Dengue Fever versus Bioterrorism

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Abstract

Viral hemorrhagic fever has ever been used as a route of bioterrorism. The mode of transmission, clinical course, and mortality of these illnesses vary with the specific viruses. In Taiwan, dengue fever is the most encountered disease of hemorrhagic fever. In the viewpoint of bioterrorism, dengue is always excluded because it is not transmissible by small-particle aerosols, and primary dengue causes hemorrhagic fever rarely. However, it still may carry great morbidity and mortality in naturally occurring outbreaks. We therein review the clinical spectrum of dengue fever and also emphasize that it is essential to teach the medical community how to diagnose and manage dengue and dengue hemorrhagic fever and to implement an emergency contingency plan to anticipate the logistical issues of hospitalizing large numbers of patients and to outline measures for community-wide vector control activities. Public education for carrying out vector control is also a determining step. *(Ann Disaster Med 2002;1 Suppl 1: S44-S58)*

Key words: dengue; hemorrhagic fever; bioterrorism

Introduction

Dengue fever becomes more and more common in southern Taiwan and south-east Asia. Will it become one of the bio-terrorism? This article will address the clinical manifestations, pathogenesis, epidemiology, diagnosis, treatment and prevention of dengue infections.

Basic information

Dengue Virus

Dengue has been called the most important mosquito-transmitted viral disease in terms of morbidity and mortality. Dengue is a homonym for the African *ki denga pepo,* which appeared in English literature during an 1827-28 Caribbean outbreak. The first definite clinical report of dengue is attributed to Benjamin Rush in 1789, but the viral etiology and its mode of transmission via mosquitos were not established until the early 20th century. As we know, dengue virus will causes dengue fever and dengue hemorrhagic fever. It is a flavivirus which is in the same family as the viruses that cause

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Japanese encephalitis. It is a single-stranded RNA virus and it has 4 serotypes known as (DEN-1, 2, 3, 4). All serotypes can cause severe and fatal disease. There is some genetic variation within those serotypes. Some genetic variants appear to be more virulent or have greater epidemic potential. And it may be possible to do that for bio-terrorism.

The Transmission Cycle

The transmission cycle of dengue virus (by the mosquito *Aedes aegypti)* starts with a dengue-infected person. This person will have viremia for about five days. In the viremic period, an uninfected female *Aedes aegypti* mosquito bites the person and ingests blood that contains dengue virus. In the extrinsic incubation period, the virus replicates in the mosquito mid-gut, ovaries, nerve tissue and fat body. It then escapes into the body cavity, and later infects the salivary glands. The virus replicates in the salivary glands and when the mosquito bites another human. Although there is some evidence of trans-ovarial transmission of dengue virus in *Aedes aegypti,* usually mosquitoes are only infected by biting a viremic person. Then, in extrinsic incubation period the virus replicates within the mosquito for eight to twelve days. The mosquito then bites another person and transmits the virus to them.

In the intrinsic incubation period, first of all the virus is inoculated into humans with the mosquito saliva. Then the virus replicates in various organs, like local lymph nodes and the liver. The virus then spread through the blood to infect white blood cells and other lymphatic tissues. Finally, another uninfected female *Aedes aegypti* bite this patient in the viremic stage, the cycle starts again. Although there is no lots of evidence prove that, trans-ovarial transmission will be a very important point because we can make “lots of dengue-infected ova” instead of “some dengue-infected mosquito”!

It is important to mention that *Aedes aegypti* is a day-time feeder and mainly bites in the morning or late in the afternoon. The *Aedes aegypti* female prefers to lay its eggs in artificial, rather than natural containers that near where people live. The life cycle is also shown in Figure 1

Epidemiology

One report estimates that nearly 80 million people are infected with a dengue virus annually. Current outbreaks can be monitored by contacting the website owner-promed @promedmail.org. Dengue occurs in tropical and subtropical areas in the world. The gray areas are those at risk for epidemic dengue--those areas infested with *Aedes aegypti* or other mosquito vectors of dengue. The black areas are those countries with recent

dengue activity. Taiwan is one in the black zone.

