The water that collects in discarded tires is an ideal -- and all too convenient -- breeding site for dengue vectors. Tire dumps like this one are proliferating globally, especially in urban areas, as automobile use rises. (Photo courtesy Sean Healy)

With 2.5 billion people at risk and estimated cases in the tens of millions, dengue is considered by many to be the second most important mosquito-borne disease in the world (surpassed only by malaria). Classic dengue and its more lethal form, dengue hemorrhagic fever (DHF), now circle the world with endemic illness and continuing threats of epidemics.

Dengue is very much an environmental disease, affecting urban and peri-urban settlements of more than 100 countries. It is characterized by seasonal outbreaks of illness carried by mosquitoes that thrive in household containers which collect water (such as flowerpots and washtubs) and in the detritus of human consumption, such as bottles, tin cans, and old tires. Children, especially in Asia, are most frequently and seriously affected by the severe form of the infection, DHF.

Mosquito control is the only effective approach to prevention, although effective case management will reduce mortality. Insecticides targetted at larval mosquitoes are effective tools, but resistance of mosquitoes to affordable and environmentally safe chemicals as well as declining political will and infrastructure have all but eliminated this approach in most countries. Vaccines are in the pipeline, but a system which could deliver them to half the world's population is probably at least a decade away. Community action—to protect containers from becoming havens for mosquito breeding and to dispose of empty containers and trash, along with surveillance and personal protection—is the best hope for transmission risk reduction.

ENVIRONMENTAL HEALTH PROJECT

Capsule Report

Number 2, January 1999

Dengue Fever: An Environmental Plague for the New Millennium?

Dengue Returns to the Americas

Although sporadic outbreaks occurred around the Caribbean in the 1960s and 1970s, intensive efforts to control *Aedes aegypti* mosquitoes rendered most North and South American countries free of major outbreaks of epidemic dengue fever for more than 50 years. In 1977, however, the spell was broken when Cuba was struck by an epidemic of classic dengue fever. While there were no recorded deaths during the outbreak, more than 500,000 people suffered the classic symptoms, including fever, malaise, joint pains, headaches, eye pain, and sporadic rashes. The outbreak, which largely affected Santiago, Cuba's second largest city, was determined to be caused by DEN 1, one of four known serotypes of dengue virus. The epidemic burned itself out in a few months, and only scattered cases were observed by the local medical authorities for the next three years.

In the spring and summer of 1981, Havana physicians started reporting outbreaks of a far more serious illness, with classic symptoms and, in addition, hemorrhages from the nose and mouth, bleeding under the skin, and occasional occurrences of shock and death. With this major announcement, dengue hemorrhagic fever (DHF) entered the Western Hemisphere. A logistics nightmare followed; thousands of people, ill from other causes, were summarily discharged from hospitals to make way for the rapidly growing number of dengue cases. During the week of highest incidence (June 30-July 6), hospital admissions for dengue averaged more than 9,000 per day. By early October, 344,000 cases of dengue, including an estimated 10,000 cases with hemorrhagic or shock symptoms, had been reported; 116,000 people were admitted to hospitals and treated. Due to the rapid response of the Cuban medical system, the case fatality rate was low: only 158 people died. Two-thirds of the dead were children.

The 1981 epidemic was caused by DEN 2, and it was speculated that the 1977 dengue epidemic had predisposed the population to DHF, which made the second outbreak more severe. The Cuban epidemics were the first indications that DHF was spreading throughout the Western Hemisphere. The number of cases in the 1980s and 1990s has risen alarmingly, particularly in Central and South America.

Dengue and DHF as Diseases

The symptoms of dengue and DHF begin in much the same way, with a fever of sudden onset, malaise, headache, and pain in the muscles and joints. The severe joint pains associated with dengue led to the name "breakbone fever," which was in common use in the earlier part of the century. Rashes, nausea, vomiting, and a very characteristic pain behind the eyes are also common dengue symptoms. A great mimic of other diseases, dengue is often mistaken for malaria, influenza, measles, hemorraghic leptospirosis, and typhoid. Specific immunological tests for dengue exist but are often unavailable within the five- to seven-day course of the infection. In the majority of cases, the symptoms of classic dengue fever resolve themselves and leave the patient weakened but with no permanent effects.

