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Outbreak Investigation - A Perspective

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Outbreak investigations, an important and challenging component of epidemiology and public health, can help identify the source of ongoing outbreaks and prevent additional cases. Even when an outbreak is over, a thorough epidemiologic and environmental investigation often can increase our knowledge of a given disease and prevent future outbreaks. Finally, outbreak investigations provide epidemiologic training and foster cooperation between the clinical and public health communities.

Investigations of acute infectious disease outbreaks are very common, and the results of such investigations are often published; however, surprisingly little has been written about the actual procedures followed during such investigations (1,2). Most epidemiologists and public health officials learn the procedures by conducting investigations with the initial assistance of more experienced colleagues. This article outlines the general approach to conducting an outbreak investigation. The approach applies not only to infectious disease outbreaks but also to outbreaks due to noninfectious causes (e.g., toxic exposure).

How Outbreaks Are Recognized

Possible outbreaks of disease come to the attention of public health officials in various ways. Often, an astute clinician, infection control nurse, or clinical laboratory worker first notices an unusual disease or an unusual number of cases of

a disease and alerts public health officials. For example, staphylococcal toxic shock syndrome and eosinophilia myalgia syndrome were first noted by clinicians (3,4). Frequently, it is the patient (or someone close to the patient) who first suspects a problem, as is often the case in foodborne outbreaks after a shared meal and as was the case in the investigation of a cluster of cases of apparent juvenile rheumatoid arthritis near Lyme, Connecticut, which led to the discovery of Lyme disease (5). Review of routinely collected surveillance data can also detect outbreaks of known diseases, as in the case of hepatitis B infection among the patients of an oral surgeon in Connecticut and patients at a weight reduction clinic (6,7). The former outbreak was first suspected when routinely submitted communicable disease report forms for several patients from one small town indicated that all of the patients had recently had oral surgery. However, it is relatively uncommon for outbreaks to be detected in this way and even more uncommon for them to be detected in this way while they are still in progress. Finally, sometimes public health officials learn about outbreaks of disease from the local newspaper or television news.

Reasons for Investigating Outbreaks

The most compelling reason to investigate a recognized outbreak of disease is that exposure to the source(s) of infection may be continuing; by identifying and eliminating the

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source of infection, we can prevent additional cases. For example, if cans of mushrooms containing botulinum toxin are still on store shelves or in homes or restaurants, their recall and destruction can prevent further cases of botulism.

However, even if an outbreak is essentially over by the time the epidemiologic investigation begins—that is, if no one is being further exposed to the source of infection—investigating the outbreak may still be indicated for many reasons. Foremost is that the results of the investigation may lead to recommendations or strategies for preventing similar future outbreaks. For example, a Legionnaires' disease outbreak investigation may produce recommendations for grocery store misting machine use that may prevent other outbreaks (8). Other reasons for investigating outbreaks are the opportunity to 1) describe new diseases and learn more about known diseases; 2) evaluate existing prevention strategies, e.g., vaccines; 3) teach (and learn) epidemiology; and 4) address public concern about the outbreak.

Once a decision is made to investigate an outbreak, three types of activities are generally involved—the epidemiologic investigation; the environmental investigation; and the interaction with the public, the press, and, in many instances, the legal system. While these activities often occur simultaneously throughout the investigation, it is conceptually easier to consider each of them separately.

Epidemiologic Investigation

Outbreak investigations are, in theory, indistinguishable from other epidemiologic investigations; however, outbreak investigations encounter more constraints. 1) If the outbreak is ongoing at the time of the investigation, there is great urgency to find the source and prevent additional cases. 2) Because outbreak investigations frequently are public, there is substantial pressure to conclude them rapidly, particularly if the outbreak is ongoing. 3) In many outbreaks, the number of cases available for study is limited; therefore, the statistical power of the investigation is limited. 4) Early media reports concerning the outbreak may bias the responses of persons subsequently interviewed. 5) Because of legal liability and the financial interests of persons and institutions involved, there is pressure to conclude the investigation quickly, which may lead to hasty decisions regarding the source of the outbreak. 6) If detection of the outbreak is de-

layed, useful clinical and environmental samples may be very difficult or impossible to obtain.

Outbreak investigations have essential components as follows: 1) establish case definition(s); 2) confirm that cases are “real”; 3) establish the background rate of disease; 4) find cases, decide if there is an outbreak, define scope of the outbreak; 5) examine the descriptive epidemiologic features of the cases; 6) generate hypotheses; 7) test hypotheses; 8) collect and test environmental samples; 9) implement control measures; and 10) interact with the press, inform the public. While the first seven components are listed in logical order, in most outbreak investigations, many occur more or less simultaneously. The importance of these components may vary depending on the circumstances of a specific outbreak.

Case Definition

In some outbreaks, formulating the case definition(s) and exclusion criteria is straightforward; for example, in an outbreak of gastroenteritis caused by Salmonella infection, a laboratory-confirmed case would be defined as a culture-confirmed infection with Salmonella or perhaps with Salmonella of the particular serotype causing the outbreak, while a clinical case definition might be new onset of diarrhea. In other outbreaks, the case definition and exclusion criteria are complex, particularly if the disease is new and the range of clinical manifestations is unknown (e.g., in a putative outbreak of chronic fatigue syndrome). In many outbreak investigations, multiple case definitions are used (e.g., laboratory-confirmed case vs. clinical case; definite vs. probable vs. possible case; outbreak-associated case vs. nonoutbreak-associated case, primary case vs. secondary case) and the resulting data are analyzed by using different case definitions. When the number of cases available for study is not a limiting factor and a case-control study is being used to examine risk factors for becoming a case, a strict case definition is often preferable to increase specificity and reduce misclassification of disease status (i.e., reduce the chance of including cases of unrelated illness or no illness as outbreak-related cases).

Case Confirmation

In certain outbreaks, clinical findings in reported cases should be reviewed closely, either directly, by examining the patients, or indirectly, by detailed review of the medical records and discussion with the attending health-care

provider(s), especially when a new disease appears to be emerging (e.g., in the early investigations of Legionnaires' disease, AIDS, eosinophilia myalgia syndrome, and hantavirus pulmonary syndrome) (4,9-11). Clinical findings should also be examined closely when some or all of the observed cases may be factitious, perhaps because of laboratory error (12); a discrepancy between the clinical and laboratory findings generally exists, which may be discernible only by a detailed review of the clinical findings.

