Surveillance for Dengue and Dengue Hemorrhagic Fever[1]

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Dengue and dengue hemorrhagic fever are emerging as major public health problems in most tropical countries. Effective prevention and control programs will depend on improved surveillance designed to provide early warning of dengue epidemics. This article outlines a reasonable approach to dengue surveillance of this kind.

Virologic surveillance should be considered the most important element in any such early warning system. Dengue virus transmission should be monitored to determine which serotypes are present, their distribution, and the type of illnesses associated with each. Other key components of an active surveillance system should include monitoring of fever activity and clinical surveillance for cases of severe and fatal disease associated with viral syndromes. Collectively, these three surveillance components can provide an early warning capability permitting emergency mosquito control measures to be implemented and major epidemics to be averted.

Dengue's importance as a public health problem for the Americas and the world has increased greatly over the past 20 years. Among other things, the Americas have seen increases in the incidence of the disease, the frequency of epidemic activity, and the number of dengue virus serotypes circulating in the Region—as well as emergence of dengue hemorrhagic fever/dengue shock syndrome (DHF/DSS), the severe and often fatal form of the disease (*1*).

The reasons for this increased dengue virus activity are complex, but basically three factors are responsible: (1) lack of effective, long-term mosquito control in most tropical countries, (2) increased urbanization in those same countries, and (3) a marked increase in air travel over the past 20 years, which has provided an ideal mechanism for transporting dengue viruses between tropical population centers—all of which has created conditions ensuring that dengue viruses will be introduced into areas suitable for epidemic transmission.

Unfortunately, this situation strongly favoring the spread of dengue viruses is unlikely to change soon. Therefore, epidemic dengue, perhaps accompanied by DHF/DSS, is likely to recur at frequent intervals during the foreseeable future.

Within this context, our options for prevention and control of epidemic dengue are limited. Eradication of the principal vector mosquito, *Aedes aegypti*, is the most effective way to prevent transmission; but unless all countries in the Americas achieve eradication, reinvasion appears inevitable. Other options include regulation of air travel and development of effective dengue vaccines; but the former is not realistic and the latter do not exist.

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[1]This article has also been published in Spanish in the *Boletín de la Oficina Sanitaria Panamericana*, Vol. 107, No. 1, 1989, pp. 22–30.

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DENGUE SURVEILLANCE IN PUERTO RICO

Puerto Rico's dengue prevention and control program relies on more effective surveillance as an early warning system that can predict epidemic dengue, and combining this with improved mosquito control measures—including both emergency and routine community-based measures—to reduce *A. aegypti* densities. This program is now in place and has been used to predict the last three dengue epidemics. Unfortunately, mosquito control measures have not been adequate to prevent epidemic transmission.

There are two basic types of surveillance for dengue and DHF/DSS, reactive and active. To date most surveillance for these diseases has been reactive—that is, it has depended upon the medical community to monitor and report clinical cases of dengue fever or DHF/DSS. This type of surveillance is typically very insensitive because of the low index of suspicion on the part of physicians and the difficulties inherent in clinical differential diagnosis. (Cases of dengue are frequently misreported as influenza, measles, or nonspecific viral syndrome.) As a result, a dengue epidemic may be near peak transmission before it is recognized. By then it is generally too late to have much impact upon epidemic transmission, even though intensive mosquito control measures may be implemented.

The advantages of such reactive surveillance are that it is logistically and organizationally easy to implement; and, once epidemic transmission is recognized, it is very easy to mobilize the government and both medical and lay communities to support epidemic control measures. However, the system's insensitivity and very slow response time provide no predictive capability or early warning, and so reactive surveillance is very costly to the community in terms of ensuing epidemic control measures, medical services, hours of work lost, and losses to tourism.

This is the type of surveillance most dengue-endemic countries have had for many years. In recent times the result has been repeated epidemics of dengue and DHF/DSS at frequent intervals, generally with each subsequent epidemic getting progressively larger. If this pattern of surveillance continues to prevail in the Americas, we can expect repeated epidemics of dengue and perhaps major epidemics of DHF/DSS instead of the sporadic disease we have had to date.

