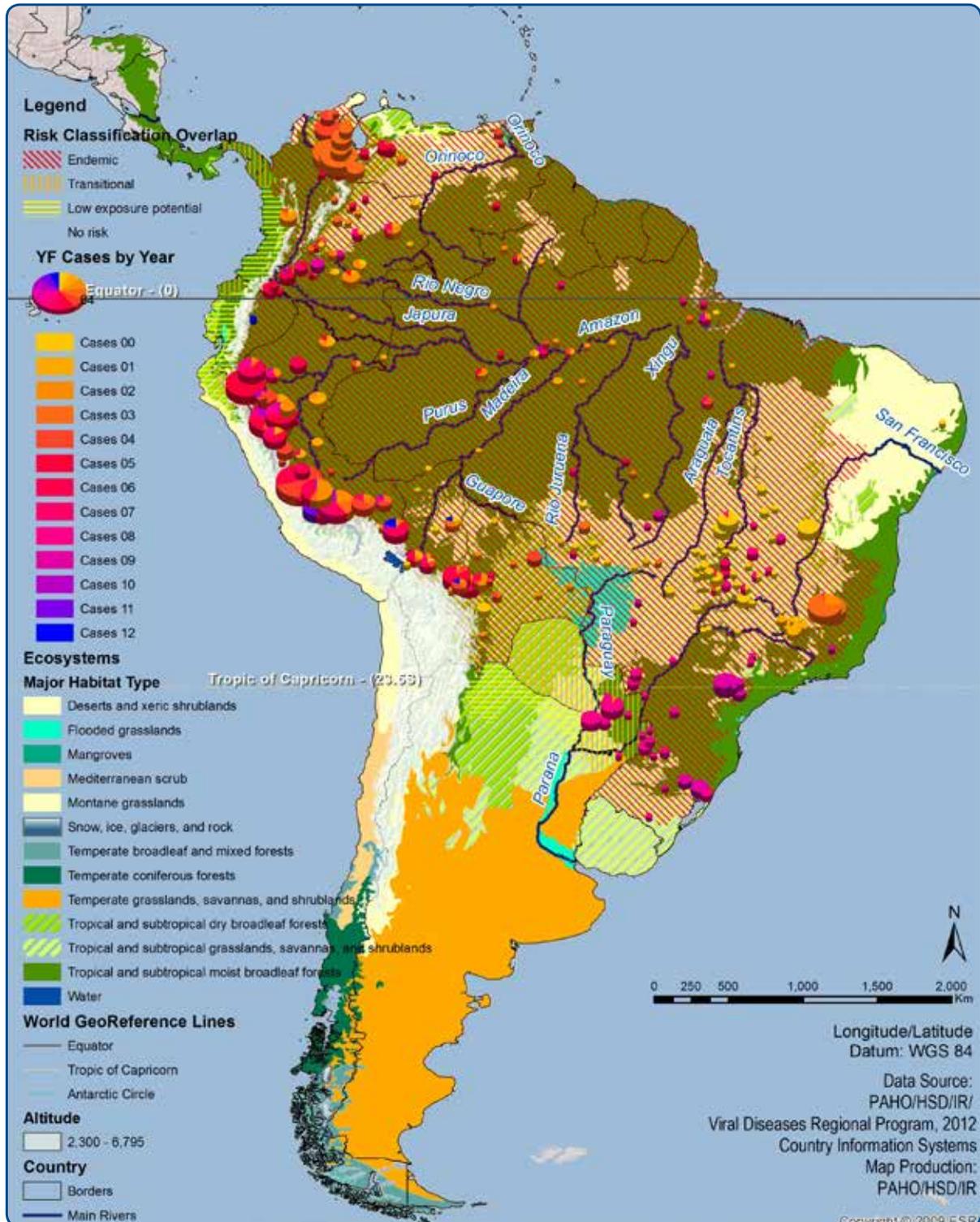
# MAP 5

## CLASSIFICATION OF SECOND-LEVEL ADMINISTRATIVE DIVISIONS FROM 13 COUNTRIES, BY YF RISK POTENTIAL AND MAJOR ECOSYSTEMS, SOUTH AMERICA AND PANAMA



## MAP 6

CLASSIFICATION OF SECOND-LEVEL ADMINISTRATIVE DIVISIONS FROM 13 COUNTRIES, BY YF RISK POTENTIAL AND CASE DISTRIBUTION, MAJOR ECOSYSTEM, AND HYDROGRAPHIC CONDITION, SOUTH AMERICA AND PANAMA



## CONCLUSIONS

Countries can make a scientific, evidence-based determination of YF risk areas for travelers by applying the best practices outlined in this document. They should strive to enhance and maintain their YF surveillance, so as to better understand the risk that this disease poses to travelers as well as to their own populations.

