2019

NATIONAL GUIDELINES ON

PREVENTION, MANAGEMENT AND CONTROL OF DENGUE IN NEPAL

Government of Nepal
Ministry of Health and Population
Department of Health Service
Epidemiology and Disease Control Division
Teku, Kathmandu

CONTENTS

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FOREWORD

It gives me an immense pleasure to present the "Revised National Guidelines on Prevention, Management and Control of Dengue in Nepal, 2019".

Dengue is a rapidly emerging disease in Nepal. The first dengue case was reported from Chitwan district in a foreigner in 2004. Since then increasing number of dengue cases have been reported from many urban cities of Nepal including several dengue outbreaks.

The first national dengue guidelines was developed based on World Health Organization (WHO) guidelines -1997 in 2008. The national guidelines was then revised in 2011. It was deemed necessary to once again revise the guideline focusing on dengue prevention, management and control using the latest internationally adopted definitions, protocols and guidelines to provide a standard technical guidance on dengue management. I hope this revised national dengue guideline would be helpful for health personnel working across the country to effectively prevent, manage and control dengue in Nepal.

I would also like to extend my appreciation to the leadership of EDCD team and to all the national and international experts for their valuable contributions in producing this excellent guideline. Finally, I would also take this opportunity to express my sincere thanks to WHO, Nepal for providing technical support in the revision of this important guideline.

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FOREWORD

Dengue is one the rapidly emerging mosquito borne viral disease causing serious problem in the lowland area in Nepal since 2006. The disease is now expanding to other areas including the hilly region and has been established as an endemic disease in Nepal. Nepal has experienced several outbreaks of dengue in recent years across many provinces in the country, requiring hospitalization of dengue cases and posing an economic burden to the patients and the health system. Timely prevention, proper case management and rapid vector control are crucial to reduce the adverse impact of the diseases.

It gives me an immense pleasure to express that the "National Guidelines on Dengue Prevention, Management and Control in Nepal 2019" has been revised according to current developments in case detection, diagnosis, treatment, vector control and management, including disease surveillance and recording and reporting of dengue.

I hope this guideline will assist program managers and health workers across the country to successfully prevent dengue using effective vector control measures and manage dengue cases in Nepal.

I would like to extend my sincere thanks to WHO country office, Nepal for providing technical assistance in preparation of this national guidelines. Finally, I would like to express my appreciation to all the national and international experts who have contributed by providing their invaluable suggestions and feedback during the development of this guidelines.

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Director

ACKNOWLEDGMENT

The Director General, Department of Health Services, Ministry of Health and Population, Nepal expresses sincere gratitude to all the authors and reviewers of this guideline particularly to World Health Organization and all the others who contributed on coming up with this comprehensive National Guidelines on Dengue Prevention, Management and Control in Nepal- Revised 2019.

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ACRONYMS AND ABBREVIATIONS

Ae.	*aedes*
AST	aspartate aminotransferase
ALT	alanine aminotransferase
BI	breateau index
BP	blood pressure
CBC	complete blood count
CO_2	carbon dioxide
CNS	central nervous system
CI	container index
DENV	dengue virus
DSS	dengue shock syndrome
ELISA	enzyme-linked immunosorbent essay
EWARS	early warning and reporting system
HIV	human immunodeficiency virus
HI	house index
HCT	hematocrit
HIA	hemagglutination inhibition assay
HMIS	health management information system
IV	intravenous
IgM	immunoglobulin M
IgG	immunoglobulin G
IGR	insecticide growth regulator
IVM	integrated vector management
NS1	nonstructural 1
NASBA	nucleic acid sequence based amplification
NSAIDS	non steroid anti-inflammatory drugs
ORS	oral rehydration solution
RNA	ribonucleic acid
RDT	rapid diagnostic test
RT PCR	reverse transcriptase polymerase chain reaction
SEAR	south east asia region
SD	standard deviation
WHO	World Health Organization
WBC	white blood cells

CHAPTER 1

INTRODUCTION

Dengue is a mosquito-borne viral disease that has rapidly spread in many countries worldwide in recent years.

In Nepal, dengue is a rapidly emerging disease. Endemic across most provinces, dengue incidence has increased in recent years largely due to expansion of the vector *Aedes aegypti* and *Aedes albopictus,* as well as the movement of people and the introduction of imported cases. All 4 dengue serotypes exist in Nepal, with DENV-1 historically contributing the highest burden.

Prevention, clinical case management, surveillance, vector control and management and outbreak response are ongoing in Nepal, however there is a need to strengthen these especially at a time of national decentralization towards a federalized system.

National dengue guidelines was first developed in Nepal in 2008 based on the World Health Organization (WHO) guidelines 1997 which was revised in 2011. This revised national guidelines on dengue prevention, management and control, 2019 aims to provide a technical 'gold-standard' advice on all aspects of dengue using the latest internationally adopted definitions, protocols and guidelines. It also provides simple, and easy to reference content, which can be printed and displayed on the walls of doctors rooms, wards or simply held in the hands of health workers who are spreading awareness on dengue within their local communities.

Aim of the guidelines

To provide current and robust guidelines for each of the core areas of seasonal and epidemic dengue prevention, management and control in Nepal.

Objectives

1. To support dengue control and prevention activities.
2. To provide pragmatic country-specific guidelines with reference to international gold standards.
3. To provide guidance and new standards to all stakeholders.
4. To provide country case studies for dengue prevention, management and control.
5. To align and build collaboration between stakeholders.
6. To provide a number of annexes that can be used as quick reference tools.

1.1. Epidemiology

Dengue is believed to have originated as a mammalian disease in non-human primates and emerged in the human population roughly 500-1,000 years ago. The disease is widespread throughout the tropics with risk factors influenced by local spatial variations of rainfall, temperature, relative humidity, degree of urbanization and quality of vector control services in urban areas. It is estimated to infect 390 million people annually (Figure 1) of which 96 million manifest clinically. One study on prevalence of dengue estimates that 3.9 billion people in 128 countries are at risk of infection with dengue viruses. Before 1970, only 9 countries had experienced severe dengue epidemics, today the disease is endemic in more than 100 countries.

Dengue is caused by a flavivirus of 4 virus serotypes (DENV1, DENV2, DENV3, DENV4). Over the past 20 years, these serotypes have spread worldwide from South East Asia and are now found throughout Asia, Africa and the Americas (Figure 2). International travel, trade, migration, decreased access to health care and urbanization are considered among the main drivers behind the rapid dissemination of all four dengue serotypes. Compounding the problem has been the global spread of the dengue mosquito vectors, *Ae. aegypti* and *Ae. albopictus,* throughout the last century.

FIGURE 1: Cartogram of the annual number of infections for all ages as a proportion of national or subnational (China) geographical area (Bhatt et al. 2013)

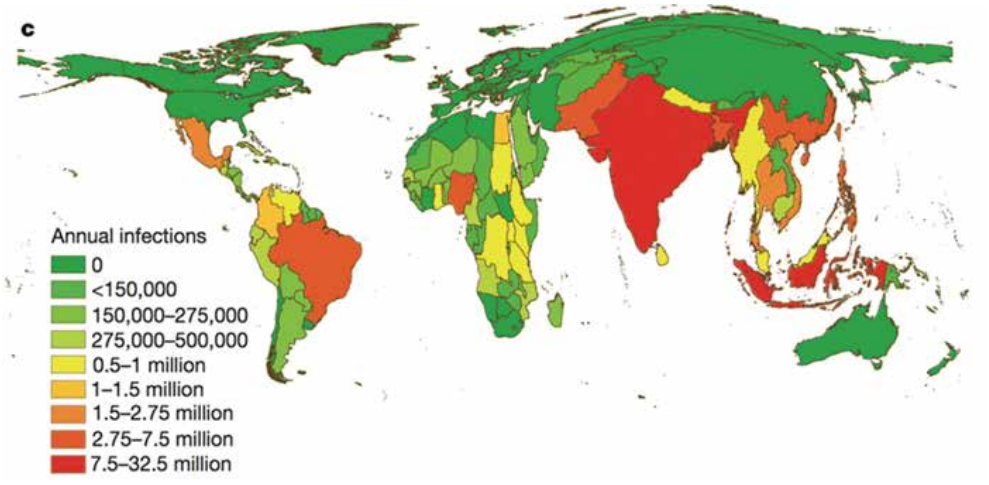
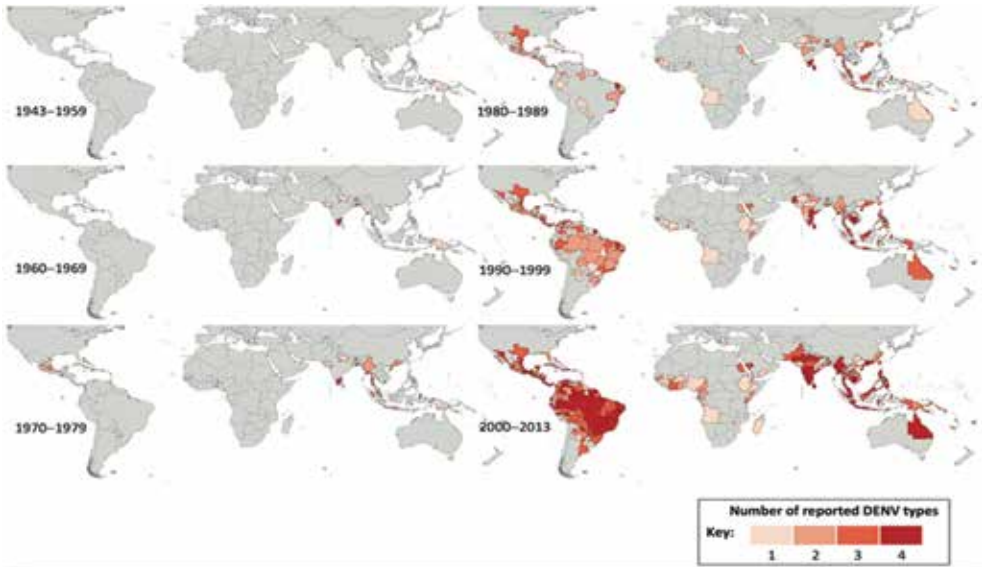


FIGURE 2: DENV Co-circulation. Cumulative number of DENV types reported by decade since 1943 in Messina et al., 2014

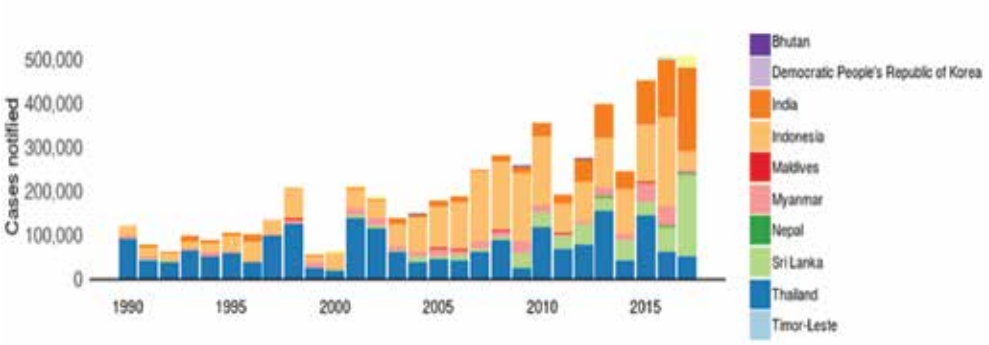


1.2. Disease Burden

Global and regional

The incidence of dengue has increased dramatically around the world in recent decades. Vast majority of cases are asymptomatic and hence actual numbers of dengue cases are under reported and many cases are misclassified. The disease is now endemic in more than 100 countries in the regions of Africa, Americas, Eastern Mediterranean, South East Asia and Western Pacific. The region of Americas, South East Asia and Western Pacific are the most seriously affected. Not only the number of cases are increasing and spreading to new areas but many outbreaks are occurring in recent years. However, many countries have reduced the case fatality rate to less than 1 % and globally, 28 % decline in case fatality have been recorded between the period of 2010-2106, largely due to improvement in case management through capacity building in countries. The number of dengue cases notified to the WHO by the member countries in South East Asia region (SEAR) has also increased substantially in recent years. The number of dengue cases has increased dramatically in the countries like India, Srilanka and Indonesia in this region. The number of cases reported by countries in this region from the period of 1990 to 2017 is provided in (figure 3) below.

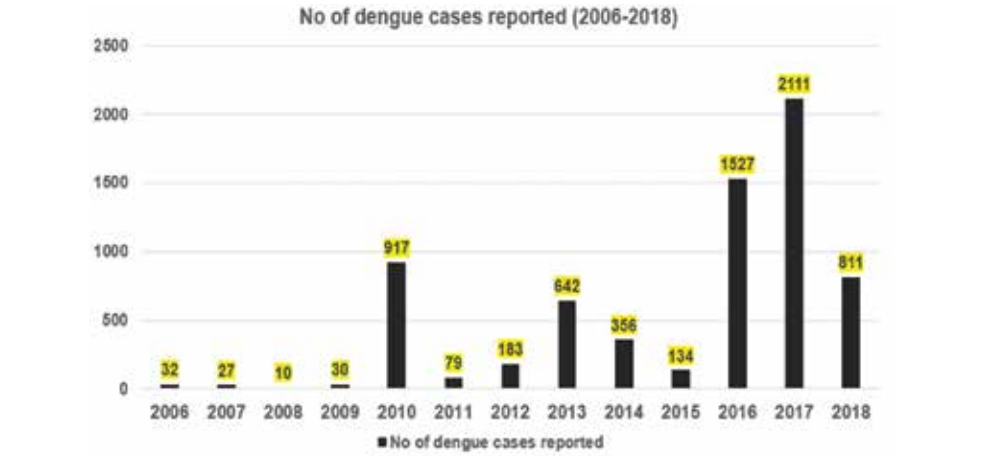
FIGURE 3: Dengue cases notified by SEAR countries to WHO during the period 1990-2017



Nepal

Dengue has been identified as one of the youngest emerging infectious diseases in Nepal. The first case of dengue was reported in 2004. In 2006, large number of probable cases and 32 laboratory-confirmed cases were reported across hospitals in central and western Terai, as well as Kathmandu during the post monsoon season. Most cases were indigenous and confirmed the presence of all 4 serotypes in Nepal. From the years 2007 to 2009, sporadic clinical cases and outbreaks were recorded. Since 2010, dengue epidemics have continued to affect lowland districts as well as mid-hill areas. This trend for increased magnitude has since continued with number of outbreaks reported each year in many districts- Chitwan, Jhapa, Parsa (2012-2013), Jhapa, Chitwan (2015-2016), Rupandehi, Jhapa, Mahottari (2017), Kaski (2018) and Sunsari (2019). The number of dengue cases reported in Nepal from the period 2006-2018 is provided in (figure 4) below.

FIGURE 4: Number of dengue cases reported in Nepal from the period 2006-2018



1.3. Transmission

1.3.1. Virus

Dengue virus (DENV) is a small single stranded RNA virus comprising four distinct serotypes (DEN-1 to DEN-4). These closely related serotypes of the dengue virus belong to the genus Flavivirus, family Flaviviridae.

They are spherical enveloped viruses that contain a single-stranded, positive RNA genome that encodes three structural proteins (capsid C, membrane M, and envelope E) and seven nonstructural proteins (NS1, NS2a, NS2b, NS3, NS4a, NS4b, and NS5). The E protein has an important function in the development of antibodies and the protective immune response, as well as in the viral immuno-amplification phenomenon. The NS1 protein appears in association with the infected cell on its surface and can be detected in the early stages of infection and mark virus replication.

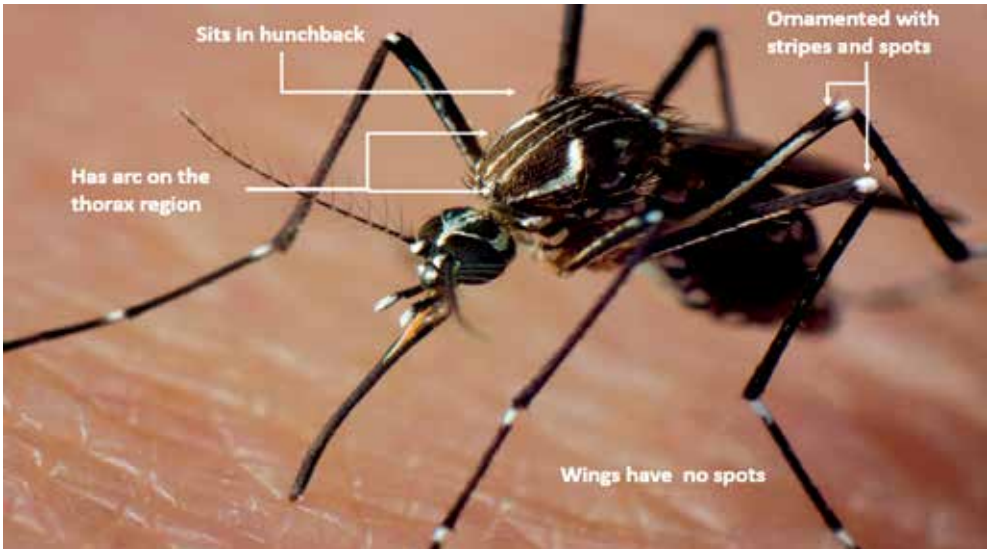
1.3.2. Vector

Aedes aegypti

Dengue is transmitted primarily by the female mosquito *Aedes aegypti* (figure 5), which thrives in and around urbanized areas. It is diurnal and highly anthropophilic, with domestic forms showing increased propensity towards exclusive human feeding. It has greater competency for transmission than *Ae. albopictus,* and coupled with short, frequent biting behavior, it can transmit dengue multiple times during a single gonotrophic cycle. It bites during the day, attracted to human odorous compounds such as CO_2, lactic acid, sulphides and ketones. Feeding occurs after an initial probing of the skin surface, and once engorged, the mosquito prefers to rest indoors to begin the gonotrophic cycle.

Subsequently, the female mosquito preferably seeks out large containers of freshwater, although most container types in and around the home are suitable. Upon reaching a container, oviposition occurs, where the female lays eggs singly just above the water's edge, even though some eggs may be found in the water. Unique to *Aedes,* the mosquito will deposit portions of her 100-200 egg batch in multiple breeding sites, perhaps as many as 11, if available- a process known as 'skip oviposition'. These eggs are particularly resistant to desiccation for prolonged periods and considering this, it is not surprising that the geographical range of *Ae. aegypti* has increased over the last century, with oceanic trade contributing to the spread of *Aedes* eggs, as well as increased prevalence of mosquito microhabitats due to urbanization of the tropics. This ability to withstand relatively extreme environmental and climatic variation has resulted in detection of the mosquito up to the spatial boundaries defined by the 10°C winter isotherms. The maximum dispersal rate of *Aedes* is 300-400 meters.