Establishing the Background Rate of Disease and Finding Cases

Once it is clear that a suspected outbreak is not the result of laboratory error, a set of activities should be undertaken to establish the background rate of the disease in the affected population and to find all the cases in a given population in a certain period. This set of activities should prove that the observed number of cases truly is in excess of the "usual" number (i.e., that an outbreak has occurred), define the scope of the outbreak geographically and temporally, find cases to describe the epidemiologic features of those affected and to include them in analytic epidemiologic studies (see below) or, most often, accomplish a combination of these goals.

When hundreds of acute onset diarrhea cases are suddenly seen daily in a single outpatient setting (10), an outbreak is clearly occurring. On the other hand, when too many hospitalized patients are dying unexpectedly of cardiac arrest (13) or the number of cases of listeriosis in a given county in recent months is moderately elevated, it may be necessary to establish the background rates in the population to determine whether an outbreak is occurring. In such situations, the period and geographic areas involved would provide the most useful baseline data, keeping in mind that the labor and time required to collect such information is often directly proportional to the length of the period and the size of the geographic area selected. Because disease incidence normally fluctuates by season, data from comparable seasons in earlier years should be included.

Establishing the background rate of a disease is generally more straightforward if confirmatory tests are available than if laboratory tests are unavailable or infrequently used. The rate of certain invasive bacterial infections (e.g., listerio-

sis and meningococcal infections) in a given area can be easily documented by reviewing the records of hospital clinical microbiology laboratories; however, cases for which specimens were not submitted to these laboratories for testing will go undetected. When a disease is less frequently laboratory-confirmed because health-care providers may not have considered the diagnosis or ordered the appropriate laboratory tests (e.g., for Legionnaires' disease), establishing the background rate of disease in a community or a hospital suspected of having an outbreak generally requires alternative case-finding strategies and is almost invariably more labor intensive. In an outbreak of a new disease, substantial effort is often necessary to determine whether or not cases of that disease had been occurring but had gone unrecognized.

Once data concerning the background rate of a disease (including case-finding for the current period) have been collected, it is generally possible to determine whether or not an outbreak is occurring or has occurred, although in some situations it may remain unclear whether or not the number of cases observed exceeds the background rate. In part, the problem may relate to how an outbreak is defined. To paraphrase a U.S. Supreme Court justice speaking about pornography, "I can't define an outbreak, but I know one when I see one." Thus, it may be difficult to detect and prove the existence of small outbreaks, but large ones are self-evident.

An outbreak can also be difficult to identify when during the period under study changes occur in the care-seeking behavior and access to care of patients; the level of suspicion, referral patterns, and test-ordering practices of health-care providers; the diagnostic tests and other procedures used by laboratories; and the prevalence of underlying immunosuppressive conditions or other host factors in the population. All these factors, which can affect the apparent incidence of a disease and produce artifactual changes perceived as increases (or decreases) in the actual incidence, need to be considered when interpreting the findings.

Descriptive Epidemiology

By collecting patient data, the case-finding activities provide extremely important information concerning the descriptive epidemiologic features of the outbreak. By reviewing and plotting on an "epidemic curve" the times of onset of the cases and by examining the characteristics (e.g., age, sex,

race/ethnicity, residence, occupation, recent travel, or attendance at events) of the ill persons, investigators can often generate hypotheses concerning the cause(s)/source(s) of the outbreak. While linking the sudden onset of gastroenteritis among scores of persons who attended a church supper to the single common meal they shared is generally not a challenge, an otherwise cryptic source can be at least hinted at by the descriptive epidemiologic features of the cases involved.

For example, in a particularly perplexing outbreak of *Salmonella* Muenchen infections ultimately traced to contaminated marijuana, the age distribution of the affected persons and of their households was markedly different from that typically seen for salmonellosis (14). Or, similarly, in the outbreak of legionellosis due to contaminated misting machines in the produce section of a grocery store, before the link to this exposure was even suspected, it was noted that women constituted a substantially higher proportion of the cases usually seen with this disease (5). The shape of the epidemic curve can also be very instructive, suggesting a point-source epidemic, ongoing transmission, or a combination of the two.

Generating a Hypothesis

The source(s) and route(s) of exposure must be determined to understand why an outbreak occurred, how to prevent similar outbreaks in the future, and, if the outbreak is ongoing, how to prevent others from being exposed to the source(s) of infection. In some outbreaks, the source and route are obvious to those involved in the outbreak and to the investigators. However, even when the source of exposure appears obvious at the outset, a modicum of skepticism should be retained because the obvious answer is not invariably correct. For example, in an outbreak of nosocomial legionellosis in Rhode Island, the results of an earlier investigation into a small number of hospital-acquired cases at the same hospital had demonstrated that *Legionella pneumophila* was in the hospital potable water supply, and a sudden increase in new cases was strongly believed to be related to the potable water (15). However, a detailed epidemiologic investigation implicated a new cooling tower at the hospital as the source of the second outbreak.

While the true source of exposure, or at least a relatively short list of possibilities, is apparent in many outbreaks, this is not the case in the more challenging outbreaks. In these

instances, hypotheses concerning the source/route of exposure can be generated in a number of ways beyond a detailed review of the descriptive epidemiologic findings. A review of existing epidemiologic, microbiologic, and veterinary data is very useful for learning about known and suspected sources of previous outbreaks or sporadic cases of a given infection or disease, as well as the ecologic niche of an infectious agent. Thus, in an outbreak of invasive *Streptococcus zooepidemicus* infections in New Mexico due to consumption of soft cheese made from contaminated raw milk, the investigation focused on exposure to dairy products and animals because of previous microbiologic and veterinary studies (16).

A review of existing data generally only helps confirm what is already known about a particular disease and is far less helpful in identifying totally new and unsuspected sources or routes of infection (i.e., marijuana as a source of *Salmonella*). When neither review of the descriptive epidemiologic features of the cases nor review of existing scientific information yields the correct hypothesis, other methods can be used to generate hypotheses about what the patients have in common. Open-ended interviews of those infected (or their surrogates) are one such method in which investigators try to identify all possibly relevant exposures (e.g., a list of all foods consumed) during a given period. For example, in an investigation of *Yersinia enterocolitica* infections in young children in Belgium, open-ended interviews of the mothers of some of the ill children showed that many gave their children raw pork sausage as a weaning food, providing the first clue as to the source of these infections (17). Similarly, in two outbreaks of foodborne listeriosis, a variant of this process led to the identification of the source of the outbreak. In one of these outbreaks, a search of the refrigerator of one of the case-patients who, as a visitor to the area, had had very limited exposure to foods there, suggested cole slaw as a possible vehicle of infection (18). In the other outbreak, an initial case-control study found no differences between cases and controls regarding exposure to a number of specific food items but showed that case households were more likely than control households to buy their food at a particular foodstore chain. To generate a list of other possible food sources of infection, investigators shopped with persons who did the shopping for case households and compiled a list of foods purchased at that foodstore chain that had not been reported

in the previous study. This approach implicated pasteurized milk from that chain as the source of the outbreak (19).