The appearance of "petechial" hemorrhages, or small black and blue areas just under the skin, may be the first sign of the more serious DHF form of the disease. Occurring in 5 to 30% of cases, the tiny hemorrhages may be accompanied by bleeding from the nose and gums, with signs of blood in the urine and the stool. The external or internal bleeding is associated with a diminution in circulating platelets that initiate blood clotting.

Loss of blood and serum leakage from the blood vessels may result in lowered blood pressure and may lead to clinical shock. It is this dengue shock syndrome (DSS) which is responsible for the majority of DHF deaths, with some 70% of fatal reactions occurring in young children (ages 0-6). In those cases where DHF is recognized as such, medical science can offer good supportive care, such as intravenous fluid replacement, to prevent shock and the risk of secondary health problems from claiming the victim. When cases come to a prepared medical care delivery system one at a time, early diagnosis, good medical practice, and supportive therapy usually result in a favorable outcome. When outbreaks are forced upon an unprepared and overburdened health care system, the results can be catastrophic. For those fortunate enough to receive timely infusions of intravenous fluids, survival is high (around 99%). For a child in a village, DHF may be a death sentence.

The Biology of Dengue and DHF

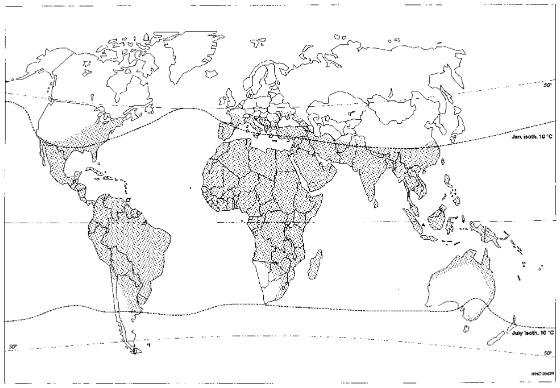
Exactly what happens to convert classic dengue to DHF is not completely understood, but risk factors that influence severity of illness include the virus strain and the immune status, age, and genetic background of the host. There are four known virus serotypes (DEN 1, DEN 2, DEN 3, and DEN 4). When a person has had classic dengue (i.e., infection by one serotype), a second infection at a later time by another serotype seems to increase the likelihood of suffering DHF. This theory, however, does not explain the small but persistent number of DHF cases that have been observed in patients with no known history of previous dengue infection. In addition, the presence of antibodies to the four dengue serotypes among people with no history of infection indicates that the majority of cases may be asymptomatic, especially in children. As mentioned above, dengue is often mistaken for other febrile maladies. Thus, there is still uncertainty surrounding the exact mechanisms through which dengue becomes DHF. But the spread of the disease in the world is clear; dengue and DHF are serious threats.

Dengue Vaccines: The Current Status

The search for a dengue vaccine began in 1944, shortly after isolation of the virus. Throughout the 1970s and 1980s, U.S. military organizations and WHO-sponsored research laboratories conducted an intensive search for a "tetravalent" vaccine—one that could be used against all four strains with a single immunization. By simultaneous immunization to all four dengue serotypes, theoretically it would be possible to eliminate the threat of DHF in the vaccinated person. Conversely, any vaccine that is *not* effective against all four serotypes might only increase the likelihood of a DHF epidemic.

Currently, medical scientists are working on several promising candidate vaccines. While they are in advanced stages of clinical testing, an approved and clinically useful vaccine that can confer immunity to infection is not yet available. At present, widespread access to protective vaccines appears to be five to ten years away.

