The Emergence of Dengue Fever
in the United States
and its Public Health Implications

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By
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CHAPTER ONE

INTRODUCTION

Dengue fever, an acute, arthropod-borne viral disease, is caused in humans by a virus transmitted by a mosquito. Human beings form the main reservoir of this infectious disease. The disease is characterized by sudden onset, severe symptoms, and short duration. Dengue fever and dengue hemorrhagic fever (caused by a secondary infection with a dengue virus serotype), especially prevalent in tropical and subtropical regions, affect more than 100 million people annually. Because of its wide distribution and devastating effects on vast numbers of people, dengue is considered by researchers to be one of the most important and serious viral infections spread by mosquitoes (Rosen et al., 1983:1108). Awareness of this potentially deadly disease, however, is masked by "more popular" diseases, such as malaria and schistosomiasis. Dengue's rate and pattern of transmission are particularly interesting and require geographical analysis.

The infectious cycle of dengue fever is perpetuated because of the nature of the disease. Explosive outbreaks usually occur in impoverished regions where people live in overcrowded and unsanitary conditions. These regions usually lack resources necessary for adequate mosquito control and public health education. Because of the high

morbidity and mortality associated with severe dengue fever outbreaks, affected regions are left socially and economically crippled and must rely on government or outside resources for community reconstruction.

This profile, unfortunately, fits most developing regions in the world's tropics. Until recently, dengue was considered solely a tropical disease because of the climatic conditions thought necessary to sustain mosquito populations. Unprecedented mobility of human populations to and from the tropics, however, has aided in transporting the virus to non-tropical regions, such as the United States. Moreover, international trade has provided a vehicle for dengue's mosquito vector to colonize in regions far from its origins.

The United States is increasingly subject to dengue outbreaks due to the following: (1) vector populations are now established in twenty-three states; (2) imported cases of dengue fever are rising in the U.S.; (3) national participation in high volume importation of commodities and people from dengue-infested and vector-infested regions; and, (4) geographic proximity of the United States to Mexico, Central and South America, and the Caribbean, where continuous and simultaneous circulation of multiple dengue virus serotypes exist. These factors suggest the potential risk of dengue fever outbreaks in the United States, and should stimulate research into the etiology, diffusion, and

control of dengue fever.

VECTORED TRANSMISSIBLE DISEASE SYSTEMS

In a vectored transmissible disease system there are three factors to consider: the agent, vector, and host. Disease usually occurs in humans when all three factors co-exist in a region, survival requirements of each are fulfilled, and communication between them transpires. It is critical, therefore, to study the interrelationship of these factors and their collective contribution to the disease cycle.

The disease-causing agent for dengue fever is a virus. This virus is protected by an envelope layer (togavirus) and can only survive parasitically. It lacks an essential nucleic acid (RNA or DNA), and therefore depends upon another organism to supplement this genetic material for protein synthesis and reproduction.

The vector in this transmissible disease system is the mosquito, an arthropod (joint-legged animal) that serves two functions: it provides either DNA or RNA for viral replication and transmits the agent between susceptible hosts. The agent-vector relationship is highly specific and must satisfy many biological conditions to ensure each organism's survival.

The host is an organism infected by a disease agent. Although a monkey reservoir of dengue fever is maintained in

forested areas of Southeast Asia, humans will be studied as the primary reservoir of infection.

DENGUE FEVER TRANSMISSION SYSTEM AS PROTOTYPE FOR OTHER VECTORED HUMAN DISEASES

Dengue fever is investigated in this thesis because it exhibits all functional components that interplay in a disease system. The dengue virus, the mosquito vector, and the human host are solidly linked in most tropical, subtropical, and some temperate regions. Although dengue may develop naturally in a region, human migration contributes greatly to the global spread of dengue. In addition, the virus and vector's considerable adaptability to changing conditions strengthens the linkage to their environment and allows for continued survival.

Gesler (1991) examines important aspects of system dynamics and their potential to form positive and negative feedback loops. A system, according to Gesler, is comprised of elements, links, and interactions. When elements in a system reinforce each other, a positive feedback loop is produced and the system is maintained. Conversely, when system elements weaken one another, a negative feedback loop is formed and the system is weakened.

Relating this model to the structure of the dengue transmission system, linkages between the virus, vector, and host, and between each element and its environment, form the

disease system. For the dengue virus to survive and replicate, it must infect a susceptible host, human or mosquito. A mosquito vector, therefore, must enter the chain of transmission, become infected, and subsequently, infect a human. When these three points of communication are maintained, the disease elements reinforce one another (positive feedback) and disease is the potential outcome.

Conversely, control of dengue outbreaks requires identifying weaker links in the transmission chain to counteract the disease cycle. Theoretically, the disease then will not occur. If certain ecological requirements of the vector are not satisfied in a region, for example, the vector cannot survive to transmit the virus to humans. Inadequate ecological environments, therefore, depress vector survival (negative feedback), and the disease cycle terminates.

It is important to know what factors propel a disease cycle, including the elements of the system and factors that influence them. Understanding the intricate relationships between virus, vector, and host, and their respective environments, therefore, is required to halt the advancement of dengue in a region.

THE ETIOLOGY OF DENGUE FEVER AND SECONDARY INFECTIONS

Dengue fever is caused by an infection with one of four dengue virus serotypes: dengue-1 - or den-1, den-2,

den-3, and den-4. Having been infected with one of the four serotypes, an individual typically develops an immunity to that serotype. Subsequent infection with one of the other three related serotypes, however, can lead to more severe forms of the disease known as dengue hemorrhagic fever (DHF) or dengue shock syndrome (DSS) (Jacobs, 1991:828).

Dengue infection initially results in a relatively mild illness. Symptoms include fever, rash, chills, headache, anorexia, nausea, vomiting, and severe joint and muscle pain (the latter being associated with dengue's alias, "breakbone fever").

Subsequent infection with dengue, however, can lead to more severe manifestations of the disease. Symptoms include bleeding gums, gastrointestinal bleeding, abdominal pain, high fever, and can result in shock and death. In fact, DHF and DSS are major causes of morbidity and mortality in children of the tropical world (CDC, 1988:1781). Treatment for dengue fever requires urgent rehydration therapy, and hospitalization for severe DHF and DSS (Lange, 1992:1161).

MOSQUITO VECTORS OF DENGUE

Two species of mosquito transmit dengue from one host to another: *Aedes aegypti* (Figure 1) and *Aedes albopictus* (Figure 2). The geographic distribution of both mosquitoes, expanding in tropical and temperate regions,

covers a wide area, including the United States.

A. aegypti, thought to have originated in Africa, was introduced to the U.S. during the early voyages to the Americas (Christophers, 1960:42). *A. albopictus*, which has now replaced *A. aegypti* in many southern and southeastern states as the principle pest mosquito, was first introduced to the United States in 1985 when a shipload of old tires from Japan arrived in Houston, Texas. Since then, the vector has appeared in twenty-three states (Lesser, 1992:9). Given the environmental conditions necessary for its survival, its persistence is likely to continue and even expand.

Figure 1. *Aedes aegypti* (pictured above right)

Figure 2. *Aedes albopictus*. The Asian Tiger Mosquito.

DENGUE WORLDWIDE

Isolated outbreaks of dengue fever have occurred worldwide since the late 1700s, with increased incidence in subsequent decades (see CHAPTER TWO - HISTORICAL MOVEMENT OF DENGUE FEVER). However, the killer form of the disease, DHF, has only been widespread throughout the tropics for the past few decades. Puerto Rico in 1951 and the Philippines in 1953 reported the first outbreaks (Meade et al., 1988:86 and CDC, 1987b:448). The disease has since become endemic in those places and in surrounding countries, as well as in parts of Mexico, Central and South America, and the Caribbean (CDC, 1989:741).

Countries such as the United States, however, have remained virtually isolated from the effects of dengue fever for several reasons: (1) geographic obstacles, such as oceans, mountains, or distance; (2) the absence of specific climatic conditions necessary for the survival of the vector; and, (3) adequate mosquito control programs.

Increased international trade, tourism, and immigration from tropical regions, however, have enabled the virus and vector to penetrate the geographic barriers that formerly isolated the U.S. from dengue fever. These three dimensions of human activity are mechanisms by which the epidemiology of dengue fever is changing in the United States and worldwide.

OBJECTIVES

The primary focus of the thesis research is to understand the etiology and diffusion (natural and human-intensified) of dengue fever in the United States. An in-depth examination of the history of dengue and its role in forming present distributions, the vector and its survival requirements, and where humans emerge as disease carriers, may reveal weaker links in the chain of dengue transmission. The objective of this thesis is to identify these weaker links as possible intervention points to curb or slow dengue transmission rates in the United States.