In some particularly perplexing outbreaks, bringing together a subset of the patients to discuss their experiences and exposures in a way that may reveal unidentified links can be useful.

Testing the Hypothesis

Whether a hypothesis explaining the occurrence of an outbreak is easy or difficult to generate, an analytic epidemiologic study to test the proposed hypothesis should be considered. While in many instances a case-control study is used, other designs, including retrospective cohort and cross-sectional studies, can be equally or more appropriate. The goal of all these studies is to assess the relationship between a given exposure and the disease under study. Thus, each exposure of interest (e.g., each of the meals eaten together by passengers on a cruise ship and each of the foods and beverages served at those meals) constitutes a separate hypothesis to be tested in the analytic study. In outbreaks where generating the correct hypothesis is difficult, multiple analytic studies, with additional hypothesis-generating activities in between, are sometimes needed before the correct hypothesis is formed and tested (19).

In interpreting the results of such analytic studies, one must consider the possibility that “statistically significant” associations between one or more exposures and the disease may be chance findings, not indicative of a true relationship. By definition, any “statistically significant” association may have occurred by chance. (When the standard cut point of $p < 0.05$ is used, this occurs 5% of the time.) Because many analytic epidemiologic studies of outbreaks involve testing many hypotheses, the problem of “multiple comparisons” arises often.

While there are statistical methods for adjusting for multiple comparisons, when and even whether to use them is controversial. At a minimum, it is important to go beyond the statistical tests and examine the magnitude of the effect observed between exposure and disease (e.g., the odds ratio, relative risk) and the 95% confidence intervals, as well as biologic plausibility in deciding whether or not a given “statistically significant” relationship is likely to be biologically meaningful. Evidence of a dose-response effect between a

given exposure and illness (i.e., the greater the exposure, the greater the risk for illness) makes a causal relationship between exposure and disease more likely. Whether the time interval between a given exposure and onset of illness is consistent with what is known about the incubation period of the disease under study must also be assessed. When illness is “statistically significantly” related to more than one exposure (e.g., to eating each of several foods at a common meal), it is important to determine whether multiple sources of infection (perhaps due to cross-contamination) are plausible and whether some of the noted associations are due to confounding (e.g., exposure to one potential source is linked to exposure to other sources) or to chance.

When trying to decide if a “statistically significant” exposure is the source of an outbreak, it is important to consider what proportion of the cases can be accounted for by that exposure. One or more of the patients may be classified as “nonexposed” for various reasons: incorrect information concerning exposure status (due to poor memory, language barriers); multiple sources of exposure or routes of transmission (perhaps due to cross-contamination); secondary person-to-person transmission that followed a common source exposure; or patients without the suspected exposure, representing background cases of the disease unrelated to the outbreak. The plausibility of each of these explanations varies by outbreak. While there is no cutoff point above or below which the proportion of exposed case-patients should fall before an exposure is thought to account for an outbreak, the lower this proportion, the less likely the exposure is, by itself, the source.

Other possibilities need to be considered when the analytic epidemiologic study finds no association between the hypothesized exposures and risk for disease. The most obvious possibility is that the real exposure was not among those examined, and additional hypotheses should be generated. However, other possibilities should also be considered, particularly when the setting of the outbreak makes this first explanation unlikely (e.g., when it is known that those involved in the outbreak shared only a single exposure or set of exposures, such as eating a single common meal). Two other explanations for failing to find a “statistically significant” link between one or more exposures and risk for illness also need to be considered—the number of persons avail-

able for study and the accuracy of the available information concerning the exposures. Thus, if the outbreak involves only a small number of cases (and non-ill persons), the statistical power of the analytic study to find a true difference in exposure between the ill and the non-ill (or a difference in the rate of disease among the exposed and the unexposed) is very limited. If the persons involved in the outbreak do not provide accurate information about their exposure to suspected sources or vehicles of infection because of lack of knowledge, poor memory, language difficulty, mental impairment, or other reasons, the resulting misclassification of exposure status also can prevent the epidemiologic study from implicating the source of infection. Studies have documented that even under ideal circumstances, memory concerning such exposures is faulty (20). However, given the usually enormous differences in rates of disease between those exposed and those not exposed to the source of the outbreak, even small studies or studies with substantial misclassification of exposure can still correctly identify the source.

Environmental Investigation

Samples of foods and beverages served at a common meal believed to be the source of an outbreak of gastroenteritis or samples of the water or drift from a cooling tower believed to be the source of an outbreak of Legionnaires' disease can support epidemiologic findings. In the best scenario, the findings of the epidemiologic investigation would guide the collection and testing of environmental samples. However, environmental specimens often need to be obtained as soon as possible, either before they are no longer available, as in the case of residual food from a common meal, or before environmental interventions are implemented, as in the case of treating a cooling tower to eradicate Legionella. Because laboratory testing of environmental samples is often expensive and labor-intensive, it is sometimes reasonable to collect and store many samples but test only a limited number. Collaborating with a sanitarian, environmental engineer, or other professional during an environmental inspection or collection of specimens is always beneficial.

While finding or not finding the causative organism in environmental samples is often perceived by the public, the media, and the courts as powerful evidence implicating or

exonerating an environmental source, either positive or negative findings can be misleading for several reasons. For example, finding Legionella in a hospital potable water system does not prove that the potable water (rather than a cooling tower or some other source) is responsible for an outbreak of Legionnaires' disease (21). Similarly, not finding the causative organism in an environmental sample does not conclusively rule out a source as the cause of the problem, in part because the samples obtained and tested may not represent the source (e.g., because of error in collecting the specimens, intervening changes in the environmental source) and in part because the samples may have been mishandled. Furthermore, in some outbreaks caused by well-characterized etiologic agents, laboratory methods of detecting the agent in environmental samples are insensitive, technically difficult, or not available, as in the case of recent outbreaks of *Cyclospora* infections associated with eating imported berries (22,23).