Approximate Actual and Potential Distribution of *Aedes aegypti* *



Source: WHO. 1997. *Dengue haemorrhagic fever* (2nd edition).

* The band between the 10°C isotherms represents potential distribution.

Dengue's Emergence as a Global Threat

Current scientific consensus is that dengue evolved from an infection of forest primates in the Malay Peninsula and spread along the early routes of commerce. The method of transport of the vector was probably by eggs deposited on the inside of water casks of sailing vessels. By the beginning of the 19th century, classic dengue was well known in the port cities of Africa, Asia, and the Americas. Even allowing for the lack of precision in diagnosis, epidemics that were likely due to dengue virus had broken out in China, Indonesia, Egypt, Panama, Mexico, Myanmar, Zanzibar, and Arabia. The success of dengue virus in infecting tens of millions of people each year is largely attributable to the ability of the vector to thrive in a variety of habitats. Within the United States, there were outbreaks in Philadelphia (1780) and in a broad band through the South, from the Carolinas to Texas (1850).

Sporadic reports of a hemorrhagic form of dengue appear in official and personal communications during the Philadelphia epidemic of 1780. Prior to World War II, hemorrhagic dengue fevers with shock and fatalities were reported from outbreaks in Australia, Lebanon, Taiwan, and Greece. While the number of hemorrhagic cases was significant in these outbreaks, they were considered to be anomalous manifestations rather than a new public health threat.

The ecologic and demographic changes that followed World War II, coupled with a new international mobility made possible by air travel, ushered in a global pandemic of dengue and DHF that rapidly spread from southeast Asia to the Indian subcontinent, to Australia and Latin America.

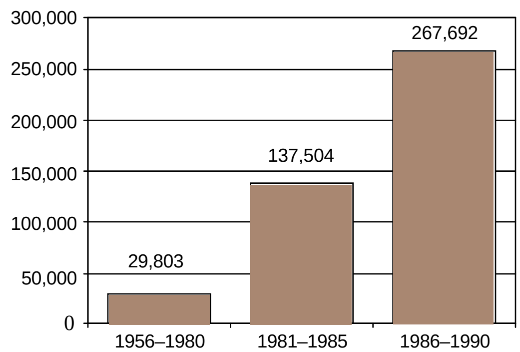
The rapidity with which dengue can establish itself in a new geographic area is best illustrated by the history of Latin America. During the postwar years (1946–1963), there were no recorded dengue epidemics in the Americas. Dengue experience was predominantly limited to periodic outbreaks of the classic non-lethal form of the disease. The disease had all but disappeared from the New World during the urban yellow fever eradication campaigns of the 1940s and 50s, since most efforts were directed toward the elimination of the *Aedes aegypti* mosquito which transmits dengue as well as urban yellow fever. Discontinuation of the eradication programs in the 1970s, however, was followed by a rapid repopulation of the region by *Ae. aegypti*. The most important disease that followed was not urban yellow fever but dengue.

By 1997, dengue was endemic in 42 American nations, and DHF cases were recorded in 24. The hemisphere is now host to all four serotypes, and recent epidemics have been recorded in Venezuela (1990), Colombia (1990), French Guiana (1991), Brazil (1992, 1994, 1996), Puerto Rico and Nicaragua (1994), Central America and Mexico (1995), and Cuba (1997).

There is little disagreement about the causes of the spread of dengue and DHF throughout the world. In 1994, Gubler and Trent summarized the major factors.

- Following a 10-year absence due to a nearly successful eradication program,

Recorded Cases of Dengue Hemorrhagic Fever Worldwide between 1956 and 1990



Source: Richard L. Guerrant. 1997. *Am J Trop Med Hyg.* 59(1).

Ae. aegypti was re-established in the Americas. More than 300 million people with little or no immunity to dengue were exposed to vectors capable of transmitting the virus.

- Most countries in which dengue is transmitted have weak mosquito control or disease monitoring infrastructures.
- Global trends in urbanization, substandard housing, intentional or unintentional water storage patterns, and population growth have created environments that favor transmission of dengue.