Research on dengue fever in tropical and subtropical regions has been on-going. To what extent dengue threatens the public's health in the U.S., however, has yet to be ascertained. Many questions emerge that remain largely unanswered. The most prominent of these are:

(1) What social, economic, and environmental conditions must prevail for dengue to become a threat to the U.S.? Do these conditions already exist in the U.S.? If not, what factors would have to change for dengue to be considered a public health threat? How likely are these changes to develop?

(2) Viewing the U.S. in the adolescent stages of dengue development, what public policies should be implemented to curb further introduction and diffusion of dengue and its vector in the U.S.? How likely is the U.S.

to follow the devastating pattern of epidemics in dengue-regions if these policies are not administered and enforced?

My objectives will be to answer the questions posed above, in addition to the following:

(1) What regions in the U.S. are high at risk for dengue fever outbreaks? What factors predispose these regions to dengue fever?

(2) What regions have a moderate or low risk? What factors are present or absent that grant this relative regional immunity?

This thesis is clearly not an exhaustive investigation of the problem of dengue fever outbreaks. Dengue remains a formidable disease globally. The thesis, however, is an overview of the potential problem of dengue fever in the U.S. It blends many theories, hypotheses, and questions facing researchers today and provides a sound model for further research on dengue fever.

METHODOLOGY

The geographical study of diseases is inherently eclectic. Spatial interactions form the foundation for research, but entomological, medical, social, and epidemiological concepts and methods are employed to fully understand disease processes. By drawing from various disciplines, a more holistic approach is used to identify the physical, cultural, environmental, and biological

interactions that make up a disease system. Understanding the interdependencies among these factors represents a more broad-based survey into the causation and diffusion of diseases.

Landscape epidemiology. Landscape epidemiology forms the bulk of research in this thesis. Using the physical and cultural landscapes to identify disease hazards and ways to control disease occurrence are the main thrusts of this approach. Ecological parameters of a region are identified as determinants of the different types of diseases that can exist.

Vital activities of the mosquito, for example, are intensified when the temperature is warm, and cease when the temperature falls below approximately 17 degrees Celsius (C) (Christophers, 1960:475). To thrive as species and transmit dengue, *A. aegypti* and *A. albopictus* must live in warmer regions. Adding to its ecological diversity, the eggs of *A. albopictus* have the biological potential to overwinter in colder temperatures, so it can transmit dengue in regions with a far broader range of climates. Defining disease environments based on the virus, vector, and host's adaptability to regional influences is the primary contribution of landscape epidemiology.

This approach also requires viewing the landscape as a potential mechanism for disease control. Humans do much to alter the landscape, either by forming barriers that slow

or curb the disease process, or by creating pathways for disease introduction. Opportunities for controlling infectious diseases, therefore, rest in understanding the ramifications when two ecological niches of disease and humans interact.

Terminology and structure. This geographical investigation into the causation and diffusion of dengue fever is a result of the cross-fertilization of many disciplines. Technical terms and concepts, therefore, are briefly explained in the context which they are used.

Chapter Two traces the historical diffusion of dengue fever from the first outbreak in 1789 in Philadelphia to the development of present distributions. The evolution of the DHF and its impact on morbidity and mortality rates of affected regions are also examined.

Survival requirements of dengue's vector are examined in Chapter Three. Several geographical influences limit the distribution of the mosquito vector, and thus the possible diffusion of dengue fever. Three ecologically diverse regions in the United States are defined based on their ability to support vector populations.

International trade, tourism, and immigration are changing the epidemiology of dengue fever to the extent that dengue can no longer be considered solely a disease of tropical and subtropical regions. Chapter Four details important concepts in the human-environmental relationship

and their interconnectedness with dengue introduction and transmission in the U.S.

Chapter Five integrates findings on the history of dengue fever, vector ecology, and human-aided diffusion. Regions in the United States will be defined according to their level of risk for dengue fever outbreaks. A summary of risk assessment was devised to clarify multiple risk factor prevalence in a region and high risk region demarcation. Effective and timely control measures of dengue are also addressed.

MAPPING DISTRIBUTIONS

The most important contributions of medical geography show where health-related phenomena are located on the surface of the earth and explain why they are so distributed (Meade, 1988:6). Maps are powerful tools for displaying phenomena in a spatial context. The dengue transmission system, for example, is perpetuated in a region when various risk factors interact; therefore, mapping these factors is critical to distinguish the topological relationships between them. By identifying spatial links and other geographical and biological associations, causality can be inferred to determine the relative health or disease of a region.

Six original maps in this thesis are used to display elements of the dengue fever transmission system in their

spatial context. The maps will supplement other data to illustrate how and where the disease can be introduced and spread in the United States. Based on these findings, high-risk regions for dengue fever outbreaks will be assessed and possible intervention points discussed.

DATA COLLECTION

Information was obtained from professional journals, books, and personal communications with medical doctors, entomologists, epidemiologists, and other health professionals from various organizations, including the Center for Disease Control (Fort Collins, Colorado and San Juan, Puerto Rico) and state health departments nationwide.

Various on-line systems, such as Nexis/Lexis, InfoTrac, Haystack,¹ Melvyl,² Medline, and U.S. Government Documents (CD-ROM) were used to retrieve publications and their locational status.

¹ California State University, Hayward computerized cataloging system for published material.

² University of California computerized cataloging system for published material.

CHAPTER TWO

HISTORIC SPREAD OF DENGUE FEVER

The history of dengue fever is a kaleidoscope of shifting patterns, distributions, and intensities. The first presumed outbreak of classic dengue fever occurred in Philadelphia in 1780, eighteen years after the yet-to-be-incriminated vector mosquito, *Aedes aegypti*, was first identified in Cairo, Egypt (Siler et al, 1926:9). The Philadelphia outbreak, as described by Rush in 1789, was the first accurate clinical description of true dengue fever (Schlesinger, 1977:9).

Before the "Golden Age of Microbiology" (1857-1914), where specific diseases could be positively linked to their associated pathogens via laboratory testing, descriptions of outbreaks were used to identify dengue fever. This is one of the simplest and least expensive methods available to compare data from the pre-germ theory era.

For two centuries it was believed that the first outbreaks of dengue occurred in 1779 in Batavia (Djakarta), Java and Cairo, Egypt. Contemporary researchers, however, have scrutinized the historical literature on dengue fever and now believe these two outbreaks were probably caused by another virus called chikungunya (Carey, 1971:243). The mistaken identity is attributed to similarities in the nature of outbreaks of both diseases and their location.

OUTBREAKS OF DENGUE FEVER AND CHIKUNGUNYA

Dengue fever is remarkably similar in terms of signs and symptoms, nomenclature, virus type, and mode of transmission to chikungunya (Carey, 1971:244). These similarities made it difficult for researchers to identify dengue virus as the culprit in the Philadelphia outbreak and other historical outbreaks (Figure 3)

(1) **Signs and Symptoms:** Chikungunya outbreaks baffled researchers because the nature of this illness and dengue fever are similar: sudden onset, fever, severe pain in the joints and knees, headaches, rash, and low mortality.

Dissimilarities between the two illnesses are chikungunya sufferers evidenced pain and swelling in the hands, had a long and debilitating convalescent period, and had no subsequent attack.

Conversely, dengue sufferers reported no pain or swelling in the hands, convalescence, although marked by periods of nausea and depression, was relatively rapid, and a subsequent attack was not unforeseen (Wragg in Carey, 1971:253).

(2) **Nomenclature:** Nomenclature used by physicians and victims to describe chikungunya and dengue in the earlier centuries also made it difficult to distinguish between epidemics. Chikungunya was referred to as 'dandy fever' in the West Indies and

southeastern United States because of the limping gait of the victim caused by a debilitating pain in the knees and ankles (Carey, 1971:249). Chikungunya was also called "dengue," "dinga," and "dyenga," in other regions. Present-day dengue was referred to as "seven-day fever," "breakbone fever," and "dengue fever," (adapted from Table I in Carey, 1971:245).

(3) Virus type and transmission: Although serologically unrelated, the structure of the viruses are similar and the mode of transmission is the same. Chikungunya is a group A togavirus (enveloped virus) and is transmitted via mosquito, specifically *Aedes aegypti*. Dengue virus, a group B togavirus, is also transmitted by *Aedes aegypti*. These diseases have similar histories and characteristics, but only virus isolation and retrospective comparisons of symptoms can discern their role in historic epidemics.

Figure 3

LOCATION AND SEASONAL OCCURRENCE OF OUTBREAKS

As the map in Figure 3 illustrates, marked similarities between chikungunya and dengue in location and time of occurrence existed. The 1964 chikungunya outbreak in Vellore, India succeeded a dengue fever outbreak in the same locale, separated by only a few months. Similarly, outbreaks of both diseases in the West Indies and southern United States virtually overlapped in time and space. These episodes are responsible for the indistinguishable nomenclature of the two diseases. Virus isolation in the former outbreaks demonstrated the viruses to be different, thus causing two different diseases.