FIGURE 5: Adult *Aedes aegypti,* PC: Dr B Nagpal, WHO



Aedes albopictus

The secondary vector, *Aedes albopictus* (figure 6) is also diurnal but less dependent on humans for blood meals. Nonetheless, it remains competent to transmit dengue. In the past it was considered a rural mosquito, often breeding in tree holes and bromeliads. However, it has emerged as a highly adaptive mosquito that can now successfully breed in man-made containers, including tyres and household receptacles, thereby increasing its potential as a serious vector of dengue.

Termed the "Asian Tiger Mosquito", its range has expanded dramatically over the last 30 years, establishing in the Americas, Australia, Africa and Europe, in part due to the used tyre trade and increasing urbanization. Accordingly, it is currently pushing the boundaries of known dengue transmission. Yet, it appears that its heterogeneous biting behavior reduces the vectorial capacity of this vector, as it is not principally responsible for large dengue outbreaks.

FIGURE 6: Adult *Aedes albopictus,* PC: Dr B Nagpal, WHO

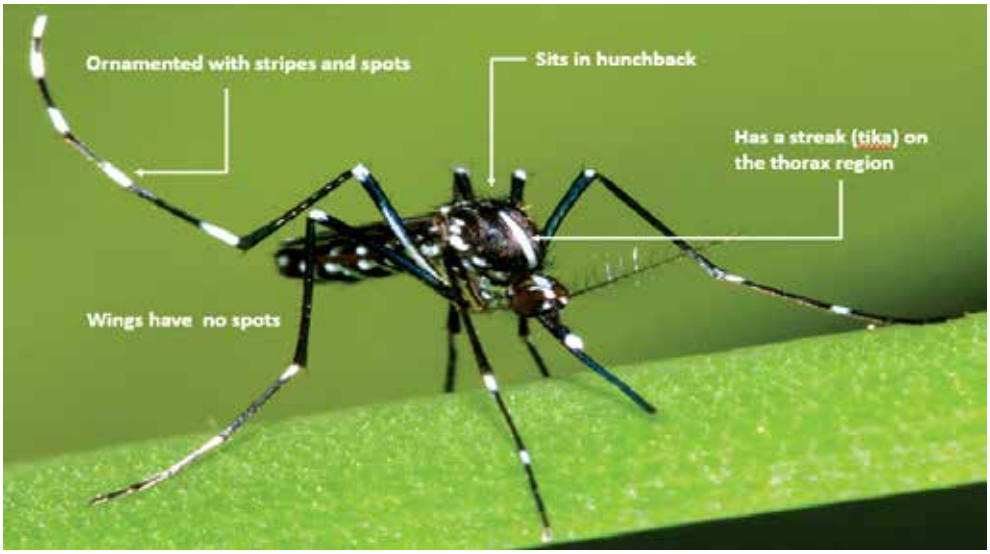
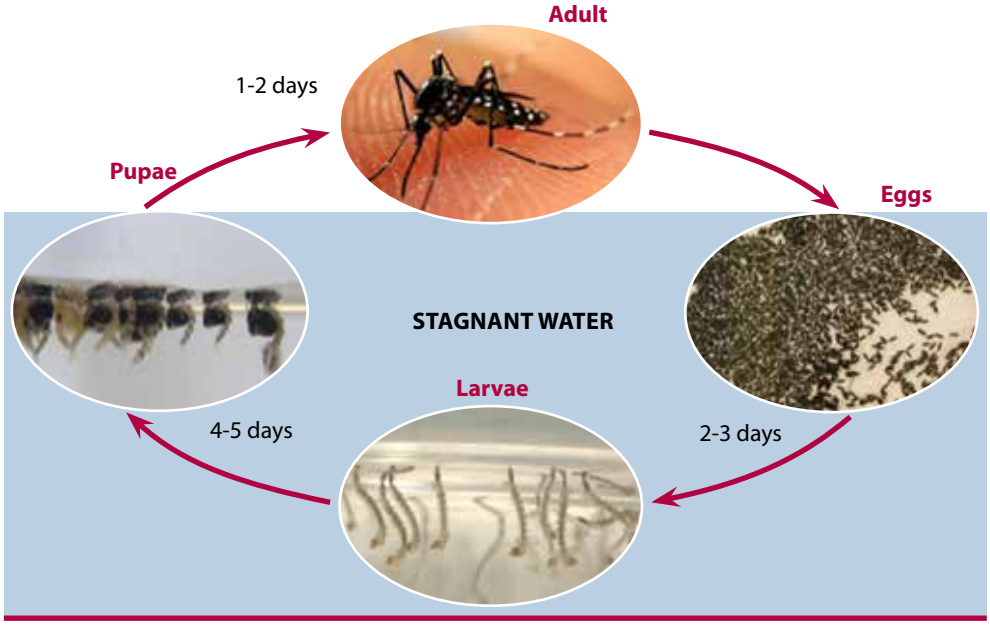


FIGURE 7: : Life cycle of *Aedes* mosquito



1.3.3. Host

Once infected, humans are the main carriers and multipliers of the virus, serving as a source of virus for the uninfected mosquitoes. The virus circulates in the blood of an infected person for 2-7 days, at approximately the same time that the person develops a fever. After an incubation period of 4- 10 days, infection with any of the four serotypes of the dengue virus can produce a wide spectrum of illness although most infections are asymptomatic or subclinical.

In humans, recovery from infection by one dengue virus provides lifelong immunity against that particular virus serotype. However, this immunity provides only partial and transient protection against subsequent infection by the other three serotypes of the virus. Some evidence show that sequential infection increases the risk of developing severe dengue. The severity of the disease is determined by the individual risk factors such as secondary infection, age and presence of co- morbid conditions like diabetes mellitus, sickle cell anaemia, renal disease, etc.

1.3.4. Transmission

Humans are the main amplifying host of the virus. The dengue virus circulating in the blood of viraemic humans is ingested by female mosquitoes during feeding. After virus incubation for 8 – 10 days, an infected mosquito is capable of transmitting the virus to susceptible individuals for the rest of its life. *Ae. Aegypti* is one of the most efficient vectors for arboviruses because it is highly anthropophilic, frequently bites several times before completing oogenesis, and thrives in close proximity to humans.

Several factors can influence the dynamics of virus transmission, including environmental and climate factors, host pathogen interactions and population immunological factors. Climate directly influences the biology of the vectors and thereby their abundance and distribution.

In Nepal, monsoon season occurs during June – August every year. The dengue season closely follows this period with seasonal cases occurring between September and November. Given the presence of a largely susceptible human population, human movement, the presence of both *Aedes* vectors and all four dengue serotypes, this trend is unlikely to reverse over the coming decades. Indeed, the burden may continue to increase likely resulting in an increasing number of severe dengue cases, particularly in and around Kathmandu, which has to date reported relatively few cases.

CHAPTER 2

CLINICAL MANIFESTATION

Dengue has a wide spectrum of clinical presentations, often with unpredictable clinical evolution and outcome. While most patients recover following a self-limiting non-severe clinical course, a small proportion progress to severe disease, mostly characterized by plasma leakage with or without hemorrhage.

The group progressing from non-severe to severe disease is difficult to define, but it is an important concern since appropriate treatment may prevent these patients from developing more severe clinical conditions.

Triage, appropriate treatment, and the decision as to where this treatment should be given (in a health facility or at home) are influenced by the case classification for dengue (Table 3). This is even more the case during the outbreaks, where health facilities are overwhelmed and need to adapt to the sudden increase in number of patients.

2.1. Natural Course of Dengue Illness

Dengue viruses cause symptomatic infections or asymptomatic seroconversion. Symptomatic dengue infection is a systemic and dynamic disease and has a wide clinical spectrum that includes both severe and non-severe clinical manifestations. After the incubation period, the illness begins abruptly and is followed by three phases. Due to the dynamic nature of the disease, the severity of the disease will usually only be apparent around defervescence i.e. transition of the febrile to afebrile phase which often coincides with the onset of the critical phase.

1. Febrile Phase
2. Critical Phase
3. Recovery Phase

2.1.1. Febrile Phase

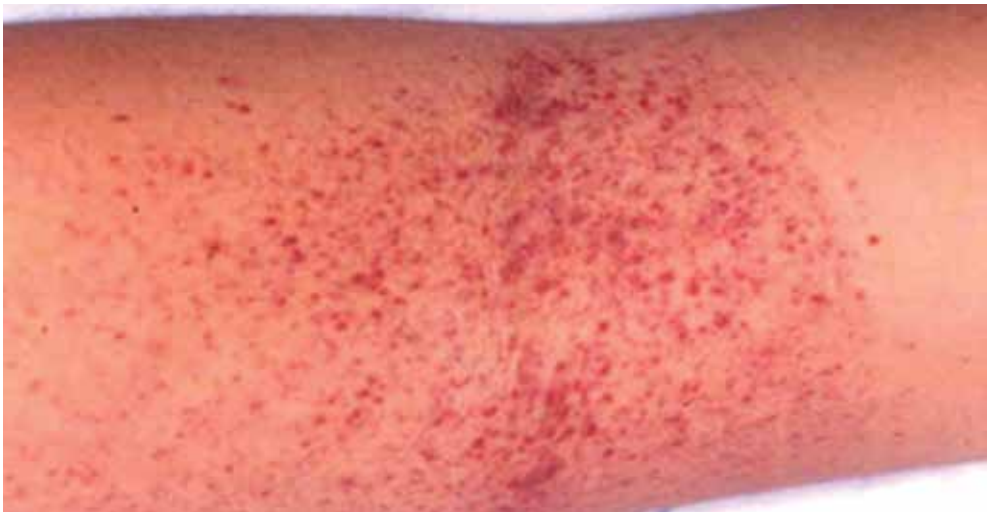
- Sudden high-grade fever usually lasts 2–7 days
- Headache
- Retro-orbital pain
- Generalized body ache, Myalgia/Arthralgia
- Facial flushing
- Skin erythema
- Photophobia
- Rubeliform exanthema
- Sore throat, injected pharynx and conjunctival injection in some patient.
- Anorexia/Nausea and vomiting-common
- Positive tourniquet test (Box 1)- increases the probability of dengue in this phase
- Mild haemorrhagic manifestations like petechiae and mucosal membrane bleeding (e.g. nose and gums) may be seen
- Easy bruising and bleeding at venipuncture site- in some cases
- Massive vaginal bleeding (in women of childbearing age) and gastrointestinal bleeding may occur during this phase but is not common.
- The liver is often enlarged and tender after a few days of fever
- Full blood count- progressive decrease in total white cell count (should alert the physician to a high probability of dengue)

It can be difficult to distinguish dengue clinically from non-dengue febrile diseases in the early febrile phase. In addition, the above clinical features are indistinguishable between severe and non-severe dengue cases. Therefore, monitoring of warning signs and other clinical parameters is important to recognize progression to the critical phase.

Box 1: Tourniquet test

- Take the patient's BP and record it, example 120/80 mm Hg
- Inflate the BP cuff to a point midway between the systolic and diastolic pressure (120+80) /2= 100 mm Hg
- Wait for 5 minutes
- The test is considered positive when 10 or more petechiae per sq. inch are observed.
- The test may be negative or only mildly positive in obese patients and during the phase of profound shock. It usually becomes positive, sometimes strongly positive after recovery from shock.

FIGURE 8: Positive tourniquet test in a dengue patient, PC: Dr S Kalyanarooj



2.1.2. Critical Phase

During the transition from the febrile to afebrile phase, patients without an increase in capillary permeability will improve without going through the critical phase. However, patients with increased permeability, instead of improving with the subsidence of high fever, may manifest with the warning signs (Table 1) mostly due to plasma leakage. The warning signs mark the beginning of critical phase. These patients become worse around the time of defervescence when the temperature drops to 37.5° C–38° C or less and remains below this level, usually on days 3–8 of illness.

- **Leucopenia and thrombocytopenia-** Progressive leukopenia followed by a rapid decrease in platelet count usually precedes plasma leakage.
- **Plasma leakage-** Around the time of subsidence of fever, an increase in capillary permeability in parallel with increasing hematocrit levels may occur. The period of clinically significant plasma leakage usually lasts 24–48 hours and the degree of plasma leakage varies. The degree of increase above the baseline hematocrit often reflects the severity of plasma leakage, however this may be reduced by early intravenous fluid therapy. Hence, frequent hematocrit determinations are essential because they signal the need for possible adjustments to intravenous fluid therapy. Pleural effusion and ascites may be clinically detectable depending on the degree of plasma leakage and the volume of fluid therapy. Hence chest x-ray and abdominal ultrasound can be useful tools for diagnosis.

- **Hemorrhagic manifestations-** In addition to plasma leakage, hemorrhagic manifestations such as easy bruising and bleeding at venipuncture sites occur frequently.
- **Shock-** Shock occurs when a critical volume of plasma is lost through leakage and is often preceded by warning signs (please refer table 1 below). The body temperature may be subnormal when shock occurs. With prolonged shock, the consequent organ hypoperfusion results in progressive organ impairment, metabolic acidosis and disseminated intravascular coagulation. This in turn leads to severe hemorrhage causing the hematocrit to decrease in severe shock. Instead of the leukopenia usually seen during this phase of dengue, the total white cell count may increase as a stress response in patients with severe bleeding.
- **Severe organ impairment-** In addition, severe organ impairment such as severe hepatitis, encephalitis or myocarditis and/or severe bleeding may also develop without obvious plasma leakage or shock.

Some patients progress to the critical phase of plasma leakage and shock without defervescence and, in these patients, a rising hematocrit and rapid onset of thrombocytopenia or the warning signs, indicate the onset of plasma leakage. Cases of dengue with warning signs will usually recover with early intravenous rehydration. Some cases will deteriorate to Severe Dengue.

TABLE 1: Dengue Warning Signs

Warning Signs Of Dengue (usually precede the manifestation of shock and appear towards the end of the febrile phase, usually between days 3-7 of illness)
■ Leucopenia, thrombocytopenia and increased hematocrit
■ Rapid and progressive decrease in platelet count to about 100,000 cells/mm^3 and a rising hematocrit above 20 % of the baseline may be the earliest sign of plasma leakage. This is usually preceded by leukopenia (< 4000 cells/mm^3)
■ Vomiting and severe abdominal pain
■ Persistent vomiting and severe abdominal pain are early indications of plasma leakage and become increasingly worse as the patient progresses to shock
■ The patient becomes lethargic but usually remains alert
■ Weakness, dizziness or postural hypotension - shock stage
■ Spontaneous mucosal bleeding or bleeding at previous venipuncture sites
■ Hepatomegaly, tender liver- frequently observed
■ Clinical fluid accumulation may only be detected if plasma loss is significant or after treatment with intravenous fluids

2.1.3. Recovery phase

As the patient survives the 24–48 hour critical phase, a gradual reabsorption of extravascular compartment fluid takes place in the following 48–72 hrs. General well-being improves, appetite returns, gastrointestinal symptoms reduces, hemodynamic status stabilizes and diuresis ensues. Some patients may have rash of "isles of white in the sea of red" (figure 9). Some may experience generalized pruritus. Bradycardia and electrocardiographic changes are common during this stage.

The hematocrit stabilizes or may be lower due to the dilutional effect of reabsorbed fluid. White blood cell count usually starts to rise soon after defervescence but the recovery of platelet count is typically later than that of white blood cell count. Respiratory distress from massive pleural effusion and ascites will occur at any time if excessive intravenous fluids have been administered. During the critical and/or recovery phases, excessive fluid therapy is associated with pulmonary edema or congestive heart failure. The various clinical problems during the different phases of dengue is summarized as in (table 2) below:

FIGURE 9: Rash of "isles of white in the sea of red" in a dengue patient, PC: Dr A Bastola

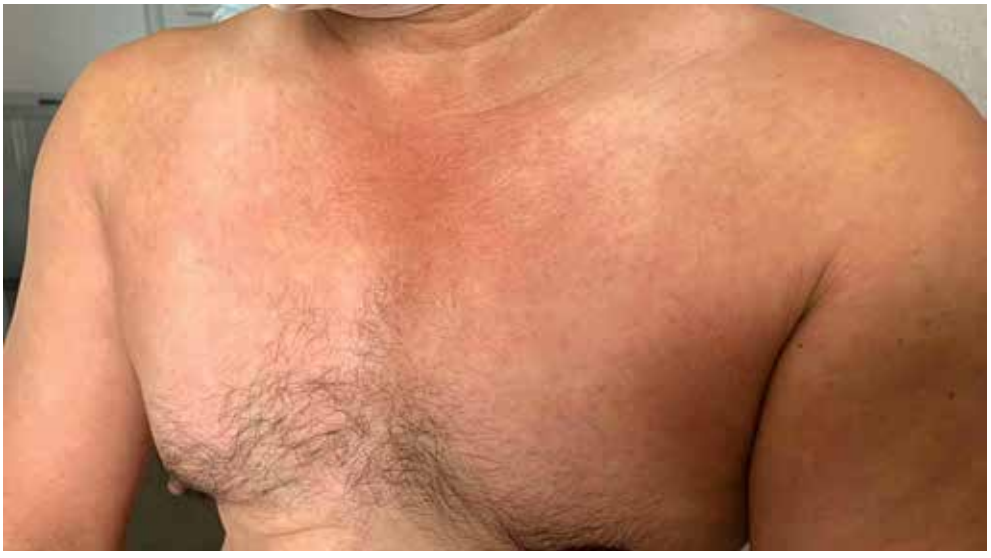
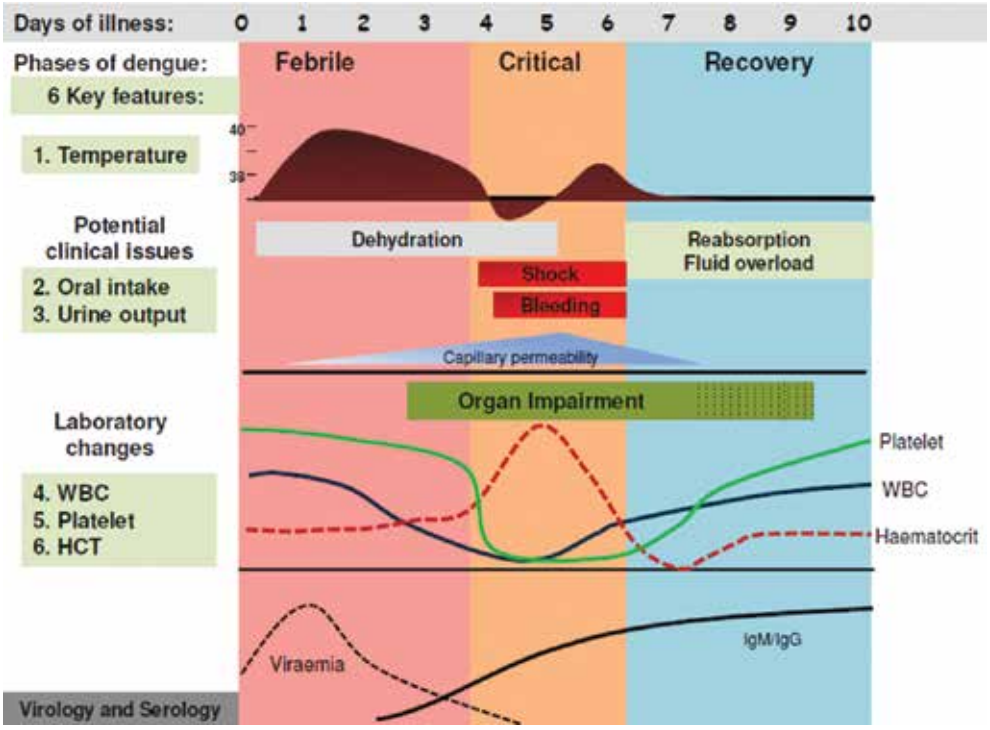


