**_Review Paper_**

# The Epidemiology of Dengue fever with Special Reference to Malaysia - emphasizing Prevention and Controlha


**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 heemorrhagic 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.

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

**Results and Conclusion:** 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; Dengue Hemorrhagic Fever (DHF); Epidemiology; prevention and control; Insect Repellents; Mosquito Nets; dengue vaccines; insecticides; insecticides (primary water-source larviciding); insecticide (aerial-spraying)




## INTRODUCTION

Dengue fever has become a menace of a mosquito-borne viral-disease, threatening over 2.5 billion humans at risk globally. Its morbidity and mortality are not small. Where once in 1970 it was endemic in only nine countries, it is now endemic in not less than 100 countries - mainly in tropical countries [1 – 12].

It is usually a benign, acute febrile illness. In a few cases dengue haemorrhagic fever (DHF) complicates, when the infection affects vascular-permeability which brings about a bleeding-diathesis and/or disseminated intravascular-coagulation (DIVC) [4].

**MATERIAL AND METHODS** The Authors here narrate from their own personal-experiences, besides reviewing existing-literature. Search-engines such PubMed, EmBase and such were used to retrieve relevant articles for discussion.

The literature consisted of original researches, systematic-reviews and narrative review. Author should comment in more depth on the weaknesses of the chosen method. This article is a narrative review which is a traditional method of integration of the literature. But, the authors realize the weaknesses of such a method – that there is no rule on how to obtain primary data and how to integrate results firstly leaving this to the subjective criterion of the reviewer. Secondly, the narrative reviewer does not synthesize quantitatively the data found in the different publications - although here in our article very little raw-data from earlier articles are being synthesized and thus susceptibility to inaccuracies and biases are very minimal.

## DISCUSSION

### Epidemiology

The *Aedes aegypti* which breeds in and around houses and buildings is the main vector. The *A. albopictus* is secondary. They are day-biting, and the peak-hours of biting are dawn, early morning and dusk [1 – 10, 12].

The *A. aegypti* is likely to cause a larger initial viral-load compared to the *A. albopictus* because the virus is found to concentrate greater in the salivary-gland of the *A. aegypti* – and viral-load is found to be a factor in the fever transforming to dengue hemorrhagic fever [13 – 15].

Major-sources of Aedes-breeding are illustrated in Fig. 1. In addition, both are noted to breed in storm-drains in residential-areas, while the *A. albopictus* is noted to breed in tree and plant folds, besides small stagnant-pools of water on the ground in shady-areas.

Globally, a total number of 50 – 100 million of dengue fever is reported by WHO estimates annually. Approximately 500, 000 (0.7%) of these result in DHF, resulting in 22,000 deaths (mostly in children) [1 – 2, 5, 6 – 9]. The World Health Organization (WHO) estimates that 40% of the world's population lives in areas endemic to dengue virus [5].

As much as 70 – 80% of dengue-infections are asymptomatic as revealed by studies in Philippines and Indonesia, although contrasting-claims, including by the US CDC, are as low as 50% [16 – 17] But in the Philippines study, only about 3% of infections were symptomatic in the age-group > 15 years [16].

Classically, the term severe dengue describes DHF and dengue shock syndrome (DSS), but a few authors include Dengue With Complications (DWC) as severe dengue. DWC mostly includes neurological-complications (commoner in children) and liver-involvement.

Presently, there isn't any specific-treatment, but effective anti-viral drugs appear to be on the line which could at least prevent mild dengue complicating to severe dengue [8 – 9].

Also, early-detection and access to proper medical-care lowers fatality-rates below 1% presently [1 – 2].

In nature, four (4) different strains of the dengue virus, DENV, exist which cause the disease – DENV1, DENV2, DENV3, and DENV4. These are distinct but closely-related sero-types. When a patient recovers from infection with one sero-type, there is lifelong-immunity against that specific-serotype – but, cross-immunity against the remaining sero-types is only partial and temporary. Subsequent infections by the remaining sero-types pose a risk of becoming DHF and DSS [1 – 9, 12].

In any region or country, the various sero-types steadily begin to predominate over the remaining sero-types over the years. The predominant strain(s) varies according to different geographies, countries, regions, seasons and over time. Presently, the predominant-strain in Malaysia is DENV3 replacing DENV1 and DENV2 in the recent years [18] Crossover of predominance in strain, as expectedly, appears to trigger an epidemic in the country as seen in Fig 2. [19].

Males are more commonly found infected in Malaysia at 57%. The total number of cases seen here is highest among those in their early twenties in age, while rising from a moderate among toddlers and then falling to a moderate in the late 40s – prior to reducing to a low in the elderly. But, the highest rate (incidence) is among the working and school-going age-groups [18].

