



A Review of Dengue Fever with Special Reference to Malaysia

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Authors' contributions

This work was carried out in collaboration between all authors. Author MAAM is the lead author and correspondence author. He is also the initiator of this Review Article and addressed much of the aspects of epidemiology including Control and Prevention and aspects of Laboratory Diagnosis. Author VK had written the preceding Review to this Article in 2006 in the Malaysian Medical Journal to which this Article is a sequel. He has also contributed to aspects of Epidemiology including Control and Prevention in this Article. Authors YYN and CLL are Internal Medicine Consultants who contributed to the Clinical Management aspects of this Article. Author CAK addressed the Entomological aspects of this Article, and addressed the part on Newer Insecticides and Innovative Methods. All authors read and approved the final manuscript.

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ABSTRACT

Introduction: Dengue is the most prevalent viral mosquito-borne disease, with over 2.5 billion humans at risk given its endemicity in more than 100 countries. Globally, 50-100 million cases of dengue occur annually, with approximately 0.7% resulting in dengue haemorrhagic fever (DHF), and 22,000 deaths. In 2017, there were 83,849 reported cases of dengue fever in endemic under-reported Malaysia, with 177 deaths.

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One of our authors (Verasingam K 2006) here, earlier published an article in the Med J Malaysia titled "Dengue Fever in Malaysia: Time for Review?" This Article is meant as a sequel.

Method: The Authors here narrate from their own personal-experiences, as well as from reviewing existing-literature.

Results and Conclusion: Clinical Management has brought about vast improvements in mortality and morbidity. Similarly, great advancements in Laboratory Diagnostics. Prevention and Control methods have been desiring of greater achievements, but also show greater promise with Newer Insecticides, Innovative Methods and Vaccines. Dengue Fever would very likely become near-eradicated just like all other vaccine-preventable diseases, once comprehensive mass-vaccination programmes are available globally, using safe and very-effective tetravalent-vaccines soon to be available.

Keywords: Dengue fever; Severe dengue; epidemiology; clinical management; laboratory diagnosis; control and prevention; dengue vaccine.

1. EPIDEMIOLOGY

Dengue is considered the most important mosquito-transmitted viral disease in terms of morbidity and mortality. It is the most prevalent viral mosquito-borne disease, with over 2.5 billion humans at risk of exposure given its endemicity in more than 100 countries, compared to nine countries in 1970 [1–11].

Dengue fever is a benign, acute febrile syndrome occurring mainly in tropical regions. In a small proportion of cases, the virus causes increased vascular permeability that leads to a bleeding diathesis or disseminated intravascular coagulation (DIVC) known as dengue haemorrhagic fever (DHF) [3].

The vectors are *Aedes aegypti*, which breeds in and around houses and buildings, and the smaller *Aedes albopictus* which breeds outdoors. They are day-biting mosquitoes, whose peak biting-hours are dawn, early morning and dusk [1–11]. Besides other factors, the bite of the *A. aegypti* is more likely to cause severe dengue (DHF and dengue shock syndrome, DSS) [12–14]. Major sources of *Aedes*-breeding are at construction sites, solid-waste dumps, open-spaces and in factories [1–11].

The WHO estimates that 50-100 million cases of dengue occur annually, with approximately 500,000 of those cases (0.7%) resulting in dengue haemorrhagic-fever (DHF), with an estimated 22,000 deaths per year, mostly in children. In 20-30% of DHF cases, the patient develops shock, known as the dengue shock syndrome (DSS). 1, 4, 5 – 8 Studies in the Philippines and Indonesia reveal that 70 – 80% of dengue infections are asymptomatic [15–16].

The term severe dengue is used classically to describe DHF and DSS, but some authors include Dengue With Complications (DWC) as severe dengue. Such complications, outside of DHF and DSS, include mostly neurological complications (which are commoner in children) and liver involvement.

There is no specific treatment for dengue/ severe dengue, although there is the promise of effective anti-viral drugs at least to prevent mild dengue converting to severe dengue. 7 – 8 Early-detection and access to proper medical care, however, lower fatality rates below 1% [1].

There are 4 distinct, but closely related, serotypes of the virus that cause dengue (DEN-1, DEN-2, DEN-3 and DEN-4). Recovery from infection by one provides lifelong immunity against that specific serotype. However, cross-immunity to the other serotypes after recovery is only partial and temporary. Subsequent infections by other serotypes increase the risk of developing severe dengue [1–11]. In Malaysia, various serotypes steadily begin to predominate in the various years – the present predominant strain being DENV3 replacing DENV1 and DENV2 [17]. The prevalence of individual serotypes varies across different geographies, countries, regions, seasons and over time [1–11].

In Malaysia, there is a male-preponderance at 57%. The number of cases steadily increases from a moderate among toddlers to a peak in the early twenties, before steadily falling to a moderate again in the late 40s, and before tapering down to a low in the elderly - although the highest incidence is among the working and school-going age groups [17,9–10].