The alternative strategy is active surveillance, which entails actively monitoring dengue infections in the community at all times. The rationale for this type of surveillance is that during interepidemic periods, or periods of sporadic or silent transmission, dengue infections are not recognized clinically. With the introduction of a new virus strain or serotype, there is usually a period of low-level transmission or "lag phase" that may last anywhere from a few weeks to several months before epidemic transmission begins (2).

The objective of active surveillance is to detect the new virus during this lag phase, well before significantly increased transmission. If effectively applied at this stage, mosquito control measures might abort an incipient epidemic. The objective here would be to reduce transmission, thereby reducing the probability of DHF/DSS. Vigilance would have to be maintained for some time, however, to ensure that the epidemic was not simply delayed. To achieve this type of predictive capability for epidemic dengue, the active surveillance system must be laboratory-based and must use rapid and sensitive laboratory diagnostic methods. Thus, a good diagnostic laboratory is essential to an effective active surveillance system.

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Five basic types of dengue surveillance are useful in an active system—these being virologic, epidemiologic, clinical, serologic, and entomologic surveillance.

VIROLOGIC SURVEILLANCE

The most important type of surveillance for predicting epidemic dengue, virologic surveillance requires a sensitive, relatively rapid, and inexpensive virus isolation system. Such a system, using mosquito cell cultures for isolation and monoclonal antibodies for virus identification, is now available (3). An efficient laboratory can process up to 200 serum samples per week for virus isolation in approximately 2.0 man-days, and dengue virus can be isolated and identified in two to three days. New methods designed to detect viral antigen in viremic sera promise even more rapid specific diagnosis, but these are not yet available for routine use (4).

In general, an active virologic surveillance system should have the following objectives:

1. To monitor the endemic dengue viruses transmitted in the area during interepidemic periods, i.e., during times when transmission is sporadic or silent.
2. To monitor the geographic distribution and movement of all dengue virus serotypes.
3. To monitor types of illness associated with dengue infection in the endemic area.

If these objectives are achieved in all communities, the introduction of new virus serotypes and possibly new virus strains can be detected without too much delay. And with this type of information in hand, epidemic transmission can be predicted and major epidemics prevented by implementing mosquito control measures immediately after detection of a new virus strain or serotype—well before increased transmission.

The surveillance program in Puerto Rico uses government health centers in selected communities around the island, chosen on the basis of the probability of dengue viruses being introduced (Figure 1). In addition, selected private physi-

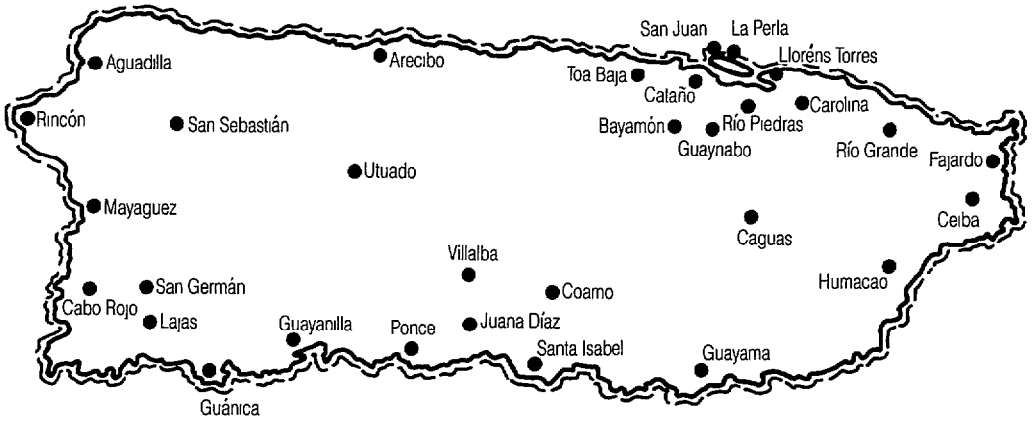

Figure 1. Puerto Rican cities where virologic surveillance is emphasized.

cians are recruited, primarily in the San Juan metropolitan area. The collaborating physicians and health centers are asked to send several acute-phase blood samples from selected patients with viral syndrome to the laboratory each week. In addition, they are asked to send blood samples from all patients with dengue-like illness and from all patients dying of any type of hemorrhagic manifestation, viral encephalitis, or viral syndrome.

