EVALUATION OF DENGUE FEVER KNOWLEDGE AMONG THE GENERAL POPULATION AND ITS PREVALENCE, CLINICAL FEATURES IN PENANG GENERAL HOSPITAL

By

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Dedication

My research is dedicated to my parents and my uncle Dr B.J. Wazir and

Auntie Aishah Wazir

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LIST OF ABBREVIATIONS

APTT	Activated partial thromboplastin time
ADEM	acute disseminated encephalomyelitis
ALT	Alanine aminotransaminase
AAT	Alanine aminotransferase
ALP	alkaline phosphatase
AMR	Americas Region
NS1	Antigen Non structural protein -1
AST	Aspartate aminotransaminase
BP	Blood pressure
CFR	Case fatality rate
CNS	Central nervous system
CSF	Cerebro spinal fluid
CRC	Clinical Research Committee
CDC	Communicable Diseases Centre
DEN	Dengue
DF	Dengue Fever
DHF	Dengue hemorrhagic fever
DSS	Dengue shock syndrome
DBP	diastolic blood pressure
DIC	Disseminated Intravascular coagulopathy
EMR	Eastern Mediterranean Region
ELISA	enzyme-linked immunosorbent assay
GGT	Gamma glutamyltransferase
GIT	gastrointestinal tract
HI	Haemagglutination Inhibition
HCT	Haemotocrit
IV	intravenous
KAP	Knowledge practice attitude
MOH	Ministry of health
NR	Normal range
NS	normal saline solution
PAHO	Pan American health organization)
PT	Platelets
PCR	Polymerase chain reaction
TDR	Research and training in tropical diseases
RT- PCR	Reverse transcriptase polymerase chain reaction
SWG	Scientific Working Group
SERI	socio-economic and environmental research institute
SEA	South- East Asian countries
SEAR	South East Asian Region
SEAR	South-East Asia Region

SPSS	statistical package for social science
SBP	systolic blood pressure
AFR	The African region
TT	Tourniquet test
UN	United Nations
WPR	Western Pacific Region
WPR	Western Pacific Region
WBCs	White blood cells
WP	working paper
WHO	World Health Organization

APPENDICES

PENILAIAN PENGETAHUAN TENTANG DEMAM DENGGI DALAM KALANGAN ORANG RAMAI SERTA PREVALENSNYA, CIRI –CIRI KLINIKAL DI HOSPITAL BESAR PULAU PINANG

ABSTRAK

Denggi merupakan salah satu daripada masalah kesihatan awam global yang amat penting, terutamanya di negara-negara Asia Tenggara. Walaupun penyakit ini telah wujud di Pulau Pinang sejak 1902, namun tiada bukti yang memperincikan tentang pengetahuan denggi dalam kalangan orang ramai. Kemunculan semula penyakit ini memerlukan suatu penilaian tentang pengetahuan yang ada pada orang ramai, prevalensnya, ciri-ciri klinikal dan pengurusan denggi di Pulau Pinang. Dalam kajian rentas-silang data dikumpul daripada orang ramai untuk menilai pengetahuan mereka tentang denggi. Seramai 862 responden terlibat dalam kajian ini, yang majoritinya (97.2%) mengetahui tentang denggi. Dapatan menunjukkan bahawa pengetahuan responden tentang denggi dan nyamuk aedes adalah mencukupi. Dari segi bangsa, didapati bahawa pengetahuan tentang denggi secara signifikannya adalah tinggi dalam kalangan responden berbangsa Melayu, dibandingkan dengan bangsa lain. Pengetahuan dalam aspek pencegahan dan gejala denggi didapati tinggi dengan perkaitan yang signifikan P=0.030 dan P=0.031 masing-masing, dengan peningkatan kumpulan umur. Suatu perkaitan yang positif ditemui di antara pengetahuan dan pendidikan. Dari segi gender, responden wanita menunjukkan pengetahuan yang lebih baik berbanding dengan responden lelaki. Dalam kajian ini, ditemui bahawa responden lelaki sama ada yang bekerja, tidak bekerja, mahupun remaja secara signifikannya tidak mempunyai pengetahuan yang mencukupi tentang denggi. Mereka ini perlu diberi perhatian khusus serta galakan untuk ikut serta dalam program pendidikan kesihatan terutamanya tentang denggi, yang akan diadakan pada masa depan. Suatu kajian retrospektif dijalankan, yang melibatkan sejumlah 756 pesakit denggi yang dimasukkan ke wad perubatan di Hospital Besar dalam tempoh Januari 2007 hingga Disember 2007. Dalam pemerhatian ini, denggi didapati dalam kalangan kanak-kanak dan orang dewasa. Ciri klinikal demam, ruam petekia (petechial rashes), ujian Hess positif, kesakitan di bahagian epigastrik, peningkatan sel darah putih, hemoglobin, hematokrit dan trombositopenia ditemui secara signifikan (P<0.001) berkaitan dengan denggi. Semua pesakit sembuh kecuali seorang meninggal kerana sindrom kejutan denggi. Demam denggi, demam denggi berdarah dan sindrom kejutan denggi sepatutnya dianggap sebagai diagnosis yang berbeza. Bagi mengelakkan komplikasi, pengurusan bendalir secara intravena adalah mandatori, yang perlu diberi dengan teknik khusus untuk mengelak daripada berlakunya lebihan cecair pada pesakit kanak-kanak dan juga pesakit dewasa.

EVALUATION OF DENGUE FEVER KNOWLEDGE AMONG THE GENERAL POPULATION AND ITS PREVALENCE, CLINICAL FEATURES IN PENANG GENERAL HOSPITAL

ABSTRACT

Dengue is one of the most important global public health problem, particularly in South East Asian countries. Despite the presence of the disease in Penang since 1902, no documented evidence existed on the knowledge of dengue among the general population. The current resurgence of the disease necessitates an evaluation of public knowledge, prevalence, clinical features and fluid management of dengue in Penang. In cross-sectional study data were collected from the general population to asses the knowledge. A total of 862 respondents of the population were participated in the study.Majority (97.2%) of the population were familiar with the disease dengue. Over all knowledge about dengue and aedes mosquito was found adequate. In terms of races knowledge on dengue was found significantly higher in Malays than the other races. Knowledge on isolated aspects like preventive measures and symptoms of dengue was found to be high with significant association (P=0.030 and P=0.031) respectively, with increasing age groups. A positive association was found between knowledge and education. On gender base female shown good knowledge compared to male. In this study the teenagers, private, unemployed people and in terms of gender male had significantly insufficient knowledge and need a special attention and to encourage these groups for meaningful participation in future health education programes regarding dengue. In retrospective study a total of 756 in patients of dengue were observed admitted to the medical ward in General Hospital during the period January 2007 to December 2007 and found that the children and adults both were affected of dengue. The clinical features fever, petechial rashes, positive Hess test, epigastric pain the rise of white blood cells (WBC), haemoglobin, haematocrit and thrombocytopenia found a significant (P<0.001) association with dengue. All patients were survived except one who was found to be died of dengue shock syndrome and circulatory failure. Dengue fever, dengue haemorrhagic fever and dengue shock syndrome should be considered in a differential diagnosis of febrile illness in patients. To avoid complications, management of intravenous fluids is mandatory to administer with special technique to avoid over load of fluids both in children as well as in adults.