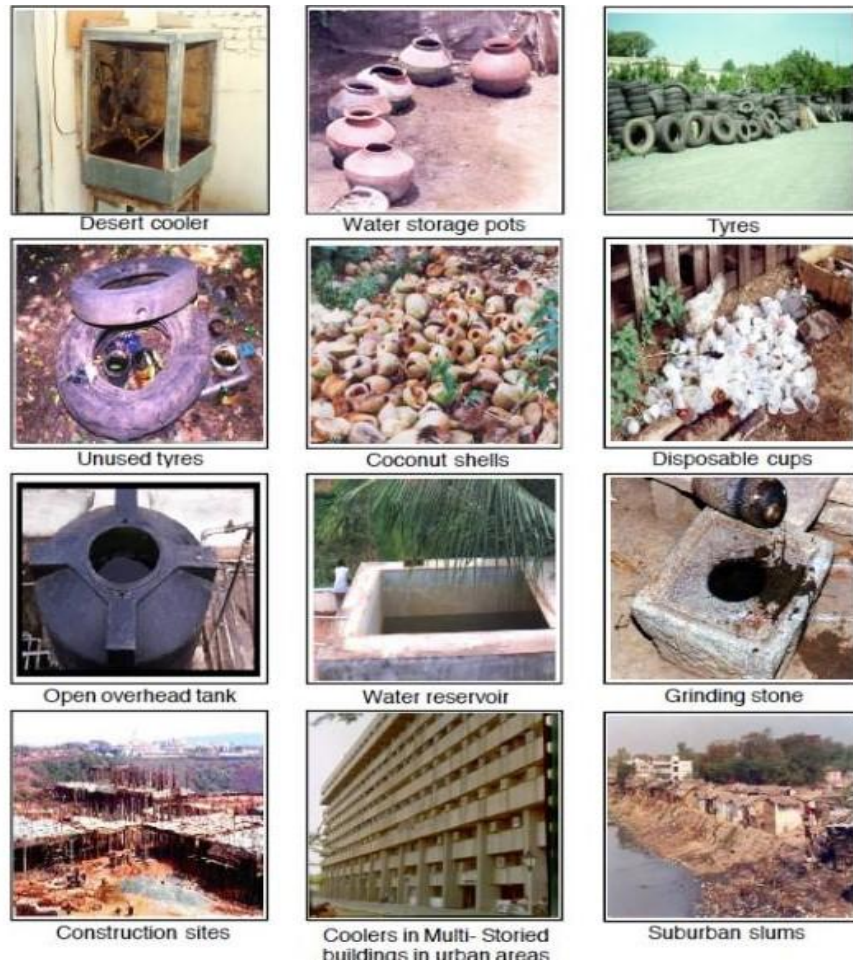


Fig .1. Common *Aedes aegypti* breeding-sites, including in Malaysia

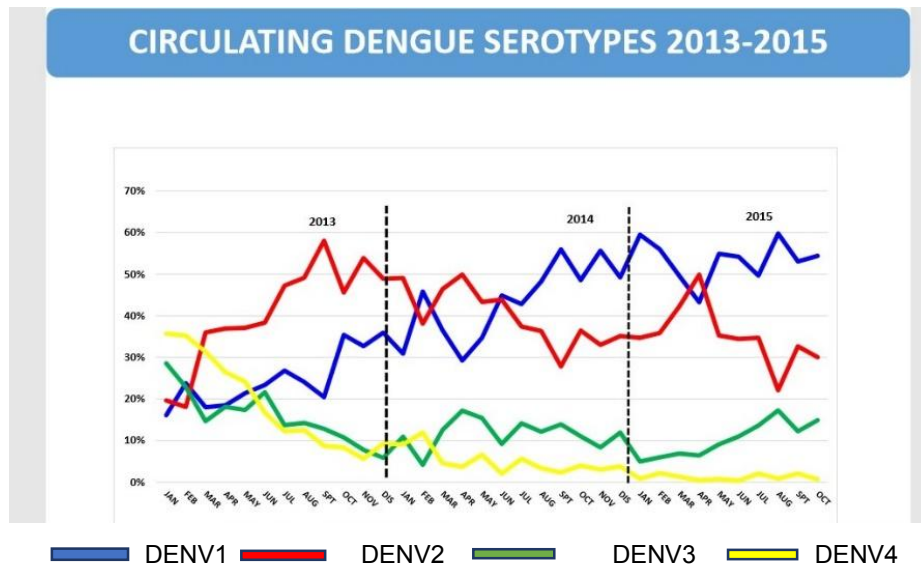


Fig. 2. Circulating dengue-serotypes in Malaysia 2013 – 2015. [17]

Severe dengue (DHF and DSS) may be commoner in females and those with co-morbidities such as diabetes-mellitus and obesity. The case-fatality rate in severe dengue appears much higher in females [18–19].

The disease is endemic in Malaysia since the 1980s [3,9–10,20–21]. Shepard DS et al. [20] say that because Malaysia has a passive-surveillance system, the number of dengue cases is under-reported [20].

In Malaysia, a “dengue outbreak” is defined as two cases occurring in an area over 14 days, while a “dengue hotspot” is when the outbreak is sustained more than 30 days [22].

Nur Azila MA et al. in studying 1000 subjects aged 35-74 years old, found 91.6% to be dengue seropositive. The sero-prevalence increased with every 10-year increase in age. Gender and ethnicity were not factors. There was no difference between urban and rural areas [23].

In 2017, there were 83,849 reported cases of dengue fever nationwide with 177 deaths, which is a conspicuous reduction from the immediate previous years [24–25].

The Health Ministry attributes its recent achievements to the integrated efforts of various ministries, agencies, society and individuals, although this reduction may be a part of the six-year pattern in the country discussed below [21,23–25].

The National Dengue Task Force (NDFTF), which comprises seven ministries and various agencies, was set up since July 2014 to mobilise agencies and members of the public in dengue prevention and control activities [24 – 25]. Besides the NDFTF, there is the National Dengue Committee [17].

It was after 2013 that a sharp increase in the incidence was noted in Malaysia, which has remained sustained [17]. The contributing factors for this sharp increase are thought to be serotype-shift, the mobility of the population, climate change, human behaviour, poor environmental sanitation and ineffectiveness of vector-control activities [3,17].