CLASSIC DENGUE FEVER AS PROLOGUE TO KILLER DENGUE HEMORRHAGIC FEVER

Dengue fever can strike in two forms—a relatively mild form, which is rarely fatal, and the killer hemorrhagic form.³ This has not always been the case, however. Historical accounts of uncomplicated dengue fever rarely, if ever, resulted in death. Up until the mid-1950s, the disease was considered debilitating, but not fatal.

Then an epidemic of an unknown hemorrhagic disease struck Manila, Philippines, in 1953. This outbreak

³ Shock and death frequently accompany the hemorrhagic form, which is referred to as dengue shock syndrome, or DSS.

struck Manila, Philippines, in 1953. This outbreak concurred with the seasonality of classic dengue fever and its mode of transmission (*A. aegypti*). Dengue was never known to be hemorrhagic in nature, so physicians were convinced that it was a new disease and named it Philippine Hemorrhagic Fever. Clinical investigations proved that this "new" hemorrhagic form was indeed dengue fever and two new strains of the dengue virus were isolated in 1956, den-3 and den-4 (Hammon in WHO, 1965:37).

Subsequent outbreaks of this deadly hemorrhagic form struck other regions where classic dengue was endemic, including Malaysia, Vietnam, Singapore, Thailand, and India. One interesting pattern in these outbreaks is that classic dengue was limited to foreigners (even where the hemorrhagic form was endemic) and was more typical in adults than children. The hemorrhagic form of the disease, however, was mostly limited to the aboriginal population, and children were most severely affected (Hammon in WHO, 1965:37).

Many possible explanations for the evolution of this potentially fatal disease have been hypothesized. Patterns of transmission recognized from dengue hemorrhagic fever outbreaks in the past help researchers understand the nature of this deadly disease. The most plausible explanations for the appearance of DHF are related to the immune response of the individual and the mutability of the virus.

IMMUNE RESPONSE AND THE EPIDEMIOLOGY OF DENGUE

For a person acquiring an infection with DHF, one prerequisite is thought to be previous infection with classic dengue fever (Hammon, 1969:164). A hypothesis that seeks to explain this phenomenon is related to the host's immune system. It is believed that repetitive infection with the virus causes the immune system to enhance replication of the virus, a phenomenon known as Antibody-Dependent Enhancement, or ADE. ADE causes the immune system to become hypersensitive to a second infection with a related serotype, resulting in the severe manifestations of the disease-DHF and DSS (Mady et al., 1991:3139).

This hypersensitive immune response may explain why foreigners in a dengue-endemic region only become infected with classic dengue. Without previous exposure to dengue, a person is not susceptible to DHF. Conversely, the natives of a "dengue-region" are deemed a high-risk group for infection with DHF if they have previously been infected with a dengue virus serotype.

Strengthening the hypothesis, individuals with a history of infection with dengue fever during childhood, who traveled back to their homeland where dengue is endemic, have become infected with DHF (Jacobs, 1991:828). According to this hypothesis, initial infection with one of the virus serotypes imparts a degree of immunity to that specific virus serotype for the victim. However, initial infection

also puts the individual at higher risk of infection with a second dengue virus serotype that can lead to the deadly hemorrhagic fever.

Children are mostly affected by DHF or DSS, a major cause of child morbidity and mortality in parts of the tropical world (CDC, 1988:1781). One explanation implicates the immaturity of the child's immune system and its inability to cope with the insults of the disease. This cannot fully explain the higher prevalence among children, however, because adults have also become infected with DHF (Hammon, 1965:56, and Jacobs, 1991:828). Susceptibility to DHF might be explained by a general weakness in the immune system, be it immature or compromised.

Another consideration is that "the biting urge [of the vector] is largely excited by the temperature of the object bitten; therefore, it is very probable that children with highly vascular skins would be especially attractive (Christophers 1960:469)." This increases a child's chances of being bitten simultaneously by virus-infected mosquitoes, thus increasing the risk of contracting DHF.

MUTABILITY OF THE DENGUE VIRUS

Since 1950, global urbanization has been rampant, much of it occurring in the tropical world (Knudsen et al., 1992:1). The myriad social implications of crowded cities, aside, uncontrolled urbanization may well encourage the

growth and mutability of certain viral populations (Langone 1990:65).

When rural inhabitants migrate to cities and introduce their virus type, opportunities exist for the virus to exchange genetic information with other serotypes. This mixing of information can create a novel form of the virus, in the case of the dengue virus, a more virulent one. Furthermore, a substantial population serves as a reservoir of infection for a variety of virus types, and the rate of dengue transmission inevitably increases.

Similarly, as urban settlements encroach previously isolated rural or suburban communities, the dengue virus must adapt to the ecological imbalances created by urbanization (eg., over-crowding, introduction of different dengue virus serotypes). The fact that DHF was first recognized in major population centers suggests that a mutant form of the virus may have evolved (Hammon, 1965:37 and WHO, 1966:21).

INCREASED VIRULENCE OF THE DENGUE VIRUS

Another way the virus is thought to become more virulent is with successive passages through a competent host (an organism capable of sustaining the virus). In the Cuban epidemic in 1981, for example, although health care personnel gained experience and improved administering care to victims during the epidemic, the case fatality rate (the

ratio of the number of fatalities to the total number of cases of dengue fever reported during the epidemic) and the "virulence" index (the ratio of the number of fatal cases to that of DSS cases) increased towards the end of the epidemic. Consecutive passage of the virus through human hosts over a several month-long epidemic is thought to account for the increase in virulence (Kouri, 1981:380).

Increased virulence of the dengue virus is a virological paradox because of the dependency of the virus on its host. A virus can only thrive parasitically. It needs the host to metabolize and replicate. If the virus mutates to a more virulent strain that can potentially kill the host, this contradicts the essence of viral existence, to propagate the microbial population.

CONCLUSION

The emergence of this "new" disease, DHF/DSS, is probably best explained by a combination of the aforementioned factors: (1) hypersensitivity of the host's immune system (2) viral mutation to resist the ecological threats of urbanization, and (3) two mosquito species that can readily harbor and transmit the virus. These factors perpetuate viral maintenance and increased virulence in human populations. Understanding the history of dengue and the destructive outbreaks can contribute to forming public health policies that intervene in the cycle of disease

transmission.

CHAPTER THREE

VECTOR ECOLOGY AND DENGUE FEVER

Vector ecology is an important consideration in determining the potential threat that dengue poses to the public's health in the United States. The two mosquito species proven to be competent vectors of dengue are *Aedes aegypti* and *Aedes albopictus*. These mosquitoes serve as the immediate host for the dengue virus; therefore, factors that affect the host also affect the virus. Understanding the relationship between the vectors and their physical and human-created cultural environment is essential to identifying effective means of intervening in the cycle of dengue transmission.

A. aegypti and *A. albopictus* require specific environmental conditions to live, breed, and therefore, transmit dengue. Latitude, climate, vegetation, water stores, and extent of urbanization are regional variables that affect the viability of these mosquitoes. Identifying biological habitats of the vectors and comparing them to environmental conditions in the United States can determine if favorable conditions exist for mosquito viability.

This evaluation will aid the researcher in projecting the threat of dengue in the United States. The inquiry will have to be at the regional level (e.g., what aggregate of states are most susceptible to dengue

introduction and diffusion?) and national level (e.g., what is the likelihood of dengue becoming a threat to the United States population as a whole?).

HOST FEEDING PATTERNS AND VECTORAL HABITAT

The female mosquito's primary source of food is blood from a vertebrate host, but she will also feed on honey or other fluids containing sugar. The male mosquito's mouthparts, however, are unsuitable for bloodfeeding, so the male mosquito feeds mostly on sweet fluids. The blood meal is required by the female to develop her eggs after fertilization has occurred. Without the blood meal, the eggs are not developed and the mosquito will not oviposit, or lay eggs (Christophers 1960:468). The female mosquito, therefore, is of primary medical importance when considering arboviral transmission and is the basis of discussion for this chapter.

A. aegypti and *A. albopictus* are highly anthropophilic; they aggressively feed on humans for blood. Although both species are considered opportunistic feeders that will feed on a wide variety of hosts, including mammals and birds (Savage et al., 1993:27 and Christophers, 1960:469), their preference for human blood makes people the main reservoir of infection for dengue in rural and urban

environments.⁴

Both species occupy a wide variety of breeding grounds and are adapted to both rural and urban environments. *A. aegypti* and *A. albopictus* breed in almost any receptacle that will hold fresh water. These containers can be natural, such as treeholes and drainage ditches, and artificial, such as bird baths and discarded tires. The latter is especially problematic in urban areas and will be considered in a later chapter.