CHAPTER ONE
INTRODUCTION

1.0 Introduction and literature review

1.1 Background

Dengue is defined as "an acute illness caused by a virus belonging to the family flaviviridae, under the genus flavivirus". Today dengue is a fast growing health problem in tropical and sub tropical countries and is the most common disease among all arthro-borne viral infection in the world today. Yearly, more than 100 million cases of dengue infection worldwide are anticipated to occur and become not only an enormous health problem but also a serious economical burden to those countries where dengue is endemic (World Health Organization, 1997).

There are four famous serotypes of dengue virus namely as Den-1, Den-2, Den-3, Den-4, which are known to cause a wide spectrum of nonspecific viral set of symptoms, ranging from fever and headache to severe and fatal hemorrhagic disease, known as dengue hemorrhagic fever and dengue shock syndrome. Dengue hemorrhagic fever is a severe febrile disease that is characterized by abnormalities of homeostasis and increased membrane permeability, also characteristic of dengue shock syndrome (Halstead, 1980). Infection with one serotype develops long life immunity against re-infection by that same serotype, but not against the other serotype.

1.2 Epidemiology and prevalence of dengue fever

Geographically the spread, incidence and severity of dengue fever (DF) and dengue hemorrhagic fever (DHF) had been increased in the Americas, South-East Asia, the Eastern Mediterranean and the Western Pacific. It was reported that 2,500 million to 3,000 million people live in the areas where dengue viruses can be transmitted. It was estimated that each year 50 million infections occurred, with 500,000 cases of DHF and at least 12,000 deaths (WHO, 2002).

An epidemiological study was conducted on dengue epidemics in 1998 Nicaragua, Central America. The dengue disease is classified on the basis of disease severity. A total of 1,027 patients were enrolled, in which 614 (60%) of the patients were found confirmed a positive cases of dengue. Out of 614, 268 (44%) were classified as dengue fever (DF), 267 (43%) defined as DF with hemorrhagic manifestations (DF hem), 40 (7%) as dengue hemorrhagic fever (DHF), 20 (3%) classified as dengue shock syndrome and 17 (3%) as dengue with signs associated (DSAS). No secondary correlation was found with DHF and DSS. In this study dengue type 3 was found to be responsible for causing dengue. It was concluded that the epidemiology can be dependent on the geographical region and viral serotype (Harris *et al*., 2000).

A retrospective study was carried out in a hospital during the outbreak of dengue in 1996 Delhi, India. Children were studied from September to November 1996 in the hospital. There were a total of 134 cases of dengue, in which 80 (60%) were males and 54 (40%) female. All these patients were diagnosed and managed according to standard protocol, 92 (67%) were detected as dengue hemorrhagic fever (DHF) and 42 (33%) as dengue shock syndrome (DSS). The symptoms observed were fever

(93%), abdominal pain (49%) and vomiting (68%). Haemorrhagic features observed were hematemsis (39%), epistaxis (36%) and skin bleed (33%). Hepatomegally was present in 97 (72%) patients and spleenomegally 25 (19%). Haematocrit (>40%) was found only in 25 (18%). So in this study it was observed that the children <6 years were more affected and was suggested that this may be due to increase in endemicity and further suggested that the DHF and DSS cases in which fluid therapy is not required isolated management protocol should be formulated (Aggarwal *et al*., 1998).

In a study carried out by Gubler, (1997) observed that the characteristic of DF in the America during the first 70 years of 20th century was the classical DF disease and that the outbreaks were caused by a single virus serotype. Dengue and dengue hemorrhagic fever geographically expanding because both the viruses and the mosquito vectors had increased the outbreaks. Gubler suggested that there is a need of community participation in dengue's programme. It was also suggested that there is a need for research and improvement of public health infrastructure. Further it was emphasized on the research needed to develop more effective preventive strategies, including new mosquito control technology and dengue vaccines, an improved public health infrastructure. These strategies will help the community-based prevention programmes to reduce the inclination of growing epidemic dengue fever (DF) and dengue hemorrhagic fever (DHF).

It was reported in a study that in 1993 in the Central America (Costa Rica and Panama), native dengue transmission was occurred and finally in 1994 dengue virus serotype 3 reappeared in Nicaragua and Panama after 17 years reported by morbidity and mortality weekly report (MMWR, 1995). In this report clinical profile were observed for 40 cases out of 46 laboratory-confirmed cases. The most commonly

reported symptoms were presented with classic dengue fever (92%), myalgia (48%), rash (48%) and headache (42%). They suggested for the health care providers to consider dengue in a differential diagnosis for all patients. They further suggested that when dengue is suspected, patients should be monitored for evidence of hypotension, hemoconcentration and thrombocytopenia. Because of the anticoagulant properties of acetylsalicylic acid (i.e., aspirin), only acetaminophen products are recommended for management of fever.

In a study conducted in Brazil, the first detected cases of dengue hemorrhagic fever was explored in Rio de Janeiro followed the isolation of DEN-2 in 1990. Upto 1991, over 50.0% (462) of all dengue hemorrhagic fever cases were diagnosed in that area. In next few years the numbers of cases of dengue were noted more and observed 112 cases per year excessive in Fortaleza, Ceara State, in Northeast Brazil. From 1995 up to 2000 Brazil had recorded few cases of dengue hemorrhagic fever and noted thousands of reported cases of classical dengue fever (DF). Majority of the people were over 15 years old that highly affected by dengue fever. They concluded that as long as a vaccine is not available, further dengue control depends on potential results from basic research and intervention evaluation studies, integrating environmental changes, community participation and education, epidemiological and virological surveillance, and strategic technological innovations aimed to stop transmission (Teixeira *et al*., 2002).