Another factor is that, from 1983 to 1994, the number of international airline passengers doubled, from 20 to 40 million (Gubler 1996). This trend greatly enhances the opportunities for international spread of dengue and other diseases.

The Current Situation

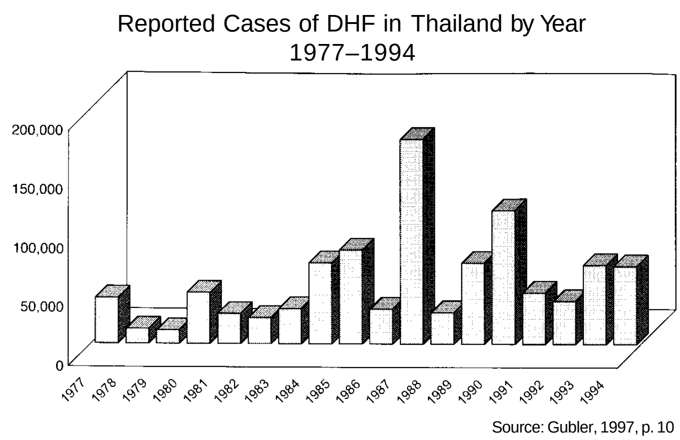
The global dengue pandemic has intensified during the past two decades until it now affects all continents except Antarctica. Dengue epidemics are increasing in frequency as well as in the degree of illness they produce. The conditions responsible for dengue's spread continue to mount. Many countries in Southeast Asia, the Pacific, and Latin America experienced unusually high levels of dengue/dengue hemorrhagic fever activity in the summer of 1998. Although there is often a seasonal increase in dengue, the level of activity in 1998 was considerably higher than in previous years. The following regional synopses are from various sources, including CDC, PAHO, and WHO.

Africa

All four dengue serotypes have been reported from Africa each year since 1980. The principal vector is *Ae. aegypti*. In 18 of Africa's 46 countries, outbreaks of classic dengue are commonplace, and hemorrhagic symptoms are seen on a regular basis. However, DHF is virtually unknown in epidemic form. The actual number of cases is unclear because of limited diagnostic capabilities and sporadic reporting. In general, dengue surveillance and reporting are given low priority by most African countries because DHF epidemics do not occur, and there are few resources to provide prevention services.

Asia and the Pacific

Since the end of World War II, 38 of 46 countries on the continent of Asia and the islands of the Pacific have experienced dengue or DHF epidemics. All four serotypes are present in virtually every country of the region, and recent epidemics of DHF have occurred in India, Sri Lanka, Pakistan, Myanmar, China, Thailand, Indonesia, the Philippines, the Maldives, Cambodia, Laos, Vietnam, Malaysia, Singapore, and many islands of the South Pacific.



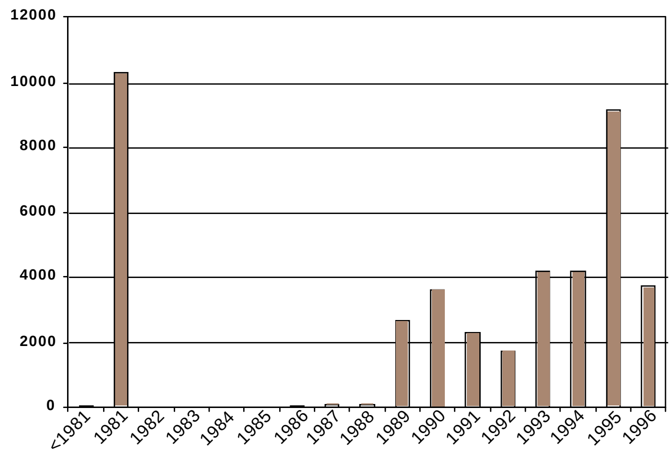
DHF is a leading cause of hospitalization and death of children in many countries of Asia, and the Pacific nations have the world's highest infection risk, with case fatality rates exceeding 13% in some areas (Gubler 1997). Once considered urban diseases, dengue and DHF are now spreading to the rural areas of the Asia/Pacific region.