Those participating in the Expert Consultation agreed on the following:

- 1.** Countries can determine YF risk areas for travelers by taking into account the evidence-based scientific information generated by their YF surveillance systems.
- 2.** Countries should adopt the best practices outlined in this document and maintain a constant, systematic surveillance system that will promptly respond to emergencies, following IHR and ITH recommendations.
- 3.** Yellow fever surveillance should be both passive and active and should be targeted at detecting YF cases in all risk areas of the country. In addition, the surveillance system should establish measurable objectives and undergo monitoring to ensure optimal system performance.
- 4.** Training and updating personnel in YF epidemiology, clinical care, entomology, and ecology is essential to allow for early detection of YF virus activity. This will improve the country's capacity to adopt preventive and control measures and to provide timely feedback at the local, national, and international levels.
- 5.** Yellow fever risk should be periodically reassessed to allow for more accurate definition of areas and populations to target for vaccination activities. Vaccination should be guaranteed to travelers entering areas at risk of YF virus transmission.

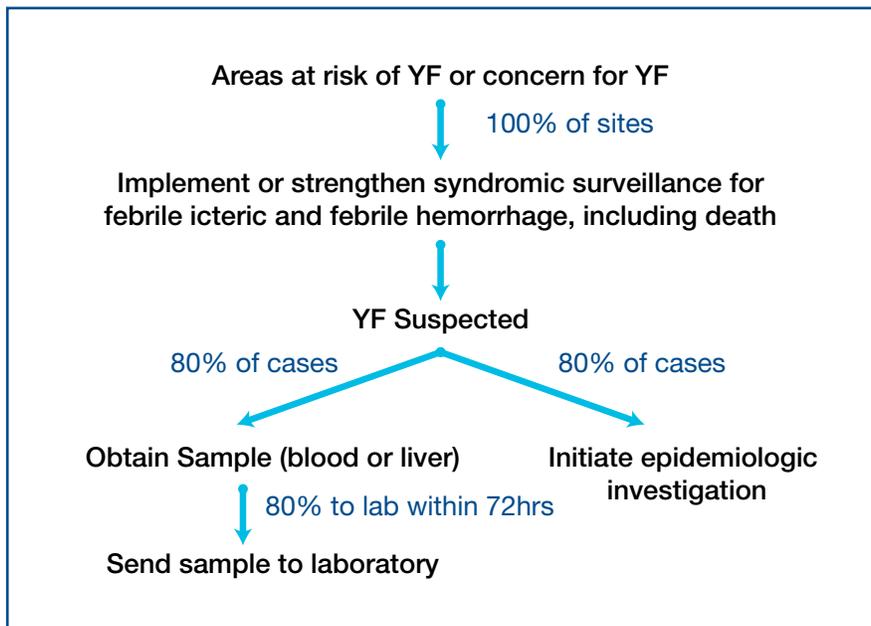
## APPENDIX

### APPENDIX I. AGENDA. EXPERTS CONSULTATION MEETING: “RECOMMENDATIONS FOR SCIENTIFIC EVIDENCE-BASED YELLOW FEVER RISK ASSESSMENT”