Control Measures

Central to any outbreak investigation is the timely implementation of appropriate control measures to minimize further illness and death. At best, the implementation of control measures would be guided by the results of the epidemiologic investigation and possibly (when appropriate) the testing of environmental specimens. However, this approach may delay prevention of further exposure to a suspected source of the outbreak and is, therefore, unacceptable from a public health perspective. Because the recall of a food product, the closing of a restaurant, or similar interventions can have profound economic and legal implications for an institution, a manufacturer or owner, and the employees of the establishments involved, acting precipitously can also have substantial negative effects. The recent attribution of an outbreak of *Cyclospora* infections to strawberries from California demonstrates the economic impact that can result from releasing and acting on incorrect information (22,23). Thus, the timing and nature of control measures are difficult. Balancing the responsibility to prevent further disease with the need to protect the credibility and reputation of an institution is very challenging.

Interactions with the Public and Press

While the public and the press are not aware of most outbreak investigations, media attention and public concern become part of some investigations. Throughout the course of an outbreak investigation, the need to share information with public officials, the press, the public, and the population affected by the outbreak must be assessed. While press, radio, and television reports can at times be inaccurate, overall the media can be a powerful means of sharing information about an investigation with the public and disseminating timely information about product recalls.

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Fish Mortality in Southeastern Caribbean Countries

A fish-kill outbreak affected several southeastern Caribbean countries from July to September 1999. As thousands of demersal reef fish washed ashore on some beaches of Barbados, Grenada, Saint Vincent and the Grenadines, and Tobago, concern grew among the national authorities of the Caribbean Community and Common Market (CARICOM), particularly for the serious direct impact of the fish-kills on the fishing industry, and their indirect effects on public health and the tourism industry.

In response to the magnitude of the problem, a Regional Meeting was convened by the Secretary General of CARICOM in Barbados in October 1999. The Pan American Health Organization (PAHO), through the Office of the Caribbean Program Coordination (CPC) in Barbados, responded in a timely manner to the request for technical cooperation from the affected countries. An epidemiological questionnaire was sent to all affected and non-affected countries and a technical team from the PAHO-CPC Office visited the countries affected by the outbreak. The purpose of this note is to present a brief description of the findings and provide recommendations to respond to similar natural or man-made disasters in the future.

Fish-kill events were reported in Grenada at the end of July, in Saint Vincent and the Grenadines on September 2, in Barbados on September 16, and in Tobago in the middle of September. The problem started to subside at the beginning of October, probably due to the depletion of the fish population at risk, to the diminution of the factor(s) associated with the kill events, or to a combination of both. Other countries affected were Guyana (in July) and Venezuela (in August). No other CARICOM Country reported fish mortality.

As estimated by the National Fisheries Division of Saint Vincent and the Grenadines, the direct economic impact amounted to a US\$192,000 loss due to the decrease in fish landing and a US\$120,000 loss of fish exports to Martinique. Additionally there was a 75 % drop in fishing and fish vending activities in comparison to the same months in previous years. There was also an unestimated loss due to a decline in the consumption of fish in the national and tourist populations. Indirect losses associated with a decrease in the number of visitors and reservation cancellations were not assessed, but highly publicized.

The following hypotheses were formulated to explain the kill events: a) volcanic eruption, b) chemical spill and/or cruise discharges, c) algae bloom, and d) pathogenic microorganisms. Hypotheses a) and b) were excluded for the following reasons: firstly, the Seismic Unit in Trinidad & Tobago did not register any significantly different seismic activity in the affected areas during the time of the outbreak as compared to data from previous years; secondly, the hypothesis of chemical spill was unsustainable, because the dilution factor would have more likely limited the fish kill to an area close to where any chemical spill would have occurred.

The hypothesis of the algae bloom – associated with an increase of the influx of nutrient-rich water from the Orinoco and Amazon Rivers in South America, an increase of water temperature, and oxygen depletion – is supported by physical observations made by fishermen from affected countries and pilots of regional airlines, indicating the presence of greenish/brownish discoloration of the sea water before and at the time of the kill events. Satellite pictures of the Caribbean presented by a technical team from Japan at the CARICOM Meeting, compared with images from previous years, clearly showed an unusual volume of the influx from the Orinoco and Amazon Rivers into the affected areas, including a gradient increase of temperature and of the sea water nutrient content as measured by chlorophyll gradient levels. This hypothesis was not confirmed by the determination of an increase in phytoplankton in the affected areas. However, it should be noted that water samples used for determination of algae blooms and physicochemical analysis were not collected in a timely manner nor using equipment allowing to sample different layers of the water column in affected areas. The samples were not preserved with lugol solution or 4 % formalin for phytoplankton studies.

In relation to the hypothesis of association with microorganisms, the Veterinary Division Laboratory of the Barbados Ministry of Agriculture, in collaboration with Dr. H. Ferguson of the University of Scotland, isolated a bacteria named *Streptococcus iniae* from 3 out of 4 specimens of moribund fish washing off the affected coast of Barbados. Histopathological studies revealed vasculitis, inflammation around the gills and pericarditis and the presence of gram+ bacteria in the liver, spleen and brain. None of the fish specimens exhibited external lesions. This finding is very significant, as *S. iniae*

has been associated with fish mortality in fresh water farming settings in various countries, and with human occupational diseases through the inoculation of the bacteria during the manipulation of fish. The Veterinary Division of the Ministry of Agriculture of Barbados has continued working on the subject and will make invaluable contributions to deal with such events in the future.

During the outbreak, the PAHO-CPC office took the following actions, together with the national authorities of all the affected countries: a) creation of inter-sectorial task forces at the national level, b) jointly with the Institute of Marine Affairs of Trinidad and Tobago, creation of an e-mail network linking the national authorities of all affected and non affected countries and international experts on the subject, including staff from PAHO's specialized centres such as the Caribbean Epidemiology Center (CAREC), the Pan American Institute for Food Protection and Zoonoses (INPPAZ), and the Pan American Center for Sanitary Engineering and Environmental Sciences (CEPIS), c) preparation of guidelines for safe disposal of dead fish, d) dissemination of a technical bulletin alerting all national health authorities in the area to the problem and its possible direct and indirect impact on public health, and e) provision of technical expertise on algae bloom, phytoplankton and marine toxins issues to all affected countries, and preparation and dissemination of a final report.