TABLE 2: Clinical problems during febrile, critical and recovery phase in dengue

S.NO.	PHASES	COMMON CLINICAL PROBLEMS
1	Febrile Phase (2-7 days)	■ High fever ■ Aches and pain o headache o retro-orbital pain o myalgia o arthralgia ■ Poor appetite ■ Nausea ■ Vomiting ■ Abdominal pain ■ Dehydration ■ Electrolyte imbalance-hyponatremia ■ Hypoglycemia ■ Febrile seizures in young children
2	Critical Phase (24-48 hrs.)	■ Plasma leakage that may lead to shock ■ Severe hemorrhage ■ Organ impairment if not properly managed ■ Common complications: acidosis, hypocalcemia, hypoglycemia
3	Recovery Phase (3-5 days)	■ Hypokalemia-due to diuresis ■ Hypervolemia- only if intravenous fluid therapy has been excessive and/or has extended into this period)

FIGURE 10: Natural course of dengue illness, adapted from WCL Yip, 1980 by Hung NT, Lum LCS, Tan LH



2.2. WHO Dengue Case Classification

TABLE 3: : WHO Dengue case classification

Dengue ± Warning Signs	Severe Dengue

Dengue without warning signs	Dengue with warning signs*	Severe Dengue
The person lived or travelled in an area of dengue transmission in the last 14 days, has a sudden high fever typically of 2 to 7 days duration, and presents TWO or more of the following manifestations: ■ Nausea, vomiting ■ Exanthema/rash ■ Myalgia/arthralgia ■ Headache, retro-orbital pain ■ Petechiae or tourniquet test positive ■ Leukopenia	Dengue (as defined to the left) with any of the following: ■ Abdominal pain or tenderness ■ Persistent vomiting ■ Clinical fluid accumulation (e.g. ascites, pleural effusion) ■ Mucosal bleeding ■ Lethargy, restlessness ■ Liver enlargement > 2 cm ■ Laboratory: increase in hematocrit, concurrent with rapid decrease in platelet count. * Requires strict observation and medical intervention	Dengue with at least 1 of the following ■ Severe plasma leakage leading to shock (dengue shock syndrome) or fluid accumulation with respiratory distress ■ Severe bleeding (as evaluated by a clinician) ■ Severe organ involvement (i.e., AST or ALT 1000 or greater, impaired consciousness, organ failure).

Severe Dengue

A case of severe dengue is defined as a suspected dengue patient with one or more of the following:

a. Severe plasma leakage that leads to shock (dengue shock) and/or fluid accumulation, with respiratory distress,

b. Severe bleeding,

c. Severe organ impairment

Severe plasma leakage and dengue shock

As dengue vascular permeability progresses and plasma leakage occurs, hypovolemia worsens and results in dengue shock syndrome. It usually takes place around defervescence, usually on day 4 or 5 (range days 3–7) of illness, often preceded by the warning signs. At this stage, patients who do not receive prompt intravenous fluid therapy progress rapidly to a state of shock.

Dengue shock presents as a physiologic continuous sequence, progressing from

symptomatic capillary leakage → compensated shock → hypotensive shock →cardiac arrest

Tachycardia (without fever during defervescence) is an early cardiac response to hypovolemia. Severe dengue should be considered if the patient is from an area of dengue risk presenting with fever of 2–7 days plus any of the following features:

- Evidence of plasma leakage
  - o high or progressively rising hematocrit
  - o pleural effusions or ascites
  - o circulatory compromise or shock (tachycardia, cold and clammy extremities, capillary refill time greater than three seconds, weak or undetectable pulse, narrow pulse pressure or, in late shock, unrecordable blood pressure)
- Significant bleeding
- Altered level of consciousness
- Severe gastrointestinal involvement
- Severe organ impairment or other unusual manifestations.

TABLE 4: Initial stage during dengue shock

Initial Stage of Shock
■ During this stage of shock, the compensatory mechanism which maintains a normal systolic blood pressure also produces tachycardia, quiet tachypnoea and peripheral vasoconstriction with reduced skin perfusion, resulting in cold extremities and delayed capillary refill time of >2 seconds and weak volume peripheral pulses. As the peripheral vascular resistance increases, the diastolic pressure rises towards the systolic pressure and the pulse pressure narrows.
■ The patient is considered to have compensated shock if the systolic pressure is maintained at the normal or slightly above normal range but the pulse pressure (i.e. the difference between the systolic and diastolic pressures) is ≤ 20 mm Hg in children or he/she has signs of poor capillary perfusion (cold extremities, delayed capillary refill, or rapid pulse rate). In adults, the pulse pressure of ≤ 20 mm Hg may indicate a more severe shock. Dengue patients in compensated shock often remain conscious and lucid. **"The inexperienced physician may measure a normal systolic pressure and a normal pulse oximetry in a conscious patient and misjudge the critical state of the patient".**

TABLE 5: Worsening Hypovolemic Shock

Worsening Hypovolemic Shock
■ Increasing tachycardia and peripheral vasoconstriction. ■ Cold and cyanosed extremities and the limbs are mottled, cold and clammy. ■ By this stage, the breathing becomes more rapid and increases in depth – a compensation for the metabolic acidosis (Kussmaul's breathing). ■ Finally, there is decompensation, both systolic and diastolic BPs disappear suddenly and dramatically, and the patient is said to have hypotensive or decompensated shock. At this time the peripheral pulses disappear while the central pulse (femoral) will be weak. ■ Hypotension develops when physiologic attempts to maintain systolic BP and perfusion are no longer effective. ■ One key clinical sign of this deterioration is a change in mental state as brain perfusion declines. The patient becomes restless, confused and extremely lethargic. Seizures may occur and agitation may alternate with lethargy. On the other hand, children and young adults have been known to have a clear mental status even in profound shock. ■ Adults have been known to be able to work until the stage of profound shock is reached. **NOTE !!** The failure of infants and children to recognize, focus or make eye contact with parents may be an early ominous sign of cortical hypoperfusion, as is the failure to respond to painful stimuli such as venipuncture. Parents may be the first to recognize these signs –but they may be unable to describe them, other than to say something is wrong. Listen to parents! Hypotension is a late finding and signals an imminent total cardiorespiratory collapse.

TABLE 6: Prolonged hypotensive shock

Prolonged Hypotensive Shock
■ Prolonged hypotensive shock and hypoxia lead to severe metabolic acidosis, multiple organ failure and an extremely difficult clinical course. ■ It may take a few hours for patients to progress from warning signs to compensated shock and another few hours for compensated shock to progress to hypotensive shock, but only minutes for hypotensive shock to progress to cardiorespiratory collapse and cardiac arrest. ■ Hypotension is associated with prolonged shock which is often complicated by major bleeding. Patients with severe dengue have varying degrees of coagulation abnormalities, but these are usually not sufficient to cause major bleeding. When major bleeding does occur, it is almost always associated with profound shock since this, in combination with thrombocytopenia, hypoxia and acidosis, can lead to multiple organ failure and advanced disseminated intravascular coagulation. Massive bleeding may occur without prolonged shock in instances when acetylsalicylic acid (aspirin), ibuprofen, or corticosteroids have been taken. Bleeding may occur in patients with previous peptic or duodenal ulcers. ■ Acute liver and renal failure and encephalopathy may be present in severe shock; sometimes even in the absence of severe plasma leakage or shock. However, most deaths from dengue occur in patients with profound and prolonged shock resulting from plasma leakage and complicated by bleeding and/or fluid overload. ■ Patients with severe plasma leakage may not have shock if prompt fluid replacement has been carried out. Instead, they manifest with respiratory distress due to massive pleural effusion and ascites, which can also be exacerbated by unguided intravenous fluid therapy.

2.3. Differential Diagnoses

A number of infectious/non-infectious diseases may mimic dengue and severe dengue. (Table 7) below summarizes a number of conditions that may mimic febrile or critical phase of dengue.

TABLE 7: Differential diagnoses of dengue

Conditions that mimic the febrile phase of dengue infection	
Flu-like syndromes	■ Influenza ■ Measles ■ Chikungunya ■ Infectious mononucleosis ■ HIV seroconversion illness
Illnesses with a rash	■ Measles/Rubella ■ Scarlet fever ■ Meningococcal infection ■ Chikungunya ■ Drug reactions
Diarrheal diseases	■ Rotavirus/Other enteric infections
Illnesses with neurological manifestations	■ Meningo/encephalitis ■ Febrile seizures
Conditions that mimic the critical phase of dengue infection	
Infectious	■ Acute gastroenteritis ■ Malaria ■ Leptospirosis ■ Typhoid ■ Typhus ■ Viral hepatitis ■ Acute HIV seroconversion illness ■ Bacterial sepsis /Septic shock
Malignancies	■ Acute leukemia and other malignancies
Other clinical pictures	■ Acute abdomen o acute appendicitis/cholecystitis o perforated viscus ■ Diabetic ketoacidosis/Lactic acidosis ■ Leukopenia & thrombocytopenia ± bleeding ■ Platelet disorders ■ Renal failure ■ Respiratory distress (Kussmaul's breathing) ■ Systemic Lupus Erythematosus

CHAPTER 3

DIAGNOSIS

It is highly recommended that this national dengue guidelines be widely used across both public and private sectors to ensure harmonization and standardization of diagnostic practice and increase the value of epidemiological data.

The objectives of the dengue laboratory diagnosis are to

- Confirm the clinical diagnosis
- Provide the information for epidemiological surveillance

Laboratory diagnosis methods for confirming dengue virus infection may involve the following depending upon which clinical phase of the disease the patient is in.

- detection of the virus
- detection of viral nucleic acids
- detection of antigens
- detection of antibodies
- or a combination of above techniques

No single diagnostic test is available to detect dengue infection across all phases of illness, thereby requiring careful selection of dengue diagnostics.

During the early stages of the disease, virus isolation, nucleic acid or antigen detection can be used to diagnose the infection. At the end of the acute phase of infection, serology is the method of choice for diagnosis.

Important Note

Laboratory diagnosis of dengue with any methods mentioned above does not guide clinical management of dengue and are therefore not recommended to perform these test for every dengue suspected cases. Use of rapid diagnostic test (RDT) kits should be rational and is discouraged to be used for each and every suspected cases.

The usefulness of available dengue diagnostics tests depends on the level of health care. Recommended diagnostic tool according to health service delivery are given below in (table 8) below.

TABLE 8: Recommended diagnostic tool according to the health service delivery level

Test methods		Primary health care centers	District/ provincial hospital	Referral or specialized hospitals	National Reference Laboratory
Virus isolation					Yes
Nucleic acid detection				Yes	Yes
NS1 Ag detection	RDT	Yes*	Yes	Yes	Yes
	ELISA			Yes	Yes
IgM detection	RDT	Yes*	Yes	Yes	Yes
	ELISA			Yes	Yes
IgG detection	RDT	Yes*	Yes	Yes	Yes
	ELISA			Yes	Yes
	Neutralization assay				Yes

* may be used in early case detection for the rapid prevention and control in the beginning of dengue outbreak

TABLE 9: Dengue diagnostics in relation to time of clinical illness

Diagnosis Method	Clinical Sample	Diagnostic Method	Methodology	Time To Results
Direct Virus detection and its components	Acute serum (1–5 days of fever) and necropsy tissues	Viral isolation	Mosquito or mosquito cell culture inoculation	One week or more
		Nucleic acid detection	RT-PCR and real time RT-PCR	1 or 2 days
		Antigen detection	NS1 Ag rapid tests	Minutes
			NS1 Ag ELISA	1 day
			Immuno-histochemistry	2–5 days
Indirect Serological response	Paired sera (acute serum from 1–5 days and second serum 15–21 days after)	IgM or IgG seroconversion	ELISA HIA	1–2 days
			Neutralization Test	Mini-mum 7 days
	Serum (after day 5 of fever)	IgM detection (recent infection)	ELISA	1 or 2 days
			Rapid tests	Minutes
		IgG detection	IgG ELISA HIA	1 or 2 days

ELISA = enzyme-linked immunosorbent assay; HIA = hemagglutination inhibition assay; IgG = immunoglobulin G; IgM = immunoglobulin M; NS1 Ag = non-structural protein 1 antigen; RT-PCR = reverse transcriptase polymerase chain reaction

Note

NS1 Ag test is positive when patients have fever. The sensitivity of the test is the highest in the first day of fever(90%), then declines as fever days. By day 5 of fever, the test is less sensitive and may be negative from day 6 onwards. The test is likely to be positive in primary infections than secondary.

3.1. Available Dengue Diagnostic Methods

3.1.1. Direct diagnostic methods

- Virus isolation
- Nucleic acid detection
- Viral antigen detection

Dengue viraemia in a patient is short; it typically occurs 2–3 days prior to the onset of fever and lasts for four to seven days of illness. During this period the dengue virus, its nucleic acid and circulating viral antigen can be detected. Although virus isolation and nucleic acid detection are more specific than antibody detection using serologic methods, they are labor intensive and costly.

Virus isolation

As dengue viraemia is short (2-3 days prior and 4-5 days after the onset of fever) virus isolation is possible only at the early phase of infection. Virus can be isolated from serum, plasma, peripheral blood mononuclear cells or from tissues during autopsy (liver, lungs, lymph nodes, thymus, bone marrow).

Since the virus is heat labile, the specimen awaiting to be transported to laboratory should be kept in refrigerator. For storage up to 24 hours specimen should be kept between 4˚-8˚ C. For longer storage specimen should be frozen at -70˚C in a dep freezer or in a liquid nitrogen container. Virus isolation is not regularly practiced in Nepal.

Nucleic acid detection

Viral nucleic acid detection is useful during early stage of the disease. Since RNA is heat labile, the specimen for nucleic acid detection must also be handled and stored as described for virus isolation.

Polymerase Chain Reaction (Reverse Transcriptase -PCR)

Detection of DENV genomic RNA in patient's sample. Several formats of PCR are available- RT-PCR, nested PCR, one step multiplex RT-PCR, real time RT-PCR (singleplex or multiplex), etc

Isothermal amplification methods

Nucleic acid sequence based amplification (NASBA)- detection of viral RNA of all serotypes in serum is available. Loop mediated isothermal amplification- simple method for RNA detection with high degree of specificity/ selectivity under isothermal conditions.

Viral antigen detection

It is useful during early phase of clinical course since the viral antigens circulate in patient's blood for longer periods than viral RNA. Most common antigen is non-structural-1 (NS1).

Methods that enable early diagnosis with high sensitivity and specificity are a support to clinical management of patients. Furthermore, early diagnosis is useful for rapidly adopting vector control measures to decrease transmission. Taking advantage of the fact that NS1 protein is a marker for viral replication that is detected in serum and plasma during the acute stage of the disease, several commercial ELISA kits and immunochromatographic strips have recently been produced. This method provides a potential opportunity to make an early and specific diagnosis of dengue, because it can detect viral replication before the development of IgM antibodies.

The sensitivity of antigen test can be variable ranging from 48-93% which is influenced by the virus serotype, the type of infection (primary or secondary), the day the sample is collected, the gold standard used in evaluations, and the affinity of the monoclonal antibodies used in the tests, among others. The quality of the results of these kits depends on the manufacturer, the geographical origin of the samples, and the composition of the serum panels analyzed, as well as the expertise of the people analyzing the tests. In general, ELISA test kits are more sensitive than rapid tests.

3.1.2. Indirect diagnostic methods

Serological test

Serological methods are widely used in routine dengue diagnosis, but are more useful when the sample is obtained three or four days after onset of symptoms or on samples subsequent to those with negative results with the direct techniques described above. In general, dengue IgM antibody analysis is recommended in samples obtained five or six days after the onset of disease or later.

IgM antibodies

Detection of IgM antibodies is the most frequently used marker of recent infection. IgM antibodies can normally be detected in the early convalescent phase of the disease, although in some cases they can be detected during the acute phase. Both rapid test and ELISA can be used for detecting IgM antibodies. IgM antibodies persists for up to 1-2 months after infection.

IgG antibodies

The presence of IgG antibodies in serum indicates past infection. However, the presence of high IgG antibody titers in a serum sample or the seroconversion, or a fourfold or greater increase in the antibody titer in paired serum samples obtained from a case of clinically suspected dengue, indicates recent infection or confirmed infection, respectively. This approach could be very useful in cases of secondary infection that show no detectable levels of IgM antibodies.

Even though the hemagglutination inhibition technique is the gold standard for IgG antibody detection, IgG ELISA is the most commonly used test that detects the presence of IgG antibodies and even determines its titer. Currently, a large number of commercial kits offer differing degrees of sensitivity and specificity for both ELISA and immunochromatographic tests using rapid test strips that detect IgM and IgG antibodies.

However, antibodies detected through HIA and ELISA show cross-reactivity among flaviviruses, an important aspect to be considered in both patient diagnosis and laboratory surveillance.

3.2. Virological and Serological Markers in Relation to Time of Dengue Infection

An incubation period of 4–10 days occurs after the mosquito bites, resulting in an asymptomatic or symptomatic dengue infection. During this period the virus replicates and an antibody response is developed.

In general, viraemia is detectable in most dengue cases at the same time when symptoms appear, and is no longer detectable at the time of defervescence. The development of IgM antibody is coincident with the disappearance of fever and viraemia. Virological and serological markers differ in time evolution and titer response and according to whether the infection is primary or secondary. Infection by a given dengue virus serotype confers prolonged immunity only against that serotype. An individual can contract up to four dengue virus infections throughout their lifetime or can also be naturally infected by other flaviviruses present.