Recognition that DHF is a major public health problem has encouraged the governments of the region to undertake prevention and control programs. WHO has been supportive of these efforts and has been a strong advocate for emergency contingency planning. Reductions in case fatality rates in some of the most heavily endemic areas demonstrate that prevention and treatment programs can be quite effective.

The Americas

As mentioned above, dengue has rapidly re-established itself in the Americas after having all but disappeared. In 1996, a total of 276,758 cases of dengue, including 4,520 cases of DHF, were reported from 41 countries. Provisional figures for 1998 from 19 countries in Central and South America report 532,469 cases of dengue and DHF, 80% of them in Brazil. Provisional reporting of DHF cases in 1998 is 9,054, the bulk of which are from Colombia and Venezuela.

Cases of Dengue Hemorrhagic Fever in the Americas, 1981–1996*



Source: WHO

* Provisional figure for 1996

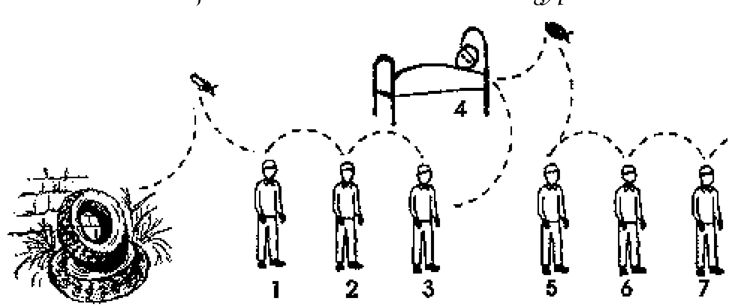
Alarming increases in *Ae. aegypti* populations, rapid urbanization, and the proliferation of slums around most of Latin America's cities have presented an environment of trash and containers ideal for *Aedes* breeding. Importation of *Ae. albopictus* has followed in the wake of brisk international trade in used automobile tires.

A PAHO survey indicates that the annual cost of dengue control activities in the American region may now exceed $200 million. This figure includes costs incurred by 23 Latin American countries in 1995 but does not include U.S. expenditures to keep dengue at bay. In 1997, a PAHO task force began work on a five-stage regional strategy which includes chemical vector control, surveillance, public education, and environmental management. Under the strategy, approximately $1.6 million per year will be allocated, a modest investment if it lowers the risk of epidemic dengue and DHF in the hemisphere.

The Mosquito

The role of *Aedes* mosquitoes in the transmission of dengue fever has been known since 1903. By 1926, investigations had incriminated both *Ae. aegypti* and *Ae. albopictus* as vectors of the disease. The mosquito becomes infected with the virus as she takes a blood meal from an infected host. The virus replicates in various tissues of the female mosquito and after 10 to 12 days, the mosquito passes along the dengue virus to her new hosts when she bites again. Blood provides proteins essential for the development of viable eggs; therefore, only the female mosquito bites and is involved in dengue transmission, as is the case with other mosquito-borne diseases such as malaria and Japanese encephalitis.

Adult female mosquitoes lay their eggs singly on the damp walls of containers, such as bottles, cans, water cisterns, and even natural containers (the axils of plants). *Ae. aegypti* prefer clean water as opposed to that contaminated with organic debris. Eggs may hatch shortly after being submerged when rain or other water fills containers; this may occur days, weeks, or even months after the eggs are laid. It may take 6-10 days for larvae to develop into adults, depending on temperature. The major factors that control *Ae. aegypti* populations are weather and the presence of natural and artificial containers for breeding. Temperature and rainfall patterns can give a marked seasonality to the vector and to dengue transmission.



Source: WHO. Preventing Dengue and Dengue Hemorrhagic Fever.