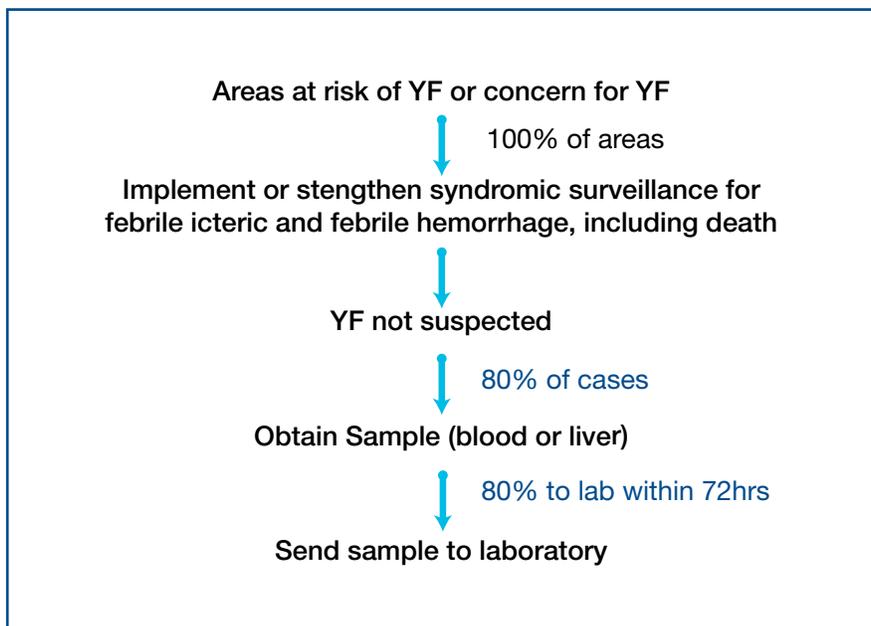
| HOUR          | JUNE 11  | HOUR          | JUNE 12  | HOUR          | JUNE 13   |
|---------------|--|---------------|--|---------------|---|
| 9:00 - 9:15   | Welcome Introductions  | 9:00 - 9:15   | YF risk mapping: methodology and results for the Americas.<br>Lic. Patricia Najera                   | 8:30 - 9:00   | <b>MEETING WITH PANAMA AUTHORITIES</b><br>Welcome Introductions   |
| 9:15 - 9:30   | <b>Objectives of the meeting</b><br>Dr. Otavio Oliva   | 9:15 - 9:30   | <b>IHR and YF countries categorization.</b><br>Dr. Sylvain Aldighieri                                | 9:00 - 9:15   | IHR and YF countries categorization<br>Dr. Sylvain Aldighieri   |
| 9:30 - 10:00  | <b>Yellow fever situation in the Americas.</b><br>Dr. Otavio Oliva   | 9:45 - 10:15  | Discussion   | 9:15 - 9:45   | <b>YF in Panama</b><br>Participant from the MOH   |
| 10:00 - 10:15 | YF vaccination: current status in the countries.<br>Dr. Alba María Ropero  | 10:15 - 10:30 | <b>Coffee break</b>  | 9:45 - 10:15  | Discussion  |
| 10:15 - 10:30 | Discussion   | 10:30 - 12:00 | Preparation of the draft: Recommendations for scientific evidence-based Yellow fever risk assesment. | 10:15 - 10:30 | <b>Coffee break</b>   |
| 10:30 - 10:45 | <b>Coffee break</b>  | 12:00 - 13:30 | <b>LUNCH</b>   | 10:30 - 11:00 | First approach: Recommendations for scientific evidence-based Yellow fever risk assessment in Panama.<br>Dr. Erin Staples |
| 10:45 - 11:15 | Best practices for human epidemiological surveillance of febrile icteric and icterohaemorrhagic syndromes.<br>Dr. Erin Staples | 13:30 - 15:30 | <i>Preparation of the draft</i>  | 11:00-11:45   | Discussion<br><b>Closing</b>  |
| 11:15 - 12:00 | Discussion   | 15:30 - 15:45 | <b>Coffee break</b>  | 12:00 - 13:30 | <b>LUNCH</b>  |
| 12:00 - 13:30 | <b>LUNCH</b>   | 15:45 - 17:00 | <i>Preparation of the draft</i>  |               |   |
| 13:30 - 14:00 | Best practices for YF non-human (epizootic) surveillance.<br>Dr. Daniel Garkauskas Ramos                                       |               |  |               |   |
| 14:00 - 14:30 | Discussion   |               |  |               |   |
| 14:30 - 15:00 | Best practices for YF Entomological surveillance: Urban and sylvatic transmission.<br>Dr. Jorge Boshell                        |               |  |               |   |
| 15:00 - 15:30 | Discussion   |               |  |               |   |
| 15:30 - 15:45 | <b>Coffee break</b>  |               |  |               |   |
| 15:45 - 16:15 | YF Laboratory surveillance.<br>Dr. Delia Enria   |               |  |               |   |
| 16:15 - 17:00 | Discussion   |               |  |               |   |

## APPENDIX II. BEST PRACTICES FOR HUMAN SURVEILLANCE AND METHODS TO USE FOR DETERMINING YELLOW FEVER RISK

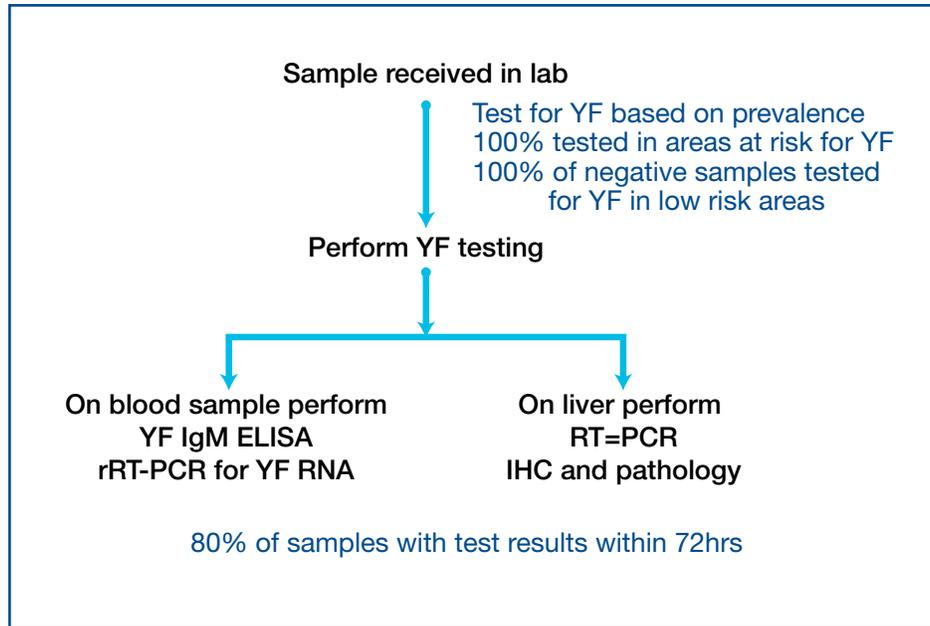
### FOR COUNTRIES WHERE YELLOW FEVER IS SUSPECTED



### FOR COUNTRIES WHERE YELLOW FEVER IS NOT SUSPECTED



## LABORATORY TESTING







Pan American  
Health  
Organization

