CLINICAL PRACTICE GUIDELIES

DECEMBER 2004 MOH/P/PAK/95.04

MANAGEMENT
OF
DENGUE FEVER IN CHILREN

MINISTRY OF HEALTH MALAYSIA

ACADEMY OF MEDICINE MALAYSIA

GUIDELINES DEVELOPMENT AND OBJECTIVES

Guidelines Development

The work group for the development of these guidelines comprised paediatricians from various Ministry of Health and Ministry of Education facilities, and a public health specialist. These guidelines are an update of the existing guidelines on dengue. For this purpose, a systematic review of current evidence was carried out. The ranking of evidence is based on a modified version of that suggested by the Catalonia Agency for Health Technology Assessment and Research (CAHTAR) Spain (Appendix 1). These guidelines have been presented to the Chairman, Health Technology Assessment and Clinical Practice Guidelines Council, Ministry of Health Malaysia for review and approval.

Objectives

The aim of these guidelines are to aid health care providers and paediatricians in clinical decision making, by providing evidence-based information on the management of children with dengue.

Clinical Questions

The clinical questions for these guidelines are:

i. What is the clinical spectrum of dengue infection?
ii. How is dengue infection diagnosed?
iii. How can patients with dengue be treated successfully?

Target Population

These guidelines are developed to apply to children with dengue.

Target Group

These guidelines are meant for all health care providers.

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1. INTRODUCTION

Dengue fever is caused by a virus belonging to the *Flaviviridae* family. There are four serotypes of dengue virus (Den 1, Den 2, Den 3, Den 4) that can be distinguished serologically. While infection by one serotype produces life-long immunity against re-infection by that same serotype, there is only temporary and partial protection against other serotypes. The incubation period of dengue varies from 3-10 days with an average of 4-6 days (WHO, 1997, *level 6;* Kabra et al, 1999, *level 8).*

The incidence of both dengue fever (DF) and dengue haemorrhagic fever (DHF) in Malaysia appears to show an increasing trend. The case fatality rates (CFR) i.e. the proportion of deaths to the total number of cases, 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 below:

Table 1: Dengue Fever in Malaysia (1999-2003)

Year	***Population (mid-year)***	***Reported cases***	***Confirmed cases***		***Incidence (/100,000)***	***Deaths***	***CFR (%)***
			DF	**DHF**			
			-	-			
1999	22,711,900	10,146	4,718		20.77	37	0.78
			3,312	411			
2000	23,226,700	7,118	3,723		16.03	45	1.21
			8,277	392			
2001	23,795,300	16,368	8,669		36.43	50	0.58
			14,694	799			
2002	24,374,300	32,767	15,493		63.56	99	0.64
			14,761	681			
2003	25,048,300	31,545	15,442		61.65	72	0.47

DF=dengue fever DHF=dengue hemorrhagic fever CFR=case fatality rate
(Source: Annual Report, Vector-Borne Diseases Section, Ministry of Health Malaysia)

Considering the age distribution, the CFR in children below 15 years of age is consistently higher than that of the adult population as seen in Table 2 below:

Table 2: 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	0.93	8,101	18	0.22
2000	373	12	3.22	1,432	19	1.33	2,291	26	1.13
2001	863	7	0.81	3,605	23	0.64	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

CFR=case fatality rate
(Source: Ministry of Health Malaysia, Vector-Borne Diseases Section, Annual Report)

2. CLINICAL DIAGNOSIS

A child with dengue virus infection may have asymptomatic infection, or present with mild undifferentiated fever (especially in the toddler age group) or with the classical signs and symptoms of dengue fever (DF), dengue haemorrhagic fever (DHF) or dengue shock syndrome (DSS). The main clinical problem in children with DHF and DSS is the increased vascular permeability causing hypovolaemia (Pancharoen et al*, 2002, level 8;* WHO, 1997, *level 3;* Lall & Dhanda, 1996*, level 8)*.

2.1 Classification

The World Health Organization (1997, *level 3*) classification of DHF and DSS and their staging is indicated in Appendix 2. However, while the sensitivity and negative predictive values were 100%, the specificity was 21.21 %, and positive predictive value 63.38% according to the WHO case definition of DF (Sawasdivorn et al, 2001, *level 6).* Recent studies have found that 18% of children with DSS failed to meet all 4 necessary criteria for DHF as per WHO case definition It has also been suggested that less emphasis be placed on bleeding or a specific platelet count (Phuong, 2004, *level 9*).

The following is a suggested classification of dengue infection:

- Dengue Fever - without increased vascular permeability
- Dengue haemorrhagic fever (DHF) - increased vascular permeability and fragility – evidence of pleural effusion or ascites or haemoconcentration > 20%

DHF can be further graded as follows:

- **DHF with no shock**
- **DHF with shock (DSS**) which can be further graded into:

  - DHF with compensated shock
  - signs of shock - tachycardia out of proportion to body temperature, decreased tissue perfusion as evidenced by cool extremities, increased capillary refill time, narrowing of pulse pressure, weak distal pulses, oliguria and altered conscious level.
  - systolic pressure within the normal range (see Appendix 3 for details of hypotension, and Appendix 4 for normal blood pressure in relation to age, height and weight)

  - DHF with decompensated shock
  - signs of shock – tachycardia, cool extremities, increased capillary refill time, weak or absent pulses, oliguria and altered conscious level.
  - systolic hypotension

2.2 Guidance for Diagnosis of Dengue Infection

The criteria for a provisional diagnosis of dengue infection are indicated below.

2.2.1 Clinical

- High fever of acute onset of 3 days or more (Kabra et al, 1999, *level 8*).
- Altered sensorium
- Shock in an afebrile patient who had fever over the previous 3-5 days
- Petechial rash - generalized flushing, with maculo-papular rash (*islets of white in a sea of red)* occurring in the convalescent phase
- Haemorrhagic manifestations
    - a positive tourniquet test***** that precedes defervescence or thrombocytopenia (Soni et al, *level 3;* Kalayanarooj, 1997, *level 5*; Kabra et al, 1999, *level 8*).
    - epistaxis (Kabra et al, 1999, *level 8*).
    - gum bleeding (Kabra et al, 1999, *level 8*).
- Convulsions
- Headache,(Kabra et al,1999,*level 8;* Srivastava et al,1990*; level 8*).backache or retro-orbital pain (in older children)
- Abdominal pain, vomiting, (Kabra et al, 1999, *level 8;* Teelucksingh et al, 1999, *level 8;* Srivastava et al, 1990, *level 8*). loose stools or diarrhoea
- Hepatomegaly (Kabra et al, 1999, *level 8;* Teelucksingh et al, 1999; *level 8;* Srivastava et al, 1990; *level 8*).