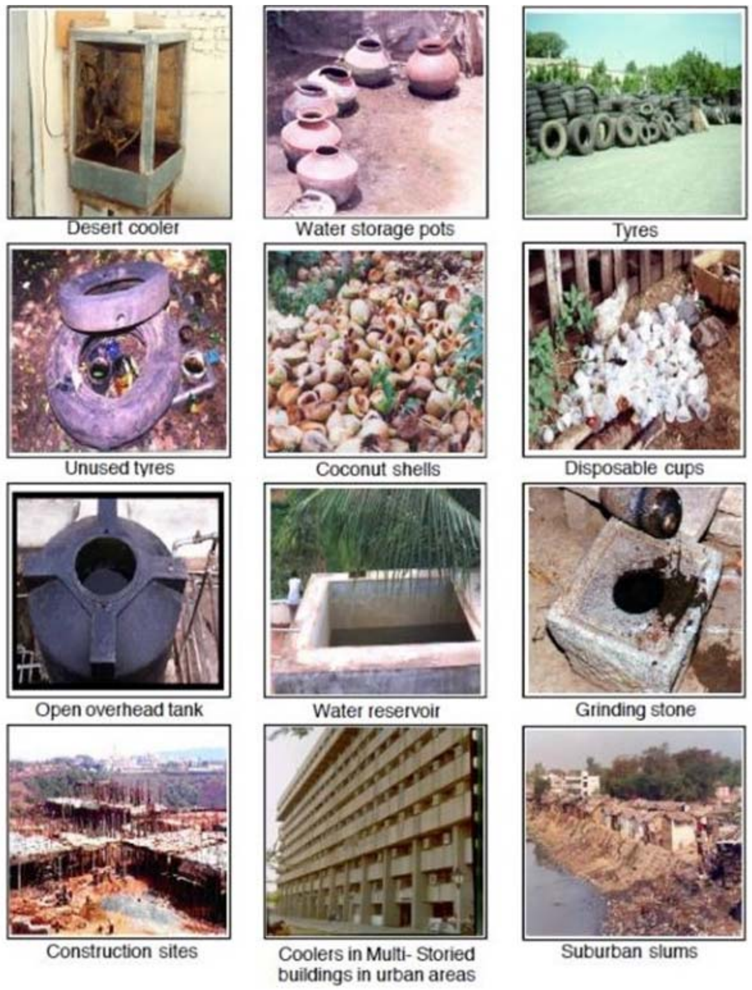


**Fig .1. Common Aedes aegypti breeding-sites, including in Malaysia**

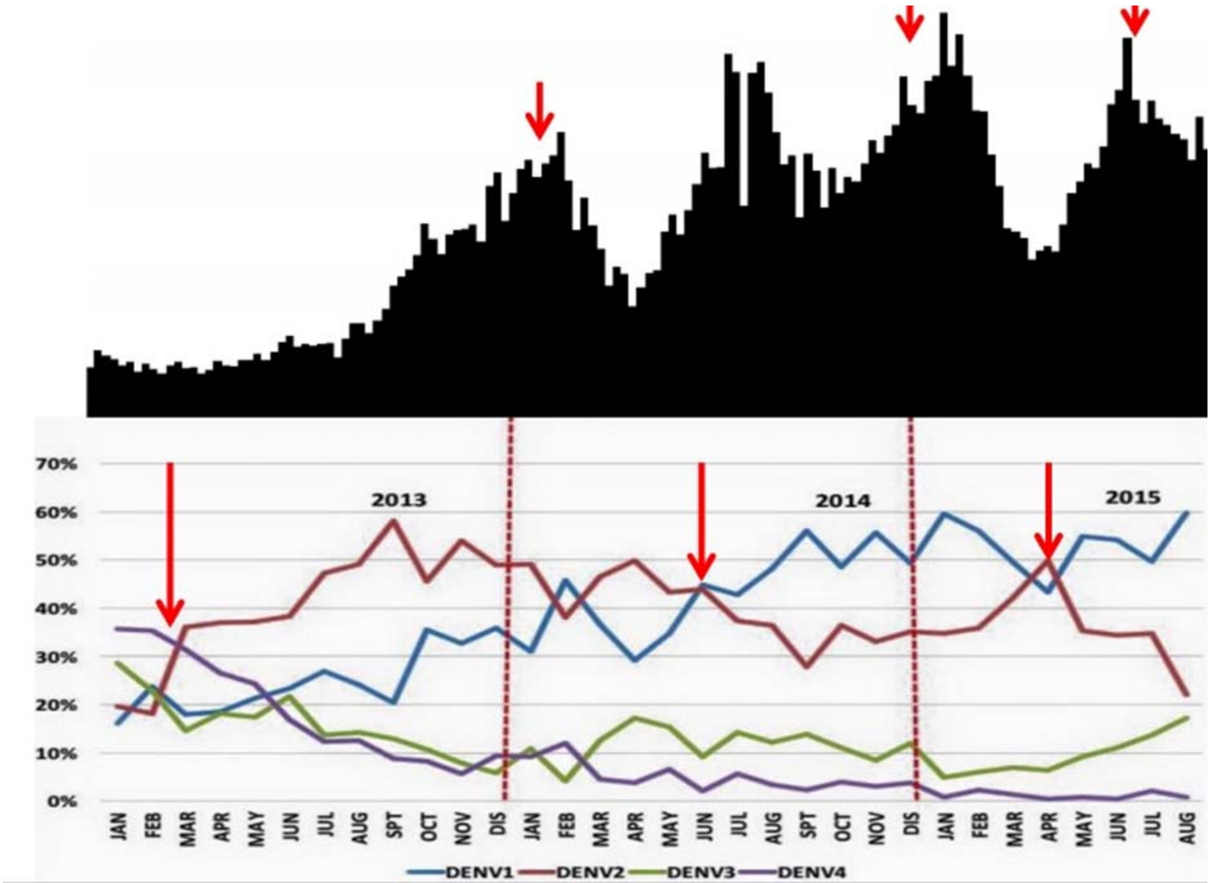


**Fig. 2. Circulating dengue-serotypes in Malaysia in relation to Cases 2013 – 2015. [19]**

The incidence of severe dengue is associated with factors related to the host (age, phenotype, presence of comorbidities, immune-genetic profile, sequential infection), to the etiological agent (serotype, strain, genotype), and to environmental aspects favoring the vector-proliferation. [20, 21, 22]. In Thailand, Halstead et al (1970) observed as much as 40% of children admitted to hospitals for dengue had DHF [21].

A retrospective epidemiological study of the Cuban epidemic of 1981 showed that DHF was seen both in children and adults. In adults, this was the first report of an epidemic of this nature. Shock was more frequent in children but more severe in adults. Serologic studies showed that DHF was seen with a frequency of 4% secondary infections in children and 1% in adults [22].

In Malaysia, Sam SS (2013) observed DHF appears commoner in females and those with co-morbids, including diabetes-mellitus and obesity. The case-fatality rate from DHF and DSS also appeared much higher in females. The researchers undertook a retrospective study to examine dengue-death cases in a hospital from June 2006 to October 2007 with a view to determine if there had been changes in the presentation of severe to fatal dengue. Nine of ten fatal cases involved adult females with a median age of 32 years. All had secondary dengue infection. The mean duration of illness prior to hospitalization was 4.7 days and deaths took place at an average of 2.4 days post-admission. Prominent presentations included acute renal failure, acute respiratory distress syndrome, myocarditis with pericarditis, and hemorrhages over the brain and heart [23].

Using secondary-data of probable cases notified in Brazil, severe dengue was reported; of in 66% of patients under the age of 15. Among the risk factors evaluated, age under 15 years old was significantly associated with severe dengue and only this age-group was significantly associated with the  of severe dengue [20].

In Malaysia, the disease is endemic since the 1980s [4, 10, 23 – 24]. Shepard DS et al state that the number of dengue-cases is under-reported here because the country has a passive-surveillance system [24] – although here the unreported cases would almost entirely be benign dengue-fever since all DHF would be diagnosed and managed at hospitals only.