Ae. albopictus, a secondary vector, is an Asian mosquito, but during the past 15 years, it has been successfully introduced and established in Latin America, Africa, the South Pacific, and the United States. Its preferred habitat is in the forest, and its food, wild animals. Extremely adaptable, *Ae. albopictus* has become urbanized and is now attracted to humans as a source of food. Cold-tolerant strains of the mosquito are able to survive the winters of northern China and even Canada, while tropical strains are being broadly distributed (e.g., into South America).

Economics of Disease vs. Control

Estimates of the cost of disease are difficult to obtain because they may (or may not) include the value of lost work, transportation for treatment, medicine and even the loss of income and productivity due to fatal illness in a wage earner. With increased competition for financial and technical resources, disease control programs must justify their costs in light of the financial burden of disease as well as in human suffering.

A 1995 study from Thailand analyzed social and economic factors surrounding 184 cases of DHF in the previous year (Sornmani *et al.*). It considered the treatment-seeking costs to the family, hospitalization and treatment expenses, and the cost of lost work for both the patient and caretakers. Even the funeral costs and permanent economic loss of wage earners were calculated. Morbidity costs ranged between $157 and $198 per case, depending on age. Mortality costs, including funeral expenses and 50 years of lost income, were in excess of $120,000 per fatal case.

The investigators went on to estimate the costs incurred in 1994 for all programs to control and prevent dengue. Combined expenditures of the Ministry of Public Health, the City of Bangkok, and the provincial governments came to $4.9 million. When the treatment cost of all 15,688 DHF patients was added to the public expenditures for prevention and control, the total came to $13.4 million, over half of which was treatment costs paid by families of patients. That calculation does not include lost work years. In contrast, based on the unit costs described in the paragraph above, the morbidity and mortality statistics of DHF, including the value of lost work for patients and caregivers as well as other treatment-seeking costs, the study's conservative estimate places the annual financial burden to the nation at $31.5 million, even in a low prevalence year. In high years, the figure would be closer to $51.5 million.

A very recent study by a group of CDC investigators summarizes more than a decade of experience with dengue in Puerto Rico from the perspective of economic impact (Meltzer *et al.* 1998). Their approach examines the disability-adjusted life years (DALYs) lost as a result of illness or death from dengue and DHF. Their analyses show a steady increase in lost work and productivity due to the two diseases, averaging 658 DALYs per one million people per year over the past 11 years. Although the mean income of the most affected groups is difficult to determine, the economic losses due to dengue and DHF are believed to be of the same order of magnitude as those from immunizable childhood diseases (polio, measles, whooping cough, tetanus), or from meningitis, hepatitis, or malaria.

What Can Be Done to Reduce the Threat of Dengue and DHF?

Dengue will continue to be a growing problem in tropical and subtropical regions of the world unless more effective measures are taken to control the main vector, *Ae. aegypti*, in these and other countries/areas. Essential elements of an effective program are integrated mosquito control with community and intersectoral involvement, surveillance, disease case management, emergency preparedness, capacity building and training, and applied research.

Integrated Mosquito Control and Community Involvement

- *Community participation to reduce the number of mosquitoes (i.e., by reducing the number of breeding sites). Ae. aegypti* mosquitoes breed in flowerpots, washtubs, drink containers, uncovered household water containers, old tires, etc. In other words, there are many potential breeding sites, particularly around homes and human settlements. To reduce the number of breeding sites, community members of all ages need to be informed of the role they can play.

Some of the containers, e.g., washtubs or household water containers, cannot be done away with, but they can be protected or dealt with in a manner which prevents them from being suitable for mosquito breeding. A recent program in Escuintla, Guatemala, emphasized scrubbing out washtubs and covering them with cloths. Other breeding sites (bottles, trash) can be eliminated, if convenient and economical solid waste or recycling programs are introduced. Encouraging and bringing about changes in household practices requires a carefully planned information program.

