GUIDE FOR DIAGNOSIS, TREATMENT AND CONTROL OF DENGUE HAEMORRHAGIC FEVER
(Second Edition)

TECHNICAL ADVISORY COMMITTEE ON DENGUE HAEMORRHAGIC FEVER for the
SOUTH EAST ASIAN AND WESTERN PACIFIC REGIONS

WORLD HEALTH ORGANIZATION
1980
A first edition of this guide was published in 1975 by the WHO South-east Asian and Western Pacific Regional Offices as "Technical Guides for Diagnosis, Treatment, Surveillance, Prevention and Control of Dengue Haemorrhagic Fever". It was prepared by a Technical Advisory Committee which met in Manila in 1974 (Annex 1) and in Bangkok in 1975 (Annex 2). In the face of extensive epidemics which developed in Burma, Indonesia, Thailand and other countries of the two WHO Regions from 1972 onwards, it was felt that such a guide could help clinicians and public health officers facing a feared disease for the first time.

Since then, dengue haemorrhagic fever has remained endemic with variable epidemic activity in the two Regions. An important factor has been its extension to rural areas, causing a primary health care problem as regards prompt recognition of the disease.

This second edition aims to present the diagnosis, treatment and control features of DHF in the simplest possible way in view of the problems that exist for primary health care services. At the same time it is desirable that clinicians and public health officers be able to find in it all the technical data they want. The challenge for the Technical Advisory Committee which met in Manila in 1978 (Annex 3) was to find a convenient compromise for this second edition. It will be noted that the Committee made little change to the criteria for diagnosis and recommended treatment, which are very similar to the 1975 edition.

WHO Headquarters, Geneva
WHO Regional Office for South-east Asia
WHO Regional Office for the Western Pacific
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1. GENERAL CONSIDERATIONS

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Dengue haemorrhagic fever (DHF) can be defined as an acute febrile illness caused by four serotypes of dengue virus and characterized clinically by haemorrhagic phenomena and a tendency to develop a shock syndrome (dengue shock syndrome - DSS) which may be fatal. Thrombocytopenia with concurrent haemoconcentration are constant findings.

1.1 Spreading outbreaks in South-east Asian and Western Pacific Regions

The classical form of dengue is an acute febrile disease with headaches and joint and muscular pains. It has been known for more than a century in the tropical areas of South-east Asia and the Western Pacific Region. However, dengue haemorrhagic fever outbreaks were recognized as a new disease first in the Philippines in 1953 (Philippine haemorrhagic fever) and in Thailand in 1958 (Thai haemorrhagic fever). These outbreaks caused some panic in the populations because of their novelty and the mystery of the causative agent until dengue viruses types 2, 3 and 4 were isolated in the Philippines in 1956 and dengue type 1, in addition, in Thailand.

Between 1953 and 1964, DHF was described in the Philippines, Thailand, Viet Nam, Malaysia, Singapore, and Calcutta in India. After a period when DHF was endemo-epidemic in Thailand and the Philippines, there was a considerable increase in reported dengue infections in the years 1971-1978 in various countries of the South-east Asian and Western Pacific Regions. DHF appeared in Indonesia and Burma. During the 1975-1978 period a total of 17,251 hospitalizations (772 deaths) was reported in Burma, 21,818 hospitalizations (916 deaths) in Indonesia, and 71,312 hospitalizations (1,676 deaths) in Thailand. In the Western Pacific Region, DHF reports were received during the 1975-1978 period from Malaysia (1,288 cases), the Philippines (836 cases), Singapore (533 cases, including dengue fever), and the Socialist Republic of Viet Nam (66,372 cases for 1976 and 1977 only).

Dengue haemorrhagic fever is an increasing public health problem in most of the countries of the tropical areas of the Western Pacific and South-east Asian Regions. This disease is among the ten leading causes of hospitalization and death in children in at least eight Asian countries in the tropics.

1.2 Other areas at risk

Other countries may be considered to be at risk of DHF outbreaks. Dengue has also been prevalent in tropical areas of Africa and the Americas and appeared episodically in the temperate regions of North America, southern Africa, and the Mediterranean region of Europe. There are indications in the literature that cases similar to DSS occurred during some earlier outbreaks.

1.3 Characteristics of outbreaks

1.4 Transmission chain of dengue

1.5 Pathogenesis of dengue haemorrhagic fever
India has serological and virological evidence of dengue infections with the four serotypes, mainly in the south-east of the country, but no DHF outbreaks have been reported since those of 1963-1965 in Calcutta. Sri Lanka has dengue activity but only sporadic DHF/DSS cases have been reported. A large number of islands in the Western Pacific Region were involved in a dengue type 1 pandemic in 1974, while outbreaks caused by serotypes 2 and 3 occurred during previous years. A somewhat similar situation is developing in the Caribbean islands of the Americas, where a pandemic caused by dengue virus type 1 occurred in 1977 following outbreaks caused by types 2 and 3. In these settings, only a few DHF cases were reported heretofore.

1.3 Characteristics of outbreaks

Outbreaks seem to have appeared suddenly in the Philippines and in Thailand. However, retrospective studies have shown that they were very probably preceded by a period when cases occurred but were not recognized. In Thailand, outbreaks occurred first in Bangkok, with a pattern of epidemic activity at two-year cycles which changed later to irregular epidemic cycles. DHF then became endemic in many large cities of Thailand and thereafter it spread gradually to smaller cities and towns during epidemic occurrences. A similar pattern has been observed in Indonesia and Burma.

A seasonal pattern of incidence, coincident with the rainy season, can be observed in some countries.

In South-east Asia, DHF has been observed mainly in children. In Bangkok, where, since 1968, there has been a trend towards reduced attack rates (constant hospital admissions with an increasing population), the modal age of hospitalized children has risen to 6-7 years but throughout the rest of Thailand the modal age is still 4-6 years. DHF is seen more frequently in females than in males.

The attack rate of DHF is difficult to evaluate as the number of dengue virus infections is most of the time unknown. A retrospective evaluation of the impact of DHF during the outbreak in Bangkok-Thonburi in May-November 1962 indicated that in a population of 870,000 children under 15 years of age there were an estimated 150,000 to 200,000 minor illnesses caused by dengue or chikungunya viruses; 4,187 were hospitalized and diagnosed as having DHF and 4,000 additional cases were treated in private clinics or at home. The incidence of shock was about one third of hospitalized DHF cases.

1.4 Transmission chain of dengue

Dengue virus infection is transmitted to man through mosquito bites and is therefore ranked among arbovirus (arthropod-borne) diseases. Man is the reservoir of virus, and studies in Malaysia have shown that the monkey is a natural reservoir (Fig. 1).
Three elements have to be considered: the virus, the vector, and the host.

The virus

The four serotypes of dengue virus - DEN-1, DEN-2, DEN-3 and DEN-4 - are antigenically very close to each other but they are different enough to elicit only partial cross-protection after infection by one of them. After an incubation period of 4-6 days (minimum 3, maximum 10), the virus is present in the blood of patients during the acute phase of the disease. This constitutes a reservoir of virus readily accessible for transmission of the disease by mosquitoes.

The vector

_Aedes aegypti_ is the most efficient amongst mosquito vectors because of its domestic habitat. The female mosquito bites man during the day. After feeding on a person whose blood contains the virus, the female _Ae. aegypti_ can transmit dengue either after an incubation period of 8-10 days, during which the virus multiplies in its salivary glands, or even immediately, by a change of host when its blood meal is interrupted. Dengue outbreaks have also been attributed to _Ae. albopictus, Ae. polynesiensis_, and several species of the _Ae. scutellaris_ complex. These species have their particular geographical distribution and in general are less efficient vectors than _Ae. aegypti_.

The host

In man, each of the four types of dengue viruses can cause either classical dengue or dengue haemorrhagic fever, and it is not known whether one virus type is more pathogenic than another. The acute phase of infection by dengue viruses, which lasts about 5-7 days, is followed by an immune response. At the first attack, neutralizing antibodies are produced predominantly against the virus type inoculated by the mosquito vector (primary dengue). The first attack gives only temporary and partial protection against the other three types and secondary or sequential infections are possible after a rather short period of time.
1.5 Pathogenesis of DHF/DSS

Two main pathophysiologic changes occur in DHF/DSS. One is an increased vascular permeability, giving rise to loss of plasma from the vascular compartment. This results in haemoconcentration, low pulse pressure and other signs of shock if and when plasma loss is critical. The second change is a disorder in haemostasis which involves all three major factors, namely vascular changes, thrombocytopenia and coagulopathy.