Here, a “dengue outbreak” is defined as two cases emerging in a defined-area in over 14 days – a “dengue hotspot” is when the outbreak remains sustained more than 30 days [Petaling Jaya City Council. 2017].

Nur Azila MA et al (2011) studied 1000 people aged 35-74 in Malaysia and found 91.6% to be sero-positive for dengue.  From a total of 13725 participants recruited into the The Malaysian Cohort (TMC) from 1 January 2008 until 31 December 2008, the researchers randomly selected 1000 and obtained serum-samples from the subjects for the study. Socio-demographic data such as gender, age, ethnicity, locality (urban/rural) were also retrieved from the TMC database The sero-positivity increased with every 10-year increase in age. This can be explained by the fact that as one grows older one is more likely to have been bitten by an infected-Aedes mosquito. The Study revealed that gender and ethnicity were not associated factors. Sero-prevalence was equal in both urban and rural areas [25].

Serum samples were measured for the presence of dengue virus-specific IgG antibodies using the PanBio Dengue IgG INDIRECT enzyme-linked immunosorbent assay (ELISA). The kit identifies antibodies to all four DENV-serotypes but does not differentiate between each serotype. A positive result of dengue-IgG antibody indicates previous exposure to DENV [25].

In 2017, there were 83,849 cases of dengue fever reported in Malaysia including 177 deaths – both a conspicuous reduction from the immediately preceding-years [26 – 27].

Such recent achievements are attributed by the Health Ministry here to the coordinated and integrated efforts of the various Ministries, agencies, civil-society and individuals. If such achievement is not sustained, it could then be attributed to the six-year pattern of reduction and resurgence observed in the country discussed below [18, 26 – 27].

The Government here set up the National Dengue Task Force (NDTF) which comprises seven Ministries and various agencies and members of the public in dengue Control and Prevention [18, 26 – 27]. Besides the NDTF, also exists here the National Dengue Committee [18].

Subsequent to 2013, a sharp increase in the incidence was noted here, which has remained sustained [18]. This could be caused by serotype-shift, population-mobility, climate-change, human- behaviour, deficient environmental-sanitation and the ineffectiveness of vector-control activities [4, 18].

In addition, health-care reforms in the late 90s which integrated the vertical organizational-structure of the Vector Borne Disease Control Programme with the general health-services resulted in loss of technical-expertise and problems in funding. In the years following such restructuring, cities like Greater Kuala Lumpur, Penang, Johore Bahru, Seremban and Melaka became hyper-endemic for dengue transmission, where more than one virus serotype are responsible [12].

It is observed by these authors that data on the dengue-incidence by States in Malaysia is difficult to search for in the internet. Table 1 below shows the incidence for the month of January 2018 (which was the only calculable, from limited-data obtained in a search). The Dengue-incidence in Malaysia appears to vary considerably between the States of Malaysia.

Norziha CH et al (2012) conclude that climate variables could have potential value in helping to predict dengue incidence in Malaysia in both time and space [28].

Monthly numbers of confirmed dengue fever cases for the states of Malaysia for the nine years from January 2001 to December 2009 were obtained from the Ministry of Health Malaysia. In total 309,003 cases were reported during this time period. Monthly mean temperature, number of rainy days and mean rainfall data were obtained from the Malaysian Meteorology Department and the data was supplemented with additional detailed-data on rainfall from the Department of Irrigation and Drainage. Nino4 is an index used to measure the strength of El Nino and La Nina events and is defined as the departure in monthly sea surface temperature (SST) from its long-term mean averaged over the Nino4 region (160 East-150 West, 5 South-5 North) which is most relevant to Malaysia. A time series of Nino4 index was obtained from the National Oceanic and Atmospheric Administration (NOAA) Climate Prediction Center for the period of the study. In general, the episodes of El Nino (warm event) and La Nina (cold event) in the study area and period were El Nino in 2008 and La Nina for the year of 2002, 2004, 2006 and 2009, with other years being neutral [28].

Initial exploratory-analyses of the data-set indicated an increasing trend in dengue incidence rate (DIR) over Malaysia as a whole over the study period. This was particularly marked in those states in the South West of the country where the main urban areas of Malaysia are located. As might be expected DIR is higher in areas where there is a higher population density. This overall increase in dengue super-imposed on an annual seasonal cycle which sees DIR peaks in January and July [28].

Geographical-differences in the pattern of DIR was evident at the state-level (both in level and to some extent in the annual cycle). This could be explained by fact that Malaysia is characterized by two monsoon regimes, namely, the Southwest Monsoon from late May to September and the Northeast Monsoon from November to March. The Northeast Monsoon brings heavy rainfall, particularly to the east coast states of Malaysia, whereas the Southwest Monsoon normally signifies relatively drier weather. Additional investigation indicated that these geographical-differences can be adequately captured without significant loss of detail by grouping the 12-states into the four broad regions of 'North East', 'South East', 'North West' and 'South West' [28].

To enable the capturing of the various influences discussed above (global trend, seasonal cycle, regional variations and the impact of population density) whilst at the same time investigating potential association with climate and lagged-climate variables, a generalized-additive models (GAM) framework was adopted (Hastie and Tibshirani, 1986) [28].

The findings were that mean rainfall three months previously has a positive relationship with DIR, but mean rainfall in the same month has a negative relationship with DIR. This could possibly be because more rainfall earlier in the year could encourage mosquito development, while heavy rainfall in the same month could wash out mosquito breeding places and lower dengue transmission. Number of rainy days both three months previously and in the same month and temperature in the same month all have a positive relationship with DIR. Meanwhile, sea surface temperature (SST) six months previously as defined by Ni˜no4 has a positive relationship with dengue [28].

In addition, the researchers state that by replacing 'observed' with 'hindcast' climate variables in a suitably refined model, dengue predictions for Malaysia could potentially be made several months ahead of the dengue-season of interest [28].

Rohani A et al (2018) conducted a study to elucidate the relationship among entomological, epidemiological and environmental factors that contributed to dengue-outbreaks in Malaysia. Entomological data were collected using ovi-traps where the number of larvae was used to reflect Aedes mosquito population-size; followed by RT-PCR (Reverse-transcriptase Polymerase Chain Reaction) screening to detect and serotype the dengue-virus in the vector. Notified-cases, date of disease-onset, and number and type of the disease-control interventions were used as epidemiological-endpoint, while rainfall, temperature, relative-humidity and air-pollution index (API) were indicators for environmental-data. The study showed that, notified-cases were related with "next-week intervention", while "conventional intervention" only happened 4 weeks after larvae were found, indicating ample time for dengue transmission [29].