The acute-phase blood samples are processed for virus isolation immediately, without regard to serology. As might be expected, most are negative during periods of low or silent transmission; but occasional cases are detected, and these few positive cases are most important for monitoring transmission in the community. The acute-phase serum specimens are also tested for antidengue IgM antibody (see below).

This system was used in Puerto Rico to detect reintroduction to the island of both dengue 1 and 2 in 1984 (Figure 2). The resulting information was employed to predict a small outbreak that occurred in late 1985. In addition, larger epidemics occurring in 1986 and 1987 were predicted several months before peak transmission. Unfortunately, support for mosquito control measures to prevent epidemic transmission could not be obtained.

Another benefit of an effective virologic surveillance system is that unpassaged viruses are available for other studies. The recent application of the RNA oligonucleotide fingerprint technique has provided a method for determining the geographic origin and distribution of newly introduced dengue viruses (*5, 6*). With this technique and the collaboration of the CDC laboratory in Fort Collins, Colorado, two distinct topotypes of dengue 2 virus have been documented in the Caribbean Basin and 14 genotypes have been described from around the world (*7, 8*). Moreover, techniques for geographic classification employing complementary deoxyribonucleic acid (cDNA) probes and antigen signature analysis have been developed recently and may be more useful for rapid characterization of newly isolated viruses (*9, 10*). These types of studies can be expected to clarify the role that virus strain differences play in epidemiology and clinical expression, and will eventually permit identification of more virulent or epidemic strains of dengue virus. Without good virologic surveillance, this type of study would not be possible.

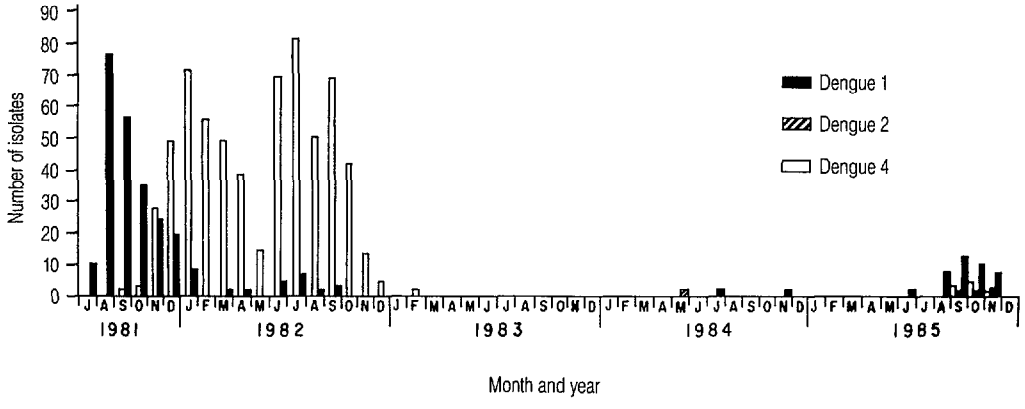

Figure 2. Dengue virus serotypes isolated in Puerto Rico from mid-1981 through 1985, by month of disease onset.

The disadvantage of active virologic surveillance is that it is difficult to motivate the medical community to cooperate and take blood samples from patients who do not appear to have dengue. Most physicians in endemic disease areas either do not know or ignore the fact that dengue frequently presents as undifferentiated, nonspecific, mild febrile illness—especially in children and during periods of low-level activity or sporadic transmission. Indeed, probably the most difficult task in this type of surveillance is to change the way health authorities and physicians think and to convince them of the need for emphasizing the interepidemic period and prevention rather than the epidemic period and control. This change in thinking is critical to development of the early warning surveillance system needed to prevent epidemics.