A constant finding in DHF/DSS which may be involved in the production of increased vascular permeability is activation of the complement system with profound depression of C3 and C5 levels. Immune complexes have been described in DHF cases associated with secondary dengue infection, which may initiate the complement activation.

One factor which may contribute to DHF/DSS is the enhancement of virus multiplication in monocytes by heterotypic antibodies. This may trigger the production by monocytes of chemical mediators of vascular permeability, activation of complement and tissue thromboplastin which initiates intravascular blood coagulation.

Research has been undertaken to understand better the pathogenic mechanisms of DHF/DSS.
2. CLINICAL DIAGNOSIS

2.1 Classical dengue fever
2.2 Dengue haemorrhagic fever
2.3 Criteria for clinical diagnosis of dengue haemorrhagic fever (DHF)/dengue shock syndrome (DSS)
2.4 Grading the severity of DHF
2.5 Differential diagnosis of DHF/DSS
2.6 Record sheet

2.1 Classical dengue fever

The clinical features of dengue fever frequently depend on the age of the patient. Infants and young children may have an undifferentiated febrile disease with maculopapular rash. Older children and adults may have either mild febrile syndromes or the classical incapacitating disease with abrupt onset and high fever, severe headache, muscular and joint pains and rash. The case fatality rate is exceedingly low.

Many epidemics of classical dengue fever are accompanied by varying frequency of bleeding complications such as petechial haemorrhage, epistaxis, gingival bleeding, gastro-intestinal bleeding and haematuria.

Classical dengue fever has to be differentiated from dengue haemorrhagic fever and chikungunya fever (see Table 1).

2.2 Dengue haemorrhagic fever

Typical cases of DHF, as commonly seen in Asian countries, are characterized by four major clinical manifestations: high fever, haemorrhagic phenomena, hepatomegaly and often circulatory failure. Moderate to marked thrombocytopenia with concurrent haemoconcentration is a distinctive clinical laboratory finding which differentiates DHF from dengue fever, including DF with haemorrhagic manifestations.

a) Dengue haemorrhagic fever without shock (DHF)

The illness commonly begins with a sudden rise of temperature which is accompanied by facial flush and other non-specific constitutional symptoms such as: anorexia, vomiting, headache and muscle or joint pains. Some patients complain of sore throat and an injected pharynx may be found on examination. Epigastric discomfort, tenderness at the right costal margin and generalized abdominal pain are common. The temperature is typically high and continues so, persisting for 2-7 days, and then falls to normal or subnormal by lysis. Occasionally, the temperature may be as high as 40-41°C and febrile convulsion may occur.

The most common haemorrhagic phenomenon is skin haemorrhage: a positive tourniquet test, easy bruisability and bleeding at venepuncture sites are present in most cases. Fine petechiae scattered on extremities, axillae, face, and soft palate may be seen during the early febrile phase. A confluent petechial rash with characteristic coin-sized areas of normal skin is sometimes seen in convalescence after temperature has been normal for 2-3 days.
Macular, maculo-papular or a rubella-type rash may be observed early or late in the disease. Epistaxis, gum bleeding are less common. Gastro-intestinal haemorrhage is infrequent and more usually follows a period of uncontrolled shock.

The liver is usually palpable early in the febrile phase. The size of the liver varies from just palpable to 2-4 cm below the costal margin. Liver size is not correlated with disease severity. The liver may be tender but jaundice is not usually observed even in patients with a big, tender liver.

In mild or moderate cases, after fever subsides, all signs and symptoms abate. Lysis of fever may be accompanied by profuse sweating and mild changes in pulse rate and blood pressure, together with coolness of extremities and skin congestion. These changes reflect mild and transient circulatory disturbances. Patients usually recover spontaneously or after fluid and electrolyte therapy.

b) Dengue shock syndrome (DSS)

In severe cases, following fever of a few days’ duration the patient’s condition suddenly deteriorates. Accompanying or shortly after the fall in temperature from the 3rd to 7th day of the disease, there are signs of circulatory failure: the skin becomes cool, blotchy and congested, circumoral cyanosis is frequently observed and the pulse becomes rapid. Although some patients may appear lethargic, they become restless and then rapidly go into a critical stage of shock. Abdominal pain is a frequent complaint shortly before the onset of shock.

Shock is characterized by a rapid and weak pulse with narrowing of the pulse pressure (20 mm Hg or less, regardless of the pressure levels, e.g. 100/90) or hypotension, with cold, clammy skin and restlessness. Patients in shock are in danger of dying if appropriate treatment is not promptly given. Patients may pass into a stage of profound shock, blood pressure and pulse becoming imperceptible. The duration of shock is short; the patient may die within 12-24 hours or recover rapidly following appropriate antishock therapy. Uncorrected shock may give rise to a more complicated course with metabolic acidosis, severe gastro-intestinal bleeding and a poor prognosis.

Convalescence in DHF with or without shock is short and uneventful. Even in cases with profound shock, when shock is overcome, the patient rapidly recovers within 2-3 days. Return of appetite is a good prognostic sign. A common finding in convalescence is bradycardia or sinus arrhythmia; absolute bradycardia is seen occasionally.

Clinical laboratory findings

Thrombocytopenia and haemoconcentration are constant findings. A platelet count of below 100,000/mm$^3$ is usually found between the third and eighth days. Haemoconcentration - an evidence of plasma leakage - is always present, even in non-shock cases, but to a lesser degree than in shock cases.
Other common findings are hypoproteinemia, hyponatremia, mildly elevated serum transaminase (SGOT) and blood urea nitrogen levels. Metabolic acidosis may be found in cases with prolonged shock.

The white blood cells count is variable, ranging from leukopenia to mild leukocytosis. Lymphocytosis with atypical lymphocytes is a common finding. A transient mild albuminuria is sometimes observed. Occult blood is often found in stool. About one third of shock cases have a prolonged prothrombin time (PT) and about half of these patients exhibit prolonged partial thromboplastin time (PTT). Assays of coagulation factors show reductions of factors II, V, VII, IX and XII in severe cases. Decreases in fibrinogen levels are also correlated with disease severity.

2.3 Criteria for clinical diagnosis of DHF/DSS

The following criteria have been selected for the clinical diagnosis of DHF and in 90 per cent of cases dengue infection has been confirmed by etiological diagnosis in the laboratory. Their use will avoid an over­diagnosis of the disease.

Clinical

a) Fever - acute onset, high, continuous and lasting 2-7 days.
b) Haemorrhagic manifestations including at least a positive tourniquet test and any of the following:
   - petechiae, purpura, ecchymosis
   - epistaxis, gum bleeding
   - haematemesis and/or melena.
c) Enlargement of liver (observed at some stage of illness in 90-96 per cent of Thai children and in 60 per cent of adults).
d) Shock - manifested by rapid and weak pulse with narrowing of pulse pressure (20 mm Hg or less) or hypotension, with the presence of cold, clammy skin and restlessness.

Laboratory

a) Thrombocytopenia (100,000/mm$^3$ or less).
b) Haemoconcentration: haematocrit (Hct) increased by 20 per cent or more.

1 Standard method using a blood pressure cuff (Wintrobe 1967) is recommended. It should be noted that in DHF patients, the test usually gives a definitely positive result, i.e. more than 20 petechiae/inch$^2$. The test may be negative or mildly positive during the phase of profound shock. It usually becomes positive and even strongly positive if looked for when recovery from shock has occurred.

2 Direct count using phase contrast microscope (normal 200,000-500,000/mm$^3$). In practice, for outpatients a qualitative count from peripheral blood smear is acceptable. In normal persons, 4-10 platelets/oil field (an average of 10 oil field readings recommended) indicates an adequate platelets level. An average of, or below, 2-3/0.F. is considerably low (approximately $<$100,000).
The presence of the first two clinical criteria plus thrombocytopenia and haemoconcentration is sufficient to establish a clinical diagnosis of DHF.