It has been found that children with the dengue illness are more likely to have anorexia, nausea and vomiting and a positive tourniquet test, with lower total white cell count, absolute neutrophil and monocyte counts, and higher plasma alanine and aspartate aminotransferase (AST) levels, than children with other febrile illnesses. Plasma AST levels were also found to be higher in children with DHF than in those with DF (Kalayanarooj, 1997, *level 6*)

Vertical transmission in newborns has also been reported (Chye et al, 1997, *level 3*).

***** In children above 4 years of age, the tourniquet test is a useful test for dengue infection, a positive reading being an indication of capillary fragility. Blood pressure cuffs of appropriate sizes should be used, with a blood pressure level between the systolic and diastolic readings being maintained for 5 min. The presence of more than 20 petechiae per sq. in.(or per 6.25 cm^2) area indicates a positive reading.

2.2.2 Laboratory

- Down-trending of platelet count on the 3^{rd} -5^{th} day of illness
- Normal white cell count or leucopenia
- Thrombocytopenia (100 000 cells per mm^3 or less) during defervescence and the critical phase of DHF/DSS (Kabra et al, 1999, *level 8*).
- Haemoconcentration (elevated haematocrit - at least 20% or more than the average for age, sex and population, which ranges from a mean of 50% at 2 weeks of life to about 38% at 7-12 years of age) (Kabra et al, 1999, *level 8*)
- Four-fold or greater change in reciprocal IgG titres to one or more dengue virus antigens in paired serum samples
- Detection of IgM antibody after the 3^{rd} -5^{th} day of illness, or after defervescence.

- Isolation of the dengue virus from serum (the virus is present in the acute phase of the disease and can be isolated in cultures for up to 5 days)
- Demonstration of the dengue virus antigen in autopsy tissue, serum or cerebrospinal fluid samples by immunohistochemistry, immunofluorescence or ELISA
- Detection of dengue virus genomic sequences in autopsy tissue serum or cerebrospinal fluid samples by polymerase chain reaction (PCR) (WHO, 1997, *level 3*)

Further details of laboratory diagnosis can be found in Appendix 5.

It is essential that the date of onset of illness as well as date of collection be indicated on all samples to assist in interpretation. Paired samples are also preferred.

3. NOTIFICATION OF DENGUE

All suspected dengue cases must be notified by telephone to the nearest health office within 24 hours, followed by written notification within a week using the standard notification format *[Borang RKPBV(AM)1 Pindaan 1/84*] as illustrated in the flow chart for dengue notification in Appendix 6 Failure to notify is liable to be compounded under the law [*Akta Pemusnahan Serangga Pembawa Penyakit, 1975 (Pindaan 2000); Prevention and Control of Infectious Diseases Act, 1988*]. Subsequent activities by public health personnel after notification are detailed in Appendix 7.

4. MANAGEMENT

4.1 Clinical Course of Dengue Haemorrhagic Fever

The clinical course consists of 3 phases:

- Febrile phase - very high body temperature, sometimes exceeding 40^{o}C,
- Critical phase – starts with defervescence***** which is towards the end of the febrile phase, and lasts for 24 to 48 hours.
- Resorption/convalescent phase - plasma that has leaked into pleural and peritoneal surfaces is reabsorbed.

***Defervescence** (abatement of fever) usually occurs on the third to fifth day of fever, when the temperature is less than 38^{o}C. It is usually preceded by vomiting, abdominal pain and restlessness. Unlike other illnesses, in DHF, the patient's condition worsens as the temperature abates. The body temperature may drop to sub-normal levels in established shock, and then rises again slightly above the baseline. The patient may have a saddle-shaped fever curve towards the end of the critical period. It is common to have 3-5 episodes of shock during this period, preceded by vomiting, abdominal pain and restlessness. There is increased vascular permeability and the platelet count begins to drop as the haematocrit rises. The viral load decreases and antibodies may begin to be detected. Studies have shown a change in the level of soluble cell surface protein and lymphokines in DHF (Kurane, 1991).

4.2. Problems during Different Phases of DHF/ DSS

- Febrile period – high fever, vomiting, diarrhoea, dehydration, seizures
- Critical period – hypovolaemic shock, multi-organ dysfunction and bleeding in cases of prolonged shock, electrolyte imbalance, metabolic acidosis (may simulate respiratory distress presenting as Kussmaul's breathing, but auscultation will indicate clear lung fields with good air entry)
- Convalescent phase – respiratory distress from massive pleural effusion and ascites, pulmonary oedema.

4.3 Ambulatory Monitoring of Suspected Dengue Patients

4.3.1 Clinical parameters:

- temperature
- oral fluid intake
- urine output
- hydration status
- bleeding including tourniquet test

4.3.2 Laboratory parameters

- haemoglobin/haematocrit
- total white cell (TWC) count , platelet count
- IgM (may be negative in the febrile phase, although virus isolation / detection may be positive)

Patients should be suspected to have dengue infection if the following are present:

- TWC is low or borderline normal
- signs of defervescence
- downward trend of platelet count

4.4 Criteria for Admission to Hospital

Any of the following should be an indication for hospitalization:

- Shock – feeble pulses, cold extremities, capillary refill time > 2 seconds, hypotension (Soni et al, *level 8)*
- Altered conscious level – lethargy, delirium, combativeness.
- Bleeding (Soni et al, *level 8;* Kabra et al, 1999, *level 8*).
- Inability to tolerate oral fluids or vomiting, diarrhoea with signs of dehydration.
- Abdominal tenderness or enlarged liver (Soni et al, *level 8;* Kabra et al, 1999, *level 8*).
- Obesity or overweight
- Falling platelet count/rising haematocrit (Soni et al, *level 8;* Kabra et al, 1999, *level 8*).
- Social factors e.g. living far from hospital, no transport, etc.

It is suggested that patients with suspected dengue infection referred by private medical practitioners be admitted to hospital for observation (Director General of Health, 2003).