URBANIZATION

The dynamics of urbanization create many favorable conditions for the proliferation of dengue's mosquito vectors. In urban areas, there is an enormous supply of discarded material that doubles as breeding containers for the mosquitoes. Treeholes, stumps, and marshes are replaced by tin cans, glass jars, and storm drains. Although preferring vegetated areas, the mosquitoes welcome the new accommodations afforded by urbanization and actively breed. Urbanization, therefore, reduces natural breeding sites for the two mosquito populations (Baumgartner, 1988:500), but increases their supply of artificial containers.

⁴ A monkey reservoir is also maintained in forested areas of Southeast Asia (Meade et al., 1988:86).

The concentration of people in urban areas also gives the mosquitoes an ample and continuous supply of blood to feed on. The mosquitoes are human-tolerant, they prefer to feed during the day when people are most active, and will live and breed in residential neighborhoods (Beier et al., 1983:76 and Savage et al., 1993:32). Furthermore, people are migrating to cities at an unprecedented rate, thus supplying nourishment to hungry mosquito populations.

An easily accessible and concentrated human population and the associated solid wastes are inevitable realities of urbanization. They create optimal conditions for the proliferation of the two adaptable mosquito vectors, therefore increasing the diffusion potential of dengue fever in urban areas.

VECTOR COMPETENCE

The successful transmission of a virus to vector (primary host) and from vector to a secondary host depends on a number of factors (Mattingly, 1969:64). For a mosquito species to be considered a competent vector of the dengue virus, the virus must undergo some biological change in the mosquito, such as growth and multiplication without killing itself or the host (Meade et al., 1988:67). The virus, therefore, inherently depends on its immediate host for survival. If this process is successful and the vector contacts and transmit the virus to a susceptible secondary

host (e.g., human host) with regularity, the mosquito is considered to be a biological vector for the dengue virus.

This relationship between virus and vector is very specific and depends on the physiological characteristics of the mosquito species and the virus. These same characteristics also make the two dengue vectors uniquely qualified at various levels of viral infection and transmission. For example, *A. albopictus* has been experimentally proven to be more susceptible to oral infection with the dengue virus than *A. aegypti*, thus increasing its efficacy in the human-vector-human transmission cycle (Rosen et al., 1985:603).

Similarly, *A. aegypti* is known to take multiple blood meals per gonotrophic (egg development) cycle rather than a single blood meal (Scott et al., 1993:98). This is an unusual occurrence for mosquitoes feeding on human blood for oviposition (Christophers, 1960:469) and increases the vectoral capacity of *A. aegypti* to contract the dengue virus or transmit it to humans.

Competency in vertical transmission (viral transmission from infected female to her offspring) of the dengue virus has also been experimentally proven for both species. This is an important consideration because it enables the maintenance of disease transmission in the absence of human reservoirs (Bosio et al., 1992:985). It also increases the infection rate among the mosquito

population, thus raising the risk of transmission when people are introduced into the disease cycle.

Regardless of degrees of efficacy, both species are confirmed vectors of the four dengue virus serotypes (Boromisa et al., 1987:378) and remain a significant health concern for infested regions.

BIOCLIMATIC REGIONS AND GEOGRAPHICAL DISTRIBUTION

Among the factors discussed, climate is the most formidable barrier the mosquitoes must overcome to become established in certain regions. Rainfall, temperature, humidity, and altitude are variables that delimit regions that favor or discourage establishment of mosquito populations. To determine which regions are susceptible to dengue infection (via *A. aegypti* and *A. albopictus*), this section will define microclimates that affect vector abundance, longevity, and distribution.

Regional water stores. There are four stages to mosquito development: egg, larval, pupal, and adult. Oviposition (egg laying) and the larval and pupal stages are aquatic for *A. aegypti* and *A. albopictus* (Horsefall, 1962:631 and 636); therefore, regional water stores are an essential component for mosquito proliferation. Annual rainfall and length of dry season determine the adequacy of water storage in a particular region. An area may have adequate annual rainfall, for example, but if the dry season

is too long, breeding grounds become scarce and eventually evaporate. Conversely, in regions with adequate rainfall and a short dry season, water stores are abundant and mosquito breeding is intensive.

Regional water storage is also determined by adequacy of drainage. Water can accumulate naturally in marshes or pastures, or be a result of human inventions, such as rain gutters, flower pots, or patio furniture. Improperly drained areas exacerbate the problem of mosquito control, which is also reflective of a region's economic status and public health awareness.

Temperature. Air temperature affects mosquito activities, such as breeding, development, and biting. The optimal temperature range for *A. aegypti* feeding and breeding is generally between 25 - 35 C (77 - 95 F). A temperature of 28 C would ensure maximum activity for this species and normal activity slows or ceases below 17 C and above 40 C (Christophers, 1960:474).

Speed of mosquito development also increases as temperature increases up to about 28 degrees C. A mosquito in the larval stage will mature faster to the pupal and adult stages in warmer temperatures, thus swelling mosquito populations.

Information on temperature affects on *A. albopictus* is minimal, but *A. aegypti* and this species are very closely related behaviorally and physiologically. *A. albopictus*,

physiologically more capable of surviving lower temperatures than *A. aegypti*, will be discussed later in this section.

Humidity. The amount of water vapor in the air affects all stages of a mosquito's life. Moist conditions are essential for regulation of body temperature and prevention of dehydration (Gordon et al., 1969:72). To counterbalance the effects of a low relative humidity, mosquitoes drink liquids such as nectar or sweat, or absorb moisture from the atmosphere. But, if the air is too dry or too cold (air temperature regulating relative humidity), desiccation can result. Normal activity and longevity is ensured when the relative humidity is high, between 70 and 90 percent. A low relative humidity (<60 percent), however, negatively affects mosquito activity and can prove fatal (Christophers, 1960:554).

Altitude. Just as temperature and humidity limit the geographic range of *A. aegypti* and *A. albopictus*, altitude is also clearly a limiting factor in their distribution. Rarely are the mosquitoes found above 7000 feet due to cooler temperatures at this elevation (Christophers, 1960:40). Also, in the mid-latitudes where temperatures are generally cooler, mosquito distribution is more limited to the lower elevations.

Temperature, therefore, ultimately limits mosquito distribution because of its interrelationship with other climatic variables. In some cases, mosquitoes have

persisted well above or below climatic ranges noted here, but climatic conditions discussed are considered favorable to mosquito vitality and proliferation.

SOUTHERN AND SOUTHEASTERN UNITED STATES

The establishment of *A. aegypti* and *A. albopictus* in the southern and southeastern United States is well-documented. The relatively wet, humid environment of these regions provide optimal conditions for mosquito populations to live long, active lives. The lengthy wet season also provides near year-round breeding grounds for the mosquitoes.

A. aegypti, introduced to North America during the period of exploration and discovery of the Americas, is now mostly confined to the southern and southeastern states, including Texas, Louisiana, Georgia, Florida, and the Carolinas. The moist, warm climate in these states enables *A. aegypti* to remain vital and potentially facilitate the disease transmission process. This species, requiring a warmer climate to remain vital, is restricted to the southern regions; it is rarely found north of the 42nd parallel in the eastern states (Christophers, 1960:40). Perennial establishment of *A. aegypti* in the southern portions of Texas and Florida is documented (CDC, 1992: 732).

WESTERN REGIONS

What remains unclear is the ability of these two species to survive in the western and northwestern regions of the United States. Studies have shown that the climate of western states (hot, dry summers and cool, wet winters) may prevent the establishment of *A. albopictus* (Washburn et al., 1992:996). Although western winters provide enough rain to support mosquito breeding, low winter temperatures prevent larval development (Washburn, 1992:1000).

Conversely, in the dry summer months when breeding sites are rarest, temperatures are most favorable for *A. albopictus* development. This interplay between adequate water stores, as defined by annual rainfall totals, and the ambient temperature required for species development are barriers to the establishment of *A. albopictus* and *A. aegypti* in the western regions.

This does not imply, however, that it is impossible for *A. albopictus* and *A. aegypti* to become established in the West. *A. albopictus*, for example, a highly adaptable species, has been found in regions with annual rainfall as low as 18 inches and 8-month-long dry seasons (Washburn 1992:995). But in regions where the drought season falls below 8 months, the survivorship of the population decreases, thus rendering it incapable of viral transmission (Washburn, 1992:1001). As of yet, however, these species are not established populations in the West.

NORTHERN REACHES

Low temperatures severely limit the geographic range of *A. aegypti* in the northern states. In the summer, this species will reach as far north as Philadelphia, but not being cold-hardy, must retreat southward in winter. Feeding, reproduction, flying and other activities of the adult mosquito generally ceases below 11 C (52 F), thereby preventing the establishment of *A. aegypti* in mid-latitude regions, where winters are longer and cooler.