EPIDEMIOLOGIC SURVEILLANCE

The aim of epidemiologic surveillance is to monitor disease activity for dengue-like illness and/or DHF/DSS in the community. The first step is to make dengue a reportable disease and have physicians make weekly reports to central health authorities. This type of epidemiologic surveillance is reactive—and therefore not very sensitive. However, it does provide statistical data for reporting.

More important for predicting epidemic dengue is the practice of reporting increased fever of unknown origin (FUO), something that is seldom done in endemic dengue areas. Increased febrile illness in a community may be due to any number of etiologic agents, including dengue. When an increase in FUO of any kind is noted by the medical community, health authorities should be notified immediately, and the cases should be investigated by epidemiologic and laboratory personnel. Specifically, blood samples should be taken and processed for virologic and/or serologic diagnosis without delay in order to determine whether dengue is the etiologic agent responsible. In countries that have the laboratory capability, these blood samples can also be used to monitor other diseases such as measles, influenza, malaria, and leptospirosis.

CLINICAL SURVEILLANCE

Clinical surveillance for classical dengue and DHF/DSS is reactive and therefore relatively insensitive, depending upon the awareness and interest of the medical community. However, surveillance for viral syndromes with a fatal outcome may be more effective in providing an early warning of epidemic activity. An example of this was observed in Indonesia, where fatal viral syndrome was monitored virologically from 1975 to 1978 (2). During the first five months of the study, only a single dengue 1 virus was isolated. In March and April of 1976, however, an increase in virologically confirmed DHF/DSS cases with fatal outcomes was observed; most of these cases were associated with dengue 3 infection. Six months later, dengue 3 virus caused a series of epidemics throughout Indonesia, suggesting that the dengue 3 virus isolated in Jakarta in the spring of 1976 was a new epidemic strain.

It has subsequently been shown by the RNA oligonucleotide fingerprint method that the dengue 3 viruses isolated from those epidemics were all the same strain (*11*). Thus, it may be feasible to detect more virulent or epidemic strains of virus well before actual epidemic transmission by monitoring viral illnesses with a fatal outcome in areas endemic for DHF/DSS.

In areas where DHF/DSS is not endemic, the disease should be defined through educational programs for the medical community. Clinical surveillance in these areas should include reporting of

all hemorrhagic disease cases in the community. In addition to permitting early detection of DHF/DSS, this activity can help define disease on the severe end of the clinical spectrum.

SEROLOGIC SURVEILLANCE

In the past, serologic surveillance was of limited use for predicting epidemic activity because it was necessary to have paired acute-phase and convalescent-phase serum samples collected 14 days apart for testing. Partly as a result, confirmation of dengue infection generally took at least four weeks, and even then the infecting serotype was usually not known. When used in conjunction with epidemiologic case reporting, however, routine serologic surveillance data are very useful in determining what proportion of reported cases actually involve dengue.

Also, development of newer methods for measuring antidengue IgM antibody in acute-phase serum samples has made serologic diagnosis faster and much more useful. IgM antibody develops somewhat faster than IgG, and by day five of illness most dengue cases have detectable IgM antibody. Moreover, specific IgM antibody disappears 60 to 90 days after the infection, and so people who are IgM-positive are known to have experienced a dengue infection sometime within the preceding three months (*12*).

In general, the IgM-capture enzyme-linked immunosorbent assay (MAC-ELISA) is useful in both endemic and nonendemic areas. In nonendemic areas it can be used in random, population-based serosurveys with the certainty that any positives detected represent recent dengue infections. Thus, a simple MAC-ELISA serosurvey can quickly determine the extent and distribution of recent dengue transmission. In endemic areas it can be used to screen large numbers of serum specimens with relatively little effort. It is especially useful for screening hospitalized patients who are generally admitted late in the course of their illness, after detectable IgM is already present in the blood.