4.5 Indications for Admission to ICU /HDU

- Impending respiratory failure
- Persistent shock not responding to 60ml/kg of fluid resuscitation
- Cerebral protection
- Need for close monitoring

4.6 Monitoring of Suspected Dengue Patients in Wards

4.6.1 Clinical parameters:

- Hydration
  - mucosal and skin turgor
  - oral fluid intake
  - urine volume, and other fluid losses such as vomiting or diarrhoea.
- Haemodynamics
  - skin perfusion – temperature of extremities
  - capillary refill time,
  - pulse volume
  - heart rate
  - blood pressure
  - pulse pressure
  - level of consciousness.
- Body Temperature

4.6.2 Bedside investigations

- Haematocrit - 4-6 hourly, depending on severity

4.6.3 Laboratory investigations

- Haematocrit - Hb, TWDC, Platelet count,
- BUSE, Creatinine
- Dengue Serology

4.7 Management of the Acute Phase

4.7.1. Fluid management

Prompt and adequate fluid resuscitation is the key to the successful management of DHF/DSS. However, fluid infusion has to be judiciously controlled to maintain an effective circulation, but at the same time, avoid over-replacement, that could lead to massive pleural effusion and ascites. Fluid therapy has to be adjusted according to

- haematocrit level (pre-existing anaemia, severe haemorrhage, and capillary leakage can affect haematocrit levels)
- urine volume – 0.5 to 1.0 ml/kg/hour
- vital signs and tissue perfusion

For children with signs of shock, two fluid therapy lines should be established:

- **first fluid line**
  - for **replacement** of fluid lost in the plasma leakage
  - in decompensated shock, rapid bolus of normal saline based on 20ml/kg body weight should be given
  - in compensated shock, normal saline based on 10-20 ml/kg body weight should be given over 30-60 minutes

  - volume and infusion rate has to be adjusted every 2-6 hours based on clinical assessment and haematocrit of the patient

- **second fluid line**
  - to administer **maintenance** fluids
  - 5% Dextrose ½ saline with or without KCl, in the maintenance volume according to the child's weight for height-centile-for-age
  - most children with DSS will be physiologically stressed, and some may not be able to handle the glucose load. Blood glucose should be checked regularly and if found to be high, dextrose should be omitted or infusion rate reduced.

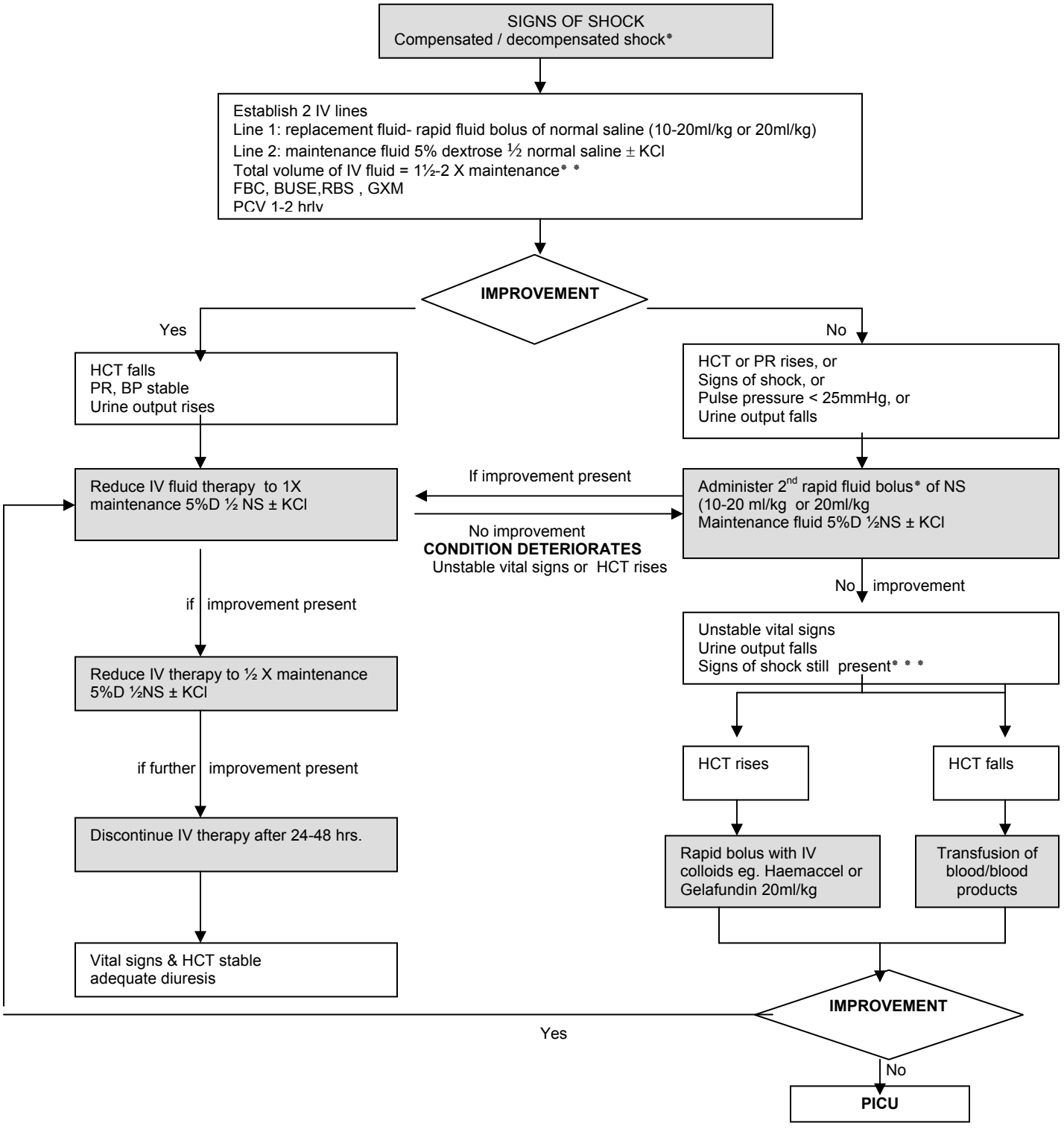
- If patient is still in shock, a second rapid normal saline bolus dose should be administered
- If still no improvement, rapid fluid bolus should be repeated with colloids or blood/blood products depending on whether there is a rise or fall in haematocrit
- When patient improves (patient is warm and has a good pulse volume), the fluid therapy is reduced to maintenance, and tapered off, finally discontinuing IV therapy, usually 24 to 48 hours after the start of plasma leakage. This is to avoid fluid overload and pulmonary oedema which may be fatal
- For obese patients, the weight adjusted to height-centile-for-age should be closely followed to avoid fluid overload.
- The use of albumin and plasma is not recommended.