Primary dengue infection: affects individuals without prior flavivirus exposure.

Secondary dengue infection: occurs mainly in individuals previously infected by any of the remaining virus serotypes or individuals immune to other flavivirus.

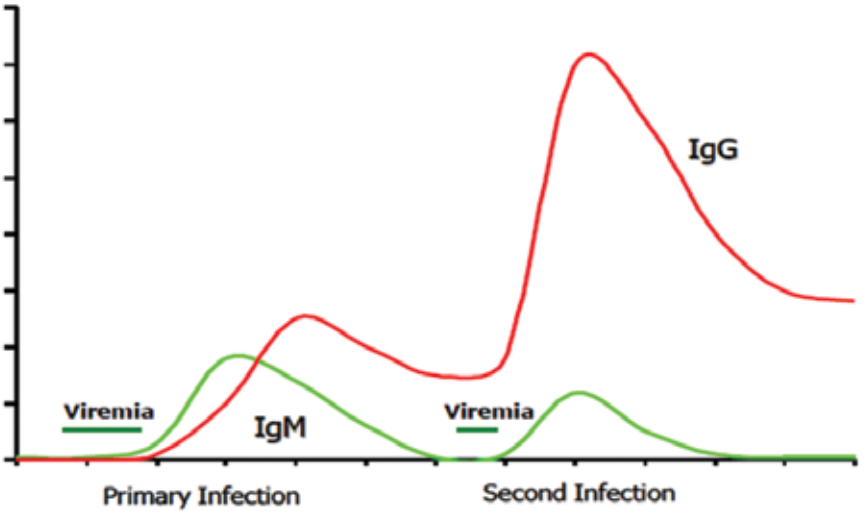
Primary infection

In a primary infection (i.e. when an individual is infected for the first time with a flavivirus), viraemia develops from 1–2 days before the onset of fever until 4–5 days after. Accordingly, anti-dengue IgM specific antibodies can be detected 3–6 days after fever onset. On average, IgM is detected in 50% of cases by days 3–5 after the onset of illness, this figure increasing to 95–98% for days 6–10. Low levels of IgM are still detectable around one to three months after fever. In addition, the primary infection is characterized by slowly increasing but low levels of dengue-specific IgG, becoming elevated at days 9–10. Low IgG levels persist for decades, an indication of a past dengue infection.

Secondary infection

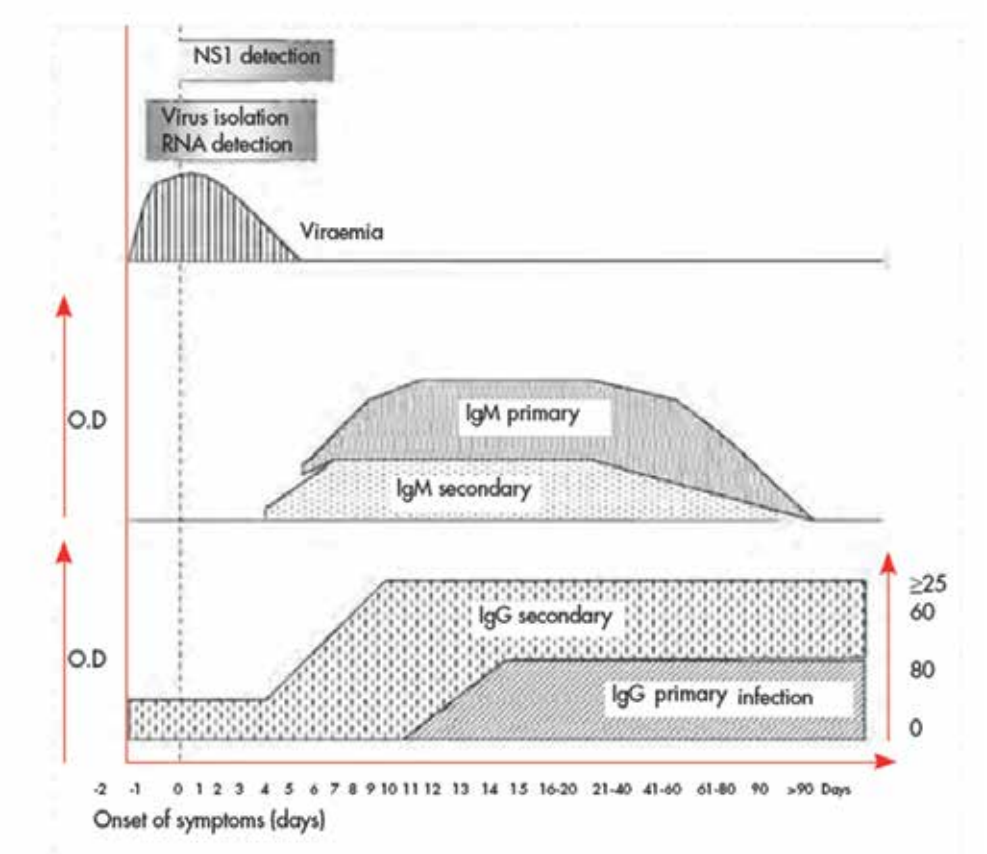
A totally different picture is observed during a secondary infection, with a rapid and higher increase of anti-dengue specific IgG antibodies and slower and lower levels of IgM. High IgG levels remain for 30–40 days. A short-lasting but higher viraemia level characterizes the secondary infection compared to the primary infection.

FIGURE 11: Virological and serological markers of dengue infection according to time of illness



IgG = immunoglobulin G; IgM = immunoglobulin M

FIGURE 12: Time-line of primary and secondary dengue virus infections and the diagnostic methods that can be used to detect infection



CHAPTER 4

CASE MANAGEMENT

Dengue infection is a systemic and dynamic disease and has a wide clinical spectrum that includes both severe and non-severe clinical manifestations. For a disease that is complex in its manifestations, management is relatively simple, inexpensive and very effective in saving lives so long as correct and timely interventions are instituted. The key is early recognition and understanding of the clinical problems during the different phases of the disease, leading to a rational approach to case management and a good clinical outcome.

Early notification of dengue cases seen in primary and secondary care is crucial for identifying outbreaks and initiating an early response.

4.1. Step wise approach for case management

TABLE 10: Steps for dengue case management

Step 1 **Overall Assessment**	1.1	History, including symptoms, past medical and family history
	1.2	Physical examination, including full physical and mental assessment
	1.3	Investigation, including routine laboratory tests and dengue-specific laboratory tests
Step 2 **Diagnosis, Assessment of Disease Phase and Severity**	2	Clinicians will diagnose whether the disease is dengue and assess its phase and severity
Step 3 **Clinical Management**	3.1	Disease notification
	3.2	Management decisions Depending on the clinical manifestations and other circumstances, patients may - be sent home **(Group A)** - be referred for hospital management **(Group B)** - require emergency treatment and urgent referral **(Group C)**

4.1.1. Step 1

TABLE 11: Step 1 Overall assessment for Dengue management

Step 1 Overall Assessment
History ■ date of onset of fever/illness ■ quantity of oral fluid intake ■ diarrhea ■ urine output (frequency, volume and time of last voiding) ■ assessment of warning signs ■ change in mental state/seizure/dizziness ■ other important relevant history, such as family or neighborhood dengue, travel to dengue-endemic areas, co-existing medical conditions.
Physical examination ■ assessment of mental state ■ assessment of hydration status ■ assessment of hemodynamic status ■ checking for quiet tachypnoea/acidotic breathing/pleural effusion ■ checking for abdominal tenderness/hepatomegaly/ascites ■ examination for rash and bleeding manifestations ■ tourniquet test (repeat if previously negative or if there is no bleeding manifestation).
Investigation Details on investigation is provided in chapter 3 ■ **CBC:** A complete blood count should be done at the first visit (it may be normal), CBC should be repeated daily until the critical phase is over. Decreasing white blood cell and platelet counts make the diagnosis of dengue very likely. ■ **Hematocrit:** The hematocrit in the early febrile phase could be used as the patient's own baseline.

Note

- Leukopenia usually precedes the onset of the critical phase and has been associated with severe disease.
- A rapid decrease in platelet count, concomitant with a rising hematocrit compared to the baseline, is suggestive of progress to the plasma leakage/critical phase of the disease. These changes are usually preceded by leukopenia (≤ 4000 cells/mm^3).
- In the absence of the patient's baseline, age-specific population hematocrit levels could be used as a surrogate during the critical phase.
- Dengue-specific laboratory tests can be performed to confirm the diagnosis. However, it is not necessary for the acute management of patients, except in cases with unusual manifestations.
- Additional tests should be considered in patients with co-morbidities and severe disease as indicated. These may include tests of liver function, glucose, serum electrolytes, urea and creatinine, bicarbonate or lactate, cardiac enzymes, electrocardiogram (ECG) and urine specific gravity.

4.1.2. Step 2

Diagnosis, assessment of disease phase and severity

On the basis of evaluations of the overall assessment as described above, clinicians should determine whether the disease is dengue, which phase it is in (febrile, critical or recovery), whether there are warning signs, the hydration and hemodynamic state of the patient, and whether the patient requires admission or not.

4.1.3. Step 3

Disease notification and management decision

Disease notification

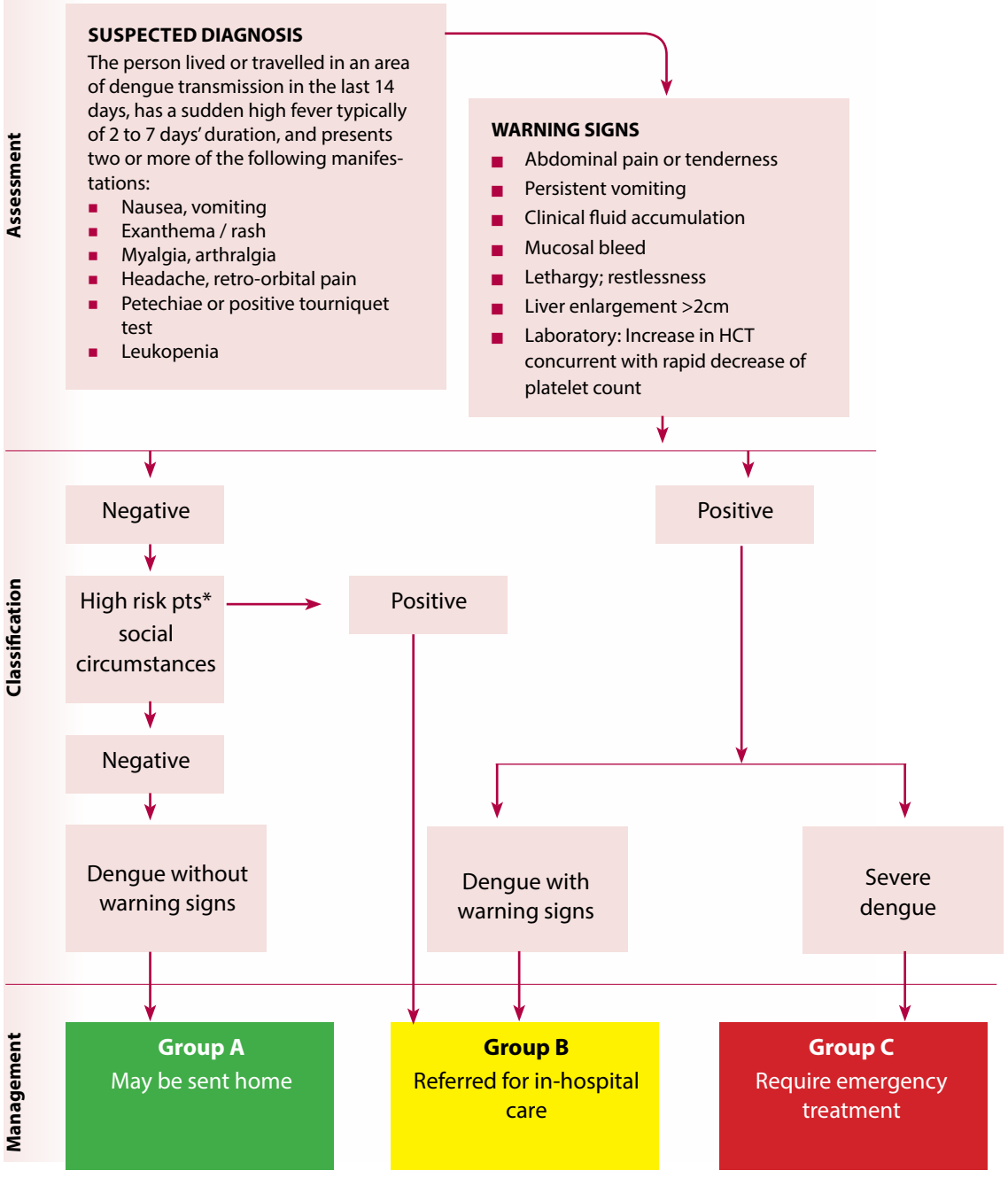
In dengue-endemic countries like Nepal, cases of suspected, probable/highly suggestive and confirmed dengue should be notified early so that appropriate public-health measures can be initiated. Laboratory confirmation is not necessary before notification, but if available should be reported. Notification of dengue is mandatory in Nepal. It is also a part of early warning and reporting system (EWARS) and should be reported accordingly.

Management decisions

Depending on the clinical manifestations and other circumstances, patients may either

- be sent home **(Group A)**
- be referred for in-hospital management **(Group B)** or
- require emergency treatment and urgent referral **(Group C)**

TABLE 12: Algorithm for Dengue case management



***High risk dengue patients**

- Infant
- Elderly
- Pregnant
- Obese patients
- Bleeding
- Underlying disease
- Confusion

Group A- MANAGEMENT

TABLE 13: Case management for Group A dengue patient

Case Management Group A* (May be sent home)	
Group criteria	■ Patients who do not have warning signs AND who are able: ■ To tolerate adequate volumes of oral fluids ■ To pass urine at least once every 6 hour
Laboratory tests	■ Complete blood Count (CBC) ■ Hematocrit (Hct)
Treatment	Advice for: ■ Adequate bed rest ■ Adequate fluid intake ■ Paracetamol, 4 gm max. per day in adults & accordingly in children Patients with stable Hct can be sent home
Monitoring	■ Daily review for disease progression: o Decreasing WBC o Defervescence o Warning signs (until out of critical period) ■ Advice for immediate return to hospital if development of any warning signs ■ Written advice of management (e.g. home care card for dengue)

Box 2: * Details on case management for Group A dengue patient

- These are patients who may be sent home. They are able to tolerate adequate volumes of oral fluids, pass urine at least once every six hours and do not have any of the warning signs (particularly when fever subsides).
- Clear, definitive advice on the care that the patient needs to receive at home: i.e. bed rest and frequent oral fluids should be given.
- Patients with ≥ 3 days of illness should be reviewed daily for disease progression (indicated by decreasing white blood cell and platelet counts and increasing hematocrit, defervescence and warning signs) until they are out of the critical period.
- Those with stable hematocrit can be sent home but should be advised to return to the nearest hospital immediately if they develop any of the warning signs and to adhere to the following action plan.
    - **Adequate oral fluid intake.** Encourage oral intake to replace fluid loss from fever and vomiting. Small amounts of oral fluids should be given frequently for those with nausea and anorexia. Oral rehydration solution or soup and fruit juices may be given to prevent electrolyte imbalance. Sufficient oral fluid intake should result in a urinary frequency of at least 4 to 6 times per day. A record of oral fluid and urine output could be maintained and reviewed daily in the ambulatory setting.
    - **Give paracetamol for high fever.** The recommended dose is 10 mg/kg/dose, not more than 3–4 times in 24 hours in children and not more than 3 g/day in adults. Sponge with tepid water if the patient still has a high fever. "Do not give acetylsalicylic acid (aspirin), ibuprofen or other non-steroidal anti-inflammatory agents (NSAIDs) or intramuscular injections, as these aggravate gastritis or bleeding".
    - **Patient should be brought to hospital immediately if any of the following occur:**
        - no clinical improvement
        - deterioration around the time of defervescence
        - severe abdominal pain/persistent vomiting
        - cold and clammy extremities
        - lethargy or irritability/restlessness
        - bleeding (e.g. black stools or coffee ground vomiting)
        - shortness of breath
        - not passing urine for more than 6 hours.
- Admission during the febrile period should be reserved for those who are unable to manage adequate oral hydration at home, infants, and those with co-existing conditions.
- Ambulatory patients should be monitored daily for temperature pattern, volume of fluid intake and losses, urine output (volume and frequency), warning signs, signs of plasma leakage and bleeding and CBC.