While climate, circulating virus-strain, urban-rural ratio, herd-immunity, population-mobility, community-behaviour, and quality of environmental-sanitation (particularly including dumping of solid-waste indiscriminately and illegally) may be the factors influencing this, existing Control and Prevention methods (particularly with reference to vector-control) may need to be scrutinized for uniformity, especially between States, in conforming to existing national-strategies, besides in the data-collection, planning, resource-allocation, implementation and evaluation.

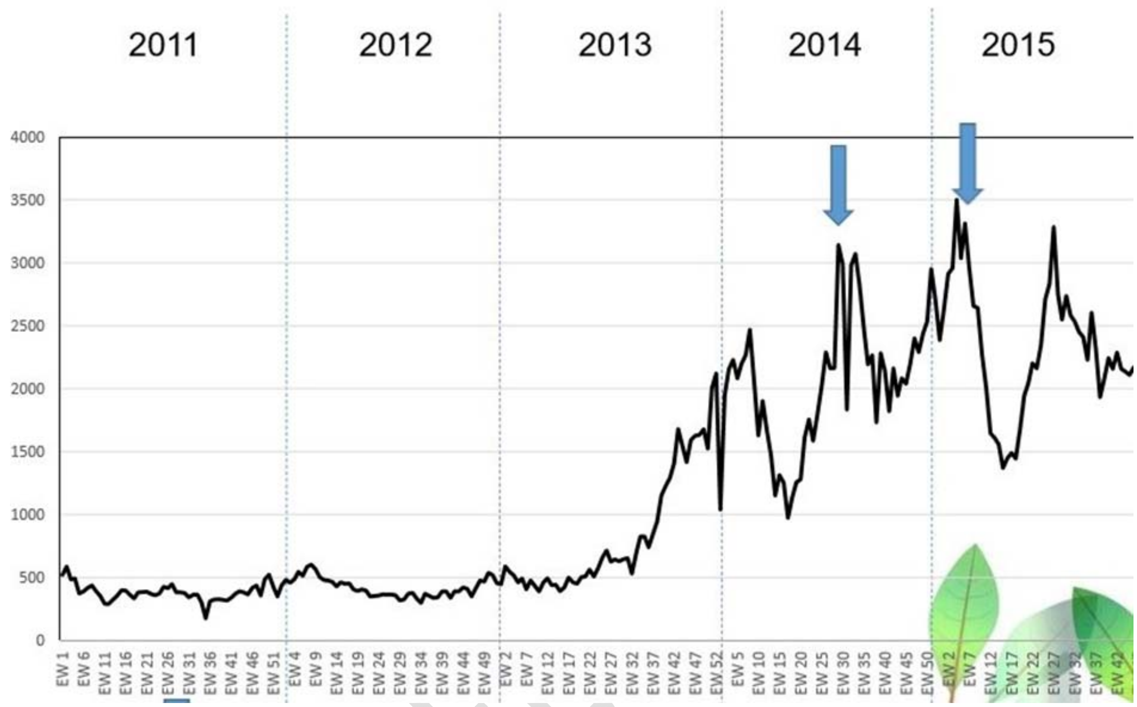


**Fig. 3. Weekly-trend in number of Dengue-cases in Malaysia, 2011 – 2015. [18]**

| | Dengue-incidence by State, Malaysia, Jan 2018 | | |
|---|---|---|---|
| State | Number of Cases | Population of State | Incidence per 100,000 |
| Perlis | 17 | 248,000 | 6.8 |
| Kedah | 77 | 2,077,000 | 3.7 |
| Penang | 286 | 1,674,000 | 17.1 |
| Perak | 175 | 2,418,000 | 7.2 |
| Selangor | 1758 | 6,169,000 | 28.5 |
| Federal Territories | 293 | 1,798,000 | 16.3 |
| Negri Sembilan | 66 | 1,085,000 | 6.1 |
| Malacca | 43 | 868,000 | 4.9 |
| Johore | 426 | 3,565,000 | 11.9 |
| Pahang | 63 | 1,581,000 | 4.0 |
| Kelantan | 72 | 1,767,000 | 4.1 |
| Terengganu | 9 | 1,147,000 | 0.8 |
| Sarawak | 45 | 2,697,000 | 1.7 |
| Sabah | 242 | 3,720,000 | 6.5 |

Source: Modified from Data of National Dengue Operations Room CPRC, Health Ministry Malaysia

**Table 1. Dengue-incidence by State in Malaysia, January 2018 (per 100,000 population)**

In the meantime, Wiwanitkit V states that the vector-control methods as applied presently are labour-intensive, require discipline and diligence and difficult in sustaining [30].

In Malaysia, epidemics of dengue tend to recur in six-year cycles which comprise high-incidence in four (4) years followed by two years of lower incidence. Although here, the annual average-incidence in successive six-year cycles has been increasing.

The economic-burden of dengue-illness in Malaysia was estimated by Shepard et al at US$56 million each year. The researchers state that the estimate could be larger if costs associated with dengue prevention and control, dengue surveillance, and long-term sequelae of dengue were included – but the researchers concede accurate estimation is difficult because of incomplete data overcoming such limitation by merging multiple data-sources to refine the estimates, “including an extensive literature review, discussion with experts, review of data from health and surveillance systems, and implementation of a Delphi process” [24].

In estimating the costs of dengue-prevention, Packierisamy PR et al state that the country spent US$73.5 million (0.03% of the GDP) on the National dengue Vector Control Program. The researchers state that where innovative-technologies for dengue-vector control prove effective, and a dengue-vaccine needed to be introduced, substantial existing-spending could be rechanneled to fund these [31].

**Prevention and Control**

The present National Dengue Strategic Plan in Control and Prevention in Malaysia (2015 – 2020) aims at strengthening the preparedness and response capacity so as to detect cases and outbreaks for an immediate action [18, 32].

The National Strategy is developed based on SWOT-analysis and the document of "Global Strategy for Dengue Prevention and Control 2012-2020“ by WHO.

SWOT-analyses 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 [33].

In Malaysia, the current new-directions in dengue-control include [18]:

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

The National Strategic Plan (2015 – 2020) is made up of strategies (totalling seven).