During rapid fluid therapy, the following need to be frequently assessed to determine the physiologic status:

- heart rate
- pulse volume and pulse pressure
- peripheral colour
- temperature
- capillary refill time
- blood pressure

A flow chart for fluid therapy in patients with DHF and DSS is indicated below (Halstead, 2002, *level 8;* Soni et al, 2001, *level 8)*.

Fluid Therapy for Patients with DHF and DSS



*** Rapid fluid bolus** **-in decompensated shock, give 20ml/kg fast**
- in compensated shock give 10-20ml/kg over 30-60 minutes if patients is warming up

*** * use weight adjusted to height –centile – for age to calculate the volume of maintenance fluids**

*** * * ensure good IV, check urinary catheter**

4.7.2. Blood transfusion

Significant haemorrhage should be recognised early, and prompt transfusion of fresh whole blood administered at 10 to 20 ml/kg. The emphasis is on fresh whole blood because of plasma loss from plasma leakage. Preventive transfusion with platelet concentrates and fresh frozen plasma in non-bleeding or fluid responsive DHF/DSS has not been shown to sustain the increase in platelet counts, prothrombin time or partial prothrombin time (PT/PPT). This practice has, in fact, been shown to increase the incidence of fluid overload and pulmonary oedema, and puts the patient at risk of blood-borne infections from multiple donors (Lum et al, 2003, *level 5*; Chuansumrit et al, 2000, *level 5*)

Bleeding should be suspected if any of the following features are present.

- shock more severe than expected for the rise in haematocrit.
- GIT bleeding which may be occult or obvious
- a drop in haematocrit with no clinical improvement e.g. a drop from 50% to 45% (or from 0.50 to 0.45)
- decompensated shock after infusion of 40 ml/kg of isotonic crystalloids or colloids
- worsening metabolic acidosis.
- history of prolonged shock (Lum et al, 2002)
- presence of multi-organ failure e.g. high creatinine, restlessness

A delay in blood transfusion and continued infusion of crystalloids or non-blood colloids (such as FFP and platelets) will give rise to more plasma leakage and a poor outcome

4.8 Management of the Convalescent Phase

Most cases of DHF will enter into the convalescent phase 24 – 48 hours after the onset of plasma leakage, and recover spontaneously with appropriate management (WHO 1997, 2001, *level 3*).

4.8.1 Indicators of patients being in the convalescent phase:

- Stable vital signs - wide pulse pressure, strong pulse, no tachycardia (warm extremities, sinus bradycardia and hypertension).
- Return of haematocrit to baseline values.
- Increase in urine output (may be delayed if tense ascites is present)
- Confluent petechial rash with multiple small, white, round areas among the rash over the extremities (islets of white in a sea of red).
- Improvement in general condition with gradual return of appetite
- Afebrile state (unless nosocomial infection is present)

4.8.2 Treatment

- Discontinuation of intravenous fluids (to avoid pulmonary oedema)
- Hypokalaemia may occur during the diuretic phase. A check should be carried out for evidence of ileus arising from hypokalaemia that may occur with diuresis. This can be corrected with fruits and fruit juices. Potassium chloride supplementation should be considered if patient refuses or is unable to take these.

- Invasive procedures such as dental extractions or intramuscular injections are not advisable during this period

4.9 Discharge Criteria for Hospitalized Patients

The following are the suggested criteria for discharge from hospital:

- visible improvement in clinical picture
- absence of fever for 24 hours without the use of antipyretics
- complete recovery from shock (after 3 days)
- stable haematocrit
- rising platelet counts greater than 50, 000/mm^3
- return of appetite
- absence of respiratory distress
- normal urine output

4.10 Complications of DHF/DSS

Primary complications

- Gastrointestinal bleeding (Hongsiriwon, 2002, *level 3)*
- Liver failure (Lum et al, 1993, *level 3)*
- Dengue encephalopathy (Solomon et al, 2000; Pancharoen et al, 2001, *level 3)*
- Acute renal failure

Secondary Complications

- Respiratory failure secondary to massive pleural effusion and gross ascites *(Soni et al, 2001, level 3)*
- Acute pulmonary oedema *(Soni et al, 2001, level 3)*
- Acute respiratory distress syndrome *(Soni et al, 2001,level 3)*
- Nosocomial infection

5. HEALTH EDUCATION

5.1 Patient and Family

The following information about the disease should be provided by health personnel to the patient and family members

- *Disease*
  - causal agent
  - signs and symptoms
  - treatment including need for follow up of ambulatory patients
  - risks and complications
  - prognosis
  - duration of infectiveness and need to stay under a mosquito net during infective phase
  - duration of hospitalisation

- *Vector*
  - *Aedes* mosquito - breeding environment, brief life cycle, role in transmission of dengue, rationale of '*Tiada Aedes Tiada Denggi*'.

- *Expected behaviour to prevent dengue* (see Appendix 9)
- *Enforcement against breeding of Aedes* – details of liability if evidence of breeding *Aedes* is found

5.2. Informational pamphlets

Information pamphlets on dengue that may be obtained from the nearest health office, should be made available and distributed widely.

6. PREVENTION STRATEGIES

6.1 Dengue Free Schools Programme

Since about 30 % of dengue cases occur among school going children between the ages of 7 and 18 years, it is hoped by this programme to turn school children into change agents for the prevention and control of dengue in the community towards. The exposure to information and prevention and control activities is started in the school environment. (Ministry of Health and Ministry of Education, 2001)

6.2 Dengue Free Health Facilities Programme

Dengue transmission can occur within health facilities (including hospitals), and so this programme was initiated in 1993 to prevent dengue transmission and *Aedes* breeding in various zones of the facilities, including living quarters and hostels. The mainstay of the programme is the setting up of work teams, daily *Aedes* larval survey and regular surveillance (Vector-Borne Diseases Section, 2002)