Community participation has to be fostered and built up intentionally, through focus group meetings and enlistment of community leaders. Finding out what the community wants and creating community awareness of the program are central to the process. Most communities clearly desire a reduction in disease, but don't know how the local environmental conditions, household practices, and individual behaviors tie in with susceptibility and transmission. Community approaches are most likely to be self-sustaining in the long run. And dengue control requires a long-term commitment.

- *Educational efforts to reduce contact between humans and* Ae. aegypti *mosquitoes.* Reducing human/vector contact includes informing those who manage households about the biting patterns of the vector. Dengue is passed to humans by the *Ae. aegypti* mosquito, which is an indoor and outdoor biting insect whose favorite times of biting are early morning and late afternoon. People who are resting indoors at those times are more likely to be bitten than those outdoors or active. Thus, small children, those who are ill, and anyone resting at those times are candidates for bites by the mosquito. Reducing the absolute number of mosquitoes is one sure approach to reducing dengue. Reducing the chances of being bitten is another. Household screening and personal protection such as mosquito nets for those already infected, mosquito coils, and residual spraying are important steps, particularly for those most vulnerable (the young and the ill).

- *Interagency coordination.* Integrated dengue control calls for management of a campaign with coordination of several (usually public) agencies: those who deal with urban planning, water and sewer services, solid waste services, household sanitary inspections, health educators and social promoters (using public media, school curriculum, community health programs or mother's groups, etc.), and clinic or health facility staff.

Emergency Preparedness

- *Hospital and facility plans.* Planning for an epidemic of dengue is very difficult in the "heat of the battle." In Cuba in 1981, hospitals were emptied out to receive dengue patients. This is not a practice that other countries would be able to emulate, or would care to attempt. Making contingency plans for how to handle a deluge of dengue cases can reduce confusion and save lives. Such planning is best carried out in workshops of decision makers and representatives of institutions that would be responsible for care of dengue patients.

- *Stockpiling the right equipment and supplies.* Stockpiling intravenous solutions and other critical care commodities can make the difference between a very low case fatality rate and a higher one. The onset of dengue shock syndrome and DHF requires fast action with appropriate fluids.

Institutional Capacity Building and Training

- *Improving diagnosis.* Dengue fever has symptoms similar to several other diseases (malaria, influenza, measles, and typhoid), which makes it difficult to diagnose. Doctors and other health care providers often don't even suspect it as a candidate disease. Identification of dengue is possible by blood test, although in many cases, the disease resolves itself even without medical care. Detection of dengue by physicians and other health care providers is crucial at the clinic level both for case management and for national surveillance and reporting.

WHO and PAHO have developed case management protocols for dengue and DHF. In-service training for health care staff in endemic countries should be a priority.

Vector Surveillance and Epidemiologic Reporting

- *Development of regional laboratories to carry out surveillance activities.* Effective dengue surveillance depends upon the continuous monitoring of three inter-related parameters:
  - Active epidemiologic tracking of dengue and DHF cases by location, age, season, and geographic setting
  - Entomologic monitoring of vector mosquito populations to assess the continued efficacy of control measures
  - Microbiologic assessment of viruses in people with respect to serotype and circulation in the environment.

Appropriate surveillance is a technical undertaking which must be conducted with precision and requires laboratory support. All affected countries should have basic diagnostic capabilities. Beyond that, the development of regional reference facilities with linkages to CDC, U.S. military research centers, or WHO collaborating laboratories, for example, would be an appropriate investment with high payoff in regional contingency planning, disease containment, and vector control.

Applied Research and Policy Issues to Address

- *Improved techniques in assessing the virus serotypes in humans and mosquitoes.*
- *Continued efforts toward development of a possible vaccine which can protect humans (even the very young) from all four types of dengue virus.*
- *Examination of the whole range of issues related to importing and recycling tires because of their role as vector breeding places.*
- *Investigation of the potential for involving multiple sectors and community members in control efforts, especially those associated with appropriate and safe water use.*

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