Clinical Manifestations of Dengue and Dengue Hemo- rrhagic Fever

Four Dengue Clinical Syndromes

There are actually four dengue clinical syndromes: 1.Undifferentiated fever; 2.Classic dengue fever; 3.DHF-Dengue hemorrhagic fever, and 4.DSS-Dengue shock syndrome. Dengue shock syndrome is actually a severe form of DHF.

Undifferentiated Fever

Undifferentiated fever is the most common manifestation. A prospective study from Thailand studied 4 to 16-year-old students in Bangkok found that most students who became infected by dengue virus--90 of 103 (87%) were asymptomatic or minimally symptom-matic. Other prospective studies including all age groups have also shown similar result.

Classical Dengue Fever

The criteria for dengue fever are: DENGUE- 1.D-Dengue hemorrhagic manifestations, which will be discussed more later. 2.E-Echymosis, maculopa-pular, petechial, or erythematous, the rash can be variable and may appear at different stages of the illness; 3.N-Nausea and vomiting; 4.G- Myalgias and arthralgias after onset of fever that can be very severe and may last for several weeks; 5.U-Unkown fever that is often sudden onset, biphasic, and last for 1-7 days; 6.E-Eye pain, severe headache, often described as retro-ocular. Some cases may develop encephalitic or encephalopathic signs and symptoms, including lethargy, confusion, and coma; seizures; nuchal rigidity; and paresis.

Hemorrhagic Manifestations of Dengue

Only some patients develop hemorrhagic manifestations, such as petechiae, purpura, and ecchymosis. The others will have gingival or nasal bleeding; hematemesis, melena, and hematochezia, the severity may vary from case to case. In some cases, however, may cause hypovolemic shock.

Clinical Definition for Dengue Hemorrhagic Fever

The four criteria, as currently stated by the World Health Organization, are: DHFS- 1.D-Drop platelet count (100,000/mm^3 or less), 2.H-Hemorrhagic manifestations, 3.F-Fever, or recent history of acute fever, 4.S-Signs of plasma leakage: including elevated hematocrit, low protein, pleural effusion or other effusions. Plasma leakage is the critical difference between dengue hemorrhagic fever and dengue fever and means that the patient requires large amounts of intravenous fluids.

Clinical Definition for Dengue Shock Syndrome

The clinical case definition for dengue shock syndrome is: 1.The four criteria for DHF. 2.Evidence of circulatory failure. There are four grades of DHF. For all grades the four criteria for DHF must be met. In Grade 1, patients will have fever, nonspecific symptoms and positive tourniquet test (which will soon be described). In Grade 2, in addition to Grade I manifestations, there is spontaneous bleeding. Grades 3 and 4 are Dengue Shock Syndrome. Grade 3 patient has mild shock. And in Grade 4, the patient has severe shock, with undetectable pulse and blood pressure.

Danger Signs in Dengue Hemorrhagic Fever

Most of the DHF patients do not go into shock. Many DHF patients have certain danger signs before circulatory failure. These danger signs include" CHAN": 1.C: Confusion; 2. H: Hypothermia, (abrupt change from fever); 3.A: Abdominal pain that is intense and sustained; and 4. N: Persistent nausea / vomiting. All of these are signs should alert clinicians that the patient needs close observation and fluids.

Warning Signs for Dengue Shock

Most patients develop DSS within 3-6 days after onset of symptoms. If the fever goes between three and six days after the symptoms began, this is a warning signal that the patient must be closely observed. Other early warning signs are including a drop in platelets, an increase in hematocrit, or other signs of plasma leakage. Though dengue fever does not often cause fatalities, a greater proportion of DHF cases are fatal. The next concern would be the danger signs--"CHAN".

Clinical Progression of Illness

On average, admission occurred at around 4-5 days. Thrombocytopenia was usually the earliest predictor of severe disease, often occurring before fever drop. The highest hematocrit, usually appears around day 5-6. After IV fluid hydration, the hematocrit returned to normal around days 7-8. During the hemoconcentration stage, shock and lowest platelet count appear. Discharge from hospital is usually at about day 11. Some unusual presentations will have high lethality without progressing through DHF. These patients may present with encephalopathy, liver failure or fulminant hepatitis, cardiomyopathy, myocarditis, or severe gastrointestinal hemorrhage.