6.3 Dengue Alerts

Dengue alerts are issued from time to time by the Director of Disease Control, or by the Vector-Borne Diseases Section, Ministry of Health Malaysia. These alerts advise through mass media on the need to take proactive action if there is a sharp rise in dengue incidence in the country or region, re-emergence of a particular dengue serotype, or when there is weather conducive to *Aedes* breeding. Action to be taken may include promotion of increased awareness, surveillance and enforcement; improved clinical vigilance at points of service and early dengue notification; organised campaigns to search for and destroy *Aedes* breeding sites including newly recognized potential breeding sites such as roof gutters; usage of larvicide in domestic water containers, and preventive insecticide fogging (Vector-Borne Diseases Section, 2004; Disease Control Division, 2004)

6.4 Circulars

The Director General of Health Malaysia also issues circulars outlining measures on dengue prevention and control. These circulars cover important issues like close monitoring of local dengue control activities at state and district level, hospital admission criteria, active case detection, case and outbreak management, and vector control management (*Ketua Pengarah Kesihatan,* 2004*)*

6.5 Insecticide Aerosol Spraying In Public Transport

Due to the spread of dengue from urban to rural areas, and the widespread use of public transport especially during festive seasons and school holidays, there is now a requirement of insecticide aerosol spraying inside public transport like school, factory, tour and express buses. The spraying should be done regularly every morning and evening. (*Ketua Pengarah Kesihatan*, 2004)

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Appendix 1

LEVELS OF EVIDENCE SCALE

Level	Strength of evidence	Study design
1	Good	Meta-analysis of RCT, Systematic review
2	Good	Large sample RCT
3	Good to Fair	Small sample RCT
4		Non-randomised controlled prospective trial
5	Fair	Non-randomised controlled prospective trial with historical control
6	Fair	Cohort studies
7	Poor	Case-control studies
8	Poor	Non-controlled clinical series, descriptive studies multi-centre
9	Poor	Expert committees, consensus, case reports, anecdotes

(*Adapted from Catalonian Agency for Health Technology Assessment & Research, [CAHTAR] Spain)*

Appendix 2

WORLD HEALTH ORGANIZATION CLASSIFICATION OF DHF AND DSS

Case Definition for Dengue Haemorrhagic Fever (WHO 1997)

The following symptoms must all be present:

- Fever, or history of acute fever, lasting 2-7 days, occasionally biphasic.
- Haemorrhagic tendencies, evidenced by at least one of the following:
  - a positive tourniquet test
  - petechiae, ecchymoses or purpura
  - bleeding from the mucosa, gastrointestinal tract, injection sites or other locations
  - haematemesis or malaena.
- Thrombocytopenia (100,000 cells per mm^3 or less)
- Evidence of plasma leakage due to increased vascular permeability, manifested by at least one of the following:
  - a rise in haematocrit $\geq$ 20% above average for age, sex and population
  - a drop in the haematocrit following volume-replacement treatment $\geq$ 20% of baseline
  - signs of plasma leakage such as pleural effusion, ascites and hypo-proteinaemia.

Case Definition for Dengue Shock Syndrome (WHO 1997)

All of the above four criteria for DHF must be present, plus evidence of circulatory failure manifested by:

- Rapid and weak pulse, and
- Narrow pulse pressure (<20 mmHg)

or manifested by:

- Hypotension for age, and
- Cold, clammy skin and restlessness

Grading of Severity of Dengue Haemorrhagic Fever (WHO 1997)

DHF is classified into four grades of severity, where grades III and IV are considered as DSS. The presence of thrombocytopenia with concurrent haemoconcentration differentiates grades I and II DHF from DF.

Grade I Fever accompanied by non-specific constitutional symptoms; the only haemorrhagic manifestation is a positive tourniquet test and / or easy bruising.

Grade II Spontaneous bleeding, in addition to the manifestations of *Grade I* patients, usually in the form of skin or other haemorrhages.

Grade III Circulatory failure manifested by a rapid, weak pulse and narrowing of pulse pressure or hypotension, with the presence of cold, clammy skin and restlessness.

Grade IV Profound shock with undetectable blood pressure or pulse.

Appendix 3

DEFINITION OF HYPOTENSION FOR AGE

(American Academy of Pediatrics and American Heart Association, Pediatric Advanced Life Support Provider Manual, 2002).

Age	**Systolic blood pressure, mmHg (5^{th} Percentile)**
< 1 month	≤ 60
1 month to 1 year	≤ 70
1 to 10 years	≤ 70 + (2 x age in years)
> 10 years	≤ 90