ENTOMOLOGIC SURVEILLANCE

Entomologic surveillance, which deals with dengue's mosquito vectors, requires knowledge of the species present, species associations, species distributions, the types and productivity of larval habitats, seasonal changes in population densities, and behavior of the principal vector involved. Once such information is available about a permissive area (where *A. aegypti* is present), constant surveillance for the mosquitoes is not necessary unless densities are very low or an active control program is under way. However, periodic larval surveys and tests for insecticide susceptibility should be carried out to determine changes in the principal vector species' distribution, larval ecology, and insecticide susceptibility.

Unless mosquito population densities are exceptionally low (with a house index of 5% or less), entomologic surveillance has little or no predictive value for epidemic transmission. However, entomologic surveillance can be employed to provide useful information on how to control *A. aegypti* in times of epidemic transmission. For this reason, detailed larval surveys should be conducted in all major cities of a permissive country to identify each city's potential problem areas, principal larval habitats, and most productive larval habitats. These data can be computerized to immediately provide detailed information about the mosquito population's ecology in the area at risk. They can also be used to formulate the most effective emergency control methods for any particular situation.

In areas where *A. aegypti* has been

eradicated, ovitrap and periodic larval surveys should be used for routine entomologic surveillance to detect reintroduced mosquitoes. Both types of surveys should give priority to areas where introductions are most likely—such as ports, airports, and used tire depots.

CONCLUDING REMARKS

In summary, several types of dengue and DHF/DSS surveillance should be conducted. The aim of active virologic surveillance, the most important element, is to monitor dengue transmission, giving emphasis to periods of sporadic or silent transmission, so as to quickly detect introduction of new virus strains or serotypes. Other important components are surveillance for increased fever activity and for viral syndromes with fatal outcomes.

Individually, none of these components is necessarily very sensitive, but collectively the three together provide the most sensitive data obtainable for predicting epidemic dengue. Furthermore, when used in conjunction with entomologic data they provide the basis for action by a rapid-response emergency vector control unit seeking to control an incipient epidemic before it spreads.

It must be emphasized that effective surveillance for dengue and DHF/DSS is not possible without a diagnostic laboratory that can perform serologic and virologic diagnostic tests that are both rapid and sensitive. This is a major problem in many dengue-endemic countries.

Another major problem in the Americas is widespread apathy about dengue/DHF/DSS among people including government officials, health officials, and private physicians. As things stand now, it is difficult to convince health officials to think about epidemic dengue before an outbreak actually occurs; and, as a result, it is impossible to obtain their support for developing a prevention and control program. Thus, one of the biggest problems in the Americas is education of the medical community. For without better understanding of the disease and increased awareness of the potential for devastating dengue/DHF/DSS epidemics, effective surveillance and therefore effective prevention and control programs cannot occur.

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PAHEF to Give Public Health Literature Award

The Pan American Health and Education Foundation (PAHEF), an independent nonprofit foundation, plans to reactivate the Fred L. Soper Award, which will be given to recognize significant contributions to the literature on health in Latin America and the Caribbean. The award, which was established several years ago but has never been given, is made possible by donations in memory of Dr. Fred L. Soper, Director of PAHO from 1947 to 1959, to honor his outstanding contributions to health in the Americas. PAHEF will administer the award fund.

To be eligible, a published work must pertain to the broad field of public health, with special relevance to the Americas. It may be a report, an analysis of new data, a new approach to analyzing available data, or a review paper. Preference will be given to studies involving more than one discipline and to papers related to infectious disease, a life-long concern of Dr. Soper. Papers that have been published or are suitable for publication in the *Boletín de la OSP* and/or the *Bulletin of PAHO* will be given priority, but papers of merit published in other journals readily available to public health personnel in the Americas will also be eligible.

The winner(s) of the award each year will be nominated by an Awards Committee and will be approved by the PAHEF Board of Trustees. The award will take the form of a certificate and a monetary prize. If the Committee and the Board agree that no contribution is worthy of the award in a particular year, it may be withheld. The duration of the fund will be indefinite.