When shock occurs with high Hct levels (except in patients with severe bleeding) and marked thrombocytopenia, the diagnosis of DHF/DSS is highly likely.

2.4 Grading the severity of DHF

The spectrum of DHF is classified according to disease severity into four grades:

- **Grade I** - Fever accompanied by non-specific constitutional symptoms; the only haemorrhagic manifestation is a positive tourniquet test.
- **Grade II** - The additional manifestation to those of Grade I is spontaneous bleeding - skin and/or other haemorrhages.
- **Grade III** - Circulatory failure manifested by rapid and weak pulse, narrowing of pulse pressure (20 mm Hg or less) or hypotension, with the presence of cold clammy skin and restlessness.
- **Grade IV** - Profound shock with undetectable blood pressure and pulse.

The presence of thrombocytopenia with concurrent haemoconcentration will differentiate Grade I and II DHF from classical dengue fever.

Grading the severity of the disease has been found clinically and epidemiologically useful in DHF epidemics in children in South-east Asia and the Western Pacific Region. However, it may not be applicable to dengue in adults.

2.5 Differential diagnosis of DHF/DSS

Early in the febrile phase, the differential diagnosis includes a wide spectrum of viral and bacterial infections. Chikungunya fever may be difficult to differentiate from dengue clinically (see Tables 2 and 3).

By the third or fourth day, usually before shock occurs, the signs and symptoms essential for diagnosis can be observed and should cause no difficulty in diagnosis under epidemic conditions. When shock develops with other manifestations, the clinical diagnosis of DHF can be made with more confidence. Endotoxic shock from bacterial infection, or meningococcemia, may resemble DSS.

The presence of marked thrombocytopenia with concurrent haemoconcentration differentiates DHF/DSS from other diseases.

2.6 Record sheet

A model record sheet for DHF is presented in Table 4.
3. TREATMENT

3.1 General considerations
3.2 Dengue haemorrhagic fever without shock
3.3 Dengue shock syndrome

3.1 General considerations

The major pathophysiological abnormality seen in DHF/DSS is an acute increase in vascular permeability that leads to leakage of plasma. Plasma volume studies revealed a reduction of more than 20 per cent in severe cases. Supporting evidence of plasma leakage includes: serious effusion found at postmortem, pleural effusion on X-ray, haemoconcentration and hypoproteinemia. In severe cases, the onset of shock is acute, haematocrit rises sharply as plasma escapes through the endothelium. Hypovolemic shock, as a consequence of critical level of plasma loss, leads to tissue anoxia, metabolic acidosis and death if uncorrected.

Haemostatic changes in DHF involve all three factors: vascular, thrombocytopenia, and coagulopathy. All patients demonstrate an increase in capillary fragility (positive tourniquet test) and moderate to marked thrombocytopenia. Almost 80 per cent of patients with DSS and 17 per cent of non-shock cases have an abnormal coagulogram suggesting disseminated intravascular coagulation (DIC), as evidenced by concomitant thrombocytopenia, increased fibrinogen degradation product (FDP) and either prolonged PTT or decreased fibrinogen level. Generally, most clotting defects result in no clinical haemorrhage. However, in cases of prolonged uncontrolled shock, DIC may cause important clinical bleeding and may play an important part in the development of lethal shock. About a third of shock cases, mostly those with refractory shock, present bleeding, mostly from gastro-intestinal tract; DIC is implicated as a cause.

In most cases, early and effective replacement of lost plasma with plasma, plasma expander and/or fluid and electrolyte solution results in a favourable outcome. The acute onset of shock, and the rapid, often dramatic, clinical recovery, together with the fact that no destructive or inflammatory vascular lesions are observed, suggests transient functional vascular changes, possibly due to a short-acting pharmacological mediator.

As in other virus infections, there is no specific anti-viral treatment but in DHF/DSS symptomatic and supportive measures are effective. Management directed at the correction of the major pathophysiologic changes is essential. With adequate fluid administration, DSS is rapidly reversible. Adequate rapid replacement will also prevent clinical DIC. The prognosis of the disease depends upon the early recognition of cases and the monitoring of pre-shock conditions.

The constant finding that a drop in the platelet count usually precedes the haematocrit rise which heralds the onset of plasma leakage is of great diagnostic and prognostic value. Serial determinations of platelet and haematocrit levels are essential for early recognition and prevention of shock.
Generally, it is not necessary to hospitalize all suspected cases, or cases, of DHF, since shock may develop in only about a third of patients. Mild and moderate cases can be treated as outpatients. For the purpose of early recognition of shock, parents should be advised to bring the patient back for platelet and haematocrit follow-up, and/or if there are any signs of clinical deterioration, warning signs of shock, e.g., restlessness and/or lethargy, acute abdominal pain, cold extremities, skin congestion, or oliguria, usually on or after the third day of illness.

3.2 Dengue haemorrhagic fever without shock

a) Thirst and dehydration result from high fever, anorexia and vomiting, thus fluid intake by mouth should be ample as tolerated. Electrolyte and dextrose solution (as used in diarrhoeal disease)\(^1\) and/or fruit juice is preferable to plain water.

b) During the febrile phase there is a risk of convulsion and antipyretic drugs may be indicated in patients with hyperpyrexia. Salicylates should be avoided since they are known to cause bleeding and acidosis. Acetaminophen is preferable at the following doses:

<table>
<thead>
<tr>
<th>Age</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>under 1 year</td>
<td>60 mg/dose</td>
</tr>
<tr>
<td>1 - 3 years</td>
<td>60-120 mg/dose</td>
</tr>
<tr>
<td>3 - 6 years</td>
<td>120 mg/dose</td>
</tr>
<tr>
<td>6 - 12 years</td>
<td>240 mg/dose</td>
</tr>
</tbody>
</table>

c) Closely observe patients for early signs of shock. The critical period is the transition from the febrile to afebrile phase which usually occurs after the third day. Haematocrit determinations are an essential guide in therapy since they reflect the degree of plasma leakage and the need for intravenous fluid. Haemoconcentration usually precedes blood pressure and pulse changes. Haematocrit should be determined daily from the third day on until the temperature becomes normal for 1 or 2 days. If haematocrit is not available, haemoglobin determination may be a less sensitive alternative.

d) Parenteral fluid therapy can be done in an O.P.D. rehydration unit in mild or moderate cases when vomiting produces or threatens dehydration or acidosis or when there are signs of haemoconcentration. The volume of fluid and its composition are similar to the fluids used in the treatment of diarrhoea with moderate dehydration. The following schedule is recommended as a guideline:

---

\(^1\) If WHO Oral Rehydration Solution (ORS - 90 mEq Na per liter) is to be used in children under 2 years of age, additional fruit juice should be given in proportion of one fruit juice (or plain water) for every two ORS volumes. The Oral Rehydration Solution consists of:

- Sodium chloride (table salt) 3.5 g
- Sodium bicarbonate (baking soda) 2.5 g
- Potassium chloride 1.5 g
- Glucose 20.0 g

dissolved in one liter of potable water.
Intravenous fluid infusion for moderate dehydration (from Ped. Clinic of North America, Nov. 1964, 11: 1093; in ml per pound body weight, with some modification):

<table>
<thead>
<tr>
<th>Weight on admission</th>
<th>&lt; 15 lbs</th>
<th>16-25 lbs</th>
<th>26-40 lbs</th>
<th>&gt;40 lbs</th>
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<tr>
<td>First day</td>
<td>100</td>
<td>75</td>
<td>60</td>
<td>40</td>
</tr>
<tr>
<td>Second day</td>
<td>75</td>
<td>60</td>
<td>40</td>
<td>40</td>
</tr>
<tr>
<td>Third day</td>
<td>60</td>
<td>40</td>
<td>40</td>
<td>40</td>
</tr>
</tbody>
</table>

or in ml per kg body weight:

<table>
<thead>
<tr>
<th>Weight on admission</th>
<th>&lt; 7 kg</th>
<th>7-11 kg</th>
<th>12-18 kg</th>
<th>&gt;18 kg</th>
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<tbody>
<tr>
<td>First day</td>
<td>220</td>
<td>165</td>
<td>132</td>
<td>88</td>
</tr>
<tr>
<td>Second day</td>
<td>165</td>
<td>132</td>
<td>88</td>
<td>88</td>
</tr>
<tr>
<td>Third day</td>
<td>132</td>
<td>88</td>
<td>88</td>
<td>88</td>
</tr>
</tbody>
</table>

The fluids shall consist of the following:

- 1/2 to 1/3 of the total fluid as physiologic saline solution (PSS)
- 1/2 to 2/3 remaining as 5 per cent glucose in water
- For acidosis: 1/4 of the total fluids shall be sixth-molar sodium bicarbonate
- Solution for fluid therapy in DHF: Lactated Ringer's (LR), 5 per cent glucose PSS, 5 per cent glucose 1/2 PSS, 5 per cent glucose 1/2 LR, 5 per cent glucose in 1/3 PSS.

Fluids as listed are calculated to be given over a 24-hour period. If the child seems severely dehydrated, half of the calculated fluid is given in the first eight hours and the second half in the next 16 hours. During rapid administration of fluids it is especially important to watch for signs of cardiac failure.

Written orders should be explicit as to the type of solution and the rate of administration. A rough estimate of flow may be derived from the formula:

\[ \text{cc/hr} = \text{drops/min.} \times 3 \]

e) Patients should be hospitalized and treated immediately when there are any of the following signs and symptoms of shock:

- restlessness/lethargy
- cold extremities and circumoral cyanosis
- rapid and feeble pulse
- narrowing of pulse pressure (20 mm Hg or less) or hypotension
- sudden rise of haematocrit or continuously elevated haematocrit despite administration of I.V. fluid (as indicated in d) above).
3.3 Dengue shock syndrome

Shock is a medical emergency. An immediate administration of intravenous fluid to expand plasma volume is most essential. Children may go into and out of shock for a 48-hour period. Close observation 24 hours a day is imperative.

a) Immediate replacement of plasma loss

Start initial fluid therapy with lactated Ringer’s or isotonic saline solution 20 ml/kg I.V. Run fluid as rapidly as possible. Positive pressure may be necessary. In case of continued or profound shock, plasma or plasma expander (Dextran, medium sized M.W. in NSS) is given following initial fluid at a rate of 10-20 ml/kg/hr. In most cases not more than 20-30 ml/kg of plasma (Dextran 10-15 ml/kg) is needed. Fluid administration is continued at this constant rate (10-20 ml/kg/hr) until improvement in vital signs is apparent.

b) Continual replacement of further plasma loss to maintain circulating volume

Intravenous fluid (5 per cent D 1/2 lactated Ringer’s or 1/2 NSS) is continued even when there is a definite improvement in vital signs and a declining Hct. The rate of fluid replacement should be slowed down to 10 ml/kg/hr and adjusted thereafter to the rate of plasma loss, which may continue for 24 or 48 hours. Microhaematocrit determination is a simple and reliable index for estimating plasma leakage. Monitoring of central venous pressure may be necessary in management of severe cases of shock that are not easily reversible.

Intravenous fluids should be discontinued when the Hct level drops to around 40 per cent and the patient gains appetite. A good urine flow indicates sufficient circulating volume. In general, there is no need for fluid therapy beyond 48 hours after shock terminates. Re-absorption of extravasated plasma takes place (manifested by a further drop in Hct after intravenous fluid is stopped) and may cause hypovolemia, pulmonary oedema or heart failure if more fluid is given. It is extremely important that a drop in Hct at this stage is not taken as a sign of internal haemorrhage. Strong pulse and blood pressure (with wide pulse pressure) and diuresis are good vital signs found at this reabsorption phase. They rule out the likelihood of gastro-intestinal haemorrhage, which is found mostly at the shock stage.

c) Other electrolyte and metabolic disturbances may need specific correction

Commonly, hyponatremia and, occasionally, metabolic acidosis occur. Electrolytes and blood gases should be determined periodically in severely ill patients and patients who do not seem to respond as promptly as expected. This will provide an estimate of the amount of electrolyte (sodium) deficit and help determine the presence and degree of acidosis. The latter, in particular, if uncorrected may lead to disseminated intravascular clotting, causing a more complicated course. The use of heparin
may be indicated in some of these cases but extreme caution should be exercised in using heparin. In general, early volume replacement and early correction of acidosis with sodium bicarbonate result in a favourable outcome with no need for heparin.

d) Sedatives

A sedative therapy is needed in some cases to restrain an agitated child. Hepatotoxic drugs should be avoided. Chlortal hydrate orally or rectally is highly recommended. In cases without lung complication, paraldehyde I.M. may be used.

Dosage: chlortal hydrate 12.5-50 mg/kg as single hypnotic dose not over 1 Gm.
paraldehyde 0.1 ml/kg I.M. not more than 10 ml.

e) Oxygen therapy

Oxygen therapy should be given to all patients in shock. The oxygen mask or tent may increase apprehension.

f) Blood transfusion

Blood transfusion is indicated in cases with significant clinical bleeding, most often haematemesis and melena. Fresh whole blood is preferable and blood should be given only in a volume up to a normal red blood cell mass. Fresh frozen plasma and/or concentrated platelets may be indicated in some cases when consumptive coagulopathy causes massive bleeding.

A persisting shock, despite an adequate fluid administration, and a decline in Hct level indicate significant clinical bleeding which requires prompt treatment. DIC is usual in severe shock and it may play an important part in the development of massive bleeding and lethal shock. Coagulogram (PT and PTT) should be studied in all shock cases to document the onset and severity of DIC, which determine the prognosis.

Blood grouping and matching should be carried out as a routine precaution for every patient in shock.

g) Monitoring of antishock therapy

Frequent recording of vital signs and Hct determination are important in evaluating results of treatment. If patients show any sign announcing a secondary shock, vigorous antishock therapy should be instituted promptly. Patients should be under constant and careful observation until there is a reasonable certainty that danger has passed. In practice:

(i) The pulse, the B.P., the respiration and the temperature should be taken every 15-30 minutes or more often, until shock is overcome.
(ii) Hct and Hb studies should be performed every two hours for the first six hours, then every four hours thereafter until stable.

(iii) A fluid balance sheet should be kept, recording the type of fluid given, the rate and amount, to evaluate the adequacy of replacement and correction of fluid and electrolytes. Frequency and volume of urine output should be recorded.
4. LABORATORY DIAGNOSIS

4.1 Serological tests
4.2 Isolation of virus

Serological tests offer the simplest and most rapid method of confirming a clinical diagnosis of dengue infection. They are also utilized for epidemiological investigations. However, their interpretation may often be difficult. Isolation of virus is the most reliable method although presently available techniques are still complicated and require time.

4.1 Serological tests

a) Collection of specimens

Physicians should be informed of the appropriate conditions for collecting specimens:

- blood samples should be drawn from suspect DHF cases on hospital admission or attendance at clinic or as soon as possible thereafter; and on discharge, or shortly before, and, if possible, 14-21 days after disease onset;

- an abbreviated case history should accompany specimens, to include, at a minimum: name, address, age, sex, date of onset of illness, date of hospitalization, and brief clinical findings.

A model of a suitable request form for arbovirus laboratory examination is given on page 20.

Two methods can be utilized for collecting specimens:

(i) Blood collection in tubes or vials

- 2 to 5 ml of venous blood are collected aseptically, preferably in a heparinized container (if blood is drawn soon after onset it can also be used for isolation of the virus).

- Use adhesive tape and pencil, indelible ink, or typewriter to label the container. Name of patient, identification number and date of collection must be indicated.

- Tubes or vials with screw caps are preferable. Fix the cap with adhesive tape, wax or other sealing material to prevent leakage during transport.

- Ship to laboratory on wet ice as soon as possible. If shipment is delayed, keep in a refrigerator at +4°C to +10°C but do not freeze as haemolysis would be an inconvenience for complement fixation.
(ii) **Blood collection on filter paper**

- With a pencil, write patient's initials or number on two or three discs or strips of standardized absorptive paper.\(^1\)

- Collect fingertip blood (or venous blood in a syringe) onto filter paper and saturate through to reverse side.

- Discs or strips are allowed to dry protected from flies.

- After dessication, place in plastic bags and staple to the laboratory examination request form. Store without refrigeration.

**Elution of filter paper blood**

- Elute the disc at 4°C overnight in 1 ml of 12.5 per cent kaolin-borate saline, pH 9.0, in a 12x75 test tube.

- In the morning, place the tube at room temperature for 20 minutes, shaking periodically.

- Centrifuge for 30 minutes at 2,000 rpm.

- For HI tests using goose erythrocytes, without removing kaolin add 0.05 ml 50 per cent goose cells to the tube, shake, without disturbing the pellet, and incubate at 37°C for 30 minutes.

- Add 1 ml borate saline, pH 9.0, to the tube.

- Centrifuge at 2,000 rpm for 10 minutes and decant supernatant.

This is approximately equivalent to a 1:30 serum dilution.

Each laboratory should standardize the correlation between results with venous blood and the filter paper disc technique in the same individuals.

b) **Haemagglutination inhibition test (HIT)**

Haemagglutination inhibition has been the serological test most widely used. The recommended technique is that of Clarke and Casals adapted to microtitre equipment and which is described in most manuals.

- Sera should be extracted with kaolin or with acetone to remove non-specific inhibitors and then absorbed with goose RBC to remove non-specific agglutinins.

\(^1\) e.g. Whatman No. 3 filter paper, discs of 1/2" or 12.7 mm diameter.
- The mode of preparation of haemagglutinating antigen described by Clarke and Casals is the most satisfactory but its extraction with acetone is laborious and expensive. A crude 20 per cent suckling mouse brain suspension in borate saline at pH 6.4 from which gross debris has been removed by 30 minutes of centrifugation at 3,000 rpm is stable for 4-6 months and has proved satisfactory.

- Paired (acute and convalescent) sera should be tested in the same run initially using 4 - 8 haemagglutinating units of a single broadly reactive antigen (usually dengue 1 or 2). If the paired sera have no antibody or do not show a significant antibody rise, both specimens may be retested against all four dengue types.

- Where chikungunya virus is known to be endemic, all paired sera should be tested against this antigen. Where chikungunya virus is not known to be present, only a small proportion of the sera need to be tested against this antigen.

- Known positive and negative sera should be included in each test to standardize results and maintain quality control. Standard reference sera are available from WHO and should be included in the test periodically for quality control.

  c) Other serological tests

  (i) Complement fixation test (CFT)

  The CFT may also be used in serological diagnosis wherever facilities for this test exist. Blood taken on filter paper is unsuitable because it is lysed.

  The CFT is useful since only anti-dengue IgG fixes complement with dengue antigens. The presence of CF antibody in early convalescent sera signifies secondary type immune response.

  (ii) Neutralization tests

  A variety of neutralization tests has been developed to measure dengue antibody. The 50 per cent endpoint plaque reduction neutralization test (PRNT) in LLC-MK2 cells has been widely used and is well described in the literature. Following primary dengue infections, relatively monotypic neutralizing antibodies are detected during early convalescence. Following secondary dengue infections, high titred neutralizing antibody is produced to two, and, most frequently, all four dengue types.

  d) Interpretation of results

  Identification of infecting virus by serological tests is often difficult in persons who have had a previous infection with other viruses of the same serological group as dengue viruses, formerly called Group B

---

1 Upon request to the Virus Diseases Unit, WHO, Geneva. A limited supply of inactivated dengue type 2, chikungunya and Japanese B encephalitis antigen is also available.
arboviruses and now called Flaviviruses. High titres of antibodies can be found to antigens from several viruses in the group. In instances when sequential infection consists of a non-dengue flavivirus and a dengue virus, the IgM serum fraction may contain antibody specific to the second infecting virus.

(i) Primary antibody response

The primary antibody response to dengue infection is characterized by slow evolution of HI antibody which is often relatively monotypic, absence of CF antibody until at least two weeks after onset of illness, and monospecific neutralizing antibody. Definitive characterization of primary response is established by demonstrating rising titres of anti-dengue IgM.

In practice, dengue HI antibody titre is generally less than 1:20 in serum obtained before the fourth day after onset of illness. There is a fourfold or greater increase in titre in convalescent specimens (1-4 weeks after onset), with antibody titre not greater than 1:1280.

(ii) Secondary antibody response

The secondary antibody response is characterized by a rapid evolution of HI and CF antibody. All antibodies are broadly reactive. Definitive characterization of a secondary response is established by demonstrating rising titres of anti-dengue IgG.

Evidence of recent infection. In practice, HI antibody to dengue antigen(s) is less than 1:20 in serum obtained before the fifth day of illness with response equal to or higher than 1:2560 in convalescent serum, or HI antibody at least 1:20 in serum obtained before the fifth day after onset of illness, with rise to $\geq 1:2560$ in convalescent serum.

Presumptive recent infection. HI antibody 1:1280 or greater in acute specimen without fourfold or greater antibody rise in convalescent specimen.

(iii) The interpretation of dengue antibodies may be summarized as follows:

<table>
<thead>
<tr>
<th>First specimen</th>
<th>Second specimen</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before 4th day $&lt; 1:20$</td>
<td>$\geq 4x$ and less than $1:2560$</td>
<td>Primary response</td>
</tr>
<tr>
<td>Before 5th day $&lt; 1:20$</td>
<td>$\geq 1:2560$</td>
<td>Secondary response</td>
</tr>
<tr>
<td>Before 7th day $\geq 1:1280$ $&lt; 4x$</td>
<td></td>
<td>Presumptive recent secondary response</td>
</tr>
</tbody>
</table>

1 These criteria were developed from an extensive experience with virologically and immunologically studied patients with dengue infections at the U.S. Army Bangkok Laboratory. If the sensitivity of the HI test system in
To interpret high-fixed titres, laboratories should establish baseline titres for the local population taken at a point of little or no dengue transmission. Titres more than twice the standard deviation of the geometric mean may be presumed to indicate recent dengue infection.

4.2 Isolation of virus

The flow chart in Table 5 shows several methods that can be used for isolation of dengue viruses. Material for isolation should be kept at +4°C to +8°C for a short period of time or frozen for a longer period of storage. In the latter case it should be maintained without risk of thawing. Wherever possible, original materials (viraemic serum or infected mosquito pools) as well as laboratory passage strains should be preserved for future study.¹

¹ WHO should be contacted concerning facilities for the storage of dengue viruses.
**ARBOVIRUS LABORATORY REQUEST FORM**

For Laboratory Use

<table>
<thead>
<tr>
<th>Name of Patient</th>
<th>Hospital No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Address</td>
<td>Hospital Name</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Age</th>
<th>Sex</th>
<th>Adnission complaint</th>
</tr>
</thead>
</table>

**Clinical findings:**
1. Fever: 39 °C or 102 °F (max) Duration ___ days
2. Turniquet test: Petechiae Epistaxis
3. Haematemesis/melena Other bleedings (Describe)
4. Hepatomegaly: (cm. at RCM). Tenderness
5. Shock: B.P. mm. Hg. Pulse ___ /min.
   Restlessness/Lethargy Coldness of extremities/body

**Clinical Laboratory findings:**

<table>
<thead>
<tr>
<th>Platelets (x10^3)</th>
<th>/mm^3 (on ___ day of illness)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haematocrit (%)</td>
<td>(max) (min)</td>
</tr>
</tbody>
</table>

(Acute) Blood specimens

<table>
<thead>
<tr>
<th>Hospital admission Date</th>
<th>Blood specimens</th>
<th>Convalescent Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospital discharge Date</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Instructions: Fill out entire form and clinical findings in duplicate. Fill filter paper discs completely so that reverse side is saturated and clip them on the form. Obtain admission and discharge specimens from all patients. If patient does not return for convalescent sample, mail promptly.

**ARBOVIRUS LABORATORY REQUEST FORM**

| To: Physician | Hospital | Patient | Hospital No. |

| Address |             |

**Clinical findings:**
1. Fever: 39 °C or 102 °F (max) Duration ___ days
2. Turniquet test: Petechiae Epistaxis
3. Haematemesis/melena Other bleedings (Describe)
4. Hepatomegaly: (cm. at RCM). Tenderness
5. Shock: B.P. mm. Hg. Pulse ___ /min.
   Restlessness/Lethargy Coldness of extremities/body

**Clinical Laboratory findings:**

<table>
<thead>
<tr>
<th>Platelets (x10^3)</th>
<th>/mm^3 (on ___ day of illness)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haematocrit (%)</td>
<td>(max) (min)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Results</th>
<th>Dates of specimens</th>
<th>HI titres</th>
</tr>
</thead>
</table>

Interpretation
5. VECTOR SURVEILLANCE AND CONTROL

5.1 Surveillance
5.2 Long-term control
5.3 Emergency control
5.4 Training

In most instances the most important, and often the only, vector of dengue haemorrhagic fever is *Aedes aegypti*. This vector should thus be the main target of surveillance and control activities wherever it occurs. Other vectors should only be considered where there is good evidence that they play an epidemiologically significant role in the transmission of the disease.

5.1 Surveillance

A number of indices have been described and are currently used to monitor *Ae. aegypti* populations in terms of dengue transmission. The most significant of these indices are those related to the abundance of adult mosquitoes expressed either as landing rates or as indoor resting density. Whenever adult collections cannot be routinely made to ensure an acceptable degree of monitoring, ovitraps can be used as a complementary method. Should the house index\(^1\) and/or Breteau index\(^2\) be used, the definition of a house should be one unit of accommodation irrespective of the number of people therein.

*Ae. aegypti* has a short flight range and a very large number of catching stations would be required to provide an accurate monitoring of the areas at risk. As this cannot usually be done, the best alternative is to concentrate the monitoring on high risk areas as determined by past experience and/or environmental conditions. Special attention should also be given to areas where control activities are carried out to evaluate their effectiveness and develop remedial measures as appropriate.

In a crowded area, many people living within the short flight range of the vector from its breeding source could be exposed to transmission even if the house index is low. Distances between houses may be of epidemiological significance especially in areas with single-storey dwellings. In multi-storey dwellings the population per unit area could be higher than in slum areas. Thus survey data for single-storey and multi-storey dwellings should be kept separate.

Emergency control measures are based on insecticide applications and it is essential to monitor periodically vector susceptibility to the insecticide most widely used for control operations, i.e. temephos (Abate) and malathion. Eggs can be sent to appropriate WHO collaborating laboratories for susceptibility testing when local facilities are not available.

---

1. Percentage of houses positive for larvae.
2. Number of positive containers per 100 houses.
In areas where *Ae. aegypti* is absent or very scarce and dengue outbreaks occur, a special effort should be made to identify the local vector(s) and develop vector surveillance and control methods accordingly.

5.2 Long-term control

Long-term control should be based on health education and community participation, supported by legislation and law enforcement wherever socio-economic conditions permit. This should be facilitated by provision of an adequate water supply to the communities concerned. Larvicides should be considered as a complementary measure, and temephos 1% sand granules can be applied at a target dose of 1 ppm (e.g. 10 g material to 100 litres of water), especially in high risk localities before periods of anticipated outbreaks.

The community should participate by undertaking the disposal of all water containers which are no longer used (e.g. old tyres, empty tins and bottles, broken jars, etc.) and by routinely changing the water in flower vases once a week. Water storage containers which can be moved should be turned upside down before refilling with water.

Water jars and drums which cannot be disposed of should be adequately covered to prevent egg laying by *Ae. aegypti*, or cleaned and scrubbed weekly. When this is not possible due to their shape or size, *Aedes* larvae should be eliminated by transferring the water from one container to another by filtering it through a cloth.

In certain areas, where vectors other than *Ae. aegypti* are present, coconut shells and husks can be buried or burned, tree holes can be filled with sand or cement, leaf axils can be punctured and the tops of bamboo fences altered to prevent accumulation of water and mosquito breeding. Large water tanks with taps in coastal areas without a piped water supply should be covered so as to allow rainwater to enter, but not egg-laying mosquitos.

Since DHF is an ever present threat, health education should be built progressively, beginning at schools and continuing throughout life, based on simple but accurate information and using all available media (school books and lectures, newspapers, radio, pamphlets, etc.). While health education should aim to cover the whole population, more specific information efforts should be directed towards key components of the community such as public health service staff and teachers. This health education should cover vector-borne diseases in general with special emphasis on DHF wherever this constitutes a major problem.

5.3 Emergency control

a) To be effective, operations must begin when the first few cases are detected or when there are sound reasons to anticipate an outbreak.

b) The size of area (or areas) to be treated should be determined through epidemiological and entomological information. If cases are scattered, adulticide space spraying should be implemented within a minimum distance of 100 metres radius from houses having cases.
c) Two adulticidal treatments should be made at 10-day intervals if resources are available or if they can be obtained. Vehicle-mounted or portable ULV aerosol generators or mist blowers can be used to apply a suitable insecticide (e.g. technical malathion or fenitrothion) at above one-half liter per hectare.

d) It is suggested that moderate size cities have at least one vehicle-mounted aerosol generator, five mist blowers, 10 swing fogs and 1,000 liters of ULV insecticides in order to be prepared to carry out rapidly adulticidal operations over a 20-kilometer-square area. With limited funds, such equipment and insecticides can be stockpiled in one city for rapid transportation to other areas when required.

e) Priority areas for vector control are those having a concentration of cases and/or a high vector density. Special attention should be focused on areas where people congregate, e.g. hospitals and schools.

f) If necessary, ULV spraying by local air force C47 aircraft or smaller agricultural type planes and helicopters can be explored.

g) Hospital rooms with DHF patients should be mosquito-proof.

5.4 Training

Medical officers and personnel who see DHF cases should receive short training courses on vector biology and ecology so that they can inform the community of the measures they can take to reduce vector breeding and biting.

Due to the expense and shortage of trained manpower to maintain special Aedes control teams, health inspectors and related personnel should be given national training courses on Aedes surveillance and control to enable them to participate in control operations.
6. EPIDEMIOLOGICAL SURVEILLANCE, CONTROL, AND PREVENTION

6.1 Factors enhancing the risk of occurrence of dengue haemorrhagic fever outbreaks
6.2 Surveillance of dengue haemorrhagic fever
6.3 Control of outbreaks
6.4 Prevention of dengue haemorrhagic fever
6.5 Exchange of information

The objectives of a surveillance programme for DHF are: (1) early detection of outbreaks, thus permitting a prompt application of control measures, and (2) monitoring all the important factors that favour an outbreak of the disease. To accomplish these, improved diagnosis and reporting, use of reliable diagnostic criteria, as well as epidemiological and entomological surveillance are needed.

6.1 Factors enhancing the risk of occurrence of dengue haemorrhagic fever outbreaks

The occurrence of DHF outbreaks is obviously linked to the density of mosquito vectors and particularly that of Aedes aegypti. The precise population density of Ae. aegypti which will sustain dengue virus epidemically or endemically in a community has not yet been determined successfully. However, a small number of active biting female mosquitoes can easily infect an entire household. The potential for virus transmission is also enhanced by the density of human populations. Uncontrolled urbanization in tropical areas has resulted in the proliferation of Ae. aegypti in densely populated areas.

Dengue viruses move with people, particularly children. Aedes aegypti has a short flight range and is less important as a means of transportation of viruses within cities than man. Schools may be important sites of dissemination of dengue viruses. Aedes aegypti bite during the day, and school children bitten by infected mosquitoes may take the virus home to other parts of the city. A second institution which can spread dengue viruses is the hospital. Visitors and patients with other diseases may be bitten by infected Aedes aegypti in hospitals.

Transportation of dengue viruses to smaller towns and rural areas is possible from large cities where the disease is epidemic or endemic. The factors of dengue transmission and maintenance in smaller towns are not well understood.

In most places there seems to be a distinct seasonal pattern in DHF outbreaks. In subtropical regions north and south of the equator, monsoon weather patterns prevail. It has been observed in Bangkok, for example, that several months following the cessation of the rains, usually during cool dry weather, DHF hospitalization rates decline. The seasonal decline in dengue transmission is not well understood. It may be related to a decrease in biting activity, a decrease in longevity of female mosquitoes, or both, and possibly to a small decrease in vector population. Whatever the cause, the phenomenon is real. During seasonal lows, virus transmission is most likely to occur only in areas of high transmission potential.
Typically, DHF cases have been associated with secondary infections and, occasionally in infants and a few children, with primary dengue infections. In Asia, DHF cases are seen in areas where a high density of *Ae. aegypti* and the presence of different types of dengue viruses cause multiple infections in children, as evidenced by a typical pattern of secondary (anamnestic) serological response. The hypothesis that DHF is associated with a secondary infection has been put forward from clinical and seroepidemiological studies in Thailand.

6.2 Surveillance of dengue haemorrhagic fever

Surveillance is indicated in all endemic areas as well as "receptive areas", defined as areas where *Ae. aegypti* is known to be present. Undoubtedly, the mere presence of this mosquito is not sufficient in itself to create potential conditions for a DHF outbreak; the biting rate, longevity and population density of the vector must be crucial factors. However, until the density level above which the situation is ready for mass transmission of dengue virus is known, the presence alone of *Ae. aegypti* is sufficient to declare an area as "receptive".

It is important to understand that, as a general rule, a great amount of silent dengue infection has preceded DHF epidemics. It has been estimated that between 150 and 200 mild or silent dengue infections occur for each case of shock seen in hospital. An understanding of this iceberg phenomenon is essential to the planning of control and prevention programmes of DHF.

Most dengue infections of young children are mild and difficult to distinguish from a common cold or other seasonal fevers. Classical dengue fever is most commonly seen in adults. In areas where dengue viruses are endemic, resident adults are generally immune. The mild nature of the vast majority of dengue infections implies that in endemic areas a fairly high level of dengue transmission may go unnoticed.

Implementation of surveillance is based on the following action:

a) Recognition of cases

Standard criteria for diagnosis should be followed, including clinical laboratory diagnosis (see 2.3, page 7).

b) Confirmation of cases

An important function of a surveillance system is to identify quickly the etiology of presumptive DHF. This should be done by submitting paired sera to a laboratory. For virus isolation, see 4.2, page 19.

c) Prospective surveys

Serological surveys may be used to detect dengue infection when this is relatively silent. They may also give an indication of the presence of specific dengue serotypes. Surveys of patients with fevers of unknown origin and suspect haemorrhagic fever cases should be undertaken, including examination of paired sera and attempts to isolate the virus.
d) **Outbreak investigation**

The geographical area affected should be defined rapidly to determine the extent of the insecticide spraying required.

e) **Reporting of cases**

Cases of DHF should be reported specifying whether with or without shock. Cases and deaths should be reported weekly by geographical area by national health authorities to the Communicable Diseases Adviser in the WHO South-east Asian (New Delhi) and Western Pacific (Manila) Regional Offices. Confirmed and unconfirmed DHF cases by age and sex should be reported annually.

6.3 Control of outbreaks

Two main operations to be carried out simultaneously are mosquito control and treatment of patients in hospitals.

a) **Emergency mosquito control**

Operations for emergency mosquito control should be carried out as indicated in 5.3, page 22. The objective is to eliminate infected mosquitoes and to break the transmission cycle by holding mosquito populations at extremely low levels during the time necessary for viraemic subjects to recover. Complete control of an epidemic may not be feasible if all adult Ae. aegypti cannot be destroyed in the entire affected area. However, a sustained reduction of mosquito populations in selected areas will inevitably result in a smaller number of cases.

b) **Organization of hospitals during epidemics**

Triage. During epidemics, outpatient and inpatient facilities may be overwhelmed and medical care staff can rapidly become exhausted. Under these conditions it is essential that only children requiring hospital care be admitted. A fever and positive tourniquet test are sufficient to produce suspicion of DHF; when possible, a microhaematocrit and platelet count should be done in the Outpatient Department. Patients with thrombocytopenia and elevated haematocrit should be sent to a rehydration ward or, on suspicion of circulatory failure, admitted to hospital. If a patient lives a long distance from hospital and nearby accommodation is not available it may be necessary to admit him for observation. Parents should be carefully instructed to return children promptly to hospital should any danger sign be observed. If properly instructed, triage can be done by paramedical workers. Competent laboratory assistance is essential. Without a laboratory, patients must be evaluated by physical examination. Cool extremities, skin congestion, circumoral cyanosis or a rapid pulse should result in hospitalization. If possible, cases should be hospitalized for observation or cautioned to remain near hospital until two days after fever terminates.

Intensive care. Patients with a similar degree of severity of illness should be grouped together. Those with shock require intensive 24-hour nursing and physician care. Paramedical workers or parents can assist in oral fluid therapy or in surveillance of the rate of intravenous fluid administration and general status of the patient.
Microhaematocrit determinations are essential in monitoring need for and success of therapy. It is recommended that all institutes providing care for DHF patients have microhaematocrit equipment available.

c) Other measures

Coordination of DHF emergency control measures can best be implemented through the establishment of a DHF committee including administrators, epidemiologists, clinicians, entomologists and virus laboratory representatives.

6.4 Prevention of dengue haemorrhagic fever

Prevention of DHF outbreaks in endemic areas is based on surveillance of virus circulation (see 6.2), together with mosquito surveillance (5.1) and anti-mosquito long-term control measures (5.2). Contingency planning should estimate populations at risk and identify the location of equipment, supplies and personnel which may be required.

Research is being carried out to develop a live tetravalent vaccine against dengue virus serotypes D₁ to D₄. Although good progress can be reported, it will be several years before an acceptable vaccine for mass use can be available.

6.5 Exchange of information

Rapid exchange of information is essential. Narrative epidemiological reports, results of clinical studies, dengue virus isolation by source and date, entomological studies, surveys for Aedes vectors, control measures planned or accomplished, new developments in insecticides and spray equipment and other pertinent information will be published in the Dengue Newsletter for the South-east Asian and Western Pacific Regions. Contributions or requests for copies may be sent to the Project Leader, WHO/VRCRU, P.B. 302, Jakarta, Indonesia. Copies of the Newsletter are available to all interested persons.
7. PRIMARY HEALTH CARE

7.1 Recognition of dengue haemorrhagic fever cases
7.2 Management of cases
7.3 Collection of specimens for laboratory examination
7.4 Mosquito control

As has been mentioned earlier, DHF tends to spread from large cities to smaller ones and to villages infested by vector mosquitoes, mainly Aedes aegypti. The case fatality rate of DHF can be considerably decreased if the appropriate replacement fluid therapy is given early in the course of the disease. Referral to a well equipped hospital is not always possible. DHF is therefore a problem for primary health care in endemic rural areas. Conditions for diagnosis, treatment and control of outbreaks are somewhat different from what have been set out heretofore. A primary health care worker, specially trained for this purpose, could be very helpful in the control of DHF.

7.1 Recognition of DHF cases

An outbreak of DHF should be suspected when:

- several children are affected with febrile diseases characterized by high continuous fever of 2-7 days duration with no response to malaria treatment;

- unexplained deaths occur with or without haemorrhage;

- patients have petechiae (red spots on the skin) or bleeding from the nose or the gums, or haematemesis or melena;

- when temperature drops, the skin becomes clammy, extremities are cold and sweaty, and children become drowsy or restless.

7.2 Management of cases

High fever should be treated by sponging. Aspirin (sali cylates) should not be given.

Oral rehydration must be attempted in early stage of fever with a sugar and salt solution used for diarrhoeal disease (see footnote page 10) and repeated small quantities should be given.

If the body temperature drops and cold extremities occur, with restlessness, refer promptly to health centre for intravenous fluid administration. If referral is not possible, enforce oral rehydration until the child urinates and the skin becomes warm.

7.3 Collection of specimens for laboratory examination

Proof that the outbreak is caused by dengue virus must be obtained as soon as the first suspect cases have been recognized.

Blood films should be taken and sent to the health centre for staining and examination for malaria parasites and platelet counting.
As indicated in 4.1, blood specimens should be collected on filter paper discs or strips and sent with clinical data to a specialized laboratory.

Recognition of cases and appropriate collection of specimens can be facilitated if a member of the community has been designated as "health communicator" to provide liaison between the community and the health care group.

7.4 Mosquito control

The disease is transmitted by mosquitos. Local mosquitos should be identified, as their breeding sites may differ according to species. If this is not possible it may be assumed that the vector is *Aedes aegypti*, a mosquito that bites during the day, rests in houses, and lays eggs in nearby water collectors, such as water jars in the house or the yard, old tyres, pots, discarded bottles and cans, shells, etc.