The following recommendations were extracted from the final report prepared by PAHO-CPC:

1) *A surveillance program should be established to monitor algae blooms and other physicochemical parameters predictor of algae bloom in affected areas and those areas that could be potentially affected in the future.*

The program should include:

- a) Active surveillance to establish trends in the environmental explanatory/predictor variables to determine the likelihood of occurrence of similar events in the future. A surveillance program should address the following points :
- When is the event occurring ? (Temporal distribution)
 - Where is it occurring? (Geographical distribution)
 - How is it occurring? If a toxic or non toxic algae bloom is suspected, it is necessary to record the following information: color changes in the water, location in the sea column (i.e., on the surface or under the surface); death of fish and shellfish; and illness or death of other living

organisms in the food chain (i.e., birds and mammals.) Characterization of the incubation period and signs/symptoms is also important if human cases are reported.

- What are the types of organisms associated with the bloom? (toxic vs. nontoxic, etc.)
 - Based on relevant epidemiological information and monitoring of key parameters, why is the problem occurring?
- b) Sampling of water for phytoplankton and microbiological analysis to detect concentration of phytoplankton species, pathogens and contaminant indicators, i.e., total coliforms, fecal *E. coli* and *S. faecalis*.
- c) Determination of appropriate physicochemical parameters.
- d) Sampling on a bi-weekly or weekly basis. The latter is highly recommended. The sampling protocol should include:
- For surface samples: use of plankton nets (pore-mesh: 25 or 30 Microns).
 - For samples at different depths (i.e., 5-10 meters), use of special bottles such as Niskin or Hansen bottles.
 - Fixation of samples with formalin or lugol. Samples fixed with formalin 4% last more than 1 year while samples fixed with lugol last approximately a month. In general, a lugol solution is used for quantitative analysis.
 - Sampling of shellfish and fish from affected reef areas for marine toxin examination. A mouse bioassay could be used for determination and measurement of Paralytic Shellfish Toxin (PSP).
- 2) *A research design should be set up to systematically collect and analyze information on variables (contributors) associated with increased kills of reef fish.* The following multivariate theoretical model was suggested:

$$FK(P) = a + b_1(x_1) + b_2(x_2) + b_3(x_3) + b_4(x_4) + b_5(x_1x_2) + \dots + e$$

where
 FK (P)= Outcome Variable or Probability of fish killing
 a= intercept
 b_1, \dots, b_n = Regression coefficients
 x_1, \dots, x_n = Variables or contributor factors
 x_1 = Temperature (degrees centigrade)
 x_2 = Phytoplankton (Number of cells per liter)
 x_3 = Toxic dinoflagellates a and b (0 or 1)
 x_4 = *S. iniae* (colony forming units (cfu) per gram)
 e = Error

This model provides room to determine the action and interaction of the variables. In the example above, the interaction between temperature and phytoplankton is expressed by $b_5(x_1 x_2)$. Other interaction factors could be included in the model. At the same time, phytoplankton concentrations and types could be used as an outcome variable.

3) *The educational strategy to the general population should receive special attention. A national task force should prepare messages to the public based on scientific evidence.* These messages must be very clear to minimize economic consequences. For example, in a scenario where an algae bloom is affecting reef areas, the consumption of fish and shellfish must be prohibited only from those affected areas.

There was not conclusive evidence associating the fish kills in the southeastern Caribbean to one single factor. These events were more likely due to the action and interaction of several physicochemical and biological environmental factors as previously discussed. Historical evidence of seasonal nontoxic and toxic algae blooms in Venezuela and in Trinidad and Tobago, and their related public health implications suggest that a surveillance and monitoring system of the likely environmental factors associated with these events should be implemented as a valuable tool to manage similar problems in the future and minimize their economic and public health impact.

The e-mail network linking national authorities from the health and agricultural sectors was very useful to exchange information on the fish kills events, and should be maintained by the Institute of Marine Affairs. Communication to the general public must be carefully managed based on risk assessment to protect public health and minimize economic consequences. PAHO/WHO and its specialized centers, CAREC and INPPAZ, in collaboration with the PAHO office in Trinidad and Tobago, held a workshop on "Analysis of Selected Foodborne Pathogens and Marine Toxins". Participants received field training on phytoplankton sampling and identification, and a demonstration of marine toxin bioassays was organized. Additionally, a Subregional Network for the control of red tides and marine toxins, now comprised of Cuba, the Dominican Republic, Guatemala, Panama and Venezuela, was created in 1990 with PAHO/WHO's cooperation. The functioning of this network should be revisited and extended to the English speaking Caribbean.

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Source: PAHO. Veterinary Public Health Program, Division of Disease Prevention and Control

Acknowledgments to the national agricultural and health authorities of all affected countries, for sharing their information and to Dr. Amelia la Barbera, of the National Fund for Research on Farming and Livestock (FONAIAP) of the State of Sucre, Venezuela, for her excellent technical support and expertise.

Meeting of the Regional Advisory Committee on Health Statistics

The Regional Advisory Committee on Health Statistics (CRAES) met in Washington, DC, from 27 to 29 March 2000. Dr. George A. O. Alleyne, Director of the Pan American Sanitary Bureau, opened the meeting and welcomed the Committee members. He recalled that beginning in the 1960s, the previous Committee had guided the Organization in achieving an improvement in vital and health statistics in the countries of the Region and he expressed satisfaction that the Committee is being revitalized.

In addition, he pointed out the difference between an expert committee and an advisory committee. Expert committees meet to deliberate on a specific subject, prepare a report, and do not meet again. Advisory Committees such as the CRAES, however, are advisors to the Director. They are long-standing and responsible for providing advice and recommendations to the Director, who in turn has the responsibility of indicating what is accepted and what is not feasible, given the conditions of the health situation of the countries and the resources available in the Organization. The use of working subcommittees by this Advisory Committee will make it possible to delve further into the critical areas required to strengthen health statistics in the Americas.

The Pan American Health Organization (PAHO), added Dr. Alleyne, has placed emphasis on the strategic use of health information. The Organization needs good-quality information not only for its own internal purposes but also to know about the health status of the population. It will never be possible to serve all the needs and it is necessary to concentrate on what the countries are currently doing and what PAHO can do to assist them. As a result, it is necessary to establish priorities using the available scientific information and pertinent analyses.