Some populations of *A. albopictus*, however, have the ability to survive through the winter months because the female lays eggs that are capable of overwintering. When exposed to shortened periods of daylight, the female lays eggs that go into diapause, an inactive state that delays hatching until spring (Hawley, 1991:57). This phenomenon allows *A. albopictus* to adapt to the shortened periods of daylight and lower temperatures characteristic of the mid-latitudes. Overwintering is a biological strategy that ensures longevity of the species, therefore, increasing its efficacy as a vector of dengue.

The map, Figure 4, illustrates regions in the United States where populations of *A. aegypti* and *A. albopictus* are established. Since the introduction of *A. albopictus* in 1985, this species has spread to many states while the intensity of infestation has increased. According to records kept by the U.S. Air Force, populations of *A.*

albopictus increased four-fold from 1989 to 1991 and have been collected at five more locations (McHugh, 1991:198). In some southern states *A. albopictus* has even replaced *A. aegypti* as the principal mosquito species (Savage et al., 1993:27).

Recent distributional records of *A. aegypti* are more scarce than that of *A. albopictus*; the map reflects this paucity of data.

Figure 4

**DISTRIBUTION OF *AEDES AEGYPTI* AND *AEDES ALBOPICTUS*
IN THE UNITED STATES - 1991**

- ▲ *Aedes albopictus*
- *Aedes Aegypti*
- ★ Both mosquito populations are prevalent

GEOGRAPHIC STRAINS OF *AEDES ALBOPICTUS*

Strains of mosquitoes refer to populations within a single species originating from the same general region. Mosquitoes possess various mechanisms for adapting to environmental conditions (Gordon et al., 1969:71) that are both behavioral (e.g., migration) and physiological (e.g., overwintering). These mechanisms manifest in mosquito activities, such as feeding, ovulation, and capacity to transmit diseases, and aid researchers in distinguishing between geographic strains.

Overwintering, in particular, has proven to be a distinguishing factor between tropical and temperate strains of *A. albopictus*. The strains of mid-latitudinal regions are known to be photoperiodic, e.g., the female's eggs hatch when exposed to long days (summer) and go into diapause when exposed to shorter days (fall). Conversely, the female eggs of tropical strains are not affected by the day's length and hatch whether exposed to long or short days. The tropical strains would not be able to survive the winters of the mid-latitudes because they are not photoperiodic; therefore, it must be assumed that the strains of *A. albopictus* found in the United States originated from the temperate zone of Asia rather than tropical regions of Southeast Asia, the Caribbean, or Mexico (Hawley, 1991:55).

It is for this reason that *A. albopictus* does well in the Great Lakes region, in Minnesota, Illinois, and

Michigan. Because of its ability to live in a wide climatic spectrum and to transmit dengue fever, *A. albopictus* increases the potential for dengue outbreaks. It is a public health concern for most regions of the United States.

IMPLICATIONS OF *AEDES ALBOPICTUS*

There are three reasons for concern over the introduction of *A. albopictus* into the U.S. and each has major public health implications. First, the addition of another vector that transmits dengue increases the efficiency of virus maintenance, therefore increasing the likelihood that people will become infected (CDC, 1988:1781). If an outbreak were to occur, the incidence of the disease would be greater with the addition of a second species that fosters and transmits the virus.

A second reason for concern also has to do with the efficacy of this mosquito species. *A. albopictus* can survive in cooler climates for longer periods of time. Consequently, its habitat is not limited to places that remain warm year-round. The geographical range of the vector would increase, therefore inflicting more people with the disease in the event of an outbreak.

Since *A. albopictus* can survive harsher winters, the disease also stands a better chance of remaining for the duration of the year without any reprieve in transmission. Disease transmission, then would no longer be cyclical

according to the change of seasons, but rather develop into a more perennial state. This third condition relates to the potential of dengue becoming endemic in the United States.

CONCLUSION

The intensity of infestation of *A. albopictus* and *A. aegypti* in the southern and southeastern United States makes dengue fever outbreaks a considerable public health concern for these areas. Northern states east of Kansas are also threatened by outbreaks due to the colonization of *A. albopictus*. Climatic conditions in the western United States presently do not favor survival of either mosquito species, so there is less of a concern for epidemic dengue.

Subsequent chapters reveal how the public health consequences of dengue become more insurmountable for southern and southeastern states when dengue virus is introduced into the disease cycle.

CHAPTER FOUR

HUMAN ACTIVITIES AND THE SCOURGE OF DENGUE FEVER

The previous chapter emphasized the physical geography of dengue fever by defining climatic controls on the physiology and behavior of dengue's propagator species, *A. aegypti* and *A. albopictus*. These variables which affect the abundance, longevity, and geographical distribution of the vectors, delimit regions with the potential for dengue outbreaks. Defining these hazard regions, based on the prevalence of the dengue virus and vector, is the basis of landscape epidemiology and will be emphasized in the remainder of this thesis.

Humans plays a significant role in the geography of dengue fever. The intent of individuals and most health programs is to avoid disease. Ironically, however, humans create disease environments by altering landscapes or by introducing hazards into a susceptible region. The latter is readily accomplished by population mobility, made easy by advanced transportation systems that facilitate the global exchange of people and goods through once-formidable geographic barriers.

To avoid further spread of dengue from the tropics, special consideration must be given to the people and goods that move to the United States from dengue-endemic regions. Owing to the high volume of international exchange of both

commodities and people, the United States is especially vulnerable to introduced diseases. Although dengue is not yet considered a major public health threat in the U.S., the recent addition of a second vector and the rising number of imported cases of dengue make U.S. health officials increasingly wary of dengue. Identifying portals of entry for the virus and the two vector species will aid researchers in defining high-risk regions for dengue fever outbreaks.

TRANSPORT MECHANISMS OF DENGUE

The occurrence of dengue in humans depends upon the convergence of three factors: the dengue virus; the mosquito vector; and, a susceptible host population. The coincidence of these factors in time and space sets the stage for disease outbreaks. Advancements in transportation and increased frequency of travel shorten the time required for these disease factors to converge. Transoceanic shipping and high-speed aircraft, for example, form a bridge between distant regions, and facilitate the exchange of disease systems between communities, states, or nations.

Spread of dengue from infected regions to uninfected regions, such as the United States, requires dengue carriers, namely infected individuals and mosquitoes. International trade, tourism, and immigration are prominent vehicles for dengue introduction and diffusion in the United

States. Persistent monitoring of these activities is a critical step in intervening in the global spread of dengue fever.

INTERNATIONAL TRADE

International trade has proven to be an effective mechanism for the diffusion of dengue. *A. albopictus*, a species native to Asia, arrived in Houston, Texas in 1985 when mosquito populations were found breeding in piles of used tires shipped from Japan. This represents the first established infestation of *A. albopictus* in the Western hemisphere (Monath, 1986:450).⁵

Retreading and recycling used tires is unpopular in Japan; therefore, Japan exports roughly one million tires a year to the United States (Craven, 1988:79). These water-filled discarded tires serve as excellent breeding grounds for mosquitoes and provided the necessary pathway for their existence in the United States. Once populations are introduced to the U.S., interstate commerce in used tires furthers the spread of this species.

⁵ Two previous introductions of *A. albopictus* occurred after World War II and the Vietnam War from the importation of used military tires from Asia; however, colonization of this species did not result (Craven, 1988:138).

Japan's exported used tires, and a quarter-billion car and truck tires the United States discards annually (Baumgartner, 1988:500) accumulate on the U.S. mainland while tire recycling programs slowly develop. Mosquitoes have ample opportunity to lay eggs in water that collects in tires permitting the continuation of mosquito breeding.

Controlling the proliferation of mosquito populations in discarded tires is difficult because it is illegal to dispose of tires in some U.S. landfills. Waste-disposal companies encourage consumers to recycle used tires for environmental purposes. Scarcity of tire recycling companies, however, and the lack of favorable alternatives discourages this practice. Piles of used tires are commonly seen on service station lots, in abandoned fields, and private backyards. Favoring the proliferation of *Aedes* populations, this practice provides breeding sites and remains a significant environmental and public health concern for surrounding neighborhoods.

A primary concern centers on countries that are importing tires. If the tires are exported from a region where dengue is endemic and populations of *A. albopictus* or *A. aegypti* are established, the possibility exists that mosquitoes shipped to the U.S. are already infected. Once a mosquito becomes infected with the dengue virus, after an eight- to eleven-day incubation period, the mosquito is infective to humans and its offspring for the rest of its

life (Horsefall, 1962:651). This may have serious ramifications for countries importing tires and is partially responsible for the diffusion of dengue from tropical to non-tropical regions.