Disease Pathogenesis

Risk Factors for DHF

Most dengue fever cases are self-limited and never progress into dengue hemorrhagic fever. The factors associated with DHF will be (1) V:

virus strain, (2) A: anti-dengue antibody. (3) G: gene, and (4) A: age. In Southeast Asia, children are most affected, but in the Americas, all age-groups are affected. It is also highly risky in patients with two or more serotypes simultaneously at high levels, which is called hyperendemic transmission. The most popular hypothesis for the increased risk of DHF in secondary infections is called "antibody dependent enhancement of viral infections". There are two possible reasons explaining why hyperendemicity may increase the probability of DHF: 1. In the situation of hyperendemicity, the risk for virulent strains is increased, which increases the probability of DHF. 2.In the situation of hyperendemic transmission, the probability of secondary infection is increased, which increases the probability of DHF.

Hypothesis on Pathogenesis of DHF

In a patient with any dengue serotype, for example- dengue type A, the immune system will respond by producing anti-A antibodies. These anti-A antibodies form homologous complexes with the type A virus, which results in the neutralization of the virus. When another new serotype dengue type B get in our body, the anti-A antibodies can form complexes with the new serotype B. However, the new serotype will not be neutralized by these antibodies. The virus with the non-neutralizing complexes, can enter more mononuclear cells where the virus replicates unchecked, thus increasing virus production and producing a massive infection. It has also been hypothesized that the infected monocytes release vasoactive mediators, resulting in the increased vascular permeability and hemorrhagic manifestations that characterize dengue hemorrhagic fever or dengue shock syndrome.

Risk Factors for DHF Pathogenesis

Dengue hemorrhagic fever most often occurs in second infections. But it seems to be mostly common in those certain dengue virus strains, or genotypes. Cohort studies in Southeast Asia have shown that secondary infections by DEN-2 or DEN-3 have greater probability of producing DHF than others. The risk is less when the second infecting virus is DEN-4 or DEN-1.

Diagnosis

In dengue-endemic areas, the season is an important consideration. In some countries and regions, the time of year with peak transmission varies, but it is usually associated with the rainy season. In non-endemic areas, it is important to determine the patient's travel history. The intrinsic incubation period for dengue is 3 to 14 days.

Therefore, if the patient developed fever more than 2 weeks after leaving the endemic location, dengue can be eliminated. The differential diagnosis of dengue includes: Influenza, Measles, Rubella, Malaria, Typhoid fever, Leptospirosis, Meningococcemia, Rick-ettsia , Bacterial sepsis and other viral hemorrhagic fevers.

Clinical Evaluation

The physical examination should include: 1.P: Permeability increased like pleural effusions or ascites. 2.T: Tourniquet test. 3.B: Bleeding. 4.P: Blood pressure. 5.H: Hydration status.

Pleural Effusion Index

In figure 3 there is a right lateral decubitus X-ray showing massive pleural effusion. The degree of plasma leakage may be quantified by "pleural effusion index". The pleural effusion index is calculated as 100 times the maximum width of the right pleural effusion, divided by the maximal width of the right hemithorax.

Tourniquet Test

The tourniquet test measures capillary fragility. You can inflate the blood pressure cuff to the point between systolic and diastolic blood pressures for five minutes. After deflating the cuff and the skin returning to its normal color, count the number of petechiae in a one-inch-square area (6.25 cm^2) on the ventral surface of the forearm. Twenty or more petechiae in the one-inch square patch means a positive test.

Laboratory Tests in Dengue Fever

In patients with dengue, the leukocyte counts are often low, even neutropenic. Thrombocytopenia can be the early warning sign, and we should do serial hematocrits to find out possible hemoconcentration. Other useful tests are serum albumin and protein, liver function tests and urine analyses. In addition, there are dengue-specific blood tests that can be performed for viral isolation and serology. The timing of samples for these tests will be discussed later.

Laboratory Methods for Dengue Diagnosis

There are several diagnostic techniques to document the Dengue infection. The most important types of analysis are virus isolation and IgM ELISA. Virus isolation is attempted to determine the virus serotype. And the IgM ELISA is the basic test for serologic diagnosis. The tests for diagnosis of dengue infection are time dependent. In the acute phase, virus isolation should be sent. Virus can be isolated most easily in the first few days. A convalescent-phase sample should also be drawn to test for IgM antibody.