Dr. Alleyne manifested his growing concern over the problems that arise from complex analytical formulations such as complex health measures or indices, many of which depend on the accuracy and validity of the underlying data. If the data used to carry out the calculations are of doubtful quality, the formulations will also be suspicious. As a result, it is necessary to pay much more attention to ensure that the basic data are of better quality.

The matter of vital statistics is not new. The word "statistics" is derived from "the needs of the state", and this is important to keep in mind, not for the historical origin of the word but because the recommendations must be of importance to the population of the states. Equity cannot be achieved without information on the health status of the

population, not only at the country level but also at other levels. The Director was pleased to observe the efforts of the countries to reach a geographical disaggregation of the basic indicators. There is still a need, however, to improve information transfer and to devote special attention to ensure that the basic data are of the best quality.

Dr. Carlos Castillo-Salgado, Chief of the Special Program for Health Analysis (SHA), expressed his satisfaction that the CRAES had been reinstated and was especially grateful that the three Collaborating Centers of the World Health Organization for the Classification of Diseases in Spanish, Portuguese and for North America, and the Division of Statistics of the United Nations were represented.

The basic points considered at this meeting of the Committee were: training of human resources, validation and consistency of information, dissemination of information and the International Classification of Diseases (ICD) and family of classifications.

During the meeting, each of the basic points was introduced with a brief presentation. Further, the results of a survey conducted between September 1999 and February 2000 to identify training programs for personnel in statistics in the Spanish-speaking countries of the Americas were presented. The following recommendations emerged from the active and fruitful discussion that followed.

Recommendations

As a result of the survey conducted in 1999-2000 and of the discussions held during the meeting, the Committee recommended the adoption of a series of measures. These recommendations are grouped by subject.

Human resources

- Training courses for technicians and professionals should be promoted and supported, tending towards professionalization. Courses for technicians should be transformed into degree programs, and complementary courses for technical personnel should be created to give them the opportunity to obtain a degree.
- PAHO should maintain and keep up-to-date a directory of the various courses and modalities offered by each country.
- An instrument should be defined to evaluate the use of the diverse training materials in health statistics, as a first step towards the possible creation of a clearinghouse for the review, recommendation, and dissemination of these materials.

- PAHO should strengthen horizontal cooperation between countries and institutions (both within and outside the country), taking advantage of previous successes in human resources training in health statistics.
- Cooperation should be encouraged between countries that have training programs for health statistics personnel and those that lack them (exchange of students and faculty).
- Courses to refresh and standardize knowledge should be conducted, especially in technology and scientific methodology, for statistical personnel that serve in health services.

Implementation of the ICD-10 in the Americas

- PAHO should obtain from WHO a clearer definition of the delegation of authority to translate (into Spanish and Portuguese), publish, print and distribute the family of classifications in the Region of the Americas.
- PAHO should encourage and support the creation of national reference groups for the International Classification of Diseases and the family of classifications in the countries of the Region. Their function would include providing advisory services and recommendations to the users of the ICD and clarifying both mortality and morbidity coding questions.
- PAHO should keep and expand the Latin American Forum of discussions on the ICD and family of classifications and, in addition, promote the creation of similar national groups using e-mail.
- The ICD subcommittee should develop a plan to obtain information on the use of the ICD and the family of classifications, and their adaptations in all the countries of the Americas. This plan should include its opinion on the action that should be taken regarding the classification of procedures in medicine.
- The ICD subcommittee should analyze the proposed list for tabulation of the leading causes of death and the tables of consistency for mortality coding, and specify the form of dissemination to be used in all the countries.

Processes of data review and validation

- PAHO should promote the preparation and dissemination of documents on the principle of obtaining good quality information, and support the visit of experts, horizontal cooperation between countries and within regions of each country.
- In each country and in a joint effort with other institutions, the improvement in vital statistics should be strengthened through joint efforts at the local levels.
- In addition to promoting the use of established validation processes in the countries of the Region, PAHO should

support and promote the implementation of specific field studies for data collection.

- PAHO should promote the exchange of the methodology for the study of the quality of medical death certification between countries.
- PAHO should give priority to the implementation of specific studies on the registry of fetal deaths to describe this event with greater precision.

Dissemination of information

- A subcommittee of the CRAES, with the participation of experts in the subject, should review the International Standards Organization (ISO) standards in order to evaluate their adequacy to health metadata.
- PAHO should prepare a directory of the various existing sources of health information in the countries' Web pages.
- PAHO should support the preparation of a guide or manual on the methodology for the analysis of mortality data based on years of life lost and widely disseminate it.
- On the occasion of the approaching celebration of PAHO's 100th anniversary, topics should be suggested for a regional study on health statistics.
- A subcommittee of the CRAES should study the feasibility and methods of including, in all Web pages of public institutions containing information on health, details related to coverage and quality that should be taken into account when using the data.

The members of the Regional Advisory Committee on Health Statistics are: Ms. Yolanda Bodnar Contreras (Departamento Administrativo Nacional de Estadísticas, Colombia), Dr. J. Peter Figueroa (Ministry of Health, Jamaica) (unable to attend), Mr. Alejandro Esteban Giusti (Instituto nacional de Estadísticas y Censos, Argentina), Ms. Marjorie S. Greenberg (WHO Collaborating Center for the Classification of Diseases for North America, USA), Prof. Ruy Laurenti (Centro Colaborador da OMS Para a Classificação de Doenças em Português, Brasil), Dr. Miguel Angel Lezana Fernández (Secretaría de Salud, Mexico), Ms. Elida Hilda Marconi (Ministerio de Salud y Acción Social, Argentina), Dr. José Miguel Mata de la Torre (Instituto de Salud Carlos III del Ministerio de Salud y Consumo, Spain), Dr. Carlos Felipe Muñoz Rojas, (Centro Colaborador de la OMS para la Clasificación de Enfermedades en Español, Venezuela), Dr. Danuta Rajs Grzebien (Instituto de Salud Pública, Chile). Other participants to this meeting were: Dr. Eduardo Arriaga (University of Córdoba, Argentina), Dr. Sonia B. Fernández Cantón (Secretaría de Salud, Mexico), Dr. F. Sam Notzon (Office of International Statistics, National Center for Health Statistics, USA), Ms. Gladys Rojas (Ministry of Health, Venezuela), Ms. Susana Schkolnik (Centro Latinoamericano de Demografía, Comisión Económica para América Latina y el Caribe, Chile) Dr. Eduardo Zacca (Ministerio de Salud Pública, Cuba), and Ms. Violeta Gonzales-Díaz (Demographic and Social Statistics Branch, Statistics Division of the United Nations).