The importation of a potentially disease-carrying insect population into the United States is a considerable public health concern. If the mosquito does not become infected in its country of origin, it may do so at its destination. Although not plagued with dengue fever, Japan is infested with populations of *A. albopictus*. The U.S. receives Japanese cargo that frequently goes uninspected. If the imported vector can be ecologically sustained in a region, it may become infected by a resident and potentially spread dengue to other individuals. The public health consequences of the United States as a receptor of foreign tire discards are real and deserve special consideration when forming trading and cargo inspection policies.

According to the U.S. Department of Commerce, the majority of used tires imported to the U.S. in 1985 and 1986 were from Asia, especially Japan and Korea (Figure 5). Dengue is not considered to be endemic in these regions, but *A. albopictus* is a native species in both Japan and Korea (Craven et al., 1988:139). Table 1 lists the numbers of tires imported into the United States in 1991. European countries have generally remained uninfested with *A. albopictus* and *A. aegypti*; however, recent infestations of

A. albopictus in parts of Italy and Albania have been reported (Lesser, 1992: 10). Proximity to these regions, therefore, warrants inclusion of other European communities in Table 1.

**TABLE 1. Number of Used Tires
Imported into the United States in 1991.**

<u>country</u>	<u>number*</u>	<u>%</u>
Mexico	34	<1
Korea	171	1
Japan	8670	60
United Kingdom	80	<1
France	716	5
Germany	3277	23
<u>Yugoslavia (former)</u>	<u>1440</u>	<u>10</u>
TOTAL	14,388	100

Source: U.S. Department of Commerce.
Tariff Schedule of the United States.
*In thousands.

Figure 5

**U.S. SHIPPING PORTS THAT RECEIVE USED TIRES
FROM VECTOR-INFESTED REGIONS - 1991**

Source: U.S. Department of Commerce. *Tariff Schedule of the United States.*

The mode of dissemination of dengue's mosquito vectors is clearly associated with human activity. Artificial breeding grounds are transported across oceans by ship and further spread around country by truck. In this example, the vector mosquito and potentially the dengue virus crosses geographic boundaries and becomes established in a region thousands of miles from its origin.

INSPECTION OF TIRES

All goods imported into the customs territory of the United States (the United States, the District of Columbia, and Puerto Rico) are subject to duty and inspection. In recognition of the potential public health problem associated with *Aedes* infestation, the Center for Disease Control, Division of Vector-Borne Infectious Diseases (CDC DVVID) in 1988 required the U.S. Public Health Service Quarantine Service to inspect used tires shipped from Asia. Although eggs of temperate-strain *A. albopictus* resist desiccation (Hawley, 1991:56), imported tires were required to arrive dry, accompanied by a certificate of treatment for killing mosquito ova. Inspections and compliance dwindled during 1990 and 1991, however, and now mosquito infestations are documented in 23 states (Lesser, 1992:11).

Mosquito infestation in used tires is clearly an international problem. Once the U.S. receives imported used tires, some are shipped to destinations outside the country.

The imported tires may arrive in the U.S. already infested with vector populations or may become infested at U.S. ports. Regardless of where the tires become infested, countries receiving used tires exported from the U.S. are also at risk for vector infestation.

POPULATION MOBILITY AND THE SPREAD OF DENGUE

The severity and frequency of dengue outbreaks are influenced by many ecological and sociological factors, such as mosquito endurance, mosquito infection rate, availability of a susceptible human population and their mobility. The latter, a critical factor in the geography of dengue, is partially responsible for the introduction and maintenance of the disease in previously unaffected regions.

Tourism and immigration, in particular, are powerful forces behind the changing epidemiology of dengue fever in the United States. The nomadic nature of Americans and the perceived "open-door" policy for foreign immigrants has forced a demographic shift in numbers and types of people who reside in the U.S. One of the ramifications of this seemingly continuous movement of people is the exchange of diseases between geographically separate regions.

DENGUE'S VOYAGE VIA AMERICAN TRAVELERS

According to the Center for Disease Control (CDC), the pattern of dengue transmission in the United States

parallels that of adjacent regions (CDC, 1987c:1712). An increase in dengue activity in the United States can be anticipated by an increase in transmission in the American tropics, especially the Caribbean and Mexico. This phenomenon can be partially explained by the increase in travel by Americans to these regions, either for visits to their homelands or for a vacation.

While traveling to and around a region where the dengue virus is well-established, an individual may get bitten by a virus-infected mosquito. The traveler may be totally unaware of the disease because of the two- to eight-day incubation period (Scully, 1989:957). Depending on the length of stay in the tropics, the individual returns home and the disease manifests in the form of any combination of symptoms; consequently, the virus has been incubated and imported into the U.S.

Furthermore, if a mosquito suitable for harboring the dengue virus were to take a blood meal from the viremic individual, the virus would multiply within the mosquito, and concentrate in its salivary glands ready for transmission to a susceptible human host (Rhodes, 1962:297). Once the virus is transported to the U.S. via travelers or immigrants, the vector furthers the spread of dengue fever.

The risk is greater for individuals who travel back to their homeland where dengue is endemic. One factor thought to be predisposing for acquiring DHF is the pre-

existence of antibodies to the dengue virus (Kouri, 1981:376) (also see CHAPTER ONE-IMMUNE RESPONSE AND THE EPIDEMIOLOGY OF DENGUE). If an individual was infected as a child with classic dengue and returns to his or her native home for a visit, he or she increases the risk of getting bitten by a virus-infected mosquito and acquiring the deadly DHF. Individuals traveling to dengue-endemic regions, therefore, are advised to follow strict precautionary measures to avoid mosquito bites (Jacobs et al., 1991:829).

HISTORIC SPREAD OF DENGUE

The mode of transmission of mosquitoes over great distances has not changed much since the introduction of sea-faring vessels. Historically, wooden ships were responsible for the widespread distribution of *Aedes* mosquitoes and dengue fever. In 1903, for example, the Hawaiian Islands recognized the first dengue outbreak when a passenger ship from China arrived in Honolulu with individuals who had been infected at a Chinese port. After initial introduction, the disease spread to other islands in the archipelago via passenger ships (Siler et al., 1926:25). Today, more efficient modes of travel expedite the process of transporting the virus and disease from one region to another.

U.S. IMMIGRANT POPULATION-CARRIERS OF DENGUE VIRUS

The mosquitoes serve only as a potential threat if they have been infected with the dengue virus, which is accomplished either trans-ovarially (from infected female to her offspring) (CDC, 1987a:166) or by taking a blood meal from an infected individual. Because this disease has mostly been confined to tropical regions, such as Southeast Asia and the Caribbean, continuous circulation of the virus in the United States requires another variable.

The increase in immigration to the U.S. from the tropics has supplied this missing transmission link and the possibility for dengue outbreaks becomes more likely. Dengue brought to the U.S. mainland via immigration is an important public health consideration because it increases the reservoir of infection, thereby perpetuating the transmission cycle.

The mobility of the dengue virus via immigration is similar to that of tourism, but on a larger scale. Substantial populations are migrating from "dengue-regions" to the United States and are bringing their virus type with them. Since dengue is endemic in many tropical regions, it is possible that many individuals in the native population have been infected. If these individuals immigrate to the U.S. during their infective period, they are likely to spread dengue, aided by *Aedes*, to others. Some regions in the U.S. support both vectoral populations and a substantial

human host population, so the pattern of dengue outbreaks may follow that of tropical regions.

The total number of U.S. immigrants has increased every decade since 1961 (U.S. Department of Justice, 1992). From 1981-1990, 76 percent of the immigrant population originated from a dengue-endemic region or from a region where outbreaks have occurred (Table 2). This accounts for a 10 percent increase from the previous decade! Moreover, 46 percent of those emigrating from "dengue-regions" are from high risk regions, such as Mexico and the Caribbean. Considering individuals who fail to gain resident or immigrant status upon arrival to the United States, the actual number reported from each country, especially Mexico, could be much higher.

**Table 2. Number of U.S. Immigrants
Originating From a "Dengue-Region," 1981-1990.**

<u>Country</u>	<u>Number</u>	<u>% of total (5,602,900)</u>
tropical Asia:	1,937,000	35
Cambodia	116,600	
China (incl. Taiwan)	451,800	
India	261,900	
Laos	145,600	
Philippines	495,300	
Thailand	64,400	
Vietnam	401,400	
Mexico	1,653,300	30
Caribbean:	892,700	16
Barbados	17,400	
Cuba	159,200	
Dominican Republic	251,800	
Haiti	140,200	
Jamaica	213,800	
Trinidad and Tobago	39,500	
Central America	458,700	8
South America:	455,900	8
Argentina	25,700	
Brazil	23,700	
Chile	23,400	
Colombia	124,600	
Ecuador	58,000	
Guyana	95,400	
Peru	64,400	
Venezuela	17,900	
East Africa (Egypt)	192,300	3
Australia	13,900	<1
TOTAL	5,603,800	

**Source: U.S. Immigration and Naturalization Service,
Statistical Yearbook, 1991.**

DEMOGRAPHIC TRENDS OF U.S. IMMIGRANTS

Subgroups of immigrants settle in different parts of the United States. The majority of Mexican nationals establish residence in California and Texas, while groups from tropical Asia cluster in California and New York. People from the Caribbean and South America are drawn towards the East Coast, in New York and Florida, and Central Americans frequently settle in California, New York, and Texas (Figure 6).