Group B- MANAGEMENT

TABLE 14: Case management for Group B dengue patient

Case Management Group B* (Referred for in hospital care)		
Group criteria	Patients with any of the following features: ■ Co-existing conditions- pregnancy, infancy, old age, diabetes mellitus ■ Social circumstances o living alone, living far from hospital	OR Existing warning signs: ■ Abdominal pain or tenderness ■ Persistent vomiting ■ Clinical fluid accumulation ■ Mucosal bleeding ■ Lethargy/ restlessness ■ Liver enlargement >2cm ■ Laboratory: increase in Hct
Laboratory tests	■ Complete blood Count (CBC) ■ Hematocrit (Hct)	■ Complete blood Count (CBC) ■ Hematocrit (Hct)
Treatment	■ Encourage oral fluids ■ If not tolerated, start intravenous fluid therapy 0,9% saline or Ringer Lactate at maintenance rate	■ Obtain reference Hct before fluid therapy ■ Give isotonic solutions - 0.9% saline or Ringer lactate start with 5-7 ml/kg/hr. for 1-2 hours, then reduce to 3- 5 ml/kg/hr. for 2-4 hr. then reduce to 2-3 ml/kg/hr. or less based on clinical response **Reassess clinical status and repeat Hct** ■ If Hct remains the same or rises only minimally continue with 2-3 ml/kg/hr. for another 2-4 hrs. ■ If worsening of vital signs and rapidly rising Hct increase rate to 5-10 ml/kg/hr. for 1-2 hours **Reassess clinical status, repeat Hct and review fluid infusion rates accordingly** ■ Reduce IV fluids gradually when the rate of plasma leakage decreases towards the end of the critical phase. This is indicated by: ■ Adequate urine output and/or fluid intake ■ Hct decreases below baseline in a stable patient
Monitoring	■ Temperature pattern ■ Volume of fluid intake and losses ■ Urine output – volume and frequency ■ Warning signs ■ Hct, WBC and platelet	■ Vital signs and peripheral perfusion (1-4 hourly until patient is out of critical phase) ■ Urine output (4-6 hourly) ■ Hct (before & after fluid replacement, then 6-12 hourly) ■ Blood glucose ■ Other organ functions (renal profile, liver profile, coagulation profile, as indicated)

Box 3: * Details on case management for Group B dengue patient

- These are patients who should be admitted for in-hospital management for close observation as they approach the critical phase. These include
  - patients with warning signs
  - patients with co-existing conditions (pregnancy, infancy, old age, obesity, diabetes mellitus, hypertension, heart failure, renal failure, chronic hemolytic diseases such as sickle-cell disease and autoimmune diseases)
  - patients with certain social circumstances (living alone or far from a health facility).
- Rapid fluid replacement in patients with warning signs is the key to prevent progression to the shock state. If the patient has dengue with warning signs or signs of dehydration, judicious volume replacement by intravenous fluid therapy from this early stage may modify the course and the severity of disease. The action plan should be as follows and applies to infants, children and adults
  - **Obtain a reference hematocrit before IV fluid therapy begins.** Give only isotonic solutions such as 0.9% saline, Ringer's lactate or Hartmann's solution (if available). Start with 5–7 ml/kg/hour for 1–2 hours, then reduce to 3–5 ml/kg/hour for 2–4 hours, and then reduce to 2–3 ml/kg/hour or less according to the clinical response.
  - **Reassess the clinical status and repeat the hematocrit.** If the hematocrit remains the same or rises only minimally, continue at the same rate (2–3 ml/kg/hour) for another 2–4 hours. If the vital signs are worsening and the hematocrit is rising rapidly, increase the rate to 5–10 ml/kg/hour for 1–2 hours. Reassess the clinical status, repeat the hematocrit and review fluid infusion rates accordingly.
  - **Give the minimum IV fluid volume required to maintain good perfusion and an urine output** of about 0.5 ml/kg/hour. IV fluids are usually needed for only 24–48 hours. Reduce IV fluids gradually when the rate of plasma leakage decreases towards the end of the critical phase. This is indicated by urine output and/or oral fluid intake improving, or the hematocrit decreasing below the baseline value in a stable patient.
  - **Patients with warning signs should be monitored by health-care providers until the period of risk is over.** A detailed fluid balance should be maintained. Parameters that should be monitored include vital signs and peripheral perfusion (1–4 hourly until the patient is out of the critical phase), urine output (4–6 hourly), hematocrit (before and after fluid replacement, then 6–12 hourly), blood glucose and other organ functions profile.
- If the patient has dengue with co-existing conditions but without warning signs, the action plan should be as follows
  - Encourage oral fluids. If not tolerated, start IV fluid therapy of 0.9% saline or Ringer's lactate with or without glucose at appropriate maintenance rate. Use ideal body weight for calculation of fluid infusion for obese /overweight patients. Patients may be able to take oral fluids after a few hrs. of IV fluid therapy. Thus, it is necessary to revise the fluid infusion frequently. Give the minimum volume required to maintain good perfusion and urine output. IV fluids are usually needed only for 24–48 hours.

Group C- MANAGEMENT

TABLE 15: Case management for Group C dengue patient

Case Management Group C*(Require emergency treatment)	
Group criteria	Patients with any of the following features. ■ Severe plasma leakage with shock and/or fluid accumulation with respiratory distress ■ Severe bleeding ■ Severe organ impairment
Laboratory tests	■ Complete blood Count (CBC) ■ Hematocrit (Hct) and other organ function tests as indicated
Treatment Compensated shock	■ Start I.V. fluid-isotonic crystalloid solutions at 5-10 ml/kg/hr. over 1 hr. ■ Reassess patient's condition **If patient improves** ■ I.V. fluids should be reduced gradually to 5-7 ml/kg/hr. for 1-2 hr. then 3-5 ml/kg/hr. for 2-4 hr. then 2-3 ml/kg/hr. for 2-4 hr. then reduced depending on hemodynamic status ■ I.V. fluids can be maintained for up to 24 - 48 hours **If patient still unstable** ■ Check Hct after first bolus-If **Hct increases/ still high** (>50%) Repeat a second bolus of crystalloid solution at 10-20 ml/kg/hr. for 1 hr. If improvement, reduce to 7-10 ml/kg/hr. for 1-2 hr. then reduce as above. **Hct decreases**-indicates bleeding & need to crossmatch & transfuse blood
Treatment Hypotensive shock	■ Initiate I.V. fluid -crystalloid /colloid solution, 20 ml/kg as a bolus for 15 min **If patient improves** ■ Give a crystalloid / colloid solution, 10 ml/kg/hr. for 1 hr. then reduce gradually as above **If patient still unstable** ■ Review the Hct taken before the first bolus-If **Hct was low** (<40% in children/adult females, < 45% in adult males) This indicates bleeding, the need to crossmatch and transfuse **Hct was high** compared to the baseline value, change to I.V. colloids at 10-20 ml/kg as a second bolus over to 1 hour; reassess after second bolus If improving reduce the rate to 7-10 ml/kg/hr. for 1-2 hours, then back to I.V. crystalloids and reduce rates as above. If condition still unstable, repeat Hct after second bolus **If Hct decreases,** this indicates bleeding, see above **If Hct increases/ remains high** (> 50%), continue colloid infusion at 10-20 ml/kg as a third bolus over 1 hr., then reduce to 7-10 ml/kg /hr. for 1-2 hours, then change back to crystalloid solution and reduce rate as above
Treatment Hemorrhagic complication	■ Give 5-10 ml/kg of fresh packed red cells or 10-20 ml/kg fresh whole blood

Box 4: * Details on case management for Group C dengue patient

- These are patients with severe dengue who require emergency treatment and urgent referral because they are in the critical phase of the disease and have
  - severe plasma leakage leading to dengue shock and/or fluid accumulation with respiratory distress
  - severe hemorrhages
  - severe organ impairment
- These patients should be admitted to a hospital with access to blood transfusion facilities. Judicious intravenous fluid resuscitation is the essential and usually sole intervention required. Please refer to above table for treatment for compensated and hypotensive shock.
- The goal of the resuscitation include
  - improving central and peripheral circulation – i.e. decreasing tachycardia, improving BP and pulse volume, warm and pink extremities, a capillary refill time < 2 seconds
  - improving end-organ perfusion – i.e. achieving a stable conscious level (more alert or less restless), and urine output ≥ 0.5 ml/kg/hour or decreasing metabolic acidosis

Box 5: When to stop intravenous fluid therapy

- Recognizing when to decrease or stop intravenous fluids as part of the treatment of severe dengue is crucial to prevent fluid overload.
- When any of the following signs are present, intravenous fluids should be reduced or discontinued:
  - signs of cessation of plasma leakage
  - stable BP, pulse and peripheral perfusion
  - hematocrit decreases in the presence of a good pulse volume
  - apyrexia (without the use of antipyretics) for more than 24–48 hours
  - resolving bowel/abdominal symptoms;
  - improving urine output.
- Continuing intravenous fluid therapy beyond the 48 hours of the critical phase will put the patient at risk of pulmonary edema and other complications such as thrombophlebitis.

Box 6: Discharge criteria for a hospitalized dengue patient

- No fever for 48 hours
- Improvement in clinical picture
- Increasing trend of platelet count
- Stable hematocrit without intravenous fluids
- No respiratory distress

4.2. Management in specific risk group

4.2.1. Dengue in the elderly

Clinical manifestations

Clinical manifestations of dengue in the elderly are similar to those of younger adults. However, rash, hepatomegaly and mucocutaneous hemorrhage are less frequent. The elderly have significantly lower incidences of fever, abdominal pain, bone pain and rashes but higher frequencies of concurrent bacteremia, gastrointestinal bleeding, acute renal failure, and pleural effusion, higher incidence of prolonged prothrombin time and lower mean hemoglobin levels than younger adult patients.

Risk of severe dengue and death

A higher incidence of plasma leakage and case fatalities has been reported in the elderly compared to young adult dengue patients.

Issues in management

- About 10% elderly dengue patients may have no complaints of fever and hence need diligent search for other manifestations.
- Elderly are more susceptible to the hypovolemic effects of plasma leakage and acute renal failure because of the effect of ageing on kidneys.
- Age related decline in cardiopulmonary function should be taken into consideration during fluid replacement and/or resuscitation in dengue illness.

4.2.2. Dengue in pregnancy

The clinical manifestations, treatment and outcome of dengue in pregnant women are similar to those of non-pregnant women but with some important differences (table 16). In order to recognize and diagnose dengue disease early in pregnancy, clinicians need to maintain a high index of suspicion when dealing with pregnant women who present with febrile illness after travelling to, or living in dengue-endemic areas.

Impact of dengue on pregnancy

- Risk of vertical transmission during the perinatal period
- Significant impact of dengue at parturition-severe bleeding

TABLE 16: Similarities and differences between normal pregnancy and dengue in pregnancy

	Normal Pregnancy	Dengue in Pregnancy
Fever	Blunted febrile response	+
Bleeding	Bleeding can be due to obstetrical cause	+ (mild to severe)
Abdominal pain	+/-	+/-
Ascites, pleural effusion	-	+ in plasma leakage
WBC	Elevated	Leukopenia
Thrombocytopenia	+	+ unique CBC changes
Haematocrit	↓ (haemodilution after the second trimester)	↑ In plasma leakage
Hemolysis	-	-
Liver enzymes	Mild ↑	Mild to severe ↑

Management of dengue during pregnancy

- Early admission for close monitoring is recommended, especially for women close to full-term/labor
- Conservative medical and obstetrical management is the treatment of choice

Challenges in recognition of dengue and plasma leakage in pregnancy

- Hyperemesis during the first trimester of pregnancy can resemble the warning signs of severe dengue and this may delay the recognition of severe dengue.
- After the second trimester of pregnancy it is normal to see an increase in circulating blood volume with generalized vasodilatation, resulting in an increased baseline heart rate and lower baseline BP, as well as a lower baseline hematocrit. This can confuse the diagnosis of dengue and therefore clinicians need to be alert to the following:
    - The lower BP and tachycardia of normal pregnancy could be misinterpreted as hypotensive shock.
    - The lower baseline hematocrit after the second trimester of pregnancy should be noted. Establishing the baseline hematocrit during the first 2–3 days of fever is essential for early recognition of plasma leakage.
    - Clinical signs of plasma leakage such as pleural effusion and ascites could be difficult to elicit in the presence of a gravid uterus.

Challenges in monitoring and management

- There is no difference in fluid therapy compared with the non-pregnant state. However, it is important to note that the growing gravid uterus may result in narrower tolerance of fluid accumulation in the peritoneal and pleural cavity from plasma leakage. Hence excessive fluid replacement should be avoided.
- The increased baseline heart rate and a lower baseline BP are normal physiological changes in late pregnancy. Targeting an inappropriate heart rate and "normal" levels of BP could result in fluid overload and respiratory distress.
- The presence of wounds or trauma during the critical phase of dengue with marked thrombocytopenia, coagulopathy and vasculopathy creates a substantial risk of severe hemorrhage. Replacement with transfusion of fresh whole blood/fresh packed red cells should be promptly instituted for severe hemorrhage.
- Prophylactic platelet transfusion is not recommended unless obstetrically indicated.
- Tocolytic agents and measures to postpone labor to a suitable time may be considered during the critical phase of dengue illness. However, there is lack of evidence on this practice.

Inevitable delivery during critical phase

- If delivery is inevitable, bleeding should be anticipated and closely monitored.
- Blood and blood products should be cross-matched and saved in preparation for delivery.
- Trauma or injury should be kept to the minimum if possible.
- It is essential to check for complete removal of the placenta after delivery.
- Transfusion of platelet concentrates should be initiated during or at delivery but not too far ahead of delivery, as the platelet count is sustained by platelet transfusion for only a few hours during the critical phase.
- Fresh whole blood/fresh packed red cells transfusion should be administered as soon as possible if significant bleeding occurs. If blood loss can be quantified, it should be replaced immediately. Do not wait for blood loss to exceed 500 ml before replacement, as in postpartum hemorrhage. Do not wait for the hematocrit to decrease to low levels.
- Ergotamine and or oxytocin infusion as per standard obstetrical practice should be commenced to contract the uterus after delivery to prevent postpartum hemorrhage.

Post delivery

- Newborns with mothers who had dengue just before or at delivery, should be closely monitored in hospital after birth in view of the risk of vertical transmission.
    - At or near-term/delivery, severe fetal or neonatal dengue illness and death may occur when there is insufficient time for the production of protective maternal antibodies.
- Congenital infection could eventually be suspected on clinical grounds and then confirmed in the laboratory.

4.2.3. Dengue in infants

Manifestations of dengue in infants

Febrile Phase

- Dengue virus can cause spectrum of outcomes in infants ranging from asymptomatic infection to mild or clinically significant severe disease as in older children and adults. Infants with dengue typically have high fever usually lasting 2-7 days same as in older children. Upper respiratory tract symptoms, vomiting, diarrhea and febrile convulsions are more common in infants. Febrile seizure, macular rash, petechiae and lower platelet counts early in the illness are significantly associated with dengue among infants with acute undifferentiated febrile illness.

Critical Phase

- An increase in capillary permeability, in parallel with increasing hematocrit levels, becomes apparent around the time of defervescence in majority of infants. During the critical phase, clinical features and laboratory findings become more prominent in infants. Skin bleeding (petechiae) and GI bleeding can occur along with hepatomegaly. Splenomegaly can occur in almost 10% of infants. Shock in infants can occur when a critical volume of plasma is lost through leakage and is preceded by warning signs. The normal values of hematocrit in infants is relatively low (28-42 %). Increase in hematocrit of ≥ 20% above the baseline hematocrit may be seen. Thrombocytopenia and leukopenia are often observed during critical phase. Liver dysfunctions are found more frequently in infants than compared to children.

Recovery Phase

- During the recovery phase, progression of infants with dengue is the same as that of children and adults which is described above.

Management of dengue in infants

Severe dengue is less common in infants but when it does occur the risk of dying is higher than in older children and adults. Infants with dengue should be referred for hospital management. Management of dengue in infants with and without warning signs can be summarized as in (table 17) below:

TABLE 17: Summary of management of dengue in infants with and without warning signs

Dengue infants without warning signs	Dengue infants with warning signs
■ Supportive treatment. ■ Oral rehydration-ORS, fruit juices and other fluids containing electrolytes and sugar. ■ Continue breastfeeding/formula feeding and/or solid food. ■ Fever control-antipyretics and tepid sponging.	■ Start IV fluid- isotonic crystalloid solutions like Ringer's lactate, Ringer's acetate or 0/9 % saline should be used. 5-7 ml/kg/hrs. for 1-2 hrs. then, adjust according to pts clinical response. ■ IV fluid therapy is only required for 24-48 hrs. then, in most infants since the capillary leak resolves spontaneously after this time.

Box 7: Points to be considered when managing infants with severe dengue

- Infant with a low baseline hematocrit of 30%, presenting with dengue shock and a hematocrit of 40%, is relatively more hemoconcentrated than another child with a baseline value of 42% and a hematocrit of 50% at the time of shock.
- In infants, IV fluids must be administered with special care to avoid fluid overload.
- Fluids account for a greater proportion of body weight in infants than children and minimum daily requirements are correspondingly higher. Infants have less intracellular fluid reserve than older children and adults. Moreover, capillary beds are intrinsically more permeable than those of older children or adults. Both early cardiovascular compromise and significant fluid overload are more likely if capillary leaks occur in these circumstances.
- Blood transfusion is only indicated in dengue infants with severe bleeding.

Vertical transmission and neonatal dengue

Dengue virus can be vertically transmitted to the fetus in utero or to the infant at parturition. Some newborns may be asymptomatic. Clinical manifestations of vertically infected neonates vary from mild illness such as fever with petechial rash, thrombocytopenia and hepatomegaly, to severe illness with clinical sepsis, pleural effusion, gastric bleeding, circulatory failure, massive intracerebral hemorrhage and death. Symptomatic and supportive treatment under close observation is the mainstay of treatment for neonatal dengue.

CHAPTER 5

VECTOR MANAGEMENT

Prevention or reduction of dengue virus transmission depends on control of the mosquito vectors or interruption of human–vector contact. Activities to control dengue transmission should target *Ae. aegypti* (main vector) or *Ae. albopictus* and other mosquito species if they are the known local vectors of dengue.

Ae. aegypti proliferates in household containers such as those used for domestic water storage, decorative plants, variety of rain-filled habitats- including used tyres, discarded food/beverage containers, blocked gutters and buildings under construction. Typically, these mosquitoes do not fly far, majority remaining within 300-400 meters of where they emerged. They feed almost entirely on humans, mainly during daylight, both indoors and outdoors. ***Ae. albopictus*** usually bite in the early morning and late afternoon. They tend to rest outdoors and inhabit both domestic and peri-domestic artificial containers as well as natural receptacles such as tree holes and plants.

Integrated vector management (IVM), "a rational decision-making process for the optimal use of resources for vector control" is the strategic approach to vector control promoted by WHO and includes control of the vectors of dengue. IVM considers five key elements.

1. advocacy, social mobilization and legislation
2. collaboration within the health sector and with other sectors
3. integrated approach to disease control
4. evidence-based decision-making
5. capacity-building

Control of *Ae. aegypti* is mainly achieved by eliminating container habitats favorable for oviposition and which allows the development of the aquatic stages. These habitats are eliminated by preventing access by mosquitoes to these containers or by frequently emptying /cleaning them, removing the developing stages using insecticides or biological control agents, by killing the adult mosquitoes using insecticides, or by combinations of these methods. Points for consideration when choosing the appropriate vector control method are:

- Local ecology and behavior of target species
- Resources available for implementation
- Cultural context in which interventions are to be carried out
- Feasibility of applying the method in a timely manner
- Adequacy of coverage

5.1. Methods of Vector Control

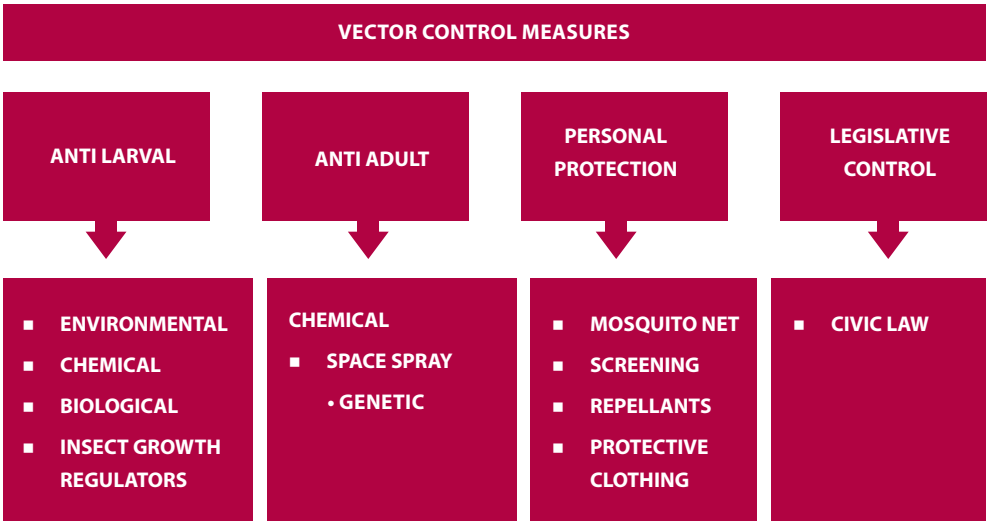
Aedes vector control should target all *Aedes* mosquito life stages (egg, larva, pupa and adult). Before deciding on which control method to use, it is important to consider the prevailing local entomological context.