In the Malaysian context, health reforms in the late nineties that integrated the vertical organizational structure of the Vector Borne Disease Control Programme with the general health services resulted in loss of technical expertise as well as constraints in funding, as

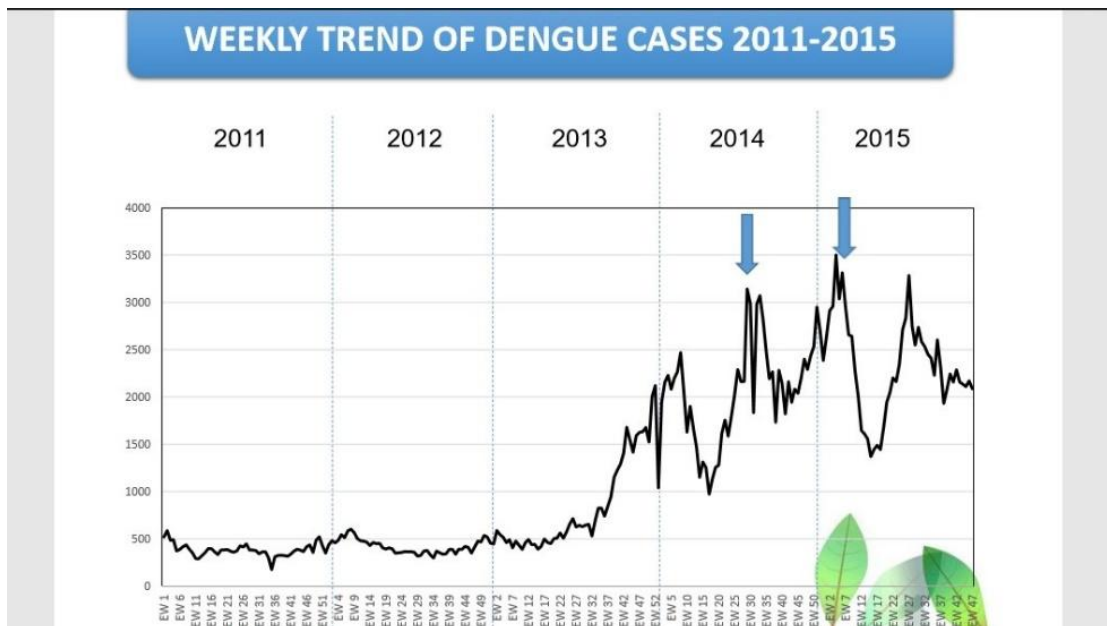


Fig. 3. Weekly-trend of Dengue-cases in Malaysia, 2011 – 2015. [17]

limited health resources were moved to other competing programmes under the Ministry of Health which is thought to be the cause of the sharp increase, coupled with local-governments being made responsible in some instances. After years of neglect, cities like Greater Kuala Lumpur, Penang, Johore Bahru, Seremban and Melaka have become hyper-endemic for dengue transmission, where more than one virus serotype are circulating [11].

While Wiwanitkit V [26] says that the application of vector-control methods is labour-intensive, requires discipline and diligence, and hard to sustain.

In Malaysia, outbreaks of dengue tend to recur in six-year cycles, consisting of four years with high numbers of cases followed by two years with relatively low numbers. However, the annual average incidence of reported dengue cases in successive six-year cycles has been increasing [21].

Shepard et al. [20] estimated an economic burden of dengue illness in Malaysia at US\$56 million per year, which is approximately US\$2.03 per capita. They say that the overall economic burden of dengue would be even higher if they had included costs associated with dengue prevention and control, dengue surveillance, and long-term sequelae of dengue.

Packierisamy PR et al. [21] estimated the costs of dengue prevention. In 2010, Malaysia spent US\$73.5 million, or 0.03% of the country's GDP, on its National Dengue Vector Control Program. If innovative technologies for dengue vector control prove efficacious, and a dengue vaccine was introduced, they say substantial existing spending could be rechanneled to fund them.

2. CLINICAL MANAGEMENT OF DENGUE

The management of dengue fever is mainly supportive, with adequate fluid replacement and antipyretics. So far there is no licensed therapeutic-drug available for the treatment of dengue, although active-research is ongoing [27–28]. Fever should be treated with paracetamol. Non-steroidal anti-inflammatory drugs (NSAIDs) should not be used as they are associated with bleeding risks and Reye's syndrome. Most patients can be managed as outpatients, with regular monitoring. It is recommended that patients be provided with a monitoring-chart [29].

The patient's hemodynamic status (blood pressure, pulse rate and volume) and full blood count (haemoglobin, haematocrit, white blood cell count, platelets count) require monitoring on a daily basis. Patients require education about warning signs and need to be advised to seek urgent medical-attention in case of warning signs. Severe abdominal-pain, recurrent vomiting and/or diarrhoea, inability to tolerate orally, lethargy, irritability and altered consciousness, cold peripheries and shortness of breath are warning signs associated with severe dengue outcome [30,33,34].

Dengue fever without warning sign typically has 2 phases, ie febrile and convalescent phase. Dengue fever with warning sign has three phases: febrile, critical (plasma leakage) and convalescent (re-absorptive) phases [8].

Leptospirosis, typhus, malaria, typhoid and other viral exanthemas (especially measles) need to be excluded as a cause of the fever. Chikungunya virus causes similar symptoms and signs and is transmitted by the same mosquito vector, *Aedes aegypti*. In studies comparing these two diseases, joint-pain was reported somewhat more often in chikungunya, whereas abdominal pain and leukopenia were more common in dengue [35–37]. The presence of typical skin rash, 'isles of white in a sea of red', thrombocytopenia, and leucopaenia supports a diagnosis of dengue.

Febrile phase: The febrile-phase occurs 4-7 days after being bitten by an infected-mosquito and it lasts between 2 and 7 days. In this phase, there is high-fever (described as saddle-back fever), headache, retro-orbital pain, myalgia, typical macular-rash and facial-flushing [38 – 39]. There may be petechiae and minor gum bleeding, leucopaenia and thrombocytopenia. After about 3 to 5 days of fever, the patient enters into the critical-phase.

Critical phase: Critical-phase occurs when the temperature settles (defer-vescence) typically during day 3 to 7 of dengue [30,38–40]. Plasma leakage may occur during this period. In a patient who is not improving clinically despite the defer-vescence, besides a rising haematocrit and the presence of pleural effusion and ascites, it suggests plasma-leakage. Plasma-leakage must be detected early and treated to prevent it from progressing to severe decompensated and intractable shock - ultimately leading to multi-organ failure and death. Patients with coexisting

conditions such as diabetes mellitus, pregnancy, obesity, renal-failure, advanced age and chronic haemolytic-anaemia have a higher risk of dengue complications. These group of patients may need hospital admission for close-observation.