The First Strategy is Disease Surveillance – and this includes in the case of dengue:

- a. eNotification, since it is a notifiable-disease under the Prevention and Control of Infectious Diseases Act, 1988
- b. Laboratory-surveillance
- c. Outbreak-management

d. Addressing new breeding-sites

e. Strengthening information-systems

f. Aspects of legislation, including considerations of imposing heavier-penalties

g. Strengthening Community Participation and Inter-sectoral Collaboration

h. Changing insecticide-fogging formulation

i. Mass-abating

j. Reducing case-fatality

The Second Strategy comprises of a National Cleanliness Policy and an Integrated Vector Management (IVM) [12, 18, 34] .

The National Cleanliness Policy is a holistic and integrated approach through the Concept of Inter-agency Blue Ocean Strategy, and emphasizes a Focus on Clean Environment – Malaysia to become among the "cleanest countries, free from Infectious Diseases".

While Integrated Vector Management includes:

a. Space spraying using Temephos EC or Bti in the hotspot areas

b. Residual spraying as a complementary measure

c. Effective waste-collection system

d. Reliable water-supply system to reduce the need for additional water-storage

e. Cleanliness-activities (Gotong Royong)

f. Advice on personal-protection

g. Inter-agency enforcement at Construction-sites

The Third Strategy addresses improved Clinical-management as discussed in the Ministry of Health/Academy of Medicine Clinical Practice Guidelines. 2014: Recommendations for Patient Safety And Minimal Monitoring Standards During Management of Dengue Infection in Adults (3rd Edition).

The Fourth Strategy involves Social Mobilisation and Communication for Dengue. This addresses two areas:

a. Community-involvement as a COMBI-volunteer (Communication for Behavioural Impact) [4, 10, 18, 34]

b. Communication through Mass-media and Social-media [4, 10, 18, 34]

The Fifth Strategy addresses Dengue Outbreak Response, and involves [18]:

a. 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

b. Early Detection of Epidemic and Response

c. Risk Communication

The Sixth Strategy addresses Dengue Research, and specifically involves [18]:

a. Focus on enhancing effectiveness, cost-effectiveness, sustainability and scale of existing interventions
b. Ideas and new methods
c. Collaboration with the National Public Health Laboratory (NPHL) and Institute for Medical Research besides other agencies

The Seventh Strategy focuses on Reduction of the Dengue Burden in Greater Kuala Lumpur where 57% of total dengue cases are encountered [18 – 26, 34]

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

A. New strategies in hotspot-areas such as:

1. **Residual-spraying and Larviciding-activity using Temephos EC or Bti:** In ensuring effective-control of the dengue-vector population, there is a need to combine several strategies - such as chemical, biological and integrated control. The chemical-insecticide is the more frequently used, since it is effective against both the larval and the adult form of the vector [10, 18, 34, 37]

The ultimate aim of insecticide-control has two parts - the control of Aedes-immatures (larvae and pupae) and the control of the adults. The control of the adults is aimed at the killing of the infective-female, especially during an epidemic. While, the control of immatures is targeted at the overall-reduction of the mosquito population-density and, at indirectly reducing the human-vector to pathogen contact in preventing transmissions [10, 18, 34, 38]

2. Different chemical-groups have been used to control the *Aedes spp* in Malaysia since the 1960s and these include organo-chlorines, organo-phosphates, carbamates and pyrethroid-insecticides. Among the main contributor to the cause of the present "raging" epidemics is the undesirable practice of routine space-spraying and thermal-fogging which do not kill 100% of the vector-populations. Because of ignorance in this, an artificial-selection happens causing chemical-resistance of concern presently – which have seriously impacted human-health following the excessive-use of the various insecticides in being used more routinely and more frequently [37 - 39].

The routine space-spraying and fogging pollutes the environment and the food chain - besides directly eliminating most of the natural-enemies of the vector also, such as ants, spiders, dragonflies, praying-mantises, lizards, frogs, birds and bats. These natural-enemies are of great value since these act as vital biological-control agents in suppressing the mosquito-population – and which control-measures must be preserved for long-term successful vector-control [37 - 39].

3. **Use of newer-generation insecticides.** 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 in the Control and Prevention of dengue-outbreaks, [37 - 39].

These are handy and of fast-action use, effective in killing all the mosquitoes and ever ready-to-use. Families and residents in dengue-hotspot communities need to pro-actively do thorough-spraying in the morning and in the evening every day within their premise, towards ensuring that there is no infective-female hiding within. For non-hotspot communities, such thorough-spraying needs to be done only once a week. The use of such aerosol insecticide-sprays need to be integrated into the overall dengue-vector control-program for maximum-results [37 - 39]

But the ordinary aerosol-insecticides are characterized by a choking-smell, besides causing staining and leaving an oily-film on surfaces, discouraging many. The new generation of the mini-aerosol spray-insecticide (equipped with metered-valve, slow-release nano-technology formulation using the active-ingredient, meto-fluthrin at 0.76%w/w) has been developed to overcome all these negative aspects – these being odourless, clean and dry, very low-volatile organic compounds (VOCs) which are non-oily, non-health-hazard and eco-friendly compared to the usual aerosol-insecticide [37 - 39].

In a standard-room of up to 30 $m^3$, one needs only to spray the four-corners of the room. Each 83ml (50g) mini aerosol-spray can deliver the fixed-amount in 800 sprays in 200 rooms, providing vector-free protection for about eight hours. In comparison, the usual 600ml (380 g) aerosol-spray can only spray about 42 rooms and provide an hour of mosquito-free protection each time. 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 also prevents the vector from being transported from one location to another. Outside-fogging can also be done [37 - 39].

4. In view of difficulties with insecticides, **innovative new-strategies** have been developed specifically to outsmart the vector. These are described in Table 1 [37 - 39].

5. **Release of genetically-modified Aedes or Wolbacchia-infected Aedes** [10, 35 – 41]:

The release of genetically-modified Aedes can be expected to be hampered by logistical-difficulty which are owed to the flight-range of *Aedes spp* in relation to release-radii in heavily built-up areas.

The same difficulty does not appear to exist with the Wolbacchia-technique because Wolbacchia-infection in the Aedes is passed onto progenies, and thus should be self-propagating – but, in practice such propagation is not found to be more than 100 meters per year.

To test this, Schmidt TL et al (2017) followed the frequency of the transinfected Wolbachia strain wMel through Ae. aegypti in Cairns, Australia, following releases at 3 non-isolated locations within the city in early 2013. Spatial spread was analysed graphically using interpolation and by fitting a statistical model describing the position and width of the wave. For the larger 2 of the 3 releases (covering 0.97 km2 and 0.52 km2), the researchers observed slow but steady spatial spread, at about 100–200 m per year, roughly consistent with theoretical predictions. In contrast, the smallest release (0.11 km2) produced erratic temporal and spatial dynamics, with little evidence of spread after 2 years. The researchers state that this is consistent with the prediction that a minimum release area is needed to achieve stable local-establishment and spread in continuous-habitats. Our graphical and likelihood analyses produced broadly consistent estimates of wave-speed and wave-width. Spread at all sites was spatially heterogeneous, suggesting that environmental heterogeneity will affect large-scale Wolbachia-transformations of urban mosquito populations [45].

Besides that, the strain of Wolbacchia shown to be effective in this method is not able to survive ambient-temperatures in the tropics.

Ross PA et al (2017) tested three Wolbachia infections: wMel, wMelPop-CLA and wAlbB strains, for their maternal transmission fidelity and ability to cause cytoplasmic incompatibility under temperature conditions that are representative of containers in the field. The researchers showed for the first time that cyclical-temperatures reaching a maximum of 37°C during development reduce the expression of cytoplasmic incompatibility in the wMel and wMelPop-CLA infections of Ae. aegypti. The researchers also found a greatly diminished Wolbachia density under these conditions. wMel and wMelPop-CLA-infected mosquitoes exposed to this regime across their life-cycle do not transmit the infection to their offspring. Conversely, the wAlbB infection is more stable in terms of its reproductive outcomes and density under cyclical temperatures. Thus, suggestions are for the need of multiple infection-types suitable for different conditions when using Wolbachia-infections in biological-control strategies [45].

The Wolbacchia-method is presently undergoing pilot-study in Selangor by the Institute for Medical Research.

6. Larviciding of primary water-sources such as water-treatment plants and water-storage, together with Aerial-spraying. [36, 38, 40 – 41, 45 - 46]:

This method would be similar to fluoridation of water using either pyripoxifen (after Environmental Impact Assessment is done) or Bti. In this, pyripoxifen has b een previously used as was done in parts of Brazil. Aerial-spraying can be carried out according to the existing US CDC Protocol. A combined-method can be implemented if a safe and cost-effective vaccine is still not found, and after a pilot-study.

7. Isolation of cases. Such would not be useful since 70-80% of infections are reported to be asymptomatic, yet infective [16 – 17, 34, 36 - 39]. Besides, diagnosis is usually made on 3rd to 5th day [1 – 10, 12]. But some authors and institutes, including the US CDC, state that only 50% of infections are asymptomatic. Thus, each region needs to ascertain the rate in their region, and then make a decision on the effectiveness of isolation, including the cost-benefit of isolating cases

| | Method | Description |
| --- | --- | --- |
| 1. | Attractant Toxic Sugar Baiting [37 – 39] | a. Attracts all the hungry and dehydrated adult-mosquitoes (male & female) when they emerge from pupae (especially first two days)<br>b. Since nectar-meals are scarce indoors, the bait is the most readily-available and attractive choice.<br>c. Only needs placement in strategic-locations indoor<br>d. Safe because no chemicals extruding into air or environment<br>e. Mostly used as supplement in control |
| 2. | Attractive Lethal Ovi-position Traps [37 – 39] | a. Makes full-use of the Aedes-vector mosquito's skip-ovi-position characteristic i.e. in using the female as mechanical-vectors to cross-contaminate the other breeding-sites which are beyond our detection.<br>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.<br>c. The formulation has the insect growth-regulator, IGR, which contaminates these female-mosquitoes - when they lay eggs in their hidden breeding-sites in the wild, they go on to cross-contaminate all the breeding-sites, and all the hidden-eggs.<br>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 |

**Table 2. Innovative new-strategy in dengue-vector control**



B. Specific protection

Primary Prevention of diseases classically comprises of Health Promotion and Specific Protection. [34, 38 – 40, 46]. Health Promotion has been extensively outlined above. Specific Protection should comprise of an appropriate Mass Vaccination Program of Endemic Areas or failing which, the 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 final two can be made available, subsidised, at Health Clinics throughout the country. Adequate Community Education in the appropriate use of these would be imperative to the success of these methods [1 – 11, 36, 40 – 42].

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 [49 – 53].

Ferguson NM et al  (2016) developed mathematical models of DENV transmission to explore hypotheses about vaccine action and to examine the potential consequences for the impact of routine use of the vaccine. The Phase III trial-results made all (any) models requiring to address the waning of vaccine-efficacy over time. Hence, the researchers fitted a “simple” model, and then a more biologically-motivated model in which the immunological effect of vaccination is comparable to a silent natural infection, to the publicly-available trial-data, with these efficacy-values assumed to be different for seropositive and seronegative vaccine-recipients. The researchers state, seronegative-recipients gain transient protective cross-reactive immunity akin to that observed for natural-infection. After this protection decays, these state lower concentrations of heterotypic-antibodies increase the risk of severe disease upon a breakthrough primary infection to the same level seen for secondary infections in non-vaccinees . Conversely, vaccination of recipients who have prior had one DENV-infection resulted in a boosting of immunity to levels comparable with someone who has had two natural infections, and their next infection will not have the higher severity associated with natural secondary infections, but rather, the much lower risk of severe disease associated with tertiary and quaternary (postsecondary) infections [51].

This model fitted well the patterns seen in both the active and long-term follow-up phases of the phase III clinical-trial, including the variation in vaccine efficacy by age, sero-status at the time of vaccination, and time since vaccination. The worst of the model-fit was with dengue seen in the 2 till 5-year-old vaccine-recipients compared with controls in the first year of the long-term follow-up in the Asian trial. But, model-predictions were still found to lie within the confidence-bounds of the data, and the model successfully reproduces a relative risk >1 for vaccine-recipients compared with controls in that age-group. Thus, had the long-term follow-up data on the outcomes of vaccination in the 2- to 5-year-old age-group not been included, the researchers state the model would still have predicted a relative risk >1 in that age group, based on trends seen in the different age-groups and the results of the active-phase [51].

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 [54].

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 [49, 54].

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 [54].

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 [54]

In a recent communication with Takeda, the authors were told that the data from TIDES will only available after completion of the Trials early this year [Hutagalung Y. Vaccines Business Unit Takeda Vaccines, Inc. January 2019]

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 [55 – 57].

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 [55 - 57].

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 tetravalent-vaccine becomes feasible and affordable.

**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.

But, 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 of the different 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.

**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 ‘ovi-position traps’. Dr. Meer Ahmad A.M. declares that he does not have any Conflict of Interest whatsoever, in writing this Article.

**REFERENCES**


1. Meer Ahmad AM, Kumarasamy V, Ngau YY, Leong CL, Koay CA. A Review of Dengue Fever with Special Reference to Malaysia. Asian Journal of Research in Infectious Diseases. 2018. Vol 1:2
2. WHO. Dengue and severe dengue. April 2017.
3. US Centers for Disease Control. Dengue. 19 Jan 2016.
4. Bains S. Severe Dengue Infection. Medscape. Oct 12, 2017.
5. WHO. Dengue control. 2018.
6. WHO REGIONAL OFFICE FOR THE WESTERN PACIFIC. THE DENGUE STRATEGIC PLAN FOR THE ASIA PACIFIC REGION. Fifty-ninth session 25 July 2008 Manila, Philippines. 22–26 September 2009.
7. WHO Western Pacific Region. WHO ASEAN Workshop on Priority Actions for Dengue Prevention and Control. 3 to 5 May 2011. Manila, Philippines
8. WHO Regional Office for South-east Asia. Comprehensive guidelines for Prevention and Control of Dengue and Dengue Haemorrhagic Fever. 2011
9. WHO. DENGUE GUIDELINES FOR DIAGNOSIS, TREATMENT, PREVENTION AND CONTROL. WHO/HTM/NTD/DEN/2009.1. Expiry date: 2014
10. Song-Quan Ong. Dengue Vector Control in Malaysia: A Review for Current and Alternative Strategies. Sains Malaysiana. 2016. 45(5): 777–785
11. Ang Kim Teng and Satwant Singh. Epidemiology and New Initiatives in the Prevention and Control of Dengue in Malaysia. Dengue Bulletin – Vol 25, 2001
12. Kumarasamy V. Dengue Fever in Malaysia: Time for Review?. Med J Malaysia. Vol 61 No. (1) March 2006
13. Paupy C, H. Delatte, L. Bagny, V. Corbel, D. Fontenille. Institute Pasteur. Aedes albopictus, an arbovirus vector: From the darkness to the light. Microbes Infect. 2009 Dec; 11 (14-15):1177-85
14. Whitehorn J, Kien DT, Nguyen NM, Nguyen HL, Kyrylos PP, Carrington LB, et al. Comparative Susceptibility of Aedes albopictus and Aedes aegypti to Dengue Virus Infection After Feeding on Blood of Viremic Humans: Implications for Public Health. J Infect Dis. 2015 Oct 15; 212 (8):1182-90.
15. Vaughn DW, Green S, Kalayanarooj S, Innis BL, Nimmannitya S, Suntayakorn S, et al. Dengue viremia titer, antibody response pattern, and virus serotype correlate with disease severity. J Infect Dis. 2000 Jan;181(1):2-9
16. Alera MT, Srikiatkhachorn A, Velasco JM, Tac-An IA, Lago CB, Clapham HE, et al. Incidence of Dengue Virus Infection in Adults and Children in a Prospective Longitudinal Cohort in the Philippines. PLoS Negl Trop Dis. 2016 Feb 4;10(2):e0004337.
17. Kosasih H, Alisjahbana B, Nurhayati, de Mast Q, Rudiman IF, Widjaja S, et al. The Epidemiology, Virology and Clinical Findings of Dengue Virus Infections in a

Cohort of Indonesian Adults in Western Java. PLoS Negl Trop Dis. 2016 Feb 12;10(2):e0004390.

18. Zailiza Suli. Dengue Prevention and Control in Malaysia. International Conference on Dengue Prevention and Control & International Dengue Expert Consultation Meeting. December 7-8 , 2015. The Magic School of Green Technologies, National Cheng Kung University, Tainan City. Ministry of Health Malaysia

19. Gill BS. Vector Borne Surveillance in Malaysia. Disease Control Division. Health Ministry Malaysia. 2017

20. José de Jesus Dias, Júnior, Maria dos Remédios Freitas Carvalho Branco, Rejane Christine de Sousa Queiroz, Alcione Miranda dos Santos, Emnielle Pinto Borges Moreira, and Maria do Socorro da Silva. Analysis of dengue cases according to clinical severity, São Luís, Maranhão, Brazil. Rev Inst Med Trop Sao Paulo. 2017; 59: e71.

21. Halstead SB, Nimmannitya S, Cohen SN, Yale J. Observations related to pathogenesis of dengue hemorrhagic fever. IV. Relation of disease severity to antibody response and virus recovered. Biol Med. 1970 Apr; 42(5):311-28.

22. Guzmán MG. Thirty years after the Cuban hemorrhagic dengue epidemic of 1981. MEDICC Rev. 2012 Apr; 14(2):46-51.

23. Sam SS, Omar SF, Teoh BT, Abd-Jamil J, AbuBakar S. Review of Dengue hemorrhagic fever fatal cases seen among adults: a retrospective study. PLoS Negl Trop Dis. 2013 May 2;7(5):e2194

24. Shepard DS, Undurraga EA, Lees RS, Halasa Y, Lum LC, Ng CW. Use of multiple data sources to estimate the economic cost of dengue illness in Malaysia. Am J Trop Med Hyg. 2012 Nov;87(5):796-805.

25. Nor Azila, Sharifah Azura Salleh, Hui-min Neoh, Syed Zulkifli Syed Zakaria and Rahman Jamal. Dengue epidemic in Malaysia: Not a predominantly urban disease anymore. BMC Research Notes. 2011, 4:216.

26. Ministry of Health Malaysia. Health Ministry: Dengue cases down in 2017 compared to 2016. The Star Online. 10 Jan 2018.

27. Ministry of Health Malaysia. Almost 83,000 dengue cases nationwide in 2017; 171 deaths. New Straits Times online. 7 April 2018.

28. Norhiza CH, Bailey TC, and Stephenson DB. Climate variability and dengue incidence in Malaysia. ResearchGate. 2012. https://www.researchgate.net/publication/282719779_Climate_variability_and_dengue_incidence_in_Malaysia

29. Rohani A, Ismail S, Wan Mohamad AWN , Omar T , Ibrahim M , and Lee HL. Factors determining dengue outbreak in Malaysia. PlosOne 2018 https://doi.org/10.1371/journal.pone.019326

30. Wiwanitkit V. Dengue Infection. In: Ganim B and Reis A, editors. Dengue Virus: Detection, Diagnosis and Control. 2010. Nova Biomedical Books. New York ISBN: 978-1-60876-398-6

31. P.Raviwharmman Packierisamy, Chiu-Wan Ng, Maznah Dahlui, Jonathan Inbaraj, Venugopalan K. Balan, Yara A. Halasa et al. Cost of Dengue Vector Control Activities in Malaysia. Am J Trop Med Hyg. 2015 Nov 4; 93(5): 1020–1027.
32. Health Ministry Malaysia. PELAN STRATEGIK PENCEGAHAN DAN KAWALAN DENGGI 2009 – 2013. BAHAGIAN KAWALAN PENYAKIT, KEMENTERIAN KESIHATAN MALAYSIA. 4 FEBRUARI 2009
33. Blayney DW. Strengths, weaknesses, opportunities, and threats. J Oncol Pract. 2008 Mar;4(2):53.
34. Meer Ahmad AM. Target real Aedes breeding grounds. The Star Online (Letter to Editor). 7 Jan 2017.
35. Meer Ahmad AM. Questions over dengue control methods. The Star Online (Letter to Editor). 8 Nov 2016.
36. Meer Ahmad AM. Dengue vaccine is still viable. The Star Online (Letter to Editor). 18 Aug 2016.
37. Bisset JA, Rodríguez MM, San Martín JL, Romero JE, Montoya R. Evaluación de la resistencia a insecticidas de una cepa de Aedes aegypti de El Salvador. Rev. Panam. Salud Publ. 2009; 26(3):229-234.
38. World Health Organization. Vector surveillance and control. In: Dengue Haemorrhagic Fever – Diagnosis, treatment, prevention and control. 2nd ed. Geneva, 1997. p. 48-59.
39. H. H. Yap, N. L. Chong, A. E. S. Foo and C. Y. Lee. Dengue vector control: Present status and future prospects. Kaohsiung J Med Sci 10: S102--Slog, 1994
40. Meer Ahmad AM. Reduce cost of dengue tests. The Star Online (Letter to Editor). 22 Jan 2016.
41. Meer Ahmad AM. Why shun the dengue vaccine? Free Malaysia Today News Portal. (Letter to Editor) 30 June 2016.
42. Meer Ahmad AM. A simple strategy to control dengue fever. Free Malaysia Today News Portal. (Letter to Editor) 12 March 2016.
43. Ross PA, Wiwatanaratanabutr, Axford JK, White VL, Endersby-Harshman NM, Hoffmann AA. Wolbachia Infections in Aedes aegypti Differ Markedly in Their Response to Cyclical Heat Stress. PLoS Pathog. 2017 Jan 5;13(1): e1006006.
44. Ye YH, Carrasco AM, Dong Y, Sgrò CM, McGraw EA. The Effect of Temperature on Wolbachia-Mediated Dengue Virus Blocking in Aedes aegypti. Am J Trop Med Hyg. 2016 Apr;94(4):812-9.
45. Schmidt TL, Barton NH, Rašić G, Turley AP, Montgomery BL, Iturbe-Ormaetxe I, et al. Local introduction and heterogeneous spatial spread of dengue-suppressing Wolbachia through an urban population of Aedes aegypti. PLoS Biol. 2017 May 30; 15(5):e2001894.
46. Alyssa Navarro. Clearing the Air: Monsanto Breaks Silence On Zika Virus, Microcephaly And Sumitomo Larvicide. Tech Times. 16 February 2016. http://www.techtimes.com/articles/133955/20160216/clearing-the-air-monsanto-speaks-out-about-zika-virus-microcephaly-and-sumitomo-larvicide.htm

47. US Centers for Disease Control. Information on Aerial Spraying; Aerial Spraying and Mosquito Control. 10 October 2017.
48. "Introduction to Epidemiology" in A Textbook of Community Medicine in South-east Asia. Phoon and Chen PCY, Editors. John Wiley & Sons Ltd. 1986
49. Meer Ahmad AM. Reveal vaccine's efficacy, safety. The New Straits Times. 21 Feb 2017.
50. Meer Ahmad AM. Doubts in the Efficacy and Safety of the CYD-TDV Dengue-Vaccine. Berita MMA Newsletter. March 2017.
51. Ferguson N, Isabel Rodríguez-Barraquer, Ilaria Dorigatti, Luis Mier-y-Teran-Romero, Daniel J. Laydon, Derek A. Benefits and risks of the Sanofi-Pasteur dengue vaccine: Modeling optimal deployment. Science. 02 Sep 2016: Vol. 353, Issue 6303, pp. 1033-1036.
52. Health Ministry Malaysia. Ministry warns of effects of Dengvaxia. The Star Online. Sunday, 3 Dec 2017.
53. Health Ministry Malaysia. Dengvaxia dengue vaccine not distributed in Malaysia, says Health DG. Malay Mail. 03 December 2017.
54. Takeda Newsroom. Takeda's Dengue Vaccine Candidate Associated with Reduced Incidence of Dengue in Children and Adolescents; New 18-Month Interim Phase 2 Data Published in The Lancet Infectious Diseases. 7 Nov 2017.
55. NIH US National Library of Medicine. Phase III Trial to Evaluate Efficacy and Safety of a Tetravalent Dengue Vaccine. Butantan Institute. ClinicalTrials.gov. 13 March 2018.
56. Whitehead SS. Development of TV003/TV005, a single dose, highly immunogenic live attenuated dengue vaccine; what makes this vaccine different from the Sanofi-Pasteur CYD™ vaccine?. Expert Rev Vaccines. 2016 Apr; 15(4): 509–517. Published online 2015 Dec 2.
57. Whitehead SS, Anna P. Durbin , Kristen K. Pierce, Dan Elwood, Benjamin D. McElvany, Ellen A. Fraser, et al. In a randomized trial, the live attenuated tetravalent dengue vaccine TV003 is well-tolerated and highly immunogenic in subjects with flavivirus exposure prior to vaccination. PLOS: Neglected Tropical Diseases. 8 May 2017.