Appendix 4

BLOOD PRESSURE TABLES FOR BOYS AND GIRLS BY AGE AND HEIGHT PERCENTILES

TABLE 3. BP Levels for Boys by Age and Height Percentile

Age, y	BP Percentile	SBP, mm Hg							DBP, mm Hg						
		Percentile of Height							Percentile of Height						
		5th	10th	25th	50th	75th	90th	95th	5th	10th	25th	50th	75th	90th	95th
1	50th	80	81	83	85	87	88	89	34	35	36	37	38	39	39
	90th	94	95	97	99	100	102	103	49	50	51	52	53	53	54
	95th	98	99	101	103	104	106	106	54	54	55	56	57	58	58
	99th	105	106	108	110	112	113	114	61	62	63	64	65	66	66
2	50th	84	85	87	88	90	92	92	39	40	41	42	43	44	44
	90th	97	99	100	102	104	105	106	54	55	56	57	58	58	59
	95th	101	102	104	106	108	109	110	59	59	60	61	62	63	63
	99th	109	110	111	113	115	117	117	66	67	68	69	70	71	71
3	50th	86	87	89	91	93	94	95	44	44	45	46	47	48	48
	90th	100	101	103	105	107	108	109	59	59	60	61	62	63	63
	95th	104	105	107	109	110	112	113	63	63	64	65	66	67	67
	99th	111	112	114	116	118	119	120	71	71	72	73	74	75	75
4	50th	88	89	91	93	95	96	97	47	48	49	50	51	51	52
	90th	102	103	105	107	109	110	111	62	63	64	65	66	66	67
	95th	106	107	109	111	112	114	115	66	67	68	69	70	71	71
	99th	113	114	116	118	120	121	122	74	75	76	77	78	78	79
5	50th	90	91	93	95	96	98	98	50	51	52	53	54	55	55
	90th	104	105	106	108	110	111	112	65	66	67	68	69	69	70
	95th	108	109	110	112	114	115	116	69	70	71	72	73	74	74
	99th	115	116	118	120	121	123	123	77	78	79	80	81	81	82
6	50th	91	92	94	96	98	99	100	53	53	54	55	56	57	57
	90th	105	106	108	110	111	113	113	68	68	69	70	71	72	72
	95th	109	110	112	114	115	117	117	72	72	73	74	75	76	76
	99th	116	117	119	121	123	124	125	80	80	81	82	83	84	84
7	50th	92	94	95	97	99	100	101	55	55	56	57	58	59	59
	90th	106	107	109	111	113	114	115	70	70	71	72	73	74	74
	95th	110	111	113	115	117	118	119	74	74	75	76	77	78	78
	99th	117	118	120	122	124	125	126	82	82	83	84	85	86	86
8	50th	94	95	97	99	100	102	102	56	57	58	59	60	60	61
	90th	107	109	110	112	114	115	116	71	72	72	73	74	75	76
	95th	111	112	114	116	118	119	120	75	76	77	78	79	79	80
	99th	119	120	122	123	125	127	127	83	84	85	86	87	87	88
9	50th	95	96	98	100	102	103	104	57	58	59	60	61	61	62
	90th	109	110	112	114	115	117	118	72	73	74	75	76	76	77
	95th	113	114	116	118	119	121	121	76	77	78	79	80	81	81
	99th	120	121	123	125	127	128	129	84	85	86	87	88	88	89
10	50th	97	98	100	102	103	105	106	58	59	60	61	61	62	63
	90th	111	112	114	115	117	119	119	73	73	74	75	76	77	78
	95th	115	116	117	119	121	122	123	77	78	79	80	81	81	82
	99th	122	123	125	127	128	130	130	85	86	86	88	88	89	90
11	50th	99	100	102	104	105	107	107	59	59	60	61	62	63	63
	90th	113	114	115	117	119	120	121	74	74	75	76	77	78	78
	95th	117	118	119	121	123	124	125	78	78	79	80	81	82	82
	99th	124	125	127	129	130	132	132	86	86	87	88	89	90	90
12	50th	101	102	104	106	108	109	110	59	60	61	62	63	63	64
	90th	115	116	118	120	121	123	123	74	75	75	76	77	78	79
	95th	119	120	122	123	125	127	127	78	79	80	81	82	82	83
	99th	126	127	129	131	133	134	135	86	87	88	89	90	90	91
13	50th	104	105	106	108	110	111	112	60	60	61	62	63	64	64
	90th	117	118	120	122	124	125	126	75	75	76	77	78	79	79
	95th	121	122	124	126	128	129	130	79	79	80	81	82	83	83
	99th	128	130	131	133	135	136	137	87	87	88	89	90	91	91
14	50th	106	107	109	111	113	114	115	60	61	62	63	64	65	65
	90th	120	121	123	125	126	128	128	75	76	77	78	79	79	80
	95th	124	125	127	128	130	132	132	80	80	81	82	83	84	84
	99th	131	132	134	136	138	139	140	87	88	89	90	91	92	92
15	50th	109	110	112	113	115	117	117	61	62	63	64	65	66	66
	90th	122	124	125	127	129	130	131	76	77	78	79	80	80	81
	95th	126	127	129	131	133	134	135	81	81	82	83	84	85	85
	99th	134	135	136	138	140	142	142	88	89	90	91	92	93	93
16	50th	111	112	114	116	118	119	120	63	63	64	65	66	67	67
	90th	125	126	128	130	131	133	134	78	78	79	80	81	82	82
	95th	129	130	132	134	135	137	137	82	83	83	84	85	86	87
	99th	136	137	139	141	143	144	145	90	90	91	92	93	94	94
17	50th	114	115	116	118	120	121	122	65	66	66	67	68	69	70
	90th	127	128	130	132	134	135	136	80	80	81	82	83	84	84
	95th	131	132	134	136	138	139	140	84	85	86	87	87	88	89
	99th	139	140	141	143	145	146	147	92	93	93	94	95	96	97

The 90th percentile is 1.28 SD, the 95th percentile is 1.645 SD, and the 99th percentile is 2.326 SD over the mean.
For research purposes, the SDs in Table B1 allow one to compute BP Z scores and percentiles for boys with height percentiles given in Table 3 (ie, the 5th, 10th, 25th, 50th, 75th, 90th, and 95th percentiles). These height percentiles must be converted to height Z scores given by: 5% = −1.645; 10% = −1.28; 25% = −0.68; 50% = 0; 75% = 0.68; 90% = 1.28; and 95% = 1.645, and then computed according to the methodology in steps 2 through 4 described in Appendix B. For children with height percentiles other than these, follow steps 1 through 4 as described in Appendix B.

TABLE 4. BP Levels for Girls by Age and Height Percentile

Age, y	BP Percentile	SBP, mm Hg							DBP, mm Hg						
		Percentile of Height							Percentile of Height						
		5th	10th	25th	50th	75th	90th	95th	5th	10th	25th	50th	75th	90th	95th
1	50th	83	84	85	86	88	89	90	38	39	39	40	41	41	42
	90th	97	97	98	100	101	102	103	52	53	53	54	55	55	56
	95th	100	101	102	104	105	106	107	56	57	57	58	59	59	60
	99th	108	108	109	111	112	113	114	64	64	65	65	66	67	67
2	50th	85	85	87	88	89	91	91	43	44	44	45	46	46	47
	90th	98	99	100	101	103	104	105	57	58	58	59	60	61	61
	95th	102	103	104	105	107	108	109	61	62	62	63	64	65	65
	99th	109	110	111	112	114	115	116	69	69	70	70	71	72	72
3	50th	86	87	88	89	91	92	93	47	48	48	49	50	50	51
	90th	100	100	102	103	104	106	106	61	62	62	63	64	64	65
	95th	104	104	105	107	108	109	110	65	66	66	67	68	68	69
	99th	111	111	113	114	115	116	117	73	73	74	74	75	76	76
4	50th	88	88	90	91	92	94	94	50	50	51	52	52	53	54
	90th	101	102	103	104	106	107	108	64	64	65	66	67	67	68
	95th	105	106	107	108	110	111	112	68	68	69	70	71	71	72
	99th	112	113	114	115	117	118	119	76	76	76	77	78	79	79
5	50th	89	90	91	93	94	95	96	52	53	53	54	55	55	56
	90th	103	103	105	106	107	109	109	66	67	67	68	69	69	70
	95th	107	107	108	110	111	112	113	70	71	71	72	73	73	74
	99th	114	114	116	117	118	120	120	78	78	79	79	80	81	81
6	50th	91	92	93	94	96	97	98	54	54	55	56	56	57	58
	90th	104	105	106	108	109	110	111	68	68	69	70	70	71	72
	95th	108	109	110	111	113	114	115	72	72	73	74	74	75	76
	99th	115	116	117	119	120	121	122	80	80	80	81	82	83	83
7	50th	93	93	95	96	97	99	99	55	56	56	57	58	58	59
	90th	106	107	108	109	111	112	113	69	70	70	71	72	72	73
	95th	110	111	112	113	115	116	116	73	74	74	75	76	76	77
	99th	117	118	119	120	122	123	124	81	81	82	82	83	84	84
8	50th	95	95	96	98	99	100	101	57	57	57	58	59	60	60
	90th	108	109	110	111	113	114	114	71	71	71	72	73	74	74
	95th	112	112	114	115	116	118	118	75	75	75	76	77	78	78
	99th	119	120	121	122	123	125	125	82	82	83	83	84	85	86
9	50th	96	97	98	100	101	102	103	58	58	58	59	60	61	61
	90th	110	110	112	113	114	116	116	72	72	72	73	74	75	75
	95th	114	114	115	117	118	119	120	76	76	76	77	78	79	79
	99th	121	121	123	124	125	127	127	83	83	84	84	85	86	87
10	50th	98	99	100	102	103	104	105	59	59	59	60	61	62	62
	90th	112	112	114	115	116	118	118	73	73	73	74	75	76	76
	95th	116	116	117	119	120	121	122	77	77	77	78	79	80	80
	99th	123	123	125	126	127	129	129	84	84	85	86	86	87	88
11	50th	100	101	102	103	105	106	107	60	60	60	61	62	63	63
	90th	114	114	116	117	118	119	120	74	74	74	75	76	77	77
	95th	118	118	119	121	122	123	124	78	78	78	79	80	81	81
	99th	125	125	126	128	129	130	131	85	85	86	87	87	88	89
12	50th	102	103	104	105	107	108	109	61	61	61	62	63	64	64
	90th	116	116	117	119	120	121	122	75	75	75	76	77	78	78
	95th	119	120	121	123	124	125	126	79	79	79	80	81	82	82
	99th	127	127	128	130	131	132	133	86	86	87	88	88	89	90
13	50th	104	105	106	107	109	110	110	62	62	62	63	64	65	65
	90th	117	118	119	121	122	123	124	76	76	76	77	78	79	79
	95th	121	122	123	124	126	127	128	80	80	80	81	82	83	83
	99th	128	129	130	132	133	134	135	87	87	88	89	89	90	91
14	50th	106	106	107	109	110	111	112	63	63	63	64	65	66	66
	90th	119	120	121	122	124	125	125	77	77	77	78	79	80	80
	95th	123	123	125	126	127	129	129	81	81	81	82	83	84	84
	99th	130	131	132	133	135	136	136	88	88	89	90	90	91	92
15	50th	107	108	109	110	111	113	113	64	64	64	65	66	67	67
	90th	120	121	122	123	125	126	127	78	78	78	79	80	81	81
	95th	124	125	126	127	129	130	131	82	82	82	83	84	85	85
	99th	131	132	133	134	136	137	138	89	89	90	91	91	92	93
16	50th	108	108	110	111	112	114	114	64	64	65	66	66	67	68
	90th	121	122	123	124	126	127	128	78	78	79	80	81	81	82
	95th	125	126	127	128	130	131	132	82	82	83	84	85	85	86
	99th	132	133	134	135	137	138	139	90	90	90	91	92	93	93
17	50th	108	109	110	111	113	114	115	64	65	65	66	67	67	68
	90th	122	122	123	125	126	127	128	78	79	79	80	81	81	82
	95th	125	126	127	129	130	131	132	82	83	83	84	85	85	86
	99th	133	133	134	136	137	138	139	90	90	91	91	92	93	93

* The 90th percentile is 1.28 SD, the 95th percentile is 1.645 SD, and the 99th percentile is 2.326 SD over the mean.
For research purposes, the SDs in Table B1 allow one to compute BP Z scores and percentiles for girls with height percentiles given in Table 4 (ie, the 5th, 10th, 25th, 50th, 75th, 90th, and 95th percentiles). These height percentiles must be converted to height Z scores given by: 5% = −1.645; 10% = −1.28; 25% = −0.68; 50% = 0; 75% = 0.68; 90% = 1.28; and 95% = 1.645 and then computed according to the methodology in steps 2 through 4 described in Appendix B. For children with height percentiles other than these, follow steps 1 through 4 as described in Appendix B.

(*National High Blood Pressure Education Programme Working Group on High Blood Pressure in Children and Adolescents).*

Appendix 5

LABORATORY DIAGNOSIS OF DENGUE

Single serum

Within 4-6 days of infection, 50-55% samples are positive for dengue IgM with a single serum sample. Almost 100 % would have seroconverted within 7 –9 days. The detection of dengue specific IgM can be carried out by EIA, either in-house or PanBio. IgM ELISA must be carried out. The dengue IgM antibody can be detected from day 3 onwards for up to 90 days in both primary and secondary infections. The turnaround time for test results depends on the kits or assay used, varying from 15 minutes to 3-4 hours.

With respect to sensitivity, the cassette tests are less sensitive (75% generally) than the ELISAs (85-90%). It is suggested that a single serology test be interpreted, taking into account clinical features, since a positive dengue IgM may indicate either an acute infection or a recent past infection.

Paired sera

This is the standard Haemagglutination Inhibition test and measures IgG antibodies. Paired samples should be at least 5-7 days apart. A four-fold or greater rise in antibody titres to one or more dengue virus antigens indicates a positive result.

Virus isolation

This is the gold standard and is the most definitive test for dengue infection. It can, however, be only performed in laboratories equipped with tissue culture facilities and a ultra-violet microscope such as reference and research laboratories like National Public Health Laboratory (NPHL), Institute for Medical Research (IMR) and University Malaya Medical Centre (UMMC). It is also sensitive only at the early acute phase of illness. The isolation of virus can be carried out from serum, whole blood, CSF, urine or biopsy specimens.

Virus amplification

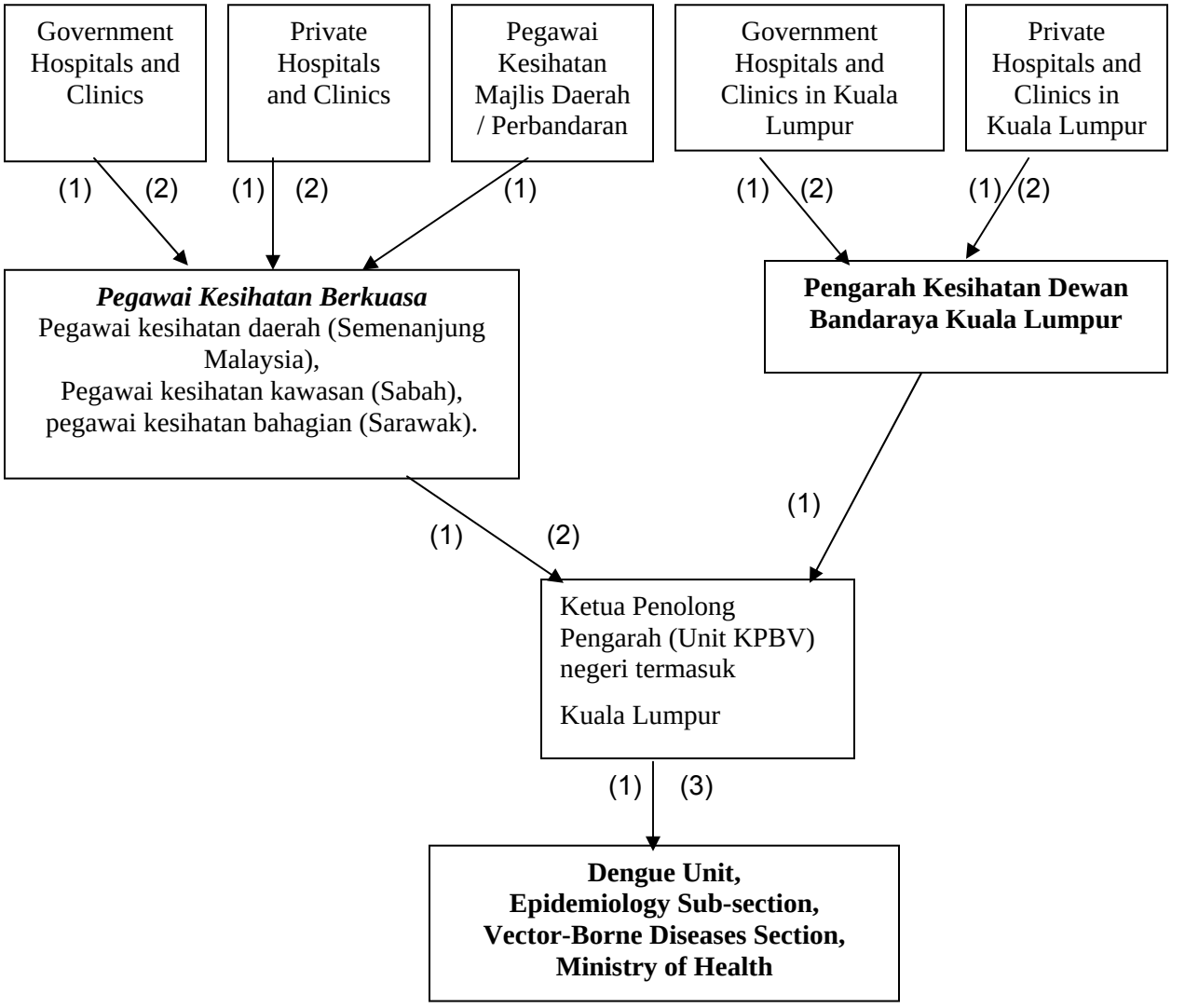
This can be carried out by standard or real time PCR techniques. Currently, National Public Health Laboratory and Institute of Medical Research (IMR) can perform the standard PCR while both tests are available at University of Malaya Medical Centre (UMMC). Samples suitable are serum, whole blood, CSF, urine and tissue biopsies, but these samples have to be sent on ice, on the day of collection.

Virus detection/isolation from autopsies

Post mortem samples include biopsies from liver, spleen and also lymph nodes and brain if possible. Bone marrow samples should be collected in saline. These should be collected in sterile containers and transported on ice. The virus laboratory performing the tests should be informed of intended test. If there is delay in dispatch, the specimens should be stored at -70˚C.

Appendix 6

FLOWCHART OF DENGUE NOTIFICATION



(Adapted from *Panduan Pencegahan dan Kawalan Penyakit Demam Denggi / Demam Denggi Berdarah: Ibu Pejabat Rancangan Kawalan Penyakit Bawaan Vektor, 1986*)

Appendix 7

ACTIVITIES AFTER NOTIFICATION

Case investigation and prevention and control activities must be initiated within 24 hours after receiving notification. Killing probably infected adult mosquitoes in the area of the notified case could be critical in cutting transmission of infection. Preventive insecticide fogging should be carried out in all high-risk areas, those with persistently high endemicity and those with potential for outbreaks (Ketua Pengarah Kesihatan, 2003). An outbreak is defined as the incidence of 2 or more dengue cases in a single locality where the onset of the cases are less than 14 days apart (Ibu Pejabat Rancangan Kawalan Penyakit Bawaan Vektor, 1986). Active case detection of dengue is useful in helping to ensure outbreaks are controlled within 14 days. This refers to the detection of dengue among contacts who live within 200 meters from a notified case or among all the population of an outbreak locality. Another measure is the use of the more potent organophosphate insecticide in outbreak control in identified problem dengue areas, such as those with high cases and difficult to control. This organophosphate insecticide is only used in 'ULV' ('ultra low volume' or 'outdoor') fogging. (*Ketua Pengarah Kesihatan, 2004.*)

Appendix 8

COMMUNITY MOBILISATION

The community has to be empowered in the prevention of dengue by being continually reminded to act out effective and critical behavioral messages such as the following (to be matched to prioritised problems in a particular locality):

1. "Examine your own home premise and surrounding area for potential *Aedes* breeding containers or sites, regularly every weekend; and destroy their *Aedes* breeding capacity."
2. "Report to the nearest health office any premise or site that you suspect to be breeding *Aedes* nearby your home premise (within 200 meters), such as an abandoned house or a dumping site."
3. "Help bring a family member or neighbour who has been down with fever to see a doctor as soon as possible."

(Vector-Borne Diseases Section, 'COMBI', 2004)