Intravenous 0.9% saline (normal saline) has been widely used as fluid-replacement. Isotonic-solutions such as 0.9% saline, Ringer's lactate or Hartman's solution is preferable for fluid-replacement. Intravenous fluid-replacement should not be for more than 24-48 hours, as the immunological-process causing plasma-leakage usually settles within that time-frame. Judicious fluid-administration must be practised to maintain good perfusion and normal vital signs, besides a minimum urine output of at least 0.5 ml/kg/hr. Haematocrit must be particularly monitored. In the absence of a baseline haematocrit (hct), the median values of a normal haematocrit among Malaysian population is used i.e. for males 60 years and below - hct 46%, males above 60 years - hct 42%, while for all females - hct 40% [41]. Additional laboratory investigations, including arterial/venous blood gas, serum lactate and bicarbonate improves the accuracy of fluid-replacement.

Studies have shown that there is no difference in overall-outcome and mortality between the use of crystalloids versus colloids [42-44]. Colloids appear to be more useful as initial-resuscitation in patients with intractable-shock as it restores cardiac-index and haematocrit faster than crystalloids. Fluid-infusions must be closely monitored and adjusted regularly. Fluids are given in excess of that required, or fluid-transfusions extending into the re-absorptive phase may cause fluid overload. There is insufficient evidence to justify the use of corticosteroids in managing dengue shock-syndrome [45].

Thrombocytopenia, endothelial-activation, liver-dysfunction and disseminated intravascular coagulation (DIVC) associated with severe dengue, all contribute to bleeding in dengue. Minor bleeding like gum-bleeding and skin-petechiae are relatively common in dengue fever. These are usually self-limiting and insignificant. Gastrointestinal (GI) bleeding, menorrhagia, epistaxis and haemoptysis may be severe and require blood-transfusion. Often, the bleeding may be occult. Significant occult-bleeding should be suspected if there are signs of intravascular hypovolemia without elevation of haematocrit. Cool peripheries, prolonged capillary refill-time

(normal less than 2 seconds), tachycardia and reduced pulse-volume, besides confusional-state are all suggestive of poor circulatory-volume and bleeding.

Prolonged-shock and metabolic-acidosis lead to severe bleeding and DIVC. In such cases, packed blood-cells, blood-component or fresh whole-blood transfusion may be required. Prophylactic platelet or freshly frozen plasma-transfusion have not been shown to produce a sustainable rise in platelet-count nor improvement in coagulation profile [46-52]. There is also an increased potential-risk of allo-immunization and transfusion-reaction.

Other than plasma-leakage and bleeding, dengue virus also has pathogenic-effects on the liver, heart and central nervous-system. Elevations of liver-enzymes are usually mild and are common in dengue [53]. Aspartate aminotransferases (AST) is usually more severely elevated compared to alanine aminotransferases (ALT). The relatively frequent isolation of dengue virus from liver-tissues of fatal-cases of dengue-hepatitis suggests that liver-injury is directly mediated by dengue virus infection of hepatocytes and Kupffer-cells.

Haemophagocytic lymphohistiocytosis (HLH) is rare but is a potentially fatal medical-condition that can occur after a patient has had severe dengue-infection. Haemophagocytic lymphohistiocytosis is characterized by hyper-inflammation, uncontrolled-proliferation of activated-lymphocytes, prolonged fever, pancytopenia, jaundice and hepato-splenomegaly. However, dengue associated HLH may be under-recognized due to overlapping signs and symptoms of HLH and dengue (e.g., fever, hepato-splenomegaly and pancytopenia). Identification of dengue-patients with, or at risk of developing, HLH is by detection of markedly-high serum-ferritin levels (≥ 500 mg/l) or serum IL2-receptor (≥ 2400 units/L). Signs and symptoms associated with HLH include hepatomegaly, splenomegaly and lymphadenopathy. Dengue with HLH usually has more prolonged fever and hospitalisation and is associated with warning-signs. Laboratory-findings include anaemia, besides raised aspartate transaminase and alanine transaminase. Treatment includes high-dose corticosteroids and IVIG with or without etoposide [54].

Neurological-complications in dengue range between 0.5% and 5.4%, and present in a wide-spectrum of clinical-conditions [55–57]. Most commonly it presents as encephalopathy and encephalitis. Other reported manifestations include meningo-encephalitis, intracranial-bleed, transverse-myelitis and Guillain-Barre Syndrome.

Convalescent (reabsorptive) phase: This phase typically occurs 24 to 48 hours after the critical phase. During this phase the patient's symptoms improve, appetite returns and hemodynamic parameters stabilise. Reabsorption of extravasated fluids occurs, and there is diuresis. Hematocrit decreases and returns to normal. It is important to recognise this phase as a continuation of fluids during this phase may lead to fluid overload and pulmonary oedema.

Despite being a leading cause of illness and mortality in the tropics and subtropics, there are no therapeutics currently available. There is an urgent need to develop an effective antiviral [58]. Newer therapeutic-approaches include direct viral-inhibitors and modifiers of virus-host interactions [59–60]. Direct-acting agents include small-molecule inhibitors of essential viral-enzymes (NS2B-3 protease, NS3 helicase, NS5 methyl-transferase, the NS5 polymerase) or small-molecule and antibody-inhibitors of viral entry/fusion.

Randomised-trials using chloroquine, lovastatin, balapiravir (a polymerase inhibitor), and celgosivir (an alpha-glucosidase inhibitor) among adults with dengue have not shown a significant benefit on viraemia, NS1 antigenaemia, or fever [61–63].