If an autopsy is performed, blood

from the heart should be collected. In addition to blood, the following tissue samples should be obtained: heart, liver, kidney, lung, intestines, spleen, lymph nodes, brain, and skin from areas where the rash occurred. If fresh tissues are available, they will be tested for virus isolation. If an autopsy has been performed and no fresh tissues are available, tissues fixed in formalin should be submitted for immunohis-tochemical studies.

Treatment

Many of these treatment recommendations are extracted from the Pan American Health Organization guidelines.

"Outpatient triage criteria" are including: 1.If the patient has no hemorrhagic and is well-hydrated, the patient can be sent home with instructions 2.If there are hemorrhagic or hydration status is borderline, the patient should be observed in the hospital. But if warning signs are present even without evidence of shock, or if DSS is present, the patient should be hospitalized. Patients who can go home should be instructed with danger signs. Repeat clinical evaluation should be considered, remembering that DSS most commonly occurs at "3-6 days" after symptom onset. Patients with bleeding manifestations should have serial hematocrit and platelet levels checked at least "daily" until their temperature is normal for 1-2 days. Mosquito barriers are only needed until the fever subsides, to prevent day-biting mosquitoes from biting viremic patients and becoming infected.

Treatment of Dengue Fever

The treatment of dengue fever consists of the following: 1.F-Fluids. Patients should be encouraged to take small, frequent sips of fluids. If the patient cannot be rehydrated by mouth, fluids should be administered intravenously. 2.A-Antipyretics, aspirin and nonsteroidal anti-inflammatory drugs such as ibuprofen should be avoided so that platelet function will not be impaired. 3.R-Rest. 4.M-Monitoring of blood pressure, urine output, hematocrit, platelet count, and level of consciousness.

The volume of fluid needed is similar to the treatment of diarrhea with mild-to-moderate isotonic dehydration (5%-8% deficit). Invasive procedures should be avoided whenever possible. There are no data in the published literature regarding the use of steroids, intravenous immune globulin, or platelet transfusions to shorten the duration or decrease the severity of thrombocytopenia.

Indications for Hospital Dis-charge

All of the following indicators should be present for hospital discharge: 1.S-Shock had been treated for 3 days,

2.H-Hematocrit had been stabilized, 3.I-Improvement in the clinical picture, 4.F-Fever had subside for 1 day, 5.T-Thrombocytopenia had been co-rrected. (>50,000 per cubic millimeter). 6.Though pleural effusions and/or ascites may still be present, there should be no distress from them.

Misconceptions about Dengue Hemorrhagic Fever

There are some common misconceptions about DHF that should be mentioned:

1. One commonly believing is that dengue plus bleeding equals dengue hemorrhagic fever. The truth is that there are four established criteria for defining DHF, and the critical difference between dengue fever and DHF is not bleeding, but the increased vascular permeability that occurs in DHF--this is what causes shock and death.
2. Another misconception is that DHF kills only by hemorrhage. Though these patients may have severe hemorrhage, the more common scenario is that the patient goes into irreversible shock because of excessive vascular permeability, and this shock is what causes fatalities.
3. A third misconception is that dengue patients who are not given adequate treatment will develop DHF. It is true that if dengue is mismanaged, the patient is more likely to develop a more severe illness. However, dengue and DHF are distinct conditions: although they are caused by the same virus, and present with the same symptoms in the first days of the illness, DHF is not just a worsening of dengue fever. Even a patient who receives the best possible care may develop DHF.
4. Another misconception is that a positive tourniquet test result equals a diagnosis of DHF. Again, the four criteria must be present for a diagnosis of DHF; the tourniquet test is a nonspecific indicator of capillary fragility.
5. Another common misconception is that dengue hemorrhagic fever is a pediatric disease. Many textbooks on dengue are based largely on the experience in Southeast Asia, where this is true, but all age-groups are involved in the Americas. Likewise, in travelers it can occur in all age-groups.
6. There is a misconception that DHF is a problem of low-income families. The truth is that all socioeconomic groups are affected.
7. Another misconception is that tourists will certainly get DHF with a second infection. The truth is that tourists, even those who have had dengue before, are at low risk for DHF.
8. About the misconception of possible bio-terrerism, Although

there is no lots of evidence prove that, trans-ovarial transmission still is the only important point because making “lots of dengue-infected ova” is easier then making “some dengue-infected mosquito”!

Dengue Vaccine?

There is now no dengue vaccine available. An effective vaccine must be tetravalent, providing protection against all four serotypes. An attenuated tetravalent vaccine in currently occurring in Thailand. However, an effective, safe and affordable vaccine is not likely to be available in the immediate future.

Disease Surveillance and Control

Surveillance

The objective of dengue surveillance system is to provide accurate and early information on disease activity: time, location, virus serotype, and disease severity. Analysis of this information provides the necessary data to predict dengue transmission and guide the implementation of control measures well in advance of peak dengue transmission. Proactive clinical surveillance must be linked with entomologic surveillance, in order to identify the time and place of transmission.

Vector Control Methods

The purpose of control is to reduce female vector and immature vector density to a level at which epidemic virus transmission will not occur. We can use chemical, biological or environmental methods. Chemical control can be targeted at the immature or adult mosquitoes. The larviciding is placing chemicals into containers to kill the mosquito larvae. Ultra-low volume, or ULV spraying of insecticides is widely practiced to kill adult mosquitoes. ULV spraying uses machines that produce very small particles of insecticide, which are carried by wind currents. The insecticide particles must come in contact with the mosquito to kill it. Unfortunately, the *Aedes aegypti* mosquito tends to reside inside houses, often resting in secluded locations such as closets that are not easily penetrable by the insecticide spray. Thus, ULV spraying from vehicles is generally ineffective, killing very few *Aedes aegypti* mosquitoes. The method is, therefore, expensive and ineffective. Commercial aerosol sprays to kill the mosquitoes found indoors are useful, but "knockdown resistance" may occur in some locations. Individual householders may note that spray insecticide has only a temporary effect, knocking down or paralyzing mosquitoes that later recover and fly away.

Biological control methods are not widely used and are primarily experimental. Environmental control

involves eliminating or controlling the container where the mosquito lays her eggs and the immature mosquitoes develop. Since chemical control is generally restricted to containers that cannot otherwise be eliminated or managed, and biological control is still experimental, environmental methods are likely to be the most effective for long-term control of *Aedes aegypti*.

Prevention

Community approaches attempt to involve groups of people in carrying out dengue prevention and control activities. Such programs are much more likely to attain sustainability. It must be remembered, however, that community programs tend to be more difficult to organize than others, and may take a relatively long time to get off the ground.

One of the first steps in achieving community participation is to make sure members of the public know the basics about dengue and the mosquito vector, such as: 1.Where *Aedes aegypti* lays her eggs, 2.The link between larvae and adult mosquitoes, and 3.General information on dengue transmission, symptoms, treatment.

Community programs are important for the possible Dengue bio-terrorism

This basic knowledge about dengue and *Aedes aegypti* is important, but knowing these facts is rarely enough to change people's behavior and involve community members in dengue prevention activities. Householders who know the dengue basics still may lack the knowledge or skills necessary to carry out the recommended behaviors--that is, they may not know where or how to find the containers where water can accumulate and mosquitoes can reproduce. Any successful program must address this skills deficit, ensuring that house-holders are confident in their ability to control mosquito reproduction in and around their homes.

Even when people know what action needs to be taken, and have the necessary skills to carry them out, they may not do so. Community programs must focus on motivating people to take action. This involves under-standing the specific barriers that may be preventing people from acting, as well as the factors that may motivate them. Barriers and motivating factors are likely to differ greatly not only from country to country, but from neighborhood to neighborhood.

Many factors can act as barriers or motivators in influencing community participation in dengue control measures. These include structural factors, such as the existence and enforcement of laws mandating the elimination of *Aedes aegypti* production sites; environmental factors, such as a lack of potable water and the need to store water, or inadequate solid

waste disposal; attitudinal factors, such as beliefs regarding causes, treatment and prevention of febrile illnesses (for example, whether people consider dengue a common illness, whether or not it is perceived as dangerous, or whether people find it hard to link the aquatic larva with the flying mosquito); and community factors, such as its history and structure, the presence of other priority problems, and the local seasonality of dengue. Any effort to help a community overcome its barriers and become motivated to participate in dengue prevention efforts must begin with an understanding of these various factors.

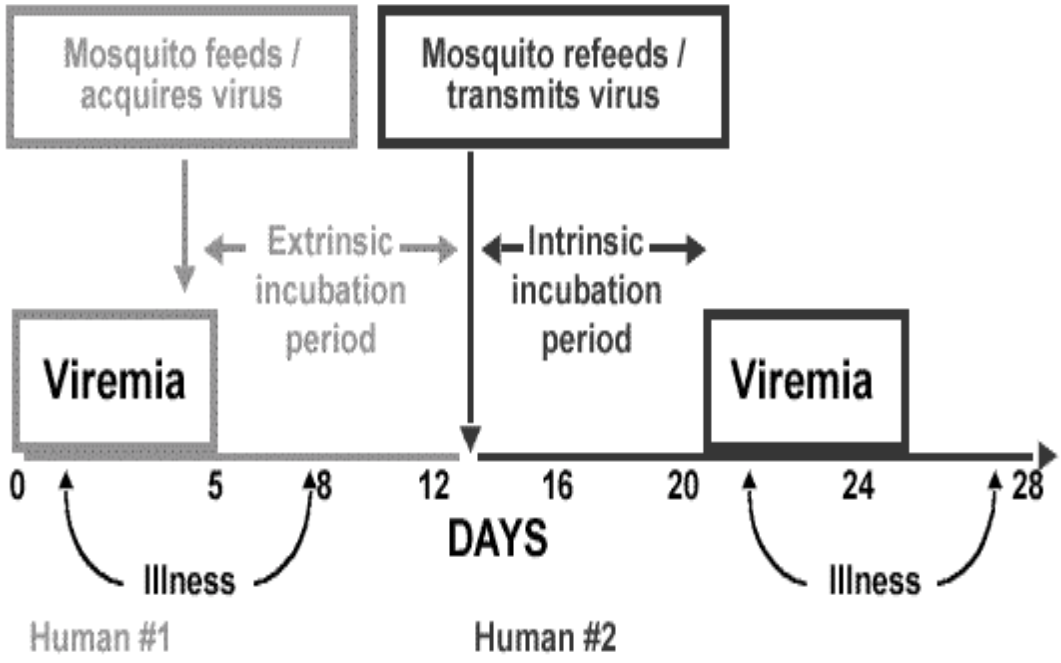

Figure 1. Transmission cycle of Dengue fever

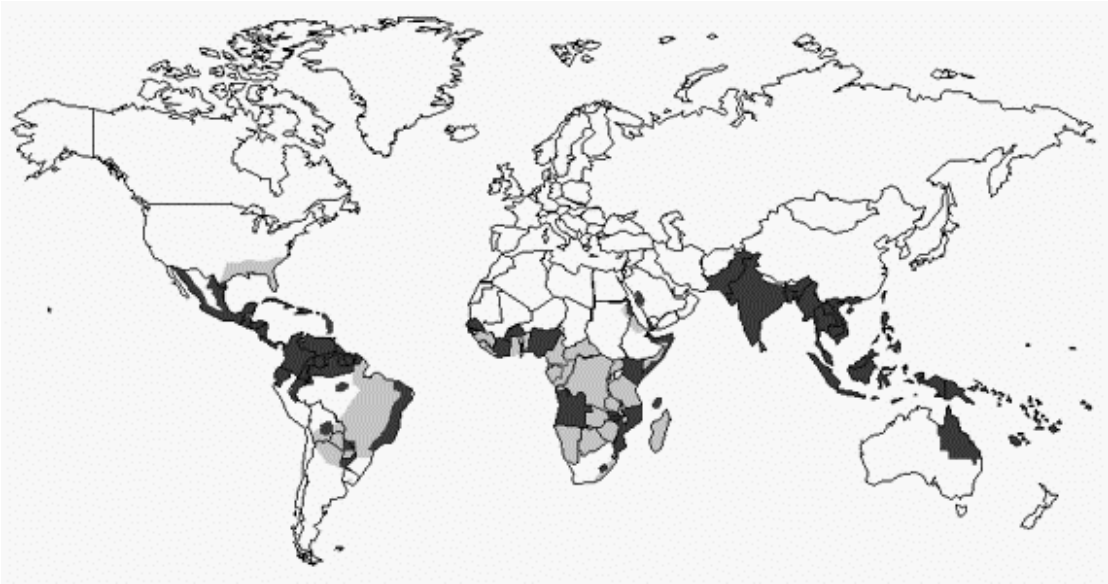

Figure 2. Areas infected with *Aedes aegypti*
Areas with *Aedes aegypti* and recent epidemic dengue

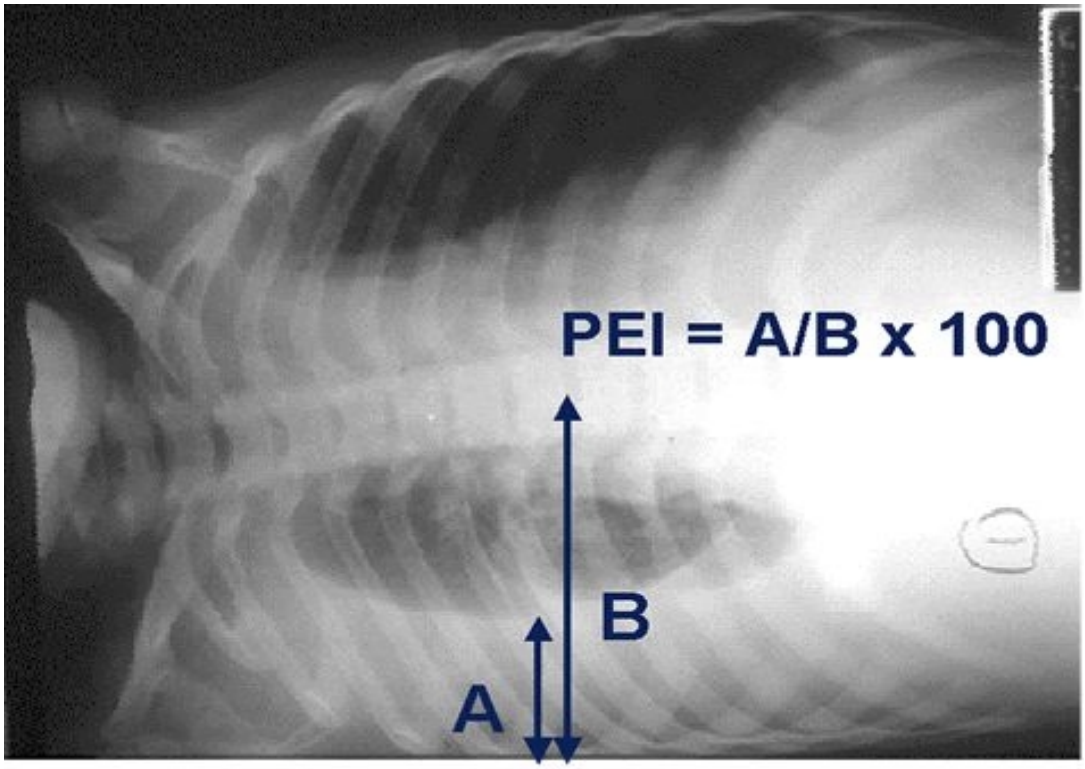

Figure 3.

Source: Vaughn DW, Green S, Kalayanarooj S, et al. Dengue in the early febrile phase: viremia and antibody responses. J Infect Dis 1997; 176:322-30

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出血熱

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摘要

病毒出血熱曾被用來作為生物戰。每一種病毒的傳染途徑，臨床病程及致死率各不相同。在台灣，登革熱是目前最常見的出血熱疾病。登革熱並非經由空氣微粒傳染，且傳染之後很少造成嚴重的出血熱，故其很少被拿來成為生物戰。但在疫情爆發之後，仍會造成許多重病及死亡的案例。在本篇文章中，我們回顧所有國內外歷年文獻，並對國內醫界再次強調其診斷及治療的特色。同時我們也強調民眾教育環境衛生及病媒控制在防治登革熱上佔有決定性的角色。
(Ann Disaster Med 2002;1 Suppl 1: S44-S58)

關鍵詞：登革熱；出血熱；生物戰

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