In addition, the U.S. resident population is increasingly urbanized. From 1950 to 1990, the population increased from 65 percent urban to 75 percent urban (U.S. Department of Justice, 1991). Urbanization, it should be emphasized, is thought to promote viral mutation and maintenance in the human population, supplying the vector with a substantial reservoir of human blood (see CHAPTER THREE-URBANIZATION).

Figure 6

U.S. IMMIGRANT POPULATION FROM DENGUE-INFESTED REGIONS: INTENDED RESIDENCE, 1981 - 1990*

* % By Highest Concentration

Source: U.S. Immigration and Naturalization Service, *Statistical Yearbook*, 1991.

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PATTERNS OF DENGUE DIFFUSION

Most large cities, with the capacity to support high volumes of trade, appear as magnets for tourists and immigrants. It is here that major transportation hubs such as airports and shipping ports are located. Because major population centers support the mass movement of people and goods, they are prime targets for dengue introduction and transmission.

Dengue diffusion is not restricted to larger cities, but follows a hierarchical diffusion pattern. Large population centers are portals of entry for the dengue virus and vector. Then the disease follows lines of communication of human transport to the outlying regions. Suburban and rural populations, therefore, are also at risk of dengue transmission.

This hierarchical diffusion pattern supports the history of dengue in many regions. Outbreaks of classic dengue fever in Southeast Asia, for instance, hit major population centers first where infestations of *A. aegypti* were high. The disease proceeded to spread to smaller communities. Then in 1954, the deadly DHF appeared in this region for the first time, and continued sporadically for many years. Now DHF is the major cause of morbidity and mortality in Southeast Asian children (Halstead, 1981:633).

The progression of dengue intensifies in a region unless proactive measures are taken to abate mosquito

populations, educate communities about personal intervention strategies, and monitor dengue transmission rates. Judging from the historical patterns of dengue in tropical Asia, and comparing them to adolescent stages of dengue in the United States, it seems clear that dengue's potential threat is very real. Although the two regions are diverse ecologically, the geography of the United States has already proven capable of supporting vector populations. The only missing link is the increased transmission of dengue fever in the United States. International trade, and increased tourism and immigration, however, are avenues for the introduction of the dengue virus and vector mosquitoes, thus increasing the potential for dengue outbreaks.

CONCLUSION

Because of civil unrest, economic strife, economic opportunity, and the desire to travel, population mobility is more prevalent today than ever before. Geographic boundaries are easier to transcend, therefore increasing the opportunity for disease introduction and diffusion. Humans have contributed to the environmental conditions that facilitate the processes of dengue transmission. It is necessary for individuals and regional health officials to maximize education and support vector control measures.

This section has illustrated how three dimensions of human activity effectively create pathways for the worldwide

spread of dengue fever: (1) International trade transports the vector (and potentially the virus) by providing artificial breeding grounds and the mechanism for movement from one region to another; (2) an increase in tourism, induced by the desire of the population and more efficient modes of transportation, encourages the mobility of dengue from one region to another via the traveler; and (3) immigration transports the dengue virus from one geographic location to another via the sheltered environment of the human body. These three manifestations of human behavior, international trade, tourism, and immigration, create a potential "flash point" of diseases by increasing the virus types and distribution in a particular locale.

CHAPTER FIVE

FORECASTING DENGUE IN THE UNITED STATES

The experience of the people and health services of the United States with dengue, fortunately has been limited. The number of laboratory confirmed cases reported is small in absolute terms, but imported cases are rising and likely to continue. For example, 67 imported cases were reported to the CDC in 1984, 94 cases were reported in 1989 (CDC, 1990:741), and 102 cases in 1990 (CDC, 1991:519). In 1991, the total number dropped to 82 imported cases of dengue fever (Figure 7) (CDC, 1992:731), but this may reflect a lull in dengue outbreaks in tropical regions. Since dengue fever is not a nationally reported disease (state health departments are not required to report suspected or confirmed cases to the CDC), the actual number of imported cases is probably much higher than the reported number.

Indigenous transmission of dengue fever was documented for the first time in the continental United States in 1922, when individuals became infected after no previous travel outside the U.S. More than 500,000 cases of dengue were estimated in Texas during the 1922 outbreak (Hafkin et al., 1982:1222).

A smaller outbreak occurred in Louisiana in 1945, and then two more episodes of indigenous transmission of dengue occurred in Texas in 1980 and 1986. In the latter

outbreaks, 27 and 9 laboratory confirmed cases were reported (Hafkin, 1982:283 and CDC, 1987c:1712). There has been no reported cases of indigenous transmission in the United States since 1986 (personal communication, Dr. Rigau, CDC, San Juan, P.R.). Continued infestation of *A. albopictus* and *A. aegypti*, however, an increase in the number of imported cases, and the continuous movement of people and goods to and from dengue-regions raise concern for the risk of indigenous dengue transmission.

THE SPILLOVER EFFECT OF DENGUE

Dengue and its vector know no political boundaries, their geographic limits are imposed ultimately by temperature and movement of the host. The relative location of the United States, and its proximity to dengue-infested regions, such as the Caribbean and Mexico, impose a higher degree of risk for bordering states. According to the CDC, the annual number of reported and confirmed cases of dengue imported to the U.S. corresponds to the amount of dengue activity in the tropics, particularly the Caribbean and Mexico (CDC, 1987c:1712). It is necessary, therefore, to consider transmission rates in neighboring regions, to accurately assess the potential risk of transmission in the U.S.

Dengue outbreaks have been on the rise in tropical regions since 1986. Latin America reported a larger number

of dengue cases in 1986 than any other year on record, both the classic type and the killer DHF (CDC, 1988:1782). Waves of epidemics hit these regions in 1989 and 1990, with an increase in the number of infections and deaths associated with DHF/DSS. This profile illustrates how dengue can evolve in a region from a low impact, mild illness to a deadly, formidable disease that covers a wider geographic area, a pattern that mirrors dengue diffusion in Southeast Asia.

CIRCULATION OF DENGUE VIRUS SEROTYPES

Because DHF is thought to be caused by a secondary infection with a serotype other than the one responsible for initial infection, circulation of multiple virus serotypes in a region is a critical concern. All four dengue virus serotypes circulate in Southeast Asia and the western Pacific region, while three of the four serotypes (DEN-1, DEN-2, DEN-4) circulate in the Caribbean region and several countries in Central and South America (CDC, 1992: 732). Epidemic activity in these areas is associated with this pattern of serotype circulation.

Although only one serotype (DEN-1) was responsible for the indigenous outbreaks in Texas, all four dengue virus serotypes have been imported into the United States since 1981 (CDC, 1987c:1712). Infecting serotypes were imported into 24 states and the District of Columbia (D.C.) and 27

states and D.C. in 1990 and 1991, respectively, by U.S. travelers from dengue-infested regions (CDC, 1991:519; and CDC, 1992:725) (Figure 7).

Imported dengue via travel or immigration is important in determining a high-risk region if the recipient region is also infested with one or both vectors. An individual, once infected with the dengue virus, remains viremic for approximately seven days. The vector, therefore, must take a blood meal within this seven-day period to become infected and transmit dengue to other susceptible individuals. If no contact between infected individuals and vector transpires once the disease is imported, the virus cannot be transmitted. To consider imported cases of dengue a regional risk factor, therefore, the region must also be infested with *A. aegypti* or *A. albopictus* or both.

Figure 7

**REPORTED AND CONFIRMED CASES OF IMPORTED DENGUE IN THE
UNITED STATES, 1989 -1991**

TOTAL REPORTED CASES: 278

HIGH RISK REGIONS IN THE UNITED STATES

Determining high-risk regions for the introduction and transmission of dengue fever in the continental United States was based on these criteria:

- (1) previous exposure to dengue fever (indigenous outbreaks or more than ten imported cases) (Figure 7);
- (2) geographic proximity to a dengue-infested region;
- (3) colonization by *A. albopictus* or *A. aegypti* or both (Figure 4);
- (4) continuous and simultaneous circulation of one or more dengue virus serotypes;
- (5) proximity to a shipping port that receives used tires from an *Aedes*-infested region (Figure 5); and,
- (6) supports large numbers of immigrants from dengue-infested regions (Figure 6).