Severe dengue is a potentially fatal form of dengue virus infection. The pathogenesis of DHF/ DSS are not clearly understood. One hypothesis concerning virus-virulence and the immune-enhancement hypothesis has been debated. Although dengue disease-severity has been associated with evidence of genetic-differences in dengue-strains, virus-virulence has been difficult to measure because of the lack of in-vivo and in-vitro models of the disease [64].

Patients with DHF/DSS are characterised by several manifestations, including severe thrombocytopenia, vascular leakage, and hepatomegaly. In addition to the effect of virus load and virus variation, abnormal immune responses of the host after Dengue-virus

infection may also account for the progression to DHF/DSS. Viral-autoimmunity is also involved in the pathogenesis of numerous viral infections, such as human immunodeficiency virus, human hepatitis C virus, human cytomegalovirus, herpes simplex virus and Epstein- Barr virus. Antibodies directed against DV non-structural protein 1 (NS1) shows cross-reactivity with human-platelets and endothelial-cells, which lead to platelet and endothelial-cell damage and inflammatory-activation. The hypothesis is that anti-DV NS1 is involved in the pathogenesis of DHF/DSS [65]

There is also evidence that the presence of certain serotypes, including primary-infection with DENV-3 in the SEA region and secondary-infection with DENV-2, DENV-3, and DENV-4 also in the SEA region, besides DENV-2 and DENV-3 from non-SEA regions, increased the risk of severe dengue [66].

3. LABORATORY DIAGNOSIS

Dengue can be diagnosed clinically. However, laboratory tests are required to confirm the diagnosis. Definitive-diagnosis is important for epidemiological-surveillance and monitoring purposes. Development of assays are ongoing and newer assays using more advanced technologies have been developed, though not fully validated [67].

Multiple sequential infections occur in dengue endemic areas. Besides, primary and secondary infection-status further cause difficulty in laboratory-diagnosis [68].

Improved disease-management requires an effective diagnostic-assay that can be used with confidence - especially in the acute early-stage and for detecting signs of severity [69].

The ideal dengue diagnostic-test would be one that is simple, rapid, and affordable having high sensitivity and specificity - which is able to differentiate between primary and secondary infections and be able to serotype the virus. The time-frame for laboratory-diagnosis is from the onset to ten days post-disease (remembering that about 2% do not seroconvert) – but, most often clinical-management needs to commence before confirmatory laboratory-diagnosis [70].

Diagnostic-tools currently are mainly serological-based, nucleic acid-based or antigen-detection [71].

The best diagnostic is the isolation of the virus or detection by direct immunofluorescence (IF), or genome-amplification via PCR [72], or detection of viral-antigens like NS1 using either ELISAs or rapid lateral-flow tests [73-74].

Very often antibodies are sought for out of convenience, but these are useful diagnostics only when results are obtained using paired samples. Currently, virus-isolation, PCR and Direct IF are done only in reference- and research-laboratories [70].

The NS1-test is more user-friendly. Apart from ELISAs, rapid-flow tests have been developed and validated [75–76].

These are useful in the first five days of symptoms when viraemia still exists. Serology is also useful in demonstrating sero-conversion from negative to positive IgM-antibody, or a four-fold increase in IgG antibody-titres in paired serum-specimens. Patients who are IgM-positive and are PCR-negative are usually classified as probable recent dengue-infection, since IgM-antibodies to dengue remain elevated for 90 days after the illness, and could have been from an infection that occurred between two and three months ago [70].

In addition, it is important to note that cross-reactivity with other flavi-viruses, including West Nile virus (WNV), St. Louis encephalitis virus (SLE), Japanese encephalitis virus (JEV), Zika virus and yellow fever virus (YFV), do occur.

However, these infections are very rare in Malaysia. Yet, a look into the patient's Recent Travel History would be helpful. A paired-sample, testing for all of the flavi-viruses, best provides a diagnosis as to which flavi-virus it is, especially in those who present late after onset of illness (> 5 days), when virus and viral antigens become undetectable [69,70].

Immune responses to dengue

Dengue virus induces the production of all classes of antibodies, primarily targeting the virus envelope-proteins. The level of antibodies primarily depends on whether the individual has a primary or a secondary dengue infection [67,72].

Fig. 4 shows the timelines of Laboratory Changes viz-a-viz Clinical-features [29].

In a primary infection, low antibody-titres are observed - while in a secondary infection, high IgG is detectable in the acute phase which sometimes masks the detection of IgM in secondary infection [29].

In a primary infection, viraemia is present through the incubation-period till the 4th Day of illness. During this viraemia-phase virus-isolation and virus-RNA detection is possible. NS1 Antigen detection is detectable through the incubation-period till the 12th Day (convalescent) of the illness [29].

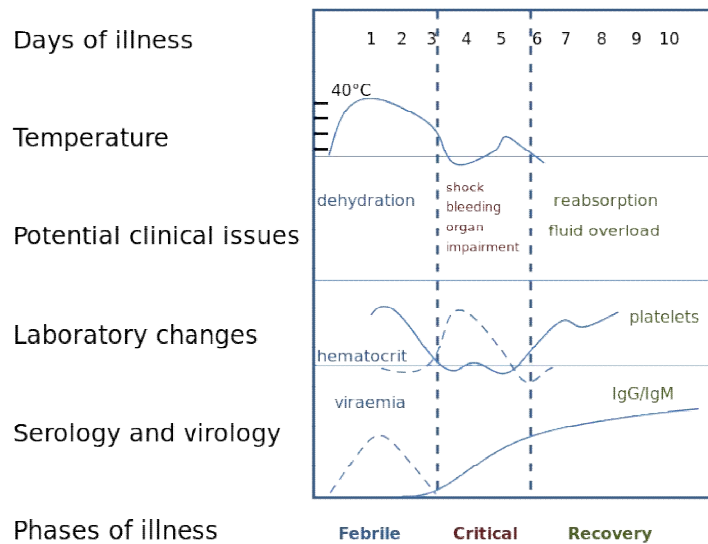


Fig. 4. Timeline of Laboratory Changes viz-a-viz Clinical-features. [29]