Source: PAHO. Special Program for Health Analysis

Update on Yellow Fever in the Americas

Yellow fever continues to be an important public health problem in the Americas. Between 1985 and 1999, Bolivia, Brazil, Colombia, Ecuador, Peru, Venezuela and French Guiana reported 2,935 cases and 1,764 deaths (see Table 1).

ling the disease. The Pan American Health Organization (PAHO)'s recommendations focus on the prevention of its re-urbanization, through surveillance, vaccination and vector control.

Table 1: Reported cases and deaths from yellow fever in the Region of the Americas, by country, 1985-2000

Country	1985-1995		1996		1997		1998		1999*		2000*	
	Cases	Deaths	Cases	Deaths	Cases	Deaths	Cases	Deaths	Cases	Deaths	Cases	Deaths
Bolivia	424	319	30	21	63	47	57	39	68	33	1	0
Brazil	202	88	15	12	3	3	34	15	75	28	66	35
Colombia	55	47	8	4	5	4	1	0	2	2		
Ecuador	45	29	8	8	31	4	3	1	5	3		
French Guiana	-	-	-	-	-	-	1	1	-	-		
Peru	1,431	914	86	34	44	20	165	49	56	33	2	1
Venezuela	2	1	-	-	-	-	15	4	1	1		
Total	2,159	1,398	147	79	146	78	276	109	207	100	69	36

* Provisional data

Source: PAHO. Division of Vaccines and Immunization

During this period, more than 80% of all yellow fever reports in the American Region came from Bolivia and Peru. In 1999, Bolivia, Brazil and Peru accounted for 33%, 36% and 27% of all cases, respectively. However, from January to May 2000, a total of 66 confirmed cases were reported in Brazil, which represent more than 90% of all the cases notified in the Region during this period. Reports from the Brazilian Ministry of Health show that most of those cases come from the State of Goiás and neighboring States, where an extensive epizootic has been taking place since the beginning of the year (see Table 2).

Table 2: Confirmed Cases of yellow fever in Brazil January-May 2000

State	Cases	Deaths
Amazonas	1	0
Bahia	8	2
Brasília, D.F.	1	1
Goiás	43	22
Mato Grosso	4	3
Minas Gerais	1	1
Sao Paulo	2	2
Tocantins	6	4
Total	66	35

Source: CENEPI-FUNASA-Ministry of Health of Brazil

All cases notified in the Region since the 1940s have been of the jungle form of yellow fever, transmitted by mosquitoes of the genus *Haemagogus*. However, the overwhelming spread of the *Aedes aegypti* mosquito threatens to re-urbanize the disease. The seriousness of the current yellow fever situation in the Region demands a firm commitment by the countries to a strong and effective strategy for control-

The establishment of a sensitive surveillance system is critical to the control and prevention of yellow fever. Currently notified cases tend to be of the severe clinical form of the disease, and therefore correspond to only a fraction of the total number of yellow fever virus infections, since as much as 50% of all cases can be asymptomatic.

In order to provide immediate protection to residents in enzootic areas and to prevent the introduction of yellow fever into nearby urban areas infested with *Aedes aegypti*, high levels of vaccination should be maintained among individuals living in both areas. During its Seventh Plenary Session in 1997, PAHO's Directing Council exhorted its Member States to include yellow fever vaccine in their national immunization programs in all areas at risk of transmission of the disease. The countries and territories that have included universal children immunization against yellow fever are Trinidad and Tobago, Guyana and French Guiana. Brazil, Ecuador and Peru have given priority to the immunization of children in enzootic areas. Trinidad and Tobago and Guyana have implemented "catch-up" campaigns in all age groups in the entire country, and Brazil and Ecuador have used the same strategy for enzootic areas and regions with a high risk of transmission of the disease. Peru, Bolivia, Suriname and Venezuela have developed plans to introduce the yellow fever vaccine in their children vaccination schedule, as well as the vaccination of all age groups in enzootic areas.

Present day control strategies against the urban vector *Aedes aegypti* are based primarily on the reduction of breeding sources through their elimination. Social communication, community participation and health education are fundamental elements in these strategies. Insecticides are widely used where there are high vector population densities.

Source: PAHO. Division of Vaccines and Immunization and Division of Disease Prevention and Control

Case definitions

Dengue Fever

Rationale for surveillance

Dengue fever, including Dengue Hemorrhagic Fever (DHF) and Dengue Shock Syndrome (DSS), is the most significant arthropod-borne viral disease worldwide. It occurs in over 100 countries and territories and threatens the health of over 2,500 million people in tropical and subtropical regions. Dengue fever is a severe disease with high epidemic potential. An estimated 500,000 patients, 90% of them below the age of 15, are hospitalized with DHF/DSS every year. The World Health Organization (WHO) aims to accelerate the final development of an attenuated dengue vaccine.

Recommended case definition

Dengue fever:

Clinical description: An acute febrile illness of 2-7 days duration with 2 or more of the following: headache, retro-orbital pain, myalgia, arthralgia, rash, hemorrhagic manifestations, leucopenia.

Laboratory criteria for diagnosis

One or more of the following:

- Isolation of the dengue virus from serum, plasma, leukocytes, or autopsy samples,
- Demonstration of a fourfold or greater change in reciprocal IgG or IgM antibody titers to one or more dengue virus antigens in paired serum samples,
- Demonstration of dengue virus antigen in autopsy tissue by immunohistochemistry or immunofluorescence or in serum samples by EIA,
- Detection of viral genomic sequences in autopsy tissue, serum or CSF samples by polymerase chain reaction (PCR).

Case classification

Suspected: A case compatible with the clinical description.

Probable: A case compatible with the clinical description with **one or more** of the following:

- supportive serology (reciprocal hemagglutination-inhibition antibody titre ≥ 1280 , comparable IgG EIA titre or positive IgM antibody test in late acute or convalescent-phase serum specimen),

- occurrence at same location and time as other confirmed cases of dengue fever.

Confirmed: A case compatible with the clinical description, laboratory-confirmed.