In another study 63% of the patients had dengue shock syndrome with haemoconcentration, thrombocytopenia and shock. There was a high percentage (80%) had gastrointestinal and in 9 (30%) had complications severe enough to cause shock and death. So in these nine cases, the gastrointestinal hemorrhage and

haematemesis began before the onset of shock and there was no evidence haemoconcentration or pleural effusion any time during hospitalization. In conclusion it was proposed that the disease should be more practically classified as dengue fever with or without hemorrhage and dengue shock syndrome (Suharyono *et al*., 1979).

Kouri and his colleagues in their study reported that dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS) cases, first were reported in Cuba in 1981. They reported a total of 344,203 of dengue and 10,312 out of that were of DHF and DSS cases and 158 cases were found critical, three main dengue outbreaks were reported in Cuba, one in 1977, produced by DEN-1 and characterized as classical dengue fever and two DHF epidemics, one in 1981 and the other in 1997, caused by DEN-2. In January 1997, a DEN-2 outbreak was evaluated in Santiago de Cuba municipality (in an eastern Cuban province). The results among adults showed that dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS) was characterized by fever (100%), gastrointestinal symptoms (90%), purpura (66%) and upper gastrointestinal bleeding (40%). Hepatomegaly (35%), abdominal pain (58%) and haematemesis (35%) were frequently recorded in fatal cases; these can be considered to be signs of a poor clinical prognosis. Thrombocytopenia (71%) and haemoconcentration (92%) were frequently observed in many cases. In children thrombocytopenia and haemoconcentration were observed in 78% and 97%, respectively. It was concluded that it should be in the notice of international community that dengue can be controlled when the principles established by (PAHO) and (WHO) to follow strictly as this done by Cuba twice (Kouri *et al*., 1989).

In 2001, a record 69 countries from the Word Health Organization (WHO) regions of South East Asia, Western pacific, and the Americas reported about the existence of dengue. In 2002, the World Health Organization (WHO) region of the Americas were reported more than 1 million cases for the first time.

It was reported by Scientific Working Group (SWG), research and training in tropical diseases (TDR) that dengue is an endemic in all of the World Health Organization Regions except the World Health Organization European Region (WHO, TDR, 2002).

In another study explored by Scientific Working Group (SWG) and (TDR) to the world health organization (WHO, 2006) that the average number of dengue cases occurred in specific time (yearly) in different countries of the world, from 1955 to 1959, 908 cases were reported, in between 1960 to 1969, 15,497 cases of, 1970 to 1979, 122,174 cases, 1980 to 1989, 295,554, cases, 1990 to 1999, 479,848 cases and from 2000 to 2005 925,896 cases of dengue were reported to the World Health Organization (WHO).

A study performed in Nakhon Pathom, Thailand on the outbreak of dengue fever (DF) and dengue hemorrhagic fever (DHF) in the year 2001 (Thaval *et al*., 2006). The total cases of dengue hemorrhagic fevers (DHF) were reported 3112 and 393 per/100,000 populations. Out of these volunteers 8.8 percent had a serum sample positive for DF and DHF virus IgM antibody. The highest prevalence was found in 15 to 40 years of age group. As a result it was found that the high prevalence of dengue virus mixed with big population, urbanization and increasing the breeding chances of

mosquitoes. It was suggested to observe the evaluation of viral transmission at the time of outbreak and later. This shows the importance to inform people and control the virus transmission and is necessary for personal protection.

In endemic Asian countries where there was a simultaneous transmission of multiple serotypes and cyclical epidemics, primary dengue infection usually occurred in young children and created few symptoms. Ocassionaly; severe dengue was noted in infants less than one year of age and was credited to the presence of maternal antibody (Kliks *et al*., 1988). In general, symptomatic dengue and severe disease, mostly associated with secondary or repeat infections, occur in older children (Burkie *et al*., 1988; Thein *et al*., 1997). As shown in the table below, 25% to 37% of symptomatic dengue requiring hospitalization was reported in children in 5 to 9 years of age.

Table 1.1 Age distribution of dengue cases from hospital based studies in hyper endemic Asian countries.

Hospital and year	Diagnosis and number (*n*)	Percentage of cases by age group			
		< 5 years	5- 9 years	10 to 14 years	> 15 years
S. L. Hospital, Manilla, Philipines ,1983 -1984 (Hayes *et al*., 1998)	Laboratory-confirmed dengue cases, n = 517	15%	36%	26%	23%
Children's Hospital No1, H. C. M. City, Vietnam 1996 (Lan *et al*., 1998)	Clinically suspected Cases, n = 4,011	34%	37%	29%	NA
M .H. Hospital and C. Hospital , Palembang, South Sumatra, Indonesia,1998 (Crown *et al*., 2001)	Clinically suspected dengue cases, n = 1,772	16%	25%	59%	NA

Table 1.2 Incidence of laboratory-confirmed symptomatic dengue from population based prospective studies in hyper endemic Asian countries

Study site	Population Size	Age range	Study period	Incidence
Yan ,Myanmar (Thein *et a*l.,1997)	12489	1 to 9 years	1984 to1988	0.3% (hospitalized dengue cases/year)
Bangkok, Thailand (Burke *et a*l.,1988)	1757	4 to 16 yrs	Jun 1980 to Jan 1981	0.7% (symptomatic dengue cases over one season)
Yogyakarta, Indonesia (Graham *et a*l.,1999)	1837	4 to 9 years	1995 to1996	3.6% (symptomatic dengue cases over one season)
Kamphaeng phet, Thailand (Endy *et a*l., 2002)	2119	7 to 11years	Jun 1998 to Nov 1998	3.3% (symptomatic dengue cases over one season)
	1928		Jun 1999 to Nov 1999	0.8% (symptomatic dengue cases over one season)
	1713		Jun 2000 to Nov 2000	

In one of the study performed on the epidemiology of dengue reported that in some of the countries gradually the older age groups became a victim of dengue attack (Guha-Sapir., 2005), this was dramatically seen in Singapore where they had successfully controlled the mosquito. Recently it was reported, that less than 1% of children 10 months to 5 years old and only 7% of those 6 to 10 years of age were found to have dengue antibodies (Ooi *et al*., 2001) and high dengue mortality was moved from children to adults (Goh,1997).

The dengue fever that was observed in children, in Latin American and Carribean countries was found to be more severe than the hyper endemic Asian countries. In these countries both adults and children were affected by dengue and in some epidemic areas only adults were affected (Guzman and Kouri, 2003).