Table 1. Current diagnostic-tests for dengue

Procedure	Description
1. Real-time RT PCR [72]	<ol style="list-style-type: none"> Positive result is definite proof of current infection Usually confirms serotype Where viral-load is high, virus can be isolated Negative PCR result should be treated as indeterminate, to be confirmed by a second sample using another marker (or quantitatively via serological tests);
2. Quantitative or Semi-quantitative Serological-tests [77 – 78]	<ol style="list-style-type: none"> Detect IgM and IgG which are best useful when conducted in pairs. Many commercially-available such tests. Such pairs enable determination of primary and secondary status as well
3. NS1 ELISA [73 – 74, 79]	<ol style="list-style-type: none"> A useful tool This test is 100% sensitive
4. The Plaque Reduction Neutralization Test (or the Fluorescent Reduction Neutralization) (PRNT/FRNT) [70]	<ol style="list-style-type: none"> Still the most sensitive serological-test But not indicative of the total antibody-levels because non-neutralizing antibodies are not detected. Indicates the level of protective antibodies labour-intensive, time-consuming, expensive and requires good standardisation
5. The Haem-agglutination Inhibition assay [80]	<ol style="list-style-type: none"> has been the gold-standard for many years requires a paired-sample – and, skill in interpreting the results. tedious, time-consuming and usually conducted by reference laboratories only

IgG and IgM start rising from the 2nd Day. IgM starts falling after the 10th to 11th Day – detectable window-period occurring from 6th Day to about 30th Day. IgG becomes detectable from about 10th to 11th Day, and remains detectable, although peaking on about the 15th Day only [29].

In secondary-infection, IgG is markedly elevated and remains elevated. IgM is not as markedly elevated as in primary infection [29].

In addition, a Microfocus-reduction Neutralization-test (based on the peroxidase/anti-peroxidase or fluorescein technique) and a Micro-neutralization Test based on an ELISA-format have been developed.

The development of rapid-assays in recent years has allowed patient-specimens to be tested at point-of-care situations. Most manufacturers of these claim that the tests are able to differentiate between primary and secondary dengue-infections [81–82].

Many biosensors are being developed as rapid-tests for dengue. They use piezoelectric, optical or electro-chemical methods [83–84].

More recently nanoparticle-beads, mass-spectrometry and micro-sequencing have been utilised and appear promising [85–86].

These rapid-tests must be properly validated.

Future dengue-assays should not only confirm serotype of virus but also have markers that are able to predict disease-severity and indicate level of immunity/protection.

4. PREVENTION AND CONTROL

The present National Dengue Strategic Plan (2015 – 2020) comprises of [17,87]:

- To strengthen the preparedness and response capacity so as to detect cases and outbreaks for an immediate action, and
- The National Strategy is developed based on the SWOT analysis as well as the document of "Global Strategy for Dengue Prevention and Control 2012-2020" by WHO

Table 2. The seven strategies under the national dengue strategic plan 2015 – 2020 [17,108]

Strategy	Description
1. Dengue Surveillance	<ol style="list-style-type: none"> 1. Includes eNotification since it is a notifiable-disease under the Prevention and Control of Infectious Diseases Act, 1988 [17, 87, 89] 2. Laboratory Surveillance [17, 87, 89] 3. Dengue Outbreak Management [17, 87, 89] 4. New breeding-sites [3,9 – 10, 17, 87, 89] 5. Strengthening information system [3,9 – 10,17, 87] 6. Legislation – heavier penalties [3,9 – 10,17, 87, 89] 7. Strengthening Community Participation and Inter-sectoral Collaboration [3,9 – 10,17, 86, 89] 8. Changing insecticide fogging formulation [3,9 – 10,17,108, 109] 9. Mass abating [3,9 – 10,17, 87] 10. Reducing case-fatality [3,9 – 10,17, 87]
2. National Cleanliness Policy (A) and Integrated Vector Management (IVM) (B) [9 – 10,17, 87, 89]	<ol style="list-style-type: none"> A. <ol style="list-style-type: none"> 1. The National Cleanliness Policy – holistic and integrated approach through Concept of Inter-agency Blue Ocean Strategy 2. Focus on Clean Environment – Malaysia to become among cleanest countries, free from Infectious Diseases B. <ol style="list-style-type: none"> 1.Space spraying using Temephos EC or Bti in the hotspot areas 2. Residual spraying as a complementary measure 3. Effective waste collection system 4. Reliable water-supply system to reduce the need for additional water-storage 5. Cleanliness activities (Gotong Royong) 6. Advice on personal protection 7. Inter-agency enforcement at Construction-sites
3. Management of Dengue Cases	See Section: Clinical Management
4. Social Mobilisation and Communication for Dengue	<ol style="list-style-type: none"> 1. Community-involvement as a COMBI-volunteer [3,9 – 10,17, 87, 89] 2. Communication through Mass-media and Social-media [3,9 – 10,17, 87, 89]
5. Dengue Outbreak Response [17-25, 87, 89]	<ol style="list-style-type: none"> 1. Epidemic Preparedness Plan: Dengue Outbreaks Operation Room at District and National-level; Inter-agency District Dengue Outbreak Committee chaired by DO; Dengue Task-force Committee at State and National-level 2. Early Detection of Epidemic and Response 3. Risk Communication
6. Dengue Research [17 – 25, 87]	<ol style="list-style-type: none"> 1. Focus on enhancing effectiveness, cost-effectiveness, sustainability and scale of existing interventions 2. Ideas and new methods 3. Collaboration with National Public Health Laboratory (NPHL) and Institute for Medical Research besides other agencies
7. Reduction of Dengue Burden in Klang Valley where 57% of total dengue cases occur [17 – 25, 87, 89]	<ol style="list-style-type: none"> 1. Strengthening cooperation and collaboration between State Government, local authorities and other agencies

The four components of a SWOT analysis examine (a) the current strengths that should be maintained and built on, (b) the weaknesses that need to be addressed, (c) the opportunities that are available for moving toward more optimal function, and (d) the threats that may prevent progress from being made [82].