Criteria for Dengue Hemorrhagic Fever/Dengue Shock Syndrome:

Dengue Hemorrhagic Fever:

A probable or confirmed case of Dengue **and** Hemorrhagic tendencies evidenced by **one or more of the following:**

- Positive tourniquet test
- Petechiae, ecchymoses or purpura
- Bleeding: mucosa, gastrointestinal tract, injection sites or other
- Haematemesis or melaena

and thrombocytopenia (100 000 cells or less per mm^3)

and evidence of plasma leakage due to increased vascular permeability, manifested by one or more of the following:

- $\geq 20\%$ rise in average hematocrit for age and sex
- $\geq 20\%$ drop in hematocrit following volume replacement treatment compared to baseline
- signs of plasma leakage (pleural effusion, ascites, hypoproteinemia)

Dengue shock syndrome:

All the above criteria, **plus** evidence of circulatory failure manifested by rapid and weak pulse, and narrow pulse pressure (≤ 20 mm Hg) or hypotension for age, cold, clammy skin and altered mental status.

Recommended types of surveillance

Areas where no dengue transmission has been detected but where Aedes aegypti occurs: surveillance of suspected cases with investigation of clusters of suspected cases for dengue.

Countries where disease is endemic with seasonal variations in transmission, and areas where epidemic dengue occurs: routine weekly/monthly reporting of aggregated data of suspected, probable and confirmed cases from peripheral to intermediate and central levels.

Recommended minimum data elements

Case-based data at the peripheral level

- Case classification (suspected/probable/confirmed), serotype, DHF/DSS present (Yes/No)
- Unique identifier, name of patient, age, sex, geographical information
- Date of onset
- Hospitalized (Yes/No)
- Outcome
- Travel history during past 2 weeks

Aggregated data for reporting

- Number of cases by age group
- Number of confirmed (and serotype)
- Number of DHF/DSS cases by age group
- Number of hospitalizations and deaths

Principal use of data for decision-making

- Target high risk areas for intervention.
- Monitor changes in serotype and rate of DHF/DSS.
- Monitor trends in endemic disease or re-emergence of disease.

Leptospirosis

Rationale for surveillance

This zoonosis with worldwide distribution occurs seasonally in countries with a humid subtropical or tropical climate. It is often linked to occupation, sometimes in outbreaks. Feral and domestic animal species may serve as sources of infection with one of the *Leptospira* serovars. Infection is transmitted to humans through direct contact with (the urine of) infected animals or a urine-contaminated environment, mainly surface waters, soil and plants. The course of disease in humans ranges from mild to lethal. Leptospirosis is probably underreported in many countries because of difficult clinical diagnosis and lack of diagnostic laboratory services. Surveillance provides the basis for intervention strategies in human or veterinary public health.

Recommended case definition

Clinical description

Acute febrile illness with headache, myalgia and prostration associated with any of the following symptoms:

- conjunctival suffusion
- meningeal irritation
- anuria or oliguria and/or proteinuria
- jaundice
- hemorrhages (from the intestines; lung bleeding is notorious in some areas)
- cardiac arrhythmia or failure
- skin rash

and a history of exposure to infected animals or an environment contaminated with animal urine.

Other common symptoms include nausea, vomiting, abdominal pain, diarrhoea, arthralgia.

Laboratory criteria for diagnosis

- Isolation (and typing) from blood or other clinical materials through culture of pathogenic leptospires
- Positive serology, preferably Microscopic Agglutination Test (MAT), using a range of *Leptospira* strains for antigens that should be representative of local strains.

Case classification

Suspected: A case that is compatible with the clinical description.

Probable: Not applicable.

Confirmed: A suspected case that is confirmed in a competent laboratory.

Note: Leptospirosis is difficult to diagnose clinically in areas where diseases with symptoms similar to those of leptospirosis occur frequently.

Recommended types of surveillance

a) Immediate case-based reporting of suspected or confirmed cases from peripheral level (hospital/general practitioner/laboratory) to intermediate level (and from intermediate level to central level for no endemic areas). All cases must be investigated.

b) In endemic areas, routine reporting of aggregated data of confirmed cases from intermediate to central level.

c) *International:* The International Society of Leptospirosis and the WHO Collaborating Centers on Leptospirosis collect data worldwide and regionally on leptospirosis.

Note:

- Hospital-based surveillance may give information on severe cases of leptospirosis.
- Serosurveillance using sera available in public health laboratories, collected for other purpose, or sera collected in programmed survey may give information on whether leptospiral infections occur or not in certain areas or populations.

Recommended minimum data elements

- Age, sex, address, occupation
- Clinical symptoms (morbidity, mortality)
- Hospitalization (Yes/No)
- History and place of exposure (animal contact, environment, occupational)
- Microbiological and serological data
- Date of diagnosis
- Meteorological data, e.g. rainfall, flooding, natural disaster

Aggregated data for reporting

- Number of cases
- Number of hospitalizations
- Number of deaths
- Number of cases by type (causative serovar/serogroup) of leptospirosis.

Principal use of data for decision-making

- Assess the magnitude of the problem in different areas and risk factors (groups/areas/conditions).
- Identify outbreaks.
- Identify animal sources of infection.
- Monitor for emergence of leptospirosis in new areas and new risk (occupational) groups.
- Design rational control or prevention methods.
- Identify new serovars and their distribution.
- Inform on locally occurring serovars for a representative range in the MAT (Monoclonal Antibody Test).



Summer Session in Intermediate Epidemiology

Under the coordination of PAHO's Special Program for Health Analysis (SHA), the Summer Session in Intermediate Epidemiology is developed annually with the College of Public Health, University of South Florida, Tampa, Florida. This is one of the most successful graduate sessions in the Region of the Americas, now in its Tenth year, and one of the few to be offered in Spanish. It is devoted to health professionals who have previous experience in epidemiology and who require more advanced training in this area.

The session consists of three integrated compulsory courses: Intermediate Methods in Epidemiology, Statistical Methods Applied to Epidemiology and Computer Software, and Use of Epidemiology in Programming and Evaluation of Health Services. The courses include lecture presentations, followed by laboratory sessions with group work and computer-based analysis. Each year an average of 30 students attend from Ibero-America.

The instructors for the Tenth session are Dr. Carlos Castillo-Salgado of PAHO's Special Program for Health Analysis, Dr. Javier Jiménez, of the Institute Carlos III of Madrid, Spain, and Jaume Canela, of the University of Barcelona, Spain.

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