These criteria measure the susceptibility of a region to dengue infection. Each criterion is a risk factor because its presence is associated with the increased probability that the disease will develop in the region. The intersection of multiple risk factors indicates a region high at risk for dengue epidemics (Figure 8).

The weighting for each criterion in defining a high-risk region will be assessed from the literature and based on patterns of outbreaks in dengue-endemic regions. There is enormous variation in economic, social, and environmental conditions between the United States and tropical and subtropical regions where dengue is prevalent. Regions

plagued with dengue, however, will provide a model for projecting the possible pattern of dengue diffusion in the United States.

SUMMARY OF RISK ASSESSMENT

This section will incorporate findings from the previous four chapters into a working model for defining a high risk region. Demarcating a region based on the prevalence and extent of risk factors will substantiate the researchers objectives in this thesis. This summary is presented in Table 3 and Figure 8, and is supplemented with the following textual information.

REGIONAL RISK FACTORS

The most important regional risk factors for dengue fever outbreaks in the U.S. are continuous circulation of dengue virus serotypes and infestation of one or both vector species. Because there have been no indigenous outbreaks reported in the U.S. since 1986, it must be assumed that the virus is not continuously circulating in any region. If a region is exposed to the dengue virus via travel or immigration, however, and supports either vector population, it is extremely vulnerable to outbreaks. Risk factor (3) coupled with (1), (2), or (6), therefore, will comprise more weight in determining a high risk region (shown in boldface type) (Table 3).

**Table 3. Summary of Risk Assessment
for Dengue Fever Outbreaks in the U.S.**

<u>STATE</u>	<u>RISK FACTORS</u>
Texas	1, 2, 3, 5, 6
Florida	1, 2, 3, 5, 6
California	1, 2, 5, 6
Georgia	1, 2, 3
Alabama	2, 3
Mississippi	2, 3
Louisiana	2, 3
South Carolina	3, 5
Illinois	3, 5
Virginia	3, 5
Minnesota, Michigan, Maryland, Delaware, Arkansas, Oklahoma North Carolina, Kentucky, Tennessee, Indiana, Missouri	3

Figure 8

DENGUE IN CALIFORNIA?

The common denominator for the states listed is vector infestation. The exception is California, which is plagued with four other risk factors. If temperate strains of *A. albopictus*, already proven to be a highly adaptable species, colonize regions within California, dengue would be easily maintained.

Although California is not infested with either species, foreign importation of used tires remains a potential source of infestation. In 1987, immature *A. albopictus* were collected in imported used tires in Oakland. Eradication measures were taken, however, and colonization did not result (Washburn et al., 1992:995). California remains a conditional risk region for dengue fever outbreaks.

GREAT LAKES REGION

Vector infestation is low in Minnesota, Michigan, Illinois, Indiana, and Ohio, and the number of dengue cases imported is low; therefore, the risk of outbreaks is relatively low. Infestation can intensify in these areas, however, due to interstate diffusion of *A. albopictus* or foreign importation of used tires, thus increasing the risk of outbreaks.

MODERATE RISK REGIONS

Regions at moderate risk for dengue outbreaks are those that support vector populations, but are lacking other significant risk factors (Figure 8). The risk of dengue transmission in those states could increase if transmission rates increased in states bordering them, imported cases into those states increased, or larger populations from dengue-endemic regions migrated there.

The potential spread of dengue is still a major concern in moderate risk regions, especially if adjacent high risk regions experience outbreaks. Outbreaks are relatively less likely, however, than that of the southern and southeastern states.

HIGH RISK REGIONS

Texas, Louisiana, Mississippi, Alabama, Georgia, and Florida are at high risk for dengue fever outbreaks. Vector infestation is high in each state, and potential for dengue virus introduction and circulation due to importation by immigrants or tourists is increasing. Strict surveillance should be implemented to ascertain viral levels in the vector and resident population.

Texas, especially counties adjacent to the Texas-Mexico boarder, is highly vulnerable to dengue fever outbreaks. Having suffered indigenous outbreaks of dengue fever several times in the past, Texas is threatened by

circulating virus serotypes. Pending epidemics are not unforeseen.

THE NEED FOR SURVEILLANCE

Adequate surveillance of dengue fever requires the involvement of the medical community and the lay community. Since 1987, the CDC has been collaborating with state health departments to improve surveillance and increase the public awareness of dengue fever (CDC, 1987c:1713). The CDC recommends individuals suspected of acquiring the infection while traveling abroad or within the United States report it to health authorities. When physicians are presented with patients suspected of being infected with dengue virus, detailed travel histories and other epidemiological information should be ascertained and reported to the state health department. This system provides information about the origin of infection and the rate of dengue transmission within the United States. The information can be used to observe patterns of introduction and diffusion associated with the disease and to make intelligent decisions concerning the development of effective intervention strategies.

Surveillance alone will not mitigate the hazard of dengue transmission in the United States. A monitoring system should also be considered to provide timely and accurate information on the emergence of the dengue virus,

including detection of its arrival and the tracking of its diffusion.

CONTROL OF MOSQUITO POPULATIONS TO REDUCE VIRAL TRANSMISSION

The best defense against a virus is a vaccine. However, a vaccine for dengue fever has not yet been developed. The best intervention strategy for minimizing transmission rates, therefore, is one that targets the vector population to sever its link to the disease cycle.

Several methods are useful in controlling mosquito populations. Ultra-low volume (ULV) applications of insecticide concentrations usually result in satisfactory levels of vector control in emergency situations (Gratz, 1991:353). In some regions, however, this method only delays the peak of the epidemic and has little impact upon disease incidence (Newton et al., 1992:709).

ULV application is not always a reliable method for decreasing vector densities due to the inability of aerosol droplets to penetrate certain materials (Perich et al., 1992:137). Moreover, the environmental impact for UVL insecticiding may have serious consequences and vector resistance to several chemicals is increasing. This method, therefore, should be reserved for emergency control (e.g., at the onset of an epidemic) of vector populations.

Monitoring mosquito populations is essential to ensure adequate control. Numbers and types of mosquitoes

fluctuate according to seasonality, regional ecology, and biology of the species. Monitoring the intensity of vector infestations demonstrates the efficacy of existing mosquito eradication methods.

COMMUNITY CONTRIBUTION IN VECTOR CONTROL AND DISEASE PREVENTION

Source reduction is the most tenable solution for vector control. Keeping natural and artificial landscapes well drained in mosquito-infested areas can drastically reduce breeding sites. Educating local communities about eliminating potential breeding grounds and reducing water storage container use is key to administering and ensuring source reduction effectiveness.

In many developing tropical countries, however, lack of funding earmarked for mosquito control and disease prevention is common. *Aedes* mosquitos breed in and around homes and people live and work unprotected against mosquito bites. Personal measures, such as wearing protective clothing, using repellents, screening homes, and eliminating breeding grounds can effectively control mosquito populations. Culturally-constructed norms and depressed economic conditions, however, are formidable obstacles to implementing mosquito management programs.

Proper burial of victims of dengue is equally important in controlling the vector's opportunity to spread

the disease. Mosquitoes, especially *A. aegypti*, will take blood meals from a corpse hours after death provided the body is still warm (Christophers, 1960:470). This could have significant consequences in the spread of dengue, especially in epidemic regions where many deaths occur in a short period of time. Depending on how long the virus remains virulent after death of the host, the mosquito may still become infected with the dengue virus and transmit it to other living individuals.

CONCLUSION

The threat of dengue fever epidemics in the United States is imminent due to the following factors:

(1) established populations of dengue's vector species, *A. aegypti* and highly adaptable *A. albopictus*, and continual infestation due to international trade in used tires; (2) reported cases of imported dengue are rising and likely to continue due to increases in tourism; (3) proximity to Latin America where dengue is endemic and continuous and simultaneous circulation of multiple virus serotypes exists (CDC, 1987c:1712); and, (4) the mass exodus of potentially virus-infected individuals from dengue-endemic areas.

The southern and southeastern states are especially high at risk for dengue outbreaks due to the elevated intensity of vector infestation and mounting danger of virus circulation. It is critical, therefore, for health

officials in these dengue "hot spots" to focus on programs that reduce vector populations, maximize public health education, and monitor dengue transmission rates in bordering regions.

The conditions outlined above threaten the public's health in the United States. Preventing explosive outbreaks of dengue fever in the U.S. requires implementing a national surveillance system for detecting the introduction of dengue and tracking its diffusion. Moreover, continuous mixing of human populations and ensuing dangers of disease exchange substantiate the need for global monitoring of dengue fever.

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