In Malaysia, the current new directions in dengue-control include [17]:

1. Having all registered dengue cases confirmed by laboratory tests,
2. Increasing source-reduction activity, and
3. Reducing fogging-activity from two cycles to one cycle

New Tools and Strategy in the Prevention and Control in Malaysia consist of:

- A. New strategies in hotspot areas such as in Table 3.

For the effective control of the dengue-vector mosquito-populations, there is a need to combine several strategies, such as chemical, biological and integrated control. The chemical-insecticide is the most commonly used, as it is effective against both the larval and the adult mosquitoes [92].

The ultimate aim of insecticide-control management has two parts i.e. the control of

Aedes-immatures and the control of the adult-mosquitoes. The control of adults especially in a dengue-epidemic situation is aimed at the killing of the infective female-mosquitoes. Whereas, the control of *Aedes*-immatures is targeted towards the overall reduction of the mosquito population-density and, indirectly reducing the human-vector pathogen-contact to prevent dengue-transmissions [85].

One of the two common chemical-controls is Larvicide-application to treat household drinking-water containers which has low-relative toxicity and is safe for humans. The other technique is space spraying (Ultra low volume, ULV or thermal fogging), which is generally employed in emergency outbreaks of dengue [93].

Different chemical groups have been used to control *Aedes spp* in Malaysia since the 1960s, including organo-chlorines, organo-phosphates, carbamates and pyrethroid-insecticides. The main contributor towards today's raging dengue epidemics is the worst practice of routine space-spraying and thermal-fogging which do not kill 100% of the vector-mosquito populations. This causes an artificial-selection due to ignorance that has led to serious chemical-resistance nowadays – and, have seriously impacted human-health following the excessive uses of various insecticides more routinely and at a higher-frequency [100].

Table 3. New strategies in hotspot areas (including concepts)

Strategy	Description/constraints
1. Residual spraying [17, 87]	Read within Text outside this Table
2. Larviciding activity using Temephos EC or Bti [9-10,17, 87, 89]	Read within Text outside this Table
3. Use of newer-generation insecticides [9-10,17, 87]	Read within Text outside this Table
4. Use of novel ovi-traps and other innovative methods [9-10,17, 87]	Read within Text outside this Table
5. Release of genetically-modified <i>Aedes</i> (A) or <i>Wolbacchia</i> -infected <i>Aedes</i> (B) [9-10, 90, 91 – 96]	A. 1. Hampered by logistical-difficulty due to flight-range of <i>Aedes</i> viz-a-viz release-radii in heavily built-up areas B. 1. Same difficulty does not exist because <i>Wolbacchia</i> -infection passed onto progenies – should be self-propagating, but in practice such propagation not found more than 100 meters per year 2. The strain of <i>Wolbacchia</i> shown to be effective in this method not able to survive ambient temperatures in the tropics. This claim is controversial. 3. The Method is undergoing pilot-study by IMR in

Selangor	
6. Larviciding of primary water-sources such as water-treatment plants (A), together with Aerial-spraying (B) [89, 91, 93 – 94, 98 - 99]	<p>A. 1. Similar to fluoridation of water 2. Pyriproxyfen (after EIA done) or Bti 3. Was done in parts of Brazil</p> <p>B. 1. Aerial-spraying using US CDC Protocol</p> <p>C. Combined method can be implemented if safe and cost-effective vaccine still not found, after pilot-study</p>
7. Isolation of Cases	<p>1. Not useful since 70-80% of infections are asymptomatic, yet infective [15 – 16, 89, 91 - 94]</p> <p>2. Besides, diagnosis is usually made on 3rd to 5th day [1 – 11]</p>

The routine space-spraying and fogging pollutes the environment and the food chain - besides also directly eliminating most of the natural-enemies of the vector-mosquitoes, such as ants, spiders, dragonflies, praying-mantises, lizards, frogs, birds and bats. These natural-enemies are of great-value as vital biological-control agents in suppressing the mosquito-populations, which control-measures must be preserved for long-term successful mosquito-control [100].

In view of the above-mentioned predicament, there are innovative new-strategies developed specifically to outsmart the dengue-vector mosquito. These are described in Table 4 [100].

In the prevention and control of dengue-outbreaks, the use of household insecticide-products (HIP), such as the insecticide aerosol-sprays have been very much a part of active and sustainable community-participation [101].

They are handy and fast-action, effective in killing all the mosquitoes and always ready-to-use. The dengue-hotspot communities should pro-actively do thorough spraying in the morning and in the evening every day within their premise, to ensure that there is no infective female Aedes-mosquitoes hiding within. For non-hotspot communities, such thorough-spraying needs to be done only once a week to ensure there is no Aedes-mosquitoes breeding inside their premise. Therefore, this aerosol insecticide-spray should be integrated into the overall dengue-vectors control-program for maximum control-results [101].

However, those ordinary aerosol-insecticide come with a choking smell, cause staining and leave an oily-film on surfaces, dissuading many. The new generation of mini-aerosol spray-insecticide, equipped with metered-valve and

Table 4. Innovative new-strategy in dengue-vector control

Method	Description
1. Attractant Toxic Sugar Baiting 100	<p>a. Attracts all the hungry and dehydrated adult-mosquitoes (male & female) when they emerge from pupae (especially first two days)</p> <p>b. Since nectar-meals are scarce indoors, the bait is the most readily-available and attractive choice.</p> <p>c. Only needs placement in strategic-locations indoor</p> <p>d. Safe because no chemicals extruding into air or environment</p> <p>e. Mostly used as supplement in control</p>
2. Attractive Lethal Oviposition Traps 100	<p>a. Makes full-use of the Aedes-vector mosquito's skip-oviposition characteristic i.e. in using the female as mechanical-vectors to cross-contaminate the other breeding-sites which are beyond our detection.</p> <p>b. Attracts gravid-mosquitoes to come and lay eggs in the special-station that contains water and a lacing-formulation of oviposition-attractants. All (100%) of these eggs cannot develop into adult-mosquitoes.</p> <p>c. The formulation has the insect growth-regulator, IGR, which contaminates these female-mosquitoes - when they lay</p>

eggs in their hidden breeding-sites in the wild, they go on to cross-contaminate all the breeding-sites, and all the hidden-eggs.