At the village level, community participation in the control of DHF, particularly in source reduction of *Aedes* mosquitos as described in 5.2, seems to be a feasible and realistic activity which can be carried out through the primary health care worker.
References


TABLE 1

Observed frequency of findings in classical Dengue fever in adults and Dengue and Chikungunya infections in Thai children diagnosed as haemorrhagic fever.

<table>
<thead>
<tr>
<th>Manifestations</th>
<th>Classical Dengue&lt;sup&gt;1&lt;/sup&gt;</th>
<th>Chikungunya Fever</th>
<th>Dengue (DHF)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Positive tourniquet test</td>
<td>++</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Petechiae or ecchymosis</td>
<td>+</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Confluent petechial rash</td>
<td>0</td>
<td>0</td>
<td>+</td>
</tr>
<tr>
<td>Hepatomegaly</td>
<td>0</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Maculopapular rash</td>
<td>++</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Myalgia/arthralgia</td>
<td>+++</td>
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<td>+</td>
</tr>
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<td>Lymphadenopathy</td>
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</tr>
<tr>
<td>Leucopenia</td>
<td>+++</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>++</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td>Shock</td>
<td>0</td>
<td>0</td>
<td>++</td>
</tr>
<tr>
<td>Gastrointestinal bleedings</td>
<td>0</td>
<td>0</td>
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</tbody>
</table>

<sup>1</sup>Data from Halstead et al. Mainly Caucasian adults.

Frequency of observation -

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<th>+</th>
<th>++</th>
<th>+++</th>
<th>++++</th>
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</thead>
<tbody>
<tr>
<td>Frequency</td>
<td>1</td>
<td>26</td>
<td>51</td>
<td>76</td>
</tr>
<tr>
<td>Percentage</td>
<td>25%</td>
<td>50%</td>
<td>75%</td>
<td>100%</td>
</tr>
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</table>
## TABLE 2

Non-specific constitutional symptoms observed in haemorrhagic fever patients with Dengue and Chikungunya infection (Modified from Nimmannitya et. al. 1969)

<table>
<thead>
<tr>
<th>Findings</th>
<th>Dengue %</th>
<th>Chikungunya %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Injected Pharynx</td>
<td>98.9</td>
<td>90.3</td>
</tr>
<tr>
<td>Vomiting</td>
<td>57.9</td>
<td>59.4</td>
</tr>
<tr>
<td>Constipation</td>
<td>53.3</td>
<td>40.0</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>50.0</td>
<td>31.6</td>
</tr>
<tr>
<td>Headache</td>
<td>44.6</td>
<td>68.4</td>
</tr>
<tr>
<td>Generalized lymphadenopathy</td>
<td>40.5</td>
<td>30.8</td>
</tr>
<tr>
<td>Conjunctonal injection</td>
<td>32.8(^1)</td>
<td>55.6(^1)</td>
</tr>
<tr>
<td>Cough</td>
<td>21.5</td>
<td>23.3</td>
</tr>
<tr>
<td>Restlessness</td>
<td>21.5</td>
<td>33.3</td>
</tr>
<tr>
<td>Rhinitis</td>
<td>12.8</td>
<td>6.5</td>
</tr>
<tr>
<td>Maculopapular rash</td>
<td>12.1(^1)</td>
<td>59.6(^1)</td>
</tr>
<tr>
<td>Myalgia/arthralgia</td>
<td>12.0(^1)</td>
<td>40.0(^1)</td>
</tr>
<tr>
<td>Enanthema</td>
<td>8.3</td>
<td>11.1</td>
</tr>
<tr>
<td>Abnormal reflex</td>
<td>6.7</td>
<td>0.0</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>6.4</td>
<td>15.6</td>
</tr>
<tr>
<td>Palpable spleen</td>
<td>6.3(^2)</td>
<td>3.1(^2)</td>
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<tr>
<td>Coma</td>
<td>3.0</td>
<td>0.0</td>
</tr>
</tbody>
</table>

\(^1\)Statistically significant difference

\(^2\)Infants under 6 months
TABLE 3

Major manifestations used as criteria for diagnosis of Dengue haemorrhagic fever - V.S. Chikungunya infection (Modified from Nimmannitya et al. 1969)

<table>
<thead>
<tr>
<th>Manifestations</th>
<th>Dengue %</th>
<th>Chikungunya %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever - duration 2 - 4 days</td>
<td>23.6</td>
<td>62.5</td>
</tr>
<tr>
<td></td>
<td>59.0</td>
<td>31.2</td>
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<tr>
<td></td>
<td>17.4</td>
<td>6.3</td>
</tr>
<tr>
<td>Haemorrhagic manifestations.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>positive tourniquet test</td>
<td>83.9</td>
<td>77.4</td>
</tr>
<tr>
<td>Petechiae scattered</td>
<td>46.5</td>
<td>31.3</td>
</tr>
<tr>
<td>Petechial rash (confl.)</td>
<td>10.1</td>
<td>0.0</td>
</tr>
<tr>
<td>Epistaxis</td>
<td>18.9</td>
<td>12.5</td>
</tr>
<tr>
<td>Gum bleeding</td>
<td>1.5</td>
<td>0.0</td>
</tr>
<tr>
<td>Melena/hematemesis</td>
<td>11.8</td>
<td>0.0</td>
</tr>
<tr>
<td>Hepatomegaly</td>
<td>90.0</td>
<td>75.0</td>
</tr>
<tr>
<td>Shock</td>
<td>35.2</td>
<td>0.0</td>
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## TABLE 4
DENGUE HAEMORRHAGIC FEVER RECORD SHEET

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<th>Day of illness</th>
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<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
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<th>9</th>
<th>10</th>
<th>11</th>
<th>12</th>
<th>13</th>
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<td>Month/Date</td>
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<td>(encircle date of hospitalization)</td>
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<td>Pulse/BP</td>
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<td>Blood for virus/sero</td>
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<td>Plasma</td>
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<td>Blood</td>
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<td>Others</td>
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</tbody>
</table>
### TABLE 5. FLOW CHART FOR DENGUE VIRUS ISOLATIONS

<table>
<thead>
<tr>
<th>SOURCE</th>
<th>MATERIAL FOR INOCULATION</th>
<th>PREPARATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Living patient</td>
<td>Blood, serum, plasma leucocytes</td>
<td>Clot homogenized, serum or plasma undiluted and 1:5 or 1:10.</td>
</tr>
<tr>
<td>Autopsy</td>
<td>Various tissues</td>
<td>Tissue homogenized as 10-20% W/V suspension in buffer with 1% protein stabilizer and antibiotics. Centrifuge at 3000 rpm 15 minutes. Use undiluted and 1:10.</td>
</tr>
<tr>
<td>Vector mosquitoes</td>
<td>♀ Mosquitoes</td>
<td>Homogenized as approximately 10% W/V suspension.</td>
</tr>
</tbody>
</table>

#### INOCULATION SYSTEMS

**A**  
- **Inoculation:** 0.2-1.0 µl intrathoracic to mosquitoes Aedes aegypti ♂  
  Ae. albopictus ♂ or ♀  
  Toxorhynchites ♂ or ♀  
- **Observation:**  
  (a) Presence of antigens in salivary glands by immunofluorescence (IF)  
  (b) Use of mosquito tissues as CF antigen in typing tests  
- **Passage material:** Further passage usually unnecessary unless strain establishment required  

**B**  
- **Inoculation:** Various cell cultures, e.g. BSC1, vero, LLC-MK2, Ae. albopictus  
- **Observation:**  
  (a) CPE in cells  
  (b) Plaque formation  
  (c) IF or PAP staining of infected foci  
- **Passage material:** Further passage usually unnecessary unless strain establishment required  

**C**  
- **Inoculation:** 0.01-0.02 ml I.C. to suckling mice < 48 hrs old  
- **Observation:**  
  (a) Presence of antigen in brain by IF on day 7  
  (b) Abnormal behaviour  
  (c) Presence of antibody in serum 3-4 weeks after inoculation  
- **Passage material:** Brain as 10% W/V suspension

---

Passage in same system and in other systems

**Identification**  
Plaque neutralization test using monotypic monkey serum as reference method.
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*Unable to attend
TECHNICAL ADVISORY COMMITTEE ON
DENGUE HAEMORRHAGIC FEVER FOR THE
SOUTH-EAST ASIAN AND WESTERN PACIFIC REGIONS

1975

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