Ae. aegypti uses a wide range of confined larval habitats, both man-made and natural. It may not be feasible or cost-effective to attempt to control the immature stages in all such habitats. Some man-made container habitats produce large numbers of adult mosquitoes, whereas others are less productive. Control activities should target the habitats that are most productive and hence epidemiologically more important rather than all types of container, especially in a resource constraints settings. Various vector control measures for dengue are as given in (table 18) below: Some of the new potential vector control tools are provided in (annexe 9)

5.1.1. Anti-Larval Measures

- Environmental management
- Chemical Control- Larvicides
- Biological larvicides
- Insect growth regulators

TABLE 18: Vector control measures for dengue vector



5.1.1.1. Environmental Management

Environmental management helps to prevent or minimize vector propagation and human contact with the vector-pathogen by destroying, altering, removing or recycling non-essential containers that provide larval habitats.

The types of environmental management are

- **Environmental modification-** Long lasting physical transformation to reduce vector larval habitats such as good piped water supply.
- **Environmental manipulation-** Temporary changes to vector habitats such as frequent emptying and cleaning of water storage containers, cleaning gutters, proper disposal of discarded containers and tyres.
- **Change in human habitation or behavior-** Mosquito screening nets in windows, doors; bed nets for sleeping during day time, etc.

Some of the environmental management methods for vector control are as follows:

- Improvement of water supply and water-storage systems
- Mosquito-proofing of water-storage containers
- Solid waste management
- Street cleansing which removes discarded water bearing containers such as plastic cups, bottles, bottle caps, plastic package covers, etc and clean drains regularly
- Legislation for building structures to reduce potential larval habitats

Environmental management actions that can be adapted in Nepal to control immature stages of *Aedes aegypti* are given in (table 19) below:

TABLE 19: Environmental management action to control immature stages of *Aedes aegypti*

Larval habitat	Empty, clean and scrub	Mosquito proof cover	Store under roof	Modify design, and/ or repair and clean	Fill (with sand, soil or concrete)	Collect, recycle and dispose	Puncture or drain
Water storage tank	+	+		+			
Drums	+	+		+			
Flower vase with water	+				+		
Potted plants with saucers	+						
Roof gutter	+			+			
Animal water container	+						
Discarded food and water containers						+	
Used tyres			+		+	+	+
Discarded buckets						+	+

FIGURE 13: Potential *Aedes* breeding sites


Open water container


Discarded containers


Discarded drums


Overhead water tanks


Plastic containers


Discarded tyres


House plants


Roof top rain water collection under house solar panel


Decorative ponds in hotels


Discarded drums


Discarded plastic containers


Water collection area in a construction site

5.1.1.2. Chemical Control-Larvicides

Chemical control should be considered as complementary to environmental management and – except in emergencies – should be restricted to containers that cannot otherwise be eliminated or managed. It is difficult and expensive to apply chemical larvicides on a long term basis. Larvicides may be impractical to apply in hard-to-reach natural sites such as leaf axils and tree holes, which are common habitats of *Ae. albopictus,* or in deep wells. The difficulty of accessing indoor larval habitats of *Ae. aegypti* (e.g. water storage containers, plant vases, saucers) to apply larvicides is a major limitation in many urban contexts.

As *Ae. aegypti* often deposits eggs in water-storage containers, the larvicides should have low toxicity to other species and should not significantly change the taste, odor or color of the water.

Insecticides

The mosquito larvicides that are suitable for treatment of drinking water are given in (table 20) below and larvicides that can be used for non-potable water containers are given below in (table 21).

TABLE 20: Insecticides for treatment of drinking water

Insecticides	Dose
Temephos	1 mg*/liter
Methoprene	1 mg*/liter
Pyriproxyfen	0.01 mg*/liter
Bacillus thuringiensis	1-5 mg/liter
*mg of active ingredient (a.i.)	

TABLE 21: WHO recommended compounds and formulations for control of mosquito larvae in container habitats[a]

Insecticide	Formulation[b]	Dosage[c]	WHO Classification of Active Ingredient[d]
Organophosphates			
Pirimiphos-methyl	EC	1	III
Temephos	EC, GR	1	U
Insect growth regulators			
Diflubenzuron	DT, GR, WP	0.02-0.25	U
rs-methoprenee	EC	1	U
Novaluron	EC	0.01-0.05	NA
Pyriproxyfene	GR	0.01	U
Biopesticides			
Bacillus thuringiensis israelensise[e]	WG	1-5 mg/l	U
Spinosad	DT, GR, SC	0.1-0.5	U

a WHO recommendations on the use of pesticides in public health are valid only if linked to WHO specifications for their quality control.
b DT= tablet for direct application; GR= granule; EC= emulsifiable concentrate; WG= water-dispersible granule; WP= wettable powder; SC= suspension concentrate.
c mg/L of active ingredient for control of container-breeding mosquitoes
d Class II = moderately hazardous; Class III = slightly hazardous; Class U = unlikely to pose an acute hazard in normal use; NA = not available.
e Can be used at recommended dosages in potable water.

Application Procedures

- Hand-operated compression sprayers- suitable for applying liquid insecticides to larger larval habitats.
- Knapsack sprayers- also suitable, especially for delivering wettable powder formulations.
- Syringe or pipette- can be used for treating indoor flower vases and ant traps.
- Direct application by protected hand- Granule and certain other solid formulations are applied directly to confined larval habitats or by a convenient standard measure (e.g. a dessert spoon or teaspoon).
- When treating containers of drinking water, sufficient insecticide should be added for the volume of the container even if the container is not full of water (e.g. 1 g of 1% temephos granules for 10 liters of container volume).

Treatment Cycle

- It will depend on the species of mosquito, seasonality of transmission, patterns of rainfall, duration of efficacy of the larvicide and types of larval habitat.
- Two or three application rounds carried out annually in a timely manner with proper monitoring of efficacy may suffice, especially in areas where the main transmission season is short.

Precautions

- Extreme care must be taken when treating drinking-water to avoid dosages that are toxic for humans.
- Label instructions must always be followed when using insecticides.

Box 8: Use of Temephos

- Tamephos is an organophosphate compound
- Safe, without any odor and color
- Residual effect with low mammalian toxicity
- Available as liquid, emulsifiable concentration and granule formulation
- Only granule formulation is used for larviciding at a dose not exceeding 1mg/L if the active ingredient

5.1.1.3. Biological Control

Biological control methods are effective only against the immature stages of vector mosquitoes in the larval habitat where they are introduced. Biological control is based on the introduction of organisms that prey upon, parasitize, compete with or otherwise reduce populations of the target species. Against *Aedes* vectors of dengue, only certain species of larvivorous fish- Gambusia affinis, Poecilia reticulata and predatory copepods– small freshwater crustaceans – have proved effective. While biological control avoids chemical contamination of the environment, there may be various operational limitations with this method.

5.1.1.4. Insect growth regulators (IGR)

Insect growth regulators are highly toxic to insect larvae or pupae interfering with development into adults. However, it is costly and limited availability.

5.1.2. Anti-Adult Measures

- Chemical
  - o Space spray (fogging)
- Genetic

Chemical control methods targeted for adult vectors are intended to impact on mosquito densities, longevity and other transmission parameters.

5.1.2.1. Space Spraying (Fogging)

This method is recommended for control **only in emergency situations** to suppress an ongoing epidemic or to prevent and incipient one. The objective of space spraying (fogging) is the massive, rapid destruction of the adult vector population. However, there has been considerable controversy about the efficacy of aerosol insecticide applications during epidemics of dengue. There is no well-documented example of the effectiveness of this approach in interrupting an epidemic. Nevertheless, if space spraying is used early in an epidemic and on a sufficiently large scale, the intensity of transmission may be reduced, which would give time for the application of other vector control measures that provide longer-term control, including larviciding and community based source reduction. Thus, if disease surveillance is sensitive enough to detect cases in the early stages of an epidemic, and if the resources are available, emergency space spraying can be initiated at the same time as source reduction measures and larviciding are intensified.

Target Area

- Since total coverage can rarely be achieved, space spraying should focus on areas where people congregate (e.g. high-density housing, schools, hospitals) and where dengue cases have been reported or vectors are abundant.
- Selective space treatment up to 400 meters from houses in which dengue cases have been reported is commonly practiced (and is sometimes also referred to as "perifocal spraying"). However, by the time a case is detected and a response mounted, the infection is likely to have spread to a wider area. Only if resources permit area-wide treatment be considered.
- Because of the indoor resting habit of *Aedes aegypti* indoor fogging can be applied to effectively target adult mosquitoes.

Insecticides

Suitable insecticides for space spraying as cold aerosol or thermal fogging are listed in the (table 22) below.

TABLE 22: Selected insecticide for cold aerosol or thermal fog application against mosquitoes

Insecticide	Chemical	Dosage of active ingredient (g/ha)		WHO hazard classification of active ingredient [a]
		Cold aerosols	Thermal fogs	
Fenitrothion	Organophosphate	250–300	250–300	II
Malathion	Organophosphate	112–600	500–600	III
Pirimiphos-methyl	Organophosphate	230–330	180–200	III
Bioresmethrin	Pyrethroid	5	10	U
Cyfluthrin	Pyrethroid	1–2	1–2	II
Cypermethrin	Pyrethroid	1–3		II
Cyphenothrin	Pyrethroid	2–5	5–10	II
d,d-trans-Cyphenothrin	Pyrethroid	1–2	2.5–5	NA
Deltamethrin	Pyrethroid	0.5–1.0	0.5 – 1.0	II
D-Phenothrin	Pyrethroid	5–20		U
Etofenprox	Pyrethroid	10–20	10–20	U
λ-Cyhalothrin	Pyrethroid	1.0	1.0	II
Permethrin	Pyrethroid	5	10	II
Resmethrin	Pyrethroid	2–4	4	III

a Class II = moderately hazardous; class III = slightly hazardous; class U = unlikely to pose an acute hazard in normal use; NA = not available.

Procedures

Details on application procedure of space spray treatments is provided in (annexe 8).

Treatment Cycle

When a rapid reduction in vector density is essential, such as in emergencies, space treatment (indoor, house to house fogging) can be done on day 0,2,7 until the cases come down and declining trend is observed. Further applications should then be made once or twice a week to sustain suppression of the adult vector population. Continuous entomological and epidemiological surveillance should be conducted, however, to determine the appropriate application schedule and the effectiveness of the control strategy.

5.1.2.2 Genetic

Some genetic control methods are available for adult mosquito control such as sterile male technique, chromosomal translocations, gene replacement/wolbachia, however, these techniques are costly and not practicable in resource poor settings like ours.

5.1.3. Personal Protection Measures

- Mosquito net
- Screening
- Repellants
- Protective clothing

Residents and travelers to dengue endemic areas should take necessary protective measures from mosquito bites. The personal protective measures for dengue include using mosquito nets when sleeping or resting during daytime, using window and door screens, using mosquito repellants to exposed skin and using protective clothing like long sleeves. People infected with the virus should also apply these measures to minimize contact with mosquito and prevent further transmission.

FIGURE 14: Personal protection measures against mosquito bites

5.1.4. Legislation

Suitable laws and byelaws should be enacted and implemented for regulating storage/ utilization of water by communities, various agencies and avoidance of mosquito genic conditions at construction sites, factories. Introduction and enforcement of legislation will require strong inter-sectoral coordination, leadership of local authorities and involvement of the judiciary.

Involvement of individuals, communities and different institutions for dengue prevention and control

Involvement of household, communities and institutions like hospitals, offices, schools, etc. for *Aedes* mosquito control is very important. There should be a continuous interaction between health personnel and the community so that people accept *Aedes* control programmes as their own programme. Community should be involved in the task of elimination of *Aedes* breeding in and around their houses for keeping houses free of larval breeding and reduction/elimination of adult mosquitoes. Behavior Change Communication (BCC) campaign is crucial to achieve this. The community must be assured that dengue is a preventable disease and they need to be empowered with the knowledge about mode of transmission, vector control options, availability of services in addition to proper treatment, so that timely and appropriate action is taken. Health education materials should be developed and widely disseminated in the form of posters, pamphlets, hoardings, radios, televisions, etc. Following actions may be taken at different levels of dengue prevention and control.

Box 9: Actions to be taken by different levels for dengue prevention and control

HOUSEHOLD LEVEL

- *Ae. aegypti* mosquito bites during daytime and the peak biting time is early morning or late afternoon. Personal protection measures as such as full sleeved clothing, mosquito nets even when sleeping during day time should be taken.
- Use of mosquito repellants.
- Use of tight fitting mesh/screens on windows and doors.
- Intensification of efforts to reduce the potential larval habitats in and around houses by
  - Covering all water containers in the house to prevent fresh egg laying by the mosquito.
  - Emptying, drying water tanks, containers, coolers, plant pots, at least once a week.
  - Regularly checking for clogged gutters and flat roofs that may have poor water drainage.
- Regular cleaning of ornamental water tanks/garden or if possible introducing larvivorous fishes (e.g., Gambusia). These small fishes eat mosquito larvae.

COMMUNITY LEVEL

- People should form groups to supplement and reinforce efforts at household level.
- Such groups can identify commercial activities such as traders dealing in used tyres or small construction projects, etc., which may be creating larval habitats for the vector.
- The groups should launch awareness campaigns on dengue and seek cooperation for prevention of mosquito breeding and protection from mosquito bites.
- Community activities against larvae and adult mosquitoes can include the following:
  - Cleaning and covering water storage containers.
  - Keeping the surroundings clean and improving basic sanitation measures.
  - Burning mosquito coils to kill or repel the mosquitoes/burning neem leaves, to repel mosquitoes and eliminating outdoor breeding sites.
  - Cleaning weeds and tall grass to reduce available outdoor resting places for adult mosquitoes near houses.
  - Promoting use of mosquito nets to protect infants and small children from mosquito bites during day time and also insecticide treated nets and curtains to kill mosquitoes attempting to bite through the nets or resting on nets and curtains.
  - Mobilizing households to cooperate during spraying / fogging if it conducted during outbreaks.

INSTITUTIONAL LEVEL
(Hospitals, Schools, Colleges, Offices, Other institutions)

In order to achieve sustainability of successful dengue vector control programme, it is essential to focus on involvement of hospitals, non-health sector departments including schools/colleges, civil society organizations and municipal bodies.

- Weekly checking for potential *Aedes* larval habitats especially overhead tanks, ground water storage tanks, air coolers, planters, flower pots, etc.
- Ensuring source elimination by:
  - Covering all water tanks with mosquito proof lids.
  - Emptying, drying water containers, coolers, plant pots at least once each week.
  - Checking for clogged gutters and flat roofs that may have poor drainage.
  - Introducing larvivorous fishes (e.g., Gambusia) in ornamental water tanks/garden if available.
- Promoting personal protection measures like wearing protective clothing (full sleeved shirts & full pants during day time), using commercially available repellents during day time as well as mosquito nets, preferably insecticide treated ones, while sleeping, particularly during day time.
- Putting tight-fitting screens/wire mesh on doors / windows.
- Supporting fogging/spraying activities if conducted by relevant authorities during outbreaks.
- In addition, notification of fever cases (suspected/confirmed) to concerned health authorities and appropriate case management by hospitals.
- These groups should be provided information on all aspects of dengue, what it is, how it spreads and the role of mosquitoes, where & how they breed/rest, and how they can be controlled.

CHAPTER 6

SURVEILLANCE

6.1. Disease Surveillance

6.1.1. Definition

Disease surveillance is an ongoing systematic collection, recording, analysis, interpretation and dissemination of data for initiating suitable public health interventions for prevention and control of the disease. It is a critical component of any dengue prevention and control programme as it provides the information necessary for risk assessment, epidemic response and programme evaluation.

6.1.2. Objectives of Dengue Surveillance

The objectives of a dengue surveillance are

- To identify high risk areas for outbreak prevention
- To detect localized transmission (clusters) of disease for prompt interventions
- To detect dengue epidemics early for preparedness and timely intervention
- To estimate the burden of dengue and provide data for the assessment of the social and economic impact of the disease on the affected community
- To monitor trends in the distribution and spread of dengue over time
- To evaluate the effectiveness of prevention and control of dengue program
- To facilitate planning and resource allocation based on the lessons learnt from programme evaluation

6.1.3. Case Definitions

Dengue case classification based on severity is given below in (table 23) and case definitions for reporting dengue cases are given below in (table 24).

TABLE 23: Dengue Case Classification

Dengue Case Classification	
Dengue without warning signs	The person lived or travelled in an area of dengue transmission in the last 14 days, has a sudden high fever typically of 2 to 7 days' duration, and presents two or more of the following manifestations: ■ Nausea, vomiting ■ Exanthema / rash ■ Myalgia, arthralgia ■ Headache, retro-orbital pain ■ Petechiae or positive tourniquet test ■ Leukopenia
Dengue with warning signs	Dengue (as defined above) with any of the following: ■ Abdominal pain or tenderness ■ Persistent vomiting ■ Clinical fluid accumulation (ascites, pleural effusion) ■ Mucosal bleeding ■ Lethargy/restlessness ■ Liver enlargement >2 cm ■ Laboratory: increase in hematocrit concurrent with rapid decrease in platelet count.
Severe dengue	Dengue with at least 1 of the following: ■ Plasma leakage leading to shock (dengue shock syndrome) or fluid accumulation with respiratory distress ■ Severe bleeding (as evaluated by a clinician ■ Severe organ involvement (i.e., AST or ALT 1000 or greater, impaired consciousness, organ failure).