1.3 Prevalence in Malaysia

Malaysia is located in the tropics, dengue is a major problem for its people. Dengue fever was first reported in 1902 in Penang (Skae, 1902) and had become a major public health problem in Malaysia. As DHF outbreak was first appeared in Penang in 1962 (Rudnick, *et al.,* 1965). Notification of DF and DHF in Malaysia was reported in 1971. It has reported that the incidence rate of clinically diagnosed DF and DHF increased from 8.5 cases/100,000 population in 1998 to 123.4 cases/100,000 population in 1998. In the year 2001, out of 16,368, 22% cases were reported among children 14 years and below. In the year 2001, the DH: DHF ratio in children to adults was found to be 6.7:1 (Ministry of Health, Malaysia, 1988-2001).

The incidence of both dengue fever (DF) and dengue hemorrhagic fever (DHF) in Malaysia has increased. The case fatality rates (CFR) however, seem to be stable. Many reported cases cannot be confirmed due to the lack of a second blood specimen. Of the confirmed cases, about 5 % were DHF as seen in Table 1.4.

Table 1.3 Dengue fever in Malaysia 1999-2003

Year	Population CFR	Reported cases	Confirmed cases		Incidence /100,000	Deaths
			DF	DHF		
1999	22,711,900	10,146.78	4,718	-	20.77	37
2000	23,226,700	71,181.21	3,312	411	16.03	45
2001	23,795,300	16,368.58	8,277	392	36.43	50
2002	24,374,300	32,767.64	14,694	799	63.56	99
2003	25,048,300	31,545.47	14,761	681	61.65	72

DF = Dengue fever, DHF = Dengue-hemorrhagic-fever, CFR = Case-fatality-rate
Adaptation, vector borne disease section, Ministry of Health, Malaysia

Table 1.4 Dengue deaths and case fatality rates by age in Malaysia (1999-2003)

Year	Age <5 years			Age 0-14 years			Age> 15 years		
	Total Cases	Total deaths	CFR	Total cases	Total deaths	CFR	Total cases	Total deaths	CFR
1999	457	3	0.66	2,045	19	0.09	8,101	18	0.22
2000	373	12	3.22	1,432	19	1.33	2,291	26	1.3
2001	863	7	0.81	3,605	23	.64	5,064	27	0.53
2002	130	17	13.08	2,284	47	2.07	13,209	52	0.39
2003	469	11	2.35	3,096	29	0.94	12,346	43	0.35

(Adaptation: Ministry of Health Malaysia, Vector-Borne Diseases Section, Annual Report)

According to the Ministry of Health, Malysia, 2007, in the below figure the number of reported dengue fever (DF) and dengue hemorrhagic fever (DHF) cases in Malaysia had increased as displayed in the figure 1.

The incidence rate also has increased from 44.3 cases/100,000 population in 1999 to 181 cases/100,000 population in 2007, Figure 2. This exceeded the national target for the incidence rate of DF and DHF which was kept less than 50 cases/100,000 population.

The incidence rate was found higher in the age group of 15 years and above (Figure 2). The highest incidence rate found among the working and school-going age groups. An increase of dengue deaths in the adult population had been observed since 2002, Figure 3.

The case fatality rates for both DF and DHF have remained below 0.3% since 2002 in Figure 4.

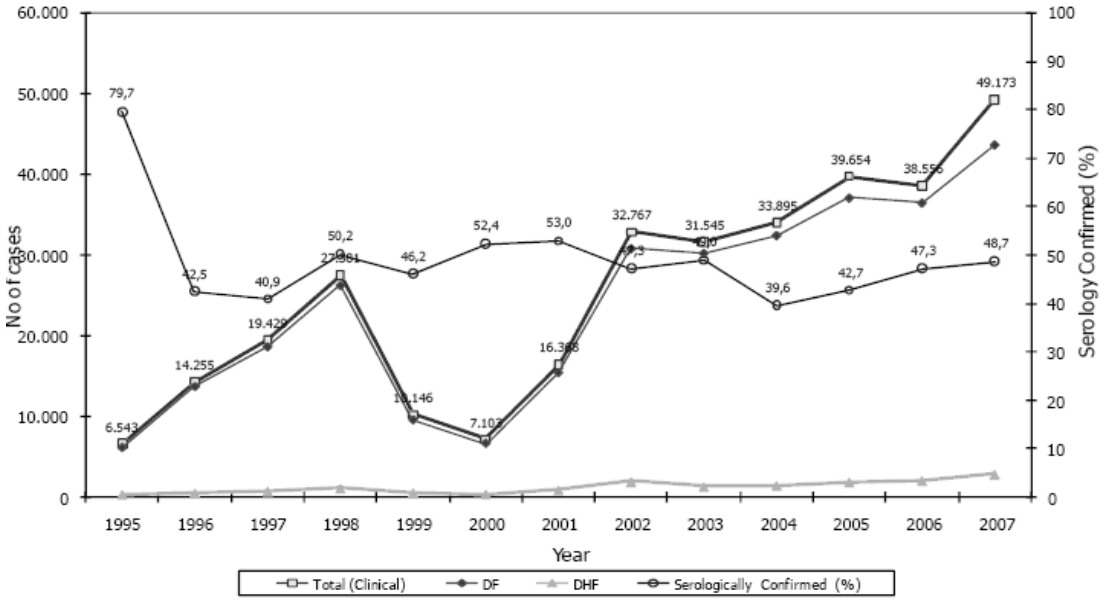

Figure 1.1 Number of dengue cases, Malaysia 1995-2007

Adapted from annual report vector borne disease section (Ministry of Health, Malaysia; 2007)