- d. All of the chemicals used in this, always stay inside the station - thus protecting all the natural-enemies of the mosquito and ensuring sustainable natural biological-control
-

slow-release nano-technology formulation (active ingredient is meto-fluthrin at 0.76%w/w) has been developed to overcome all these negative aspects – they are odourless, clean and dry, very low-volatile organic compounds (VOCs), non-oily, non health-hazard and eco-friendly compared to the ordinary aerosol-insecticide [101].

In the standard room of up to 30 m³, one needs to spray at the four corners. Each 83ml (50g) mini aerosol-spray can deliver the fixed-amount in 800 sprays of protection in 200 rooms, providing mosquito-free protection for up to 8 hours. In comparison, the ordinary 600ml (380 g) aerosol-spray could only spray up to 42 rooms and provide an hour of mosquito-free protection. For smaller spaces like in a car, this mini spray can be sprayed once in the car to ensure no mosquitoes while driving. In this manner, it is also a great tool in preventing mosquitoes being transported from one location to another. Outside-fogging can also be done [101]

B. Specific protection

Primary Prevention of diseases classically comprises of Health Promotion and Specific Protection. [91], [95 – 97, 103]. Health Promotion has been extensively outlined above. Specific Protection should comprise of an appropriate Mass Vaccination Program of Endemic Areas, appropriate use of effective mosquito-repellents such as DEET, lemon eucalyptus or picaridin, and the appropriate use of mosquito-nets by day-sleeping children, the elderly and the infirm. The last two can be made available, subsidised, at Health Clinics throughout the country [1 – 10, 91,95–97].

In late 2015 and early 2016, the first dengue vaccine, Dengvaxia (CYD-TDV) by Sanofi Pasteur, was registered in several countries for use in individuals 9-45 years of age living in endemic areas. But overall, the much waited-for dengue-vaccine has been a disappointment both in its efficacy and its safety [104–108].

If a sufficiently effective and safe vaccine can be found, it will transform dengue fever into a

vaccine-preventable disease, and the disease can be quickly brought to near-eradication levels just like all other previous vaccine-preventable diseases.

Takeda Pharmaceutical Company Limited, (“Takeda”) in November 2017 announced the data from an 18-month interim analysis of the ongoing Phase 2 DEN-204 trial of its live, attenuated tetravalent dengue vaccine-candidate, TAK-003 (also referred to as TDV). This interim-analysis showed that children and adolescents who received TAK-003 had a relative-risk of symptomatic-dengue of 0.29 (95% CI: 0.13–0.72) compared to children and adolescents in the placebo control-group [109].

TAK-003 was found to be safe and well-tolerated in terms of solicited local-reactions and systemic adverse-events, relative to the placebo control-group [104].

In participants who were sero-negative at baseline, a second-dose given at Month 3 improved the tetravalent sero-positivity rate at Month 6 to 86%, compared to 69% in the one-dose group. A booster dose at Month 12 resulted in a 100% tetravalent sero-positivity rate at Month 13 in participants who were sero-negative at baseline [109].

TAK-003 is currently under evaluation in the Tetravalent Immunization against Dengue Efficacy Study (TIDES), a large-scale Phase 3 efficacy-trial being conducted in eight dengue-endemic countries. Data from TIDES will be available in late 2018 [109].

The US National Institute of Allergy and Infectious Diseases (NIAID) has developed the LATV dengue vaccines TV003/TV005. A single dose of either TV003 or TV005 induced sero-conversion to four DENV serotypes in 74-92% (TV003) and 90% (TV005) of flavivirus-seronegative adults and elicited near-sterilizing immunity to a second dose of vaccine administered 6-12 months later [110–112].

The Phase III clinical-trial of the TV003 commenced in February 2016 among 17,000

volunteers in multiple locations in Brazil with the aim of determining its efficacy and safety. The estimated primary-completion date is June 2018, and the estimated study-completion date is December 2022 [110–112].

When vaccines are available which afford greater than 90% protection against all four strains, the risk of antibody-directed enhancement (ADE) in subsequent natural-infections, causing severe dengue, becomes remote because secondary infections would be rare. Dengue fever very likely will become reduced to sporadic-outbreaks of mostly the Sylvan-type, just like yellow-fever, once a successful mass-vaccination program of a safe and highly-effective vaccine becomes feasible and affordable.

5. CONCLUSION

In conclusion, dengue fever and its complications have been a serious scourge of mankind for too long in recent history, affecting countries across the globe. The case-fatality rate of the disease in these countries, including Malaysia, is not negligible.

However, Clinical Management has brought about vast improvements in mortality and morbidity. Similarly, great advancements in Laboratory Diagnostics have been seen. Prevention and Control methods have been desiring of greater achievements, but also show greater promise with comprehensive re-evaluated programmes, newer insecticides, innovative methods and vaccines. Dengue fever would very likely become near-eradicated just like all other vaccine-preventable diseases, once comprehensive mass-vaccination programmes are available globally, using safe and very-effective tetravalent-vaccines soon to be available.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

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COMPETING INTERESTS

Dr. CA Koay declares that he is Technical Manager of a Firm that sells one brand of the 'mini-aerosol spray-insecticide', one brand of the 'attractant baiting' and one brand of the 'oviposition traps'. The remaining Co-authors declare that they have no Conflict of Interest whatsoever, in writing this Article.

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