Dengue cases can be defined as suspected, highly suggestive or confirmed based on the following criteria given below:

TABLE 24: Classification of dengue cases as suspected, highly suggestive or confirmed

Dengue Case Classification	
Suspected	■ A person who lived or travelled in an area of dengue transmission in last 14 days and has a sudden onset of high fever typically of 2-7 days duration and presents with two or more of the following manifestations: nausea, vomiting, exanthema/ rash, myalgia/arthralgia ,headache, retro-orbital pain, petechiae or positive tourniquet test, leukopenia, any warning signs or any criterion of severe dengue, but laboratory tests (NS1 Antigen, IgM anti-DENV and molecular testing) after the onset of illness not performed, awaited or negative.
Highly Suggestive	■ Any suspected dengue case with laboratory results indicative of highly suggestive such as IgM+ in a single serum sample OR IgG+ in a single serum sample with a HIA titer of 1280 or greater or NS1 antigen+
Confirmed	■ Any suspected dengue case with one of the confirmatory laboratory results positive: PCR OR Viral Culture, OR IgM seroconversion in paired sera* OR IgG seroconversion in paired sera OR four fold IgG titer increase in paired sera*.

* paired sera- acute serum from (1-5) days and second serum from (15-21) days

6.1.4. Surveillance Strategy

I. Characteristics of a robust surveillance system for dengue

1. Objectives of the surveillance system(s) should be clear to all stakeholders with a shared goal of reducing the burden of the disease.
2. National guidelines for dengue/disease surveillance should be available.
3. All suspected, highly suggestive/probable and confirmed dengue cases should be reported.
4. Clear data flow, including timely information feedback, defined responsibilities and linkage to response should be in place.
5. Sensitivity of disease surveillance for an early alert can be increased by including the private sector, all health units including outpatient departments, all age groups.
6. Terminology of dengue surveillance should be described and consistent.
7. Dengue notification should be mandatory.
8. Timeliness of all reporting steps should be optimized
9. Usage of easy to apply notification forms, standardized data entry processes and electronic-based reporting.
10. The specificity of dengue information can be improved by quality controlled laboratory support.
11. During outbreaks a small fraction of suspected cases should be tested (e.g. 10% to 30%).
12. Continuous data analysis by a defined team of epidemiologists should be ensured.
13. Regular internal and external evaluations of the routine surveillance system to improve quality standards should be organized.
14. Regular training for epidemiologists, clinicians, laboratory staff and others should be ensured. Staff should be knowledgeable about the case definitions and case management, through capacity building.
15. Alarm signals with a threshold level ('trigger') to initiate activities should be identified (example: excess of reported dengue cases >2 standard deviation of the five-years average)

II. Types of surveillance

The following aspects are of importance in the national dengue surveillance system:

- To use a simplified and standardized case definition. (table 24)
- To improve laboratory support through standardized and quality controlled test procedures.
- To add active/enhanced/syndromic surveillance components.

Passive Disease Surveillance

Passive surveillance is the routine reporting of diseases, where the health care provider provides notification of the disease. In Nepal, dengue case can be reported by health facilities through the health management information system (HMIS).

Passive routine reporting of dengue cases, monitors the spatial and temporal distribution of dengue in its different clinical forms, determines the 'hot spots' and priority areas for interventions and serves as a trigger for outbreak alert. However, passive surveillance is not very sensitive because not all clinical cases are correctly diagnosed specially during season of low transmission. Moreover, many patients with mild, nonspecific viral syndrome who do not formally seek treatment at hospitals are not reported through this passive surveillance system. By the time dengue cases are detected and reported under a passive surveillance, substantial transmission has already occurred and could even reach high peak. In these circumstances it is often too late to control the epidemic.

Enhanced Disease Surveillance

Routine surveillance is the backbone of dengue information but there are other tools that strengthen the information system. These systems either contribute with additional alarm signals or increase data quality and/or timeliness. The potential value of enhanced surveillance lies in combining tools that complement the routine reporting but do not replace it. Enhanced surveillance during the inter-epidemic period includes:

- epidemiological sub-analysis of routinely reported data
- syndromic surveillance
- laboratory-based dengue reporting
- other active surveillance approaches

Syndromic surveillance

Syndromic surveillance can be used for early detection of outbreaks, to follow the size, spread, and speed of outbreaks, to monitor disease trends, and to provide reassurance that an outbreak has not occurred.

Syndromic surveillance systems use existing health data in real time to provide immediate analysis and feedback to investigation staff and decision makers and follow-up of potential outbreaks. Stakeholders need to understand the advantages and limitations of syndromic surveillance systems. However, syndromic surveillance does not replace traditional public health surveillance, nor does it substitute for direct physician reporting of unusual or suspect cases of public health importance.

Other active surveillance approaches

Sentinel surveillance

Sentinel surveillance involves collecting case data from a sample of providers and then extrapolating them to a larger population. The advantage is that it is less expensive (being restricted to small areas) and produces data of higher quality. The disadvantage is the inability to ensure that the sample population is representative. It is often performed in sentinel sites, mainly major hospitals.

Active case finding

Active case finding involves outreach by the public authority, such as regular telephone calls or visits to laboratories, hospitals and providers to stimulate reporting of specific diseases. It requires intensive demands on resources and should be limited to specific purposes.

An active surveillance system allow health authorities to monitor dengue transmission in a community and tell, at any point in time, where transmission is occurring, which virus serotypes are circulating, and what kind of illness is associated with the dengue infection. However, to accomplish this, the system must be active and have good diagnostic laboratory support. Effectively managed, such a surveillance system should be able to provide an early warning or predictive capability for epidemic transmission.

Active case finding around a dengue index case is appropriate to confirm local transmission or to investigate an imported case. Also it could help to assess the size of a local outbreak.

III. Monitoring and evaluation

Periodic internal and external evaluation of the surveillance system is needed to assess the minimum requirements for achieving the objectives of disease surveillance. These evaluations include: information on the system's purpose, process, outcome attributes, analysis and use of collected data as well as public health impact. Opportunities for improvement should be identified and reacted on.

6.2. Vector Surveillance

6.2.1. Sampling methods

Vector surveillance is used for the following purposes

- to determine changes in geographical distribution of vectors
- to monitor and evaluate control programmes
- to obtain relative measurements of the vector population over time and
- to facilitate appropriate and timely decisions regarding interventions

These vector surveillance data will enable the selection and use of the most appropriate vector control tools, and can be used to monitor their effectiveness. In areas where the vector is no longer present, vector surveillance is critical in to detect new introductions rapidly before they become widespread and difficult to eliminate. Monitoring of the vector population's susceptibility to insecticide should also be an integral part of any programme that uses insecticides. There are several methods for detection and monitoring of larval and adult population. Various sampling methods for vector surveillance are given in (table 25) below:

TABLE 25: Various sampling methods for larval and adult mosquitoes

	Sampling methods
1	Larvae and pupae sampling
2	Pupal demographic surveys
3	Larvae and pupae passive collection
4	Adult mosquito population sampling ■ Landing collections ■ Resting collections ■ Sticky trap collection ■ Ovipositioning population sampling

1. Larvae and Pupae Sampling

The most common survey method is larval sampling including pupal than egg or adult collections. Larval surveillance during the pre-monsoon and monsoon is important to find out the prevalence of vectors in an area. The basic sampling unit is the house, which is systematically searched for water-holding containers. Containers are examined for the presence of mosquito larvae, pupae, and larval and pupal skins. Laboratory examination is usually necessary to confirm the species. The following three indices are commonly used to record *Ae. aegypti* infestation levels (table 26):

- House Index
- Container Index
- Breteau Index

TABLE 26: Types of indices used for larval and pupal sampling

House Index (HI)	Percentage of houses infested with larvae and/or pupae.	$\frac{\text{Infested houses}}{\text{Houses inspected}}$ X 100
Container Index (CI)	Percentage of water-holding containers infested with larvae and/or pupae	$\frac{\text{Containers positive}}{\text{Containers inspected}}$ X 100
Breteau Index (BI)	Number of positive containers per 100 houses inspected	$\frac{\text{Number of positive containers}}{\text{Houses inspected}}$ X 100

House Index

- Used most widely for measuring population levels.
- Does not take into account the number of positive containers or the productivity of those containers.

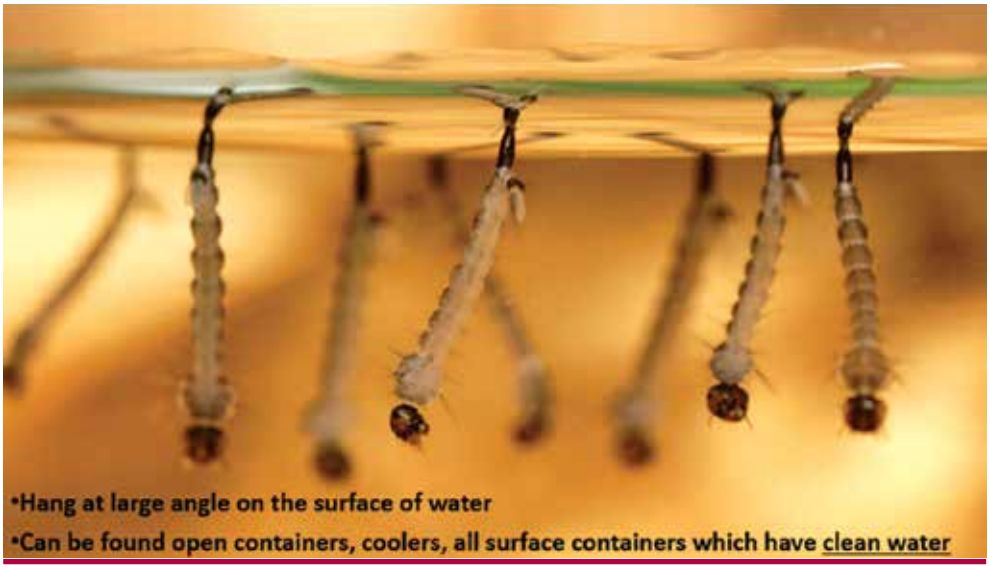
Container Index

- Provides information only on the proportion of water-holding containers that are positive.

Breteau Index

- It establishes a relationship between positive containers and houses, and is considered to be the most informative.
- But it does not give information on container productivity.
- Nevertheless, in the course of gathering the basic information for calculating the Breteau index, it is possible (and highly desirable) to obtain a profile of the larval habitat characteristics by simultaneously recording the relative abundance of the various container types either as potential or actual sites of mosquito production (e.g. the number of positive drums per 100 houses, the number of positive tyres per 100 houses).These data are particularly relevant for focusing larval control efforts on the management or elimination of the most common habitats and for the orientation of educational messages for community-based initiatives.

FIGURE 15: *Aedes* larvae



2. Pupal Demographic Surveys

Pupal/demographic surveys measure the total number of pupae in different classes of containers in a given community. If the classes of containers with the highest rates of adult mosquito emergence are known in a community, their selective targeting for source reduction or other vector control interventions can be the basis for the optimized use of limited resources. However, pupal surveys are far more labor intensive than the above-mentioned larval surveys and are not envisaged for the routine monitoring of *Ae. aegypti* populations.

3. Passive Collection of Larvae And Pupae

Funnel traps have been used for sampling *Aedes* species and other container-breeding organisms in sites with poor or difficult access, such as wells.

4. Adult Mosquito Population Sampling

Adult vector sampling can provide valuable data for studies of seasonal population trends or evaluation of adulticiding measures. However, results are less reproducible than those obtained from sampling of immature stages. Adult mosquitoes collection also are labor-intensive and depend heavily on the collector's proficiency and skill. Various methods for adult mosquito population sampling are given below:

Landing Collections

Landing collections on humans are a sensitive means of detecting low-level infestations and for studying the biting times and places of host attraction. Both male and female *Ae. aegypti* are attracted to humans. Because adult mosquitoes, especially males, have low dispersal rates, their presence can be a reliable indicator of proximity to hidden larval habitats. Rates of capture, typically using hand nets or aspirators as mosquitoes approach or land on the collector, are usually expressed in terms of landing rates per man-hour. However, the method is both labor-intensive and expensive and poses safety and ethical issues in areas endemic for disease.

Resting Collections

During periods of inactivity, adult *Ae. aegypti* typically rests indoors, especially in bedrooms, and mostly in dark places such as clothes closets and other hidden sites. Resting collections involve the systematic searching of these sites with the aid of a flashlight and the capture of adults using mouth- or battery-powered aspirators and hand-held nets. Backpack aspirators powered by rechargeable 12-volt batteries have proven to be an efficient and effective alternative means of collecting resting adult mosquitoes in and around human habitation. Following a standard collection routine, densities are recorded as the number of adult mosquitoes per house (females, males, or both) or the number of adults per man-hour of effort. Where infestation levels are low, the percentage of houses positive for adults is sometimes used.

Sticky Trap Collections

Various sticky trap devices can be used for sampling adult *Ae. aegypti.* The traps are designed to be visually attractive, odor-baited, or both, or are simply located at constricted access points through which adult mosquitoes pass. Age and viral infection have been determined in adult mosquitoes collected with sticky traps though mainly in a research context.

Sampling the Ovipositioning Population

Oviposition traps

Oviposition traps or "ovitraps" are a sensitive and economical method for detecting the presence of *Ae. aegypti* and *Ae. albopictus* in situations where infestations are low and larval surveys are generally unproductive (e.g. when the Breteau index is <5) or for the early detection of new infestations in areas from which the mosquito has been eliminated.

The standard ovitrap is a wide-mouth 0.5 liter glass jar painted black on the outside and equipped with a hardboard or wooden paddle that is clipped vertically to the inside with its rough side facing inwards. The jar is partially filled with clean water and is appropriately placed in a rain-sheltered site – usually outdoors and close to habitation.

Ovitraps are usually serviced weekly and the paddles are examined for the presence of *Ae. aegypti* eggs. The percentage of positive ovitraps provides the simplest index of infestation levels. Ovitraps are inexpensive and it is possible to install and service them over large areas relatively quickly. Ovitraps can be used by people without specialized training.

Enhanced CDC Ovitraps

Enhanced CDC ovitraps is more attractive to ovipositioning females and yields many more *Ae. aegypti* eggs than the standard version. In this double ovitrap method, one jar contains an olfactory attractant made from a "standardized" 7-day-old hay infusion, while the other contains a 10% dilution of the same infusion.

Unlike the original version, with which positivity rates and egg counts are seldom sufficiently high, the enhanced ovitrap has proved suitable for monitoring changes in the adult female populations daily rather than weekly and has been successfully used to assess the impact of adulticidal space spraying on adult females.

Tyre section larvitraps

Tyre section larvitraps like water-filled radial section of a tyre can be used for monitoring oviposition activity. A prerequisite for any tyre section larvitrap is that it facilitates either visual inspection of the water in situ or the ready transfer of the contents to another container for examination. Tyre larvitraps differ functionally from ovitraps in that water level fluctuations caused by rainfall induce the hatching of eggs, and it is the larvae that are counted rather than the eggs deposited on the inner surfaces of the trap.

6.2.2. Monitoring Insecticide Resistance

Information on susceptibility of *Ae. aegypti* to insecticides is of fundamental importance for the planning and evaluation of vector control. The status of resistance in a population must be carefully monitored in a number of representative sentinel sites depending on the history of insecticide usage and eco-geographical context, to ensure that timely and appropriate decisions are made on the use of alternative insecticides or alternative control strategies. It is, therefore, advisable to obtain baseline data on insecticide susceptibility before insecticidal control operations are begun, and to continue periodically monitoring susceptibility levels of larval or adult mosquitoes.

6.2.3. Sampling Strategies

Only in certain situations when the objective is vector eradication or when larval infestation level is reduced to very low level, larval surveys of every houses are needed. In other situations, the number of houses to be inspected should be based on considerations of available resources, the desired level of precision of the results, and the total number of houses in the locality.

Systematic Sampling

Every "n"th (where n equals an agreed number) house is examined throughout the community or along linear transects. For example, if a sample of 5% of the houses must be inspected, every 20th house would be inspected. This is a practical option for rapid assessment of vector population levels, especially in areas where there is no house numbering system.

Simple Random Sampling

The houses to be examined are obtained from a table of random numbers (obtained from statistical textbooks or from a calculator or computer-generated list). This is a more laborious process, as detailed house maps or lists of street addresses are a prerequisite for identifying the selected houses.

Stratified Random Sampling

This approach minimizes the problem of under- and over-representation by subdividing the localities into sectors or "strata". Strata are usually based on identified risk factors, such as areas without piped water supply, areas not served by sanitation services, and densely-populated areas. A simple random sample is taken from each stratum, with the number of houses inspected being in proportion to the number of houses in that sector.

Cluster Sampling

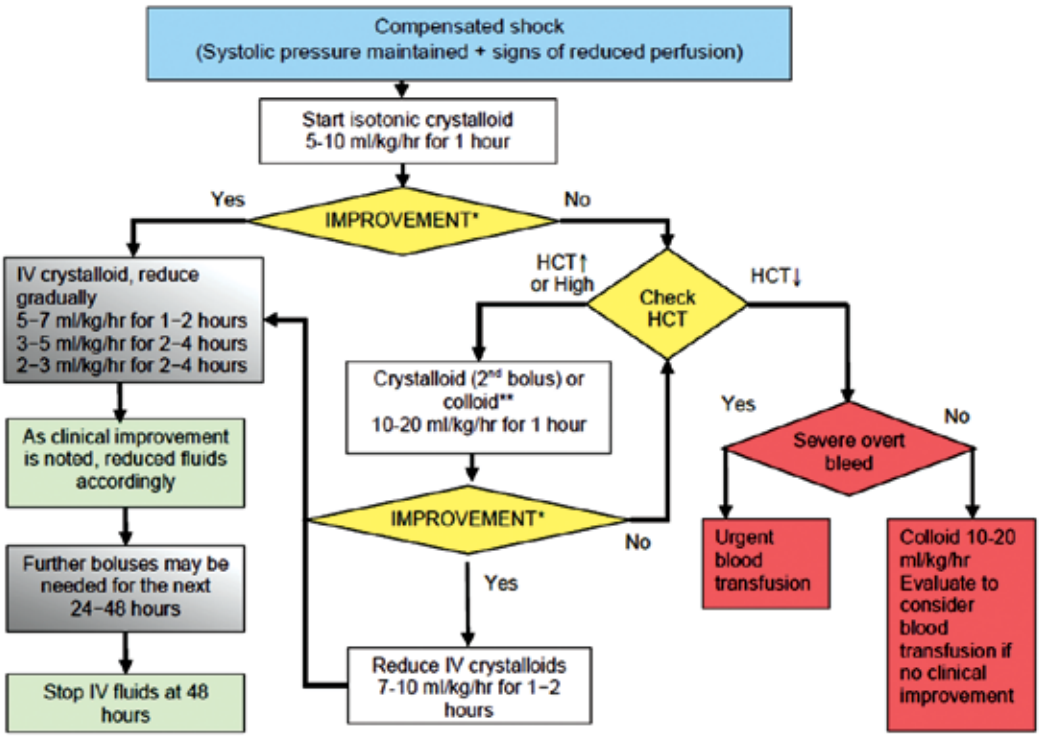
This method can be conducted in large cities or geographical areas where it may be difficult or impossible to use random or systematic sampling because of limitations of time, money and personnel, or because of other logistical constraints. In these circumstances, the sample may be selected in two stages in order to minimize the resources needed for the survey. The first stage is obtained by simple or stratified random sampling of population groups or clusters (e.g. city blocks, villages, or administrative districts). Having identified these clusters, simple or stratified random sampling procedures are again applied to identify the specific houses within each cluster for inclusion in the survey.

