

~ CHAPTER 1 ~

INTRODUCTION

1.1 Overview

To begin this paper without a journey into the past of dengue infection would be inadequate. This chapter starts by outlining the history and characteristics of the infamous dengue disease. The repercussion of the disease on the global scale as well as within the Malaysian context is also briefly discussed. The current status of dengue infection in Malaysia and the various preventive and control measures will also be covered in the later part of the chapter, following which, the objectives and significance of this study will be presented.

1.2 History of Dengue

Dengue is a viral infection typified by fever, bone or joint and muscular pains, rash, leucopenia, haemorrhagic manifestation and in severe cases, circulatory failure which can be fatal. The first account of dengue infection was rather obscure. According to Professor Susumu Hotta (1969) of Kobe University, towards the end of eighteenth century, such syndrome, now known as dengue, had been labeled as *Coup de barre* in French West India (1635), *Knokkel-Koorts* in Indonesia (1779), *Abu rokab* or *Mal de genoux* in Egypt (1779) and *Break-bone fever* or *Bilious remitting fever* in North America (1780). Some called it the “dandy fever” to describe the acute febrile disease. The Germans named it *hundskrankheit* due to the bloodshot eyes that comes with the infection (Meers et al, 1995). Dengue, as it is widely known as today, was believed to

have lent its name from Spanish, which means prudish or affected. Since the late nineteenth century, enormous progress and discoveries on dengue had been made. One such important accomplishment was made by Bancroft in 1906 who implicated *Aedes aegypti* as a vector of dengue virus, later confirmed by Ashburn and Craig (Hotta, 1969).

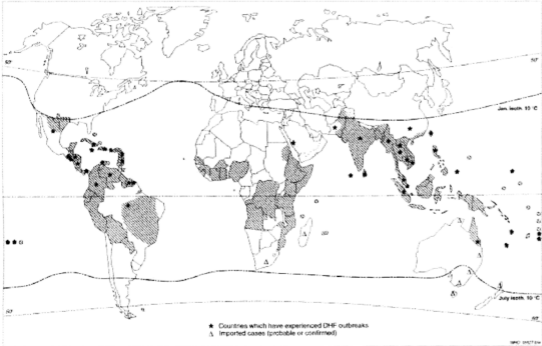
Hotta (1969) cited a few major outbreaks observed in the southern portions of North America in 1922, Greece in 1927-28, on the western coast of Australia in 1925-26, 1942 and 1954-55, Japan in 1942, Vietnam in 1960, Puerto Rico in 1963, and Venezuela in 1964 where some hundred thousand of cases were involved in these pandemics and endemics. According to him, the total easily surpassed a million.

Post World War II, the “bleeding” type of dengue infection or “haemorrhagic fever” was discovered in the Western Pacific Islands as well as the Southeast Asia. Dengue with haemorrhages and cardiovascular shock symptoms was first observed in the Philippines and Thailand in 1954-56. Such versions of dengue, now known as Dengue Haemorrhagic Fever and Dengue Shock Syndrome, were subsequently recognized in the regions of South Asia, China and several Pacific Island groups.

Today, dengue is primarily distributed in the tropical and subtropical regions of the world. Non-immune populations in these areas are constantly exposed to the risk of infection. Tremendous increase in the incidence and geographical distribution of dengue haemorrhagic fever has been observed over the past 20 years. In some South-East Asian countries, epidemics occur almost every year (WHO, 1998).

The sequence of dengue infection is more or less the same in areas of frequent transmission involving multiple dengue serotypes. The first commonly observed pattern started with sporadic cases of dengue haemorrhagic fever, followed by dengue haemorrhagic fever epidemics that gradually become more and more frequent until major explosive epidemic occurs. The disease then follows a pattern of epidemic activity every 2 to 5 years. The second frequently observed pattern is in areas of low endemicity, where multiple serotypes are being transmitted at a rate below 5% of the population per year (WHO, 1997a).

Figure 1.1: The general distribution of dengue fever and/or dengue haemorrhagic fever, 1975 – 1996



Source: World Health Organization, (1997a).

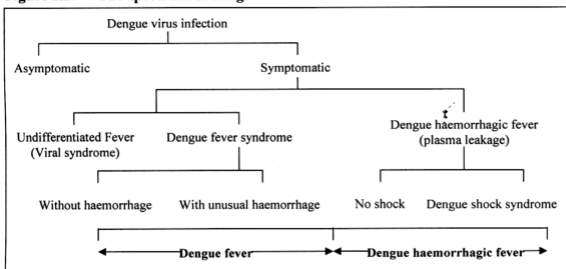
1.3 Dengue Infection

They are four serotypes of the dengue virus recognized as DEN-1, DEN-2, DEN-3 and DEN-4. These viruses, also known as the arbovirus (arthropod or insect borne virus), are transmitted to humans through the bite of infected *Aedes* mosquitoes. Most infections are carried out by *Aedes aegypti*. The less efficient but able vectors for such virus are *Aedes albopictus*, *Aedes polynesiensis*, and several species of *Aedes scutellaris* complex. All the virus serotypes have been linked to dengue fever and dengue haemorrhagic fever and humans are the primary amplifying host for these viruses. Individuals infected by one serotype acquire life-long immunity against reinfection by the same serotype, but not long-lasting cross-immunization. In other words, one can get up to four dengue infections in a lifetime (WHO, 1997a).

Dengue virus infection can be subclinical with no detectable symptom or it may lead to undifferentiated fever, dengue fever (DF) or dengue haemorrhagic fever (DHF) that if untreated, may develop into dengue shock syndrome (DSS), causing circulatory collapse which is fatal (Figure 1.2).

Currently, there are no vaccine or antiviral drugs for dengue infection. Patients essentially self-recuperate. Besides symptomatic treatment, the main treatment is by way of plasma replacement through intravenous means. While it may not be necessary to hospitalize all patients with suspected dengue infection, careful monitoring of infected patient is important so that prompt treatment can be made in case of shock.

Figure 1.2: The spectrum of dengue virus infection



Source: World Health Organization, (1997a).

1.4 Global Impact of Dengue

According to WHO (1997a), dengue infection is estimated at 20 million cases annually, with around 24,000 of deaths per annum. About 2.5 to 3.0 billion people lived in areas at risk of dengue infection as at 1996. In the 1960s and 1970s, about 1.07 million cases and 42,808 deaths were reported. For the decade of 1980s, there were 1.95 million cases and 23, 793 deaths documented in the Western Pacific and Southeast Asia regions alone. Table below shows the global reports of dengue infection.

Table 1.1: Reports of dengue and dengue haemorrhagic fever for the world, 1956 – 1995

Time Interval	No. of years	No. of cases	Mean no. of cases per year
1956 – 1980	25	1,547,760	61,910
1981 – 1985	5	1,304,304	260,861
1986 – 1990	5	1,776,140	355,228
1991 – 1995	5	1,704,050	340,810

Source: World Health Organization, (1997a).

WHO reported a cost estimate of US\$103 million for the 1981 Cuban epidemic of DHF/DSS where 344,203 dengue cases were reported. The estimate includes the cost of control measures and medical services. The epidemics in Puerto Rico since 1977 have cost more than US\$150 million thus far. According to the same source, the estimated direct costs for the 1987 Thailand epidemic were some US\$16 million and the annual spending ranges from US\$19 million to US\$51 million per year depending on the severity of outbreak.

In Malaysia, the cost for Aedes surveillance and control has increased tremendously over the years. According to Shaari (2001) of the Vector and Pest Division of Kuala Lumpur, the figure has increased from RM2 million in 1996 to RM6 million in 1998 for surveillance and control measure alone. In 2000, a budget of RM10 million was allocated for such purpose.

1.5 Situation of Dengue in Malaysia

The earliest account of dengue fever (DF) epidemic in Malaysia was in Singapore in the late 1901 (Rudnick, 1986). At about the same time, an epidemic in Penang involving a large proportion of native population and many Europeans, mostly in the native part of the town, was documented by Skae in 1902. Then in March 1954, an outbreak of dengue fever with rash occurred at a girls' school in Kuala Lumpur with 40 suspected cases. The much dreaded Dengue Haemorrhagic Fever (DHF) epidemic made its debut in Penang and Kuala Lumpur in 1963. Ten years later, in 1973, another DHF

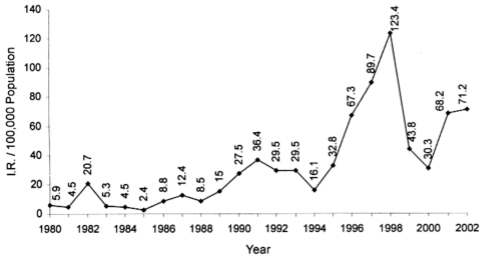
epidemic took place nationwide; 969 cases were reported with 54 deaths, all confined to the urban and semi-urban areas. About 67% of the reported cases were confirmed by the laboratory. Half of the total cases were under 14 years of age. Of all the severe cases, 73% were in the 5 – 14 age-group. In 1982, there was another major epidemic with 3005 cases notified and 35 deaths. About one third of the total notified cases were laboratory-confirmed. It was noted that more than 80% of the cases were from the urban areas (Smith, 1986). This time there was a shift towards the older age-groups. Such phenomenon was perhaps due partly to the dengue control program started in 1974, which managed to reduce the Aedes Index (percentage of premise positive of *Aedes* out of total premises inspected) for houses via house inspection. Pre-school children and the elderly at home were no longer the main affected groups. In fact, most cases now come from the middle age group who work outside (Singh, 2001).

The 1973 DHF outbreak called for an immediate action plan to prevent and control the disease. For that, the Dengue Control Programme was initiated in 1973 under the Public Health Services Division of the Ministry of Health. The program aims to reduce the morbidity and mortality of DF/DHF and to subdue the breeding of *Aedes* mosquitoes to a level below 1% of Aedes Index. In addition, it also seeks to increase public support and participation in the prevention and control of dengue (Singh, 2001).

The Destruction of Disease Bearing Insect Act (1975) was introduced to control the breeding of all vectors that transmit diseases. Under the act, individuals found to be breeding mosquitoes are issued with compound notice of the offence (Pawanchee, 2001).

Today, dengue remains an urban disease. From 1990 to 1998, urban cases made up an average of 82% of total dengue cases reported annually in the country. During the 1980's, improved epidemiological surveillance, vector control and public health education manage to keep dengue at an endemic level with occasional outbreaks. Nevertheless, beginning 1990, the Incidence Rate (IR) per 100,000 population appears to be trending upwards as observed in Figure 1.3. Singh (2001) related such pattern to the rapid urbanization and population growth, disposing of non-biodegradable containers, rapid transportation and poor living conditions which gave rise to the increased breeding of *Aedes* mosquitoes.

Figure 1.3: Incidence Rate (I.R. per 100,000 population) of reported dengue in Malaysia, 1980-2002^a



^a Values for 2000 and 2001 are computed from the Annual Report 2001, Ministry of Health, Malaysia, while the 2002 value is computed from the online statistics published by the Ministry of Health, Malaysia at www.moh.gov.my.

Source: Modified from Singh, S., (2001).

Under the current Eighth Malaysian Plan 2001-2005, the targets set for controlling DF/DHF are:

- *Not more than 50 cases of DF per 100,000 population*
- *Not more than 2 cases of DHF per 100,000 population*
- *Case Fatality Rate of DF/DHF (total death over total DF & DHF cases) not more than 0.2%*
- *Case Fatality Rate of DHF (total death over total DHF cases) not more than 1.0%*

In the bid to achieve the above targets, the Prevention and Control of Infectious Diseases Act (1988) requires that all medical officers to notify all clinically diagnosed dengue cases within 24 hours to the nearest District Health Office, even without laboratory confirmation. The District Health Office will then inform the Senior State Health Officer, who will in turn notify the Epidemiology Department at the headquarters. Such prompt notification through the proper channels is crucial to allow immediate and timely control measures to prevent outbreak (Singh, 2001).

Rapid screening tests are also employed in order to speed up the diagnosis and confirmation of dengue infection. Under the vector control program, houses and premises are inspected periodically through the “search and destroy” activities. Fogging is carried out in areas of reported dengue, areas of outbreak as well as those identified as high risk. Larviciding is also performed regularly by the health personnel to destroy the larval stages of *Aedes* mosquitoes. Other important measures proven effective in preventing and controlling dengue include public education and community participation (Ewe, 2001). Activities such as exhibitions, demonstrations and distributions of

educational materials are carried out through mass media and individual approach. Anti-dengue campaigns (1997) and National Cleanliness and Anti-mosquito Campaign (1999) are launched by government nationwide to control dengue outbreaks. In school, the “Dengue Free School” program educates children about the disease so they can be the “change agents” in the future. Various Quality Assurance tools are also introduced to improve the management and control of dengue outbreaks. Training and research in this area are also intensified under the government initiatives (Singh, 2001).

Table 1.2: Number of reported dengue cases and death in Malaysia, 1997-2002

	1997	1998	1999	2000	2001	2002
DF	18,642	26,240	9,403	6,715	15,360	15,493
DHF	787	1,133	605	403	908	1,960
Total	19,429	27,373	10,008	7,118	16,268	17,453
Death	52	82	37	37	50	69

Source: Compiled from the Annual Report 2001 and online statistics (www.moh.gov.my) published by Ministry of Health, Malaysia.

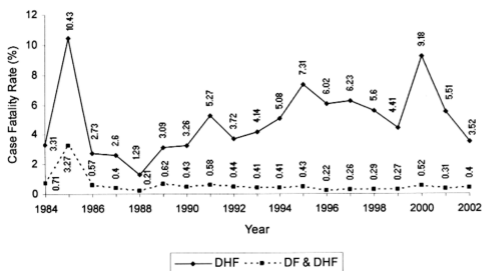
Singh (2001) commented that the drop in the total DF/DHF cases since 1999 (Table 1.2 and Figure 1.3) can be attributed to the success of the “National Cleanliness and Anti-mosquito Campaign” launched in April 1999 with the objective to increase awareness of mosquito-borne diseases. Moreover, the pre-dominance of DEN-2 virus in the preceding years might also contribute to herd immunity to this virus, thereby causing a reduction of cases after 1998.

Ironically, despite the sharp decline in 1999, the Incidence Rate of DF/DHF quickly bounced back to about 70 cases per 100,000 population in 2001 and 2002 (Figure 1.3);

way above the target of 52 cases set under the Eighth Malaysian Plan as mentioned earlier.

From 1990 to 2002, the case fatality rate for DF and DHF combined (total deaths over total DF and DHF cases) hovered in the range of 0.22-0.58% as observed in Figure 1.4; consistently above the target of 0.2%. The case fatality rate for DHF likewise fluctuated above the target of 1.0% throughout the period shown.

Figure 1.4: Case Fatality Rate according to DHF and DF & DHF in Malaysia, 1984-2002^a



^a Values for 2000-2002 are computed from the online statistics published by the Ministry of Health, Malaysia at www.moh.gov.my.

Source: Modified from Singh, S., (2001).

1.6 Objectives of the Study

Broadly speaking, the intention of this paper is to understand the various clinical and laboratory manifestation in relation to dengue infection. To achieve that, the explicit objective of this study is three-fold and they are:

1. To understand the significance of various dengue symptoms in adults and children clinically diagnosed as having dengue fever and dengue haemorrhagic fever.
2. To explain the variation in the dengue serology test outcome for the clinical dengue patients at the University Malaya Medical Centre (UMMC).
3. To classify patients into category of dengue fever or dengue haemorrhagic fever in the context of UMMC.

1.7 Significance of the Study

This case study on the dengue patients at UMMC for the year 2002 can provide an updated understanding on the clinical presentation of dengue infection that keeps changing every now and then as claimed by George (1993) in tracking the clinical pattern of the disease since early 1960's. The study also allows surveillance on the current practice and management of dengue cases at UMMC in area such as the admission rate, notification of dengue cases and proportion of suspected dengue patients who underwent dengue serology test. Through the study, symptoms significant in the differential diagnosis of dengue infection (positive dengue serology) versus other non-dengue viral infection (negative dengue serology) can be identified. In addition, dengue symptoms

significant in the classification of clinical DF and DHF cases at UMMC can be studied and compared against various guidelines and protocol for the purpose of such diagnosis.

1.8 Organization of the Paper

Subsequent to the above introduction to dengue infection, Chapter 2 provides a concise review of the literature and studies made in this area pertinent to the objectives of this study.

Chapter 3 goes a step further by introducing the data and discussing the statistical methodologies employed throughout the study.

Chapter 4 describes the profile of dengue patients in this study alongside the various statistics pertaining to the management of dengue cases at UMMC. The chapter also looks into the various clinical and laboratory symptoms of dengue infection in children and adults diagnosed with DF and DHF.

Chapter 5 presents the logistic model for prediction and classification of dengue infection defined as either positive or negative result in the dengue serology test. Probability of dengue infection is computed under hypothetical conditions while odds ratios are depicted for understanding of relative risk. Essential tests of significance and diagnostic analysis will also be discussed in complement to the statistical modeling process.

Chapter 6 provides the discriminant function for the classification of DF and DHF clinical diagnosed by the medical officers at UMMC. Various measures of model fit and significance are reviewed.

Chapter 7 wraps up the paper with a summary of the salient findings in this study. The chapter also puts forth some discussions on the critical findings of the study as well as its limitations. Suggestions on future study are also furnished herewith.

For the convenience and greater appreciation of the analyses and findings herein, the definition of the medical terms commonly quoted in the paper is provided in the Appendix.