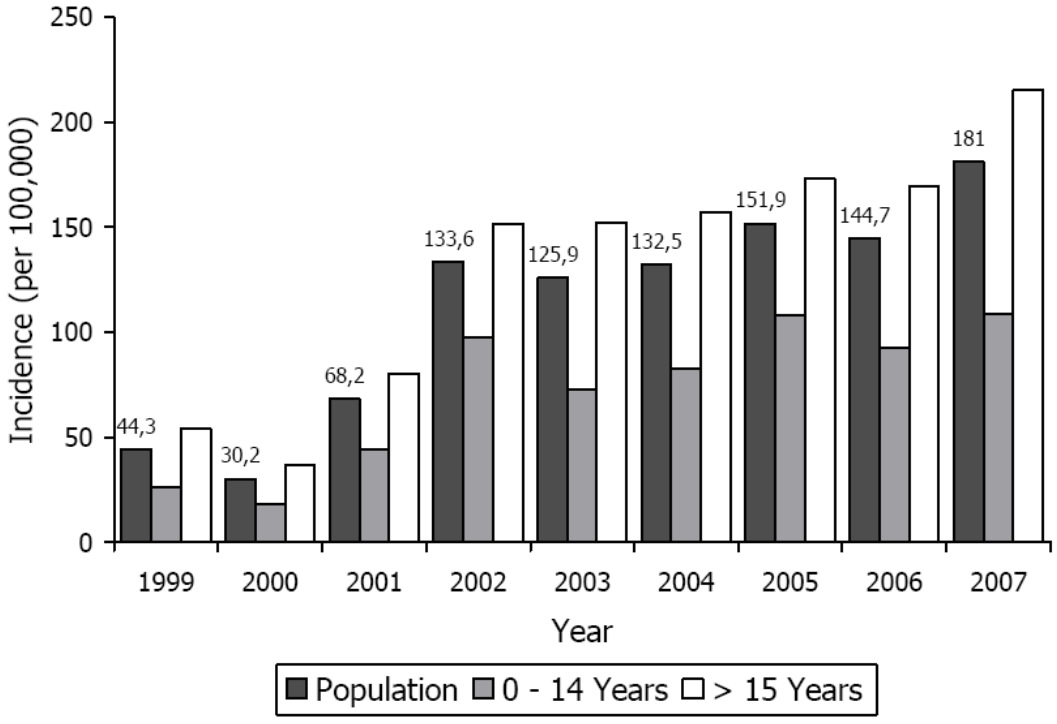

Figure 1.2 Dengue incidence rate by age group in Malaysia, 2003, 2007

Adapted from annual report vector borne disease section (Ministry of Health, Malaysia; 2007).

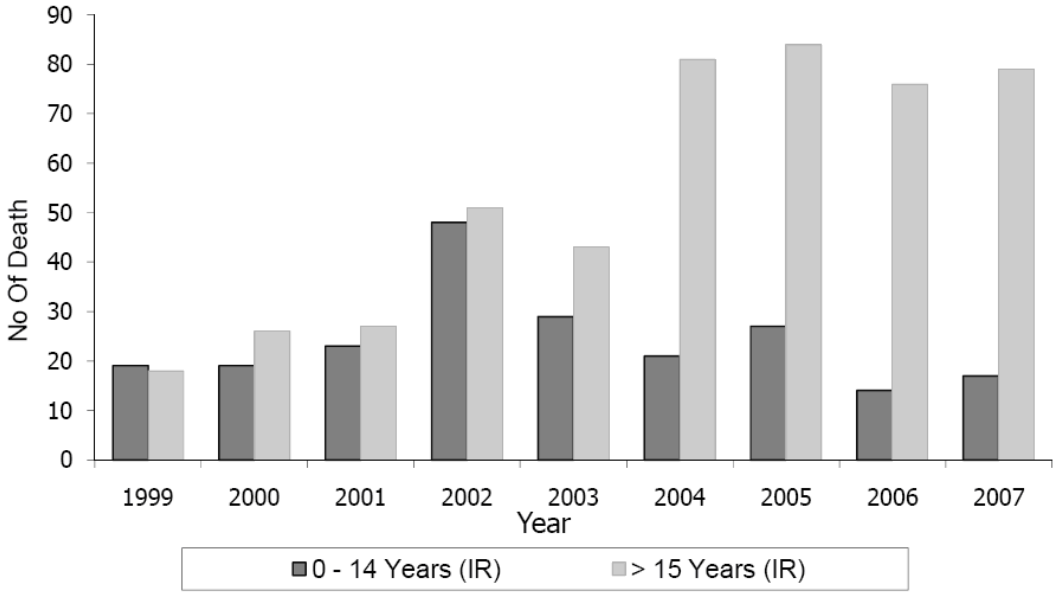

Figure 1.3 Dengue deaths by age group, Malaysia

Adapted from annual report vector borne disease section (Ministry of Health, Malaysia; 2007).

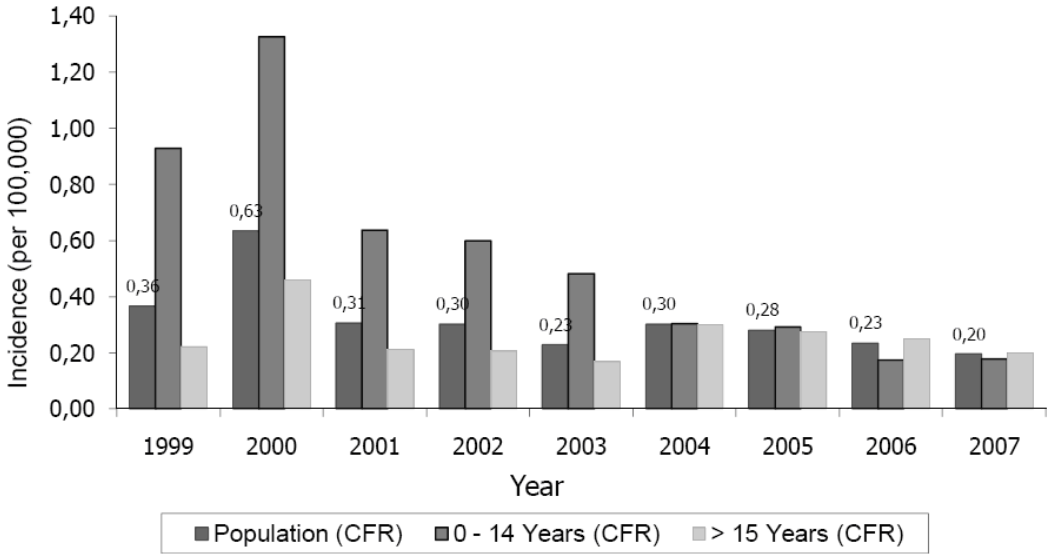

Figure 1.4 Dengue case fatality rate (CFR) by age group, Malaysia

Adapted from annual report vector borne disease section (Ministry of Health, Malaysia; 2007).

1.4 Disease Transmission

The bite of an infectious female mosquito transmits dengue to humans. The *Aedes aegypti* mosquito usually rests in dark, indoor sites such as closets and under beds and is primarily a day time feeder, biting mainly in the morning or late afternoon. The female mosquito lays its eggs often in the artificial containers. Larvae are often found in the containers with relatively clean water, such as discarded tires, buckets, flowerpots and flower vase, drums, blocked rain gutters. Larvae can also found in natural sites such as bromeliads (types of plants) and tree holes.

The transmission cycle of dengue virus begins when the female mosquito bites a viremic person. Eight to twelve days that is extrinsic incubation period to pass before the mosquito becomes infective. It can then transmit the virus throughout its lifetime whenever it bites or even search the skin of another person. Once the virus is inoculated into the susceptible human, it replicates in the local lymph nodes and the liver (Gubler e*t al.,* 1979). The virus is then released from these tissues and infects white blood cells (WBCs) and distant lymphatic tissues, circulates in the blood and is eventually cleared by the host immune response. The incubation period for disease in humans (intrinsic incubation period) may range from 3 to 14 days and most often lasts between 4 and 7 days.

The virus is transmitted by the *Aedes* mosquito, of which the *Aedes aegypti* is the principal vector (Pang, 1983). *Aedes aegypti* is mostly domesticated mean found in urban areas. While another vector *Aedes* albopictus mostly survive in the rural setting (Lam, 1993). Dengue viruses are transmitted to humans by the bite of infective female mosquitoes of the genus *Aedes*, although *Aedes albopictus* and *Aedes*

polynesienses are both also involved in dengue outbreaks. It has been estimated that 50 to 100 million cases of dengue fever and 500,000 cases of dengue hemorrhagic fever (DHF) and as a result approximately 24,000 deaths take place, are reported annually (Porter e*t al.,* 2005; WHO,1997).

1.5 Virology

Dengue infection is caused by dengue virus which is a mosquito-borne flavivirus. Dengue transmitted by *Aedes aegypti* and *Aedes albopictus*. Growth of the population, rural–urban migration, no proper urban infrastructure and growth of consumerism are responsible for favorable conditions, causing viral transmission by the mosquito vector, *Aedes aegypti* (WHO, 1997). There are four distinct serotypes, DEN-1, 2, 3 and 4. Each infection induces a life-long protective immunity to the homologous serotype but gives a partial and brief protection against succeeding infection by the other three serotypes. Secondary infection is a major risk factor for DHF due to antibody-dependent enhancement. Other important contributing factors for DHF are involved viral virulence, host genetic background, T-cell activation, viral load and auto-antibodies.

According to MOH annual report, 2007 in the analysis of dengue serotypes from 1991 – 2007 all four serotypes are found in Malaysia. But DEN-3 was the predominant serotype in 1993 and then declined. It was then reproduced, reaching the peak in 2001. Other serotypes were also observed co-circulating at the same time (Annual report 2007; Ministry of Health, Malaysia).

1.6 Clinical features (manifestations) and pathophysiology

1.6.1 Spectrum of dengue infection

The incubation period for dengue infection is 4-7 days (ranging 3-14) reported by 2nd edition, WHO, 1997. This disease can be asymptomatic or may result in a spectrum of illness starting from undifferentiated mild febrile illness towards severe disease, with or without plasma leakage and different organ impairment. Symptomatic dengue infection is a systemic and active disease with clinical, hematological and serological profiles changing from day to day. These changes speed up by the hour or even minutes during the critical phase, particularly in those with plasma leakage.

1.6.2 Clinical course of dengue infection

Dengue infection is an active disease. Its clinical route changes as the disease grows. After the incubation period, the illness begins rapidly and will be followed by 3 phases, febrile, critical and recovery phase (Nimmannitya, 1987; Gubler, 1998).

1.6.2.1 Febrile phase

Normally patients develop high grade fever suddenly. In this acute febrile phase the fever usually lasts 2-7 days and the face becomes flush, other characteristics skin erythema, generalized body ache, myalgia, arthralgia and headache (Nimmannitya, 1987; Gubler, 1998). Some patients may suffer of sore throat, injected pharynx and conjunctival injection. Anorexia, nausea and vomiting are common features. These clinical features were indistinguishable between DF and DHF (Kalayanarooj e*t al.,* 1997). Mild hemorrhagic manifestations like positive tourniquet test or petechia and mucosal membrane bleeding can be seen in DF and DHF (Kalayanarooj e*t al.,* 1997; Balmaseda *et al*., 2005). Per vaginal bleeding is common among young female adults. Vast vaginal bleeding and gastrointestinal bleeding may occur during this phase but

are not common (Hammond *et al*., 2005; Balmaseda *et al*., 2005). The liver is often enlarged and tender after a few days of fever in DHF (Kalayanarooj *et al*., 1997).

1.6.2.2 Critical Phase

This critical phase occurs at the time of late febrile phase (often after 3rd day of fever) or around defervescence (usually between 3rd day to 5th day of illness but may go up to 7^{th} day) when a rapid drop in temperature may match with an increase in capillary permeability in some patients. In other viral infections, the patient's condition improves as the temperature falls down but different in DHF. At this point the patient will either become better or least plasma leak occurs or worse if critical volume of plasma is lost (Nimmannitya, 1987; Gubler, 1998; Guzman *et al.*, 1997; Rigau, 2006).

The critical phase remains for about 24 to 48 hours. In less severe cases, these changes are least and for short time. Many of these patients recover spontaneously, or after a short period of fluid or electrolyte therapy. In more severe form of plasma leakage, the patients could sweat, become restless, have cool extremities and prolonged capillary fill up time. The pulse rate increases, diastolic blood pressure increases and the pulse pressure narrows. Abdominal pain and vomiting, restlessness, altered conscious level and a sudden change from fever to subnormal temperature were stated as the clinical alarm signals of shock (Rigau and Laufer ,2006; Ong *et al*., 2007; Wichmann e*t al.,* 2004). The patient can progress rapidly to deep shock and death if on time fluid resuscitation is not administered.

Leucopenia with relative lymphocytosis, clotting abnormalities, elevation of transminases (typically the level of aspartate aminotransaminase (AST) is about 2-3 times the level of alanine aminotransaminase (ALT), hypoproteinaemia and hypoalbuminaemia are usually observed stated by (Nimmannitya, 1987; Gubler, 1998; Kalayana-rooj *et al.*, 1997).

1.6.2.3 Recovery phase

After 24 to 48 hours of defervescence, plasma leakage stops and is followed by reabsorption of extravascular fluid. Patients' generally improves, appetite returns, gastrointestinal symptoms decrease, hemodynamic status stabilizes and diuresis develops. Some patients may have a classical rash of "island of white in the sea of red" (Nimmannitya, 1987).

Some may have generalized pruritus. Bradycardia and electrocardiographic changes may occur during this stage. It is important to note that during this phase, haematocrit (Hct) level stabilizes or drops further due to haemodilution following reabsorption of extravascular fluid. The recovery of platelet count is typically preceded by recovery of WBC count.

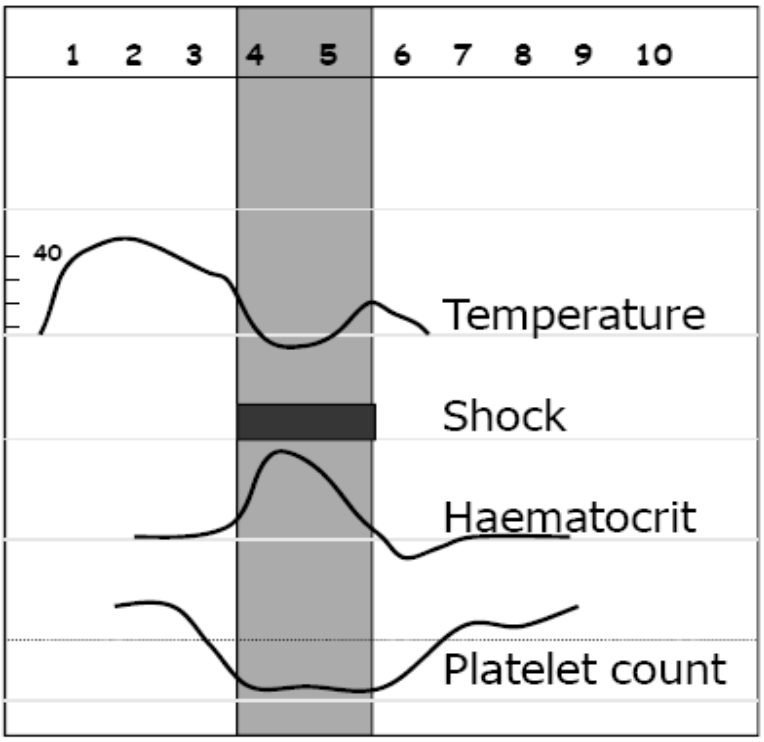

Fig 1.5 Clinical course of dengue of DHF (Nimmannitya, 1987; Gubler. 1998)

Clinical worsening mostly happens at the time of the critical phase (plasma leakage) therefore, it is significant to identify the onset of this phase. The onset of critical phase is manifest by plasma leakage and usually occurs around the beginning of defervescence. Indication of plasma leakage includes raised Hct (early marker), hemodynamic instability, fluid accumulation in extra vascular space (rather late marker) or hypoproteinemia. Abdominal pain and vomiting, restlessness, altered conscious level and a sudden change from fever to subnormal temperature are the clinical alarm signals of shock.

1.7 Pathophysiology of plasma leakage in dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS).

The primary pathophysiological abnormality seen in DHF and DSS is a quick increase in vascular permeability that leads to leakage of plasma into the extra vascular compartment, resulting as a haemoconcentration and hypovolaemia or shock (Cohen e*t al.,* 1987; Gubler, 1998). Hypovolaemia leads to reflex tachycardia and generalized vasoconstriction due to increased sympathetic output; (Pongpanich, 1973; Ganong, 2005). Clinical manifestations of vasoconstriction in various systems are as follows:

a. Skin - coolness, pallor and delayed capillary refill time.

b. Cardiovascular system - raised diastolic blood pressure and a narrowing pulse pressure.

c. Renal system - reducing urine output

d. Gastrointestinal system - vomiting and abdominal pain

e. Central nervous system – lethargy, restlessness, apprehension, reduced level of consciousness.

f. Respiratory system – tachypnoea (respiratory rate > 20/min)

In those patients whose consciousness is not mentally dulled, powerful thirst is another important symptom. At the same time, the inadequate perfusion of the tissue leads to increased anaerobic glycolysis and resultant lactic acidosis. If the hypovolaemia is not corrected quickly, the patient will progress to refractory shock state. The tissue perfusion would not respond to vasopressor drugs, even if the blood pressure and intravascular volume were to be restored and cardiac output would remain depressed.

The resultant lactic acidosis further depresses the myocardium and worsens the hypotension (Ganong, 2005). The common late complications of prolonged shock are huge, bleeding, disseminated intravascular coagulopathy (DIC) and multi organ failure which are mostly lethal.

Table 1.5 A ranges of pathophysiological changes from normal circulation to compensated and decompensated hypotensive shock by Ganong WF, 2005

Normal circulation	Compensated shock	Decompensated hypotensive shock
Clear consciousness	Clear consciousness –shock can be missed if you do not touch the patient	Change of mental state – restless, aggressive or lethargy
Fast capillary refill time <2 sec	Prolonged capillary refill time >2 sec	Mottled skin, very prolonged capillary refill time
Warm and pink extremities	Cool extremities	Cold, clammy extremities
Good volume peripheral pulses	Weak & thready peripheral pulses	Feeble or absent peripheral Pulses
Normal heart rate for age	Tachycardia	Severe tachycardia with bradycardia in late shock
Normal blood pressure for age	Normal systolic pressure with raised diastolic pressure postural hypotension	Hypotension/ unrecordable BP
Normal pulse pressure for age	Narrowing pulse pressure	Narrowed pulse pressure (<20 mmHg)
Normal respiratory rate for age	Tachypnoea	Metabolic acidosis/ hyperpnoea/ Kussmaul's breathing

The pathogenetic mechanism which is responsible for the increased vascular permeability in DHF/DSS is not yet known. There are no clear destructive vascular lesions to describe for this increased vascular permeability but on post-mortem (microscopically), perivascular oedema and loss of integrity of endothelial junctions with endothelial dysfunction are found (Bhamarapravati, 1967; Sahaphong e*t al.*, 1980). Abnormal immune response involving the production of cytokines or

chemokines, activation of T-lymphocytes and disturbances of haemostatic system are the major changes seen in DHF. Mediators including C3a, C5a, tumor necrosis factor-α, interleukin 2, 6 and 10, interferon-α and histamine are elevated (Gubler, 1998; Chuansumrit and Tangnararatchakit, 2006).

Secondary infection with a heterotypic dengue virus is associated with increased risk of developing dengue hemorrhagic fever (DHF). It is believed that DHF is occured due to antibody-dependent enhancement phenomenon (Halstead, 1970; Sangkawibha e*t al.,* 1984; Guzman e*t al.,* 2002). The sub-neutralizing concentration of the cross-reacting antibody from the previous infection may opsonise (making the virus susceptible) and enhances the virus uptake and replication in the macrophage or mononuclear cells. The level of T-cell activation is also enhanced. Profound T-cell activation with cell death during acute dengue infection may suppress or delay viral elimination, leading to the higher viral loads and increased immunopathology found in patients with DHF (Gubler, 1998, Chuansumrit e*t al.,* 2006).

1.8 Assessment of the WHO classification and case definitions

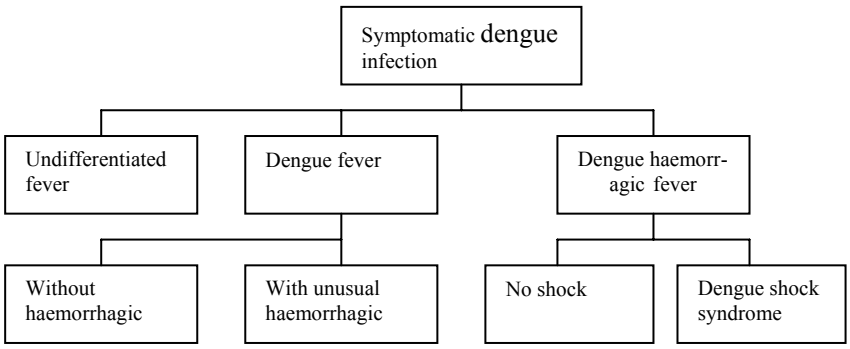

Figure 1.6 World health organizations (WHO) Dengue classification

The WHO case definitions of dengue fever (DF), dengue hemorrhagic fever (DHF), and dengue shock syndrome (DSS) are described below. Due to the unpredictability in the clinical illness associated with dengue infection, the WHO guidelines stress the need for laboratory confirmation (WHO, 1997).

Probable dengue fever (DF) is an acute febrile illness with two or more of the following manifestations.

Headache, retro-orbital pain, myalgia, arthralgia, rash, hemorrhagic manifestations, leucopenia and supportive serology or occurrence at the same location and time as other confirmed cases of dengue.

Confirmed DF is characterized by laboratory criteria (isolation of dengue virus, four fold or greater change in antibody titres, demonstration of the dengue virus antigen or genomic sequence.)

To fulfill the WHO case definition for DHF, the following must all be present.

i) History of acute fever, lasting 2-7 days, occasionally biphasic.

ii) Bleeding (hemorrhagic tendencies), evidenced by at least one of the following

A positive tourniquet test (TT), petechiae, ecchymosis, or purpura, bleeding, bleeding from the mucosa, gastrointestinal tract, injection sites or other locations, haematemesis or melena, thrombocytopenia (100,000 cells per mm^3 or less).

iii) Evidence of plasma leakage due to increased vascular permeability, manifested by at least one of the following.

A rise in the haematocrit equal or greater than 20% above average for age, sex and population. A drop in the haematocrit following volume replacement treatment equal to or greater than 20% of baseline. Signs of plasma leakage such as pleural effusion, ascites and hypoproteinemia.

iv) To fulfill the case definitions for DSS, the four criteria above for DHF (fever, hemorrhaged tendencies, thrombocytopenia and plasma leakage) must all be present plus evidence of circulatory failure manifested as: rapid and weak pulse, narrow pulse pressure (<20mmHg) or hypotension for age (this is defined as systolic pressure <80mmHg for those less than five years of age, or <90mmHg for those of five years of age or older.

v) Cold sweaty skin and restlessness.

In the WHO guidelines, DHF is also classified on the basis of severity. Grade I is defined as fever and non-specific legitimate signs and symptoms; the only hemorrhagic manifestation is a positive tourniquet test and/or easy bruising.

Grade II is the same as grade I but it includes spontaneous bleeding, usually in the form of skin or other haemorrhages. Grade III is manifested by circulatory failure, by a rapid, weak pulse and narrowing of the pulse pressure or hypotension, along with cold, clammy skin and restlessness. Grade IV is profound shock with undetectable blood pressure or pulse (For Grades III and IV define DSS (WHO, 1997).

In addition, the WHO guidelines provided a list of indicators that may be used to guide the diagnosis of DHF/DSS. These indicators may be helpful for clinicians to establish an early diagnosis, ideally before the onset of shock but are not proposed to be alternate for the case definitions. The listed indicators of DHF/DSS are: high fever of acute onset, hemorrhagic manifestations (at least a positive TT), hepatomegaly, shock, thrombocytopenia and haemoconcentration. The first two clinical observations, plus one of the laboratory findings establishes a temporary diagnosis of dengue hemorrhagic fever (DHF). The presence of shock in a patient with a provisional (interim) diagnosis of DHF supports the diagnosis of DSS (WHO, 1997).

1.9 Tourniquet test (TT)

One of the criteria for diagnosis included in the WHO case definition and in published protocols is the tourniquet test (TT), which is a measure of capillary fragility and thrombocytopaenia. The WHO guidelines specify that a blood pressure cuff should be inflated on the upper arm to a point midway between the systolic and diastolic pressures for five minutes and then the number of resulting petechiae in an area 6.25 cm^2 (2.5×2.5 cm) should be counted. The TT is considered positive when 20 or more petechiae are observed within the square inch (WHO, 1999; Phuong e*t al.,* 2004).

1.10 Other important manifestations

The following manifestations are important in dengue infection but are often under-recognized or misdiagnosed.

1.10.1 Acute abdomen:

Acute abdominal pain is a common symptom in dengue infection. It can be due to hepatitis, acalculous cholecystitis, shock and occasionally misdiagnosed as acute appendicitis (Khor e*t al.,* 2006; Premaratna e*t al.,* 2007). The history of onset of fever before that of abdominal pain and laboratory findings of leucopenia, thrombocytopenia or prolonged APTT with normal PT help to differentiate acute abdominal pain due to dengue infection from other surgical causes (Khor e*t al.,* 2006). Furthermore, in shock cases, the abdominal pain is relieved by the intravenous fluid therapy.

1.10.2. Hepatitis and liver failure*:*

Hepatitis is common in patients having DF and DHF and may be mild or severe in spite of the degree of plasma leakage. In some cases, liver failure may occur (Badyopadhyay *et al.,* 2006). The patients with liver failure have high tendency to bleed especially gastrointestinal bleeding (Nguyen, 1999; Wichmann, 2004).

1.10.3. Neurological manifestation:

Patients with dengue infection may have neurological manifestations (<1%) mainly encephalitis or encephalopathy (Solomon *et al.,* 2000). Other unusual manifestations include myelitis and Guillain Barre Syndrome (Soares e*t al.,* 2006).