Annexes

Annexe 1

Algorithm for fluid management of compensated shock in adults

TABLE 27: Algorithm for fluid management of compensated shock in adults

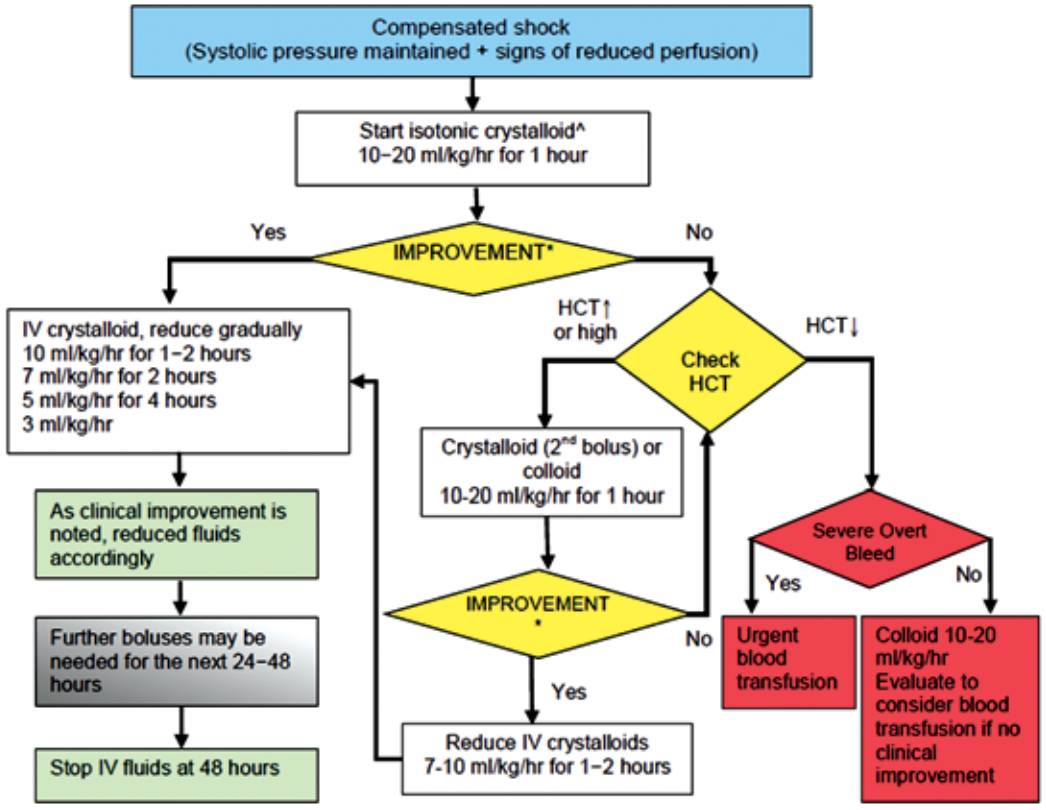


*Reassess the patient's clinical condition, vital signs, pulse volume, capillary refill time and temperature of extremities.
**Colloid is preferable if the patient has already received previous boluses of crystalloid
-IV: intravenous, HCT: haematocrit, ↑: increased, ↓: decreased.

Annexe 2

Algorithm for fluid management of compensated shock in infants and children

TABLE 28: Algorithm for fluid management of compensated shock in infants and children

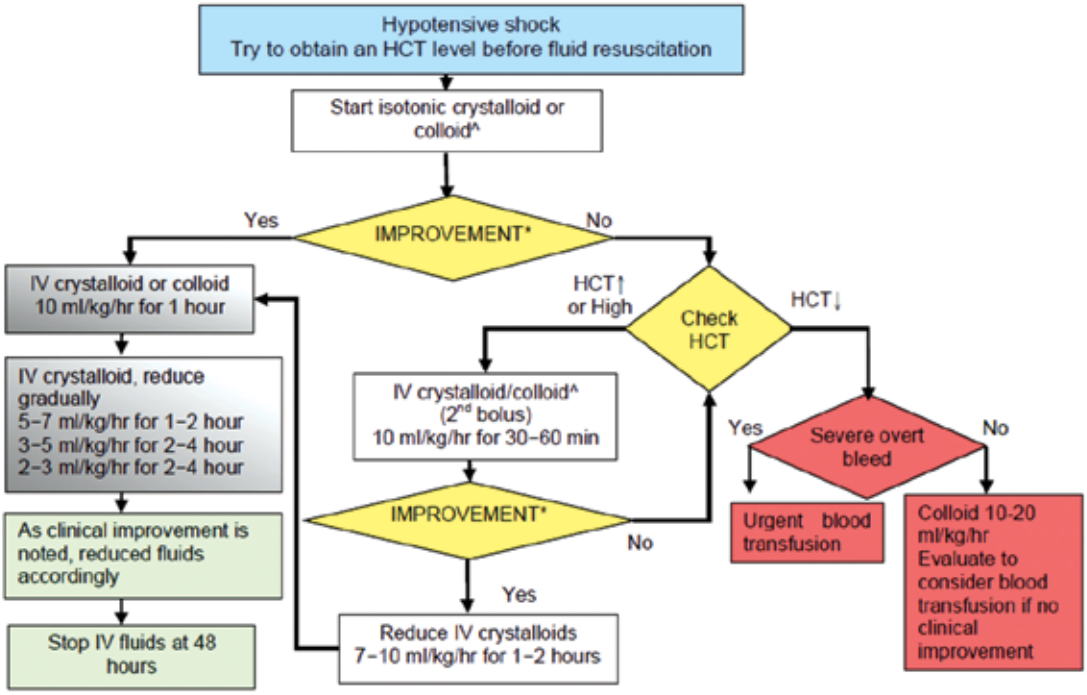


^Colloid is preferable if the patient has already received previous boluses of crystalloid
*Reassess the patient's clinical condition, vital signs, pulse volume, capillary refill time and temperature of extremities.IV = intravenous; HCT = haematocrit; ↑ = increased; ↓ = decreased

Annexe 3

Algorithm for fluid management of hypotensive shock in infants, children and adults

TABLE 29: Algorithm for fluid management in hypotensive shock in infants, children and adults



^Colloid is preferable if the patient has already received previous boluses of crystalloid
*Reassess the patient's clinical condition, vital signs, pulse volume, capillary refill time and temperature of extremities.
IV = intravenous; HCT = haematocrit; ↑ = increased; ↓ = decreased

Annexe 4

Good and bad clinical practices

Good practices (recommended)	Bad practices (not recommended)
Assessment and follow-up of patients with dengue and instructions to carefully monitor warning signs and how to identify them.	Discharging patients with dengue with no follow-up or inadequate instructions.
Administration of paracetamol to the patient with fever and pain.	Administration of aspirin or NSAIDs.
Obtaining a hematocrit level before and after each fluid bolus.	Ignoring the relationship between hematocrit levels and fluid therapy.
Clinical assessment of the patient's hemodynamic status before and after each fluid bolus.	Not monitoring patient response to fluid therapy.
Interpretation of hematocrit levels in the context of fluid administration hemodynamic monitoring.	Interpretation of hematocrit levels independent of patient's clinical status.
Administration of intravenous fluids for persistent vomiting or a rapid elevation of hematocrit.	Administration of intravenous fluids to any patient with dengue.
Use of isotonic solutions in cases with severe dengue or dengue with warning signs.	Use of hypotonic solutions in cases with severe dengue or dengue with warning signs.
Administration of sufficient intravenous fluid volume in order to maintain effective circulation during the period of plasma leakage in cases with severe dengue.	Excessive or prolonged intravenous fluid administration in cases with severe dengue or dengue with warning signs.
Avoiding intramuscular injections to patients.	Administration of intramuscular injections to patients.
Adjusting intravenous fluid therapy according to monitoring of vital signs, patient's hemodynamic condition, and hematocrit measurement.	Maintaining a fixed rate of intravenous fluid infusions in patients with severe dengue without changing its frequency according to patient monitoring and hematocrit measurements during hospitalization.
Discontinuation or reduction of intravenous fluid therapy once hemodynamic condition stabilizes.	Not modifying intravenous fluid therapy once hemodynamic condition stabilizes or at the end of the critical phase.

Annexe 5

DO's and DONT's for dengue patients

- If you or your family member is suffering from suspected dengue, it is very important to carefully watch yourself or your relative for the next few days. The disease can sometimes rapidly become very serious and lead to a medical emergency.
- The complications associated with dengue usually appear between 3rd and 5th day of the illness. It is important to watch yourself or your relative for two days even after the fever has disappeared.

WHAT TO DO

- Keep body temperature below 390C. Give paracetamol but not more than four times in 24 hours.
- Give large amount of fluids like water, soup, milk, juice along with the patient's normal diet.
- Take complete rest.
- Immediately consult a doctor if any of the following manifestations appear
  - Red spots on the skin
  - Bleeding from the nose or gums
  - Frequent vomiting
  - Vomiting with blood
  - Black stools
  - Sleepiness
  - Constant crying (child)
  - Abdominal pain
  - Excessive thirst (dry mouth)
  - Pale, cold or clammy skin
  - Difficulty in breathing

WHAT NOT TO DO

- Do not wait and immediately consult a doctor in case the above symptoms appear. It is very important to quickly get treatment in case of these complications.
- Do not take Aspirin or Ibuprofen

Annexe 6

Choice of intravenous fluids for resuscitation

There is no clear advantage to the use of colloids over crystalloids in terms of the overall outcome. Crystalloid solutions are the choice for resuscitation of a dengue patient. However, colloids may be the preferred choice if blood pressure has to be restored urgently, i.e. in those with pulse pressure less than 10 mm Hg. Colloids have been shown to restore the cardiac index and reduce the level of hematocrit faster than crystalloids in patients with intractable shock.

Crystalloid solution

0.9% saline solution: 0.9% saline solution (normal saline) has an osmolarity of 308 mOsmol/L and contains a high sodium and chlorine level (154 mmol/L, each). Normal plasma chloride ranges from 95–105 mmol/L. 0.9% saline is a suitable option for initial fluid resuscitation; however, administration of large volumes of 0.9% saline may lead to hyperchloremic acidosis, which may aggravate or be confused with lactic acidosis from prolonged shock. Monitoring the chloride and lactate levels should be done. When the patient's serum chloride level exceeds the normal range, it is advisable to change to other alternatives such as Ringer's lactate.

Ringer's lactate/acetate: This has lower sodium (131 mmol/L) and chloride (115 mmol/L) contents and an osmolarity of 273 mOsm/L. It may not be suitable for resuscitation of patients with severe hyponatremia. However, it is a suitable option to complete the treatment after 0.9% saline has been administered and the patient's serum chloride level has exceeded the normal range.

Colloid solution

Colloids are gelatin-, dextran-, or starch-based solutions. The reason not to administer colloids to dengue patients or to do so only exceptionally is that whichever colloid solution is used, it will filter into the extravascular space and increase the oncotic pressure in that space. This can perpetuate shock and make it irreversible. Another major concern regarding their use is their impact on coagulation. Dextrans have an antithrombotic activity when acting on primary hemostasis (decrease platelet aggregation) and coagulation factors (facilitate lysis of the thrombus). These effects appear four to six hours following their administration and last about 24 hours. Of all the colloids, gelatin has the least effect on coagulation, but the highest risk of allergic reactions. Allergic reactions such as fever and chills have also been observed with Dextran 70. Dextran 40 can potentially cause an osmotic renal injury in hypovolemic patients.

Monitoring chart for Dengue

Name:
Date of onset of fever:
Weight:
Date and approx. time of onset of warning signs:

Date									
Time									
Vitals									
Tempº C									
BP mm Hg									
PR / min									
RR /min									
Lab investigations									
HCT									
Platelet									
WBC									
Intake									
Crystalloids ml/kg/hr.:									
Cumulative volume:									
Colloids ml/kg/hr.:									
Cumulative volume									
Blood products ml/kg/hr.:									
Cumulative volume									
Oral intake									
Cumulative volume									
TOTAL									
Output									
Urine hourly									
Vomit/Bleed									
TOTAL									

Annexe 8

Application procedure-space spraying (fogging) during emergency

- Space sprays can be applied as thermal fogs at 10-50 l/ha or as ultra-low volume applications of undiluted or slightly diluted technical-grade insecticide in the form of a cold aerosol of droplets of controlled size (15–25 µm) at a rate of 0.5–2.0 l/ha.
- Portable or vehicle-mounted thermal or cold-fog generators can be used for ground application.
- Areas to be sprayed should be planned and the local population should be prior informed, encouraging them to open their doors /windows in order to improve the effectiveness of the spraying programme.
- Application rates vary with the susceptibility of the target species and environmental considerations. Wind speed has a strong effect on droplet distribution and contact with insects. In most situations, a wind speed of 1–4 meters per second (approximately 3.6–15 km/h) is needed to drift droplets downwind from the line of travel.
- Furthermore, space sprays should be applied when there are temperature inversions – i.e. colder air closer to the ground – which occur early in the morning or in the evening when the ground temperature begins to fall.
- Space spray applications should correspond to the activity of the target species. *Ae. aegypti* and *Ae. albopictus* are active during the day, with peak flight activity in the morning and afternoon. For these species, spraying outdoors is therefore usually carried out in the early morning or late afternoon. Indoor treatments are particularly effective against Ae. aegypti because its resting behavior is mainly indoors. Indoor treatments are the only choice where there is no access for vehicles.

Precautions to be taken when applying space sprays

- Operators conducting house-to-house space spraying using portable equipment should wear face masks in addition to normal protective clothing and should operate the equipment for short periods only.

Annexe 9

New Innovative Vector Control Tools

New innovative vector control tools	
Several promising new vector tools have been reviewed in the context to response to Dengue	
Wolbachia Biocontrol	■ Natural bacterium present in different species of insects around us, including some mosquitoes. ■ When introduced into *Ae. aegypti* populations, it reduces mosquitoes' ability to transmit dengue virus to humans by reducing viral replication within mosquitoes and also delays appearance of virus in mosquito saliva.
Genetically Modified Mosquitoes	■ New strategy to control mosquito borne diseases ■ Mosquitoes are bred to express certain traits ■ These bred mosquitoes are released into the wild ■ The released mosquitoes mate with wild mosquitoes ■ The next generation of wild mosquitoes is altered, their offspring inherit the self-limiting trait. ■ The resulting offspring will die before reaching adulthood, and the local mosquito population will decline.
Sterile Insect	■ Involves the mass production, sex-separation and sterilization of male mosquitoes. ■ Sterile males released into the wild mate with wild female mosquitoes of the same species, resulting in production of unviable eggs leading to a decline in wild mosquito populations.
Attract and kill baits/ Attractive Toxic Sugar Bait (ASTB)	■ Novel application method involving use of insecticide classes that act as stomach poisons for mosquitoes. ■ This technology is based on an "attract and kill" principle, where mosquito attractants are combined with oral toxins that kill the target insects.

Annexe 10

Safe use of insecticides

All pesticides are toxic to some degree and safety precautions should be taken as follows:	
■ Instructions on pesticide labels should be followed carefully	■ Spray operators should be provided with at least two uniforms to allow for frequent changes
■ Safety gloves, goggles and masks should be used for high-exposure activities such as machine calibration	■ Changing and washing facilities should be available
■ All work clothes should be removed at the end of each day's operations and a shower or bath taken	■ Work clothes should be washed regularly, preferably daily
■ During and immediately after indoor space spray operations, householders and pets must remain outside the dwelling	■ Spray operators should wash their hands and face before eating and should not smoke during work hours.
■ Spray operators should not be exposed to toxic material for periods that are longer than recommended	■ Care must be taken in disposing of used insecticide containers

Dengue reporting form

			No. of supected dengue cases*	No. of probable/highly suggestive dengue cases**	No. of confirmed dengue cases***	No. of deaths due to dengue
Age	≤14 years	M				
		F				
	≥ 15 years	M				
		F				
Total						

* A person who lived or travelled in an area of dengue transmission in last 14 days and has a sudden onset of high fever typically of 2-7 days duration and presents with two or more of the following manifestations: nausea, vomiting, exanthema/rash, myalgia/arthralgia ,headache, retro-orbital pain, petechiae or positive tourniquet test, leukopenia, any warning signs or any criterion of severe dengue, but laboratory tests (NS1 Antigen, IgM anti-DENV and molecular testing) after the onset of illness not performed, awaited or negative.

** Any suspected dengue case with laboratory results indicative of highly suggestive such as IgM+ in a single serum sample OR IgG+ in a single serum sample with a HIA titer of 1280 or greater or NS1 antigen +

***Any suspected dengue case with one of the confirmatory laboratory results positive: PCR+ OR Viral Culture+, OR IgM seroconversion in paired sera OR IgG seroconversion in apaired sera or four fold IgG titer increase in paired sera.


HOME CARE FOR DENGUE
HOW TO CARE FOR A LOVED ONE WITH DENGUE
GIVE THEM PLENTY TO DRINK
PARACETAMOL CAN HELP WITH FEVER, HEADACHES, ACHES AND PAINS
ENSURE THEY GET A LOT OF REST
HAVE THEM REST OR SLEEP UNDER A NET AND WEAR REPELLENT
LEARN THE WARNING SIGNS OF SEVERE DENGUE- IF THE SIGNS ARE PRESENT, TAKE THEM TO THE HOSPITAL IMMEDIATELY!
WHILE TAKING CARE OF OTHERS, TAKE CARE OF YOURSELF: USE REPELLENT AND WEAR LIGHT CLOTHES THAT COVER MOST OF YOUR BODY


No mosquitoes = no dengue
So do your part by cleaning up mosquito breeding sites!
Empty water storage containers, scrub the insides and reseal carefully after refilling
Clean the insides of flower vases, plant pots or pet bowls and change the water
Clean drains and gutters
Dispose of any unused containers and objects that can accumulate water
Turn over any containers that cannot be thrown away and protect them from rain
once a week
Even a bottle cap can contain enough water for a mosquito to breed!

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TECHNICAL SUPPORT BY: