Review Paper

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

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; control and prevention; mosquito-repellents; mosquito-nets; dengue vaccine; primary water-source larviciding; aerial-spraying

EPIDEMIOLOGY

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].

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 – 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].

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].

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 – 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 [10 – 11, 18].

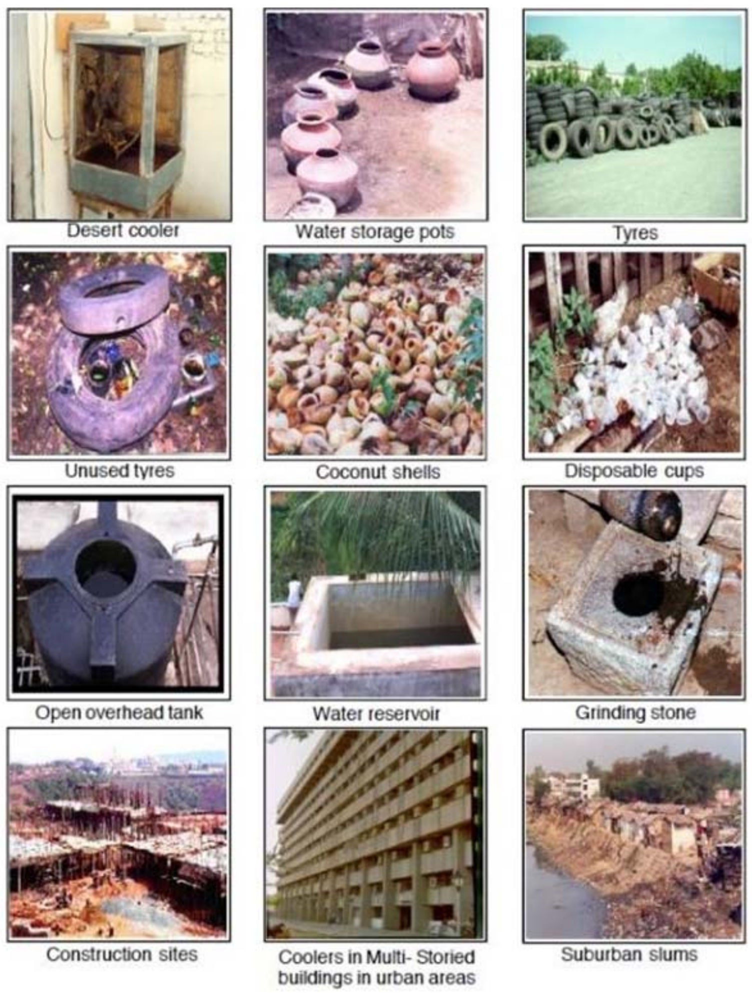

Fig .1. Common Aedes aegypti breeding-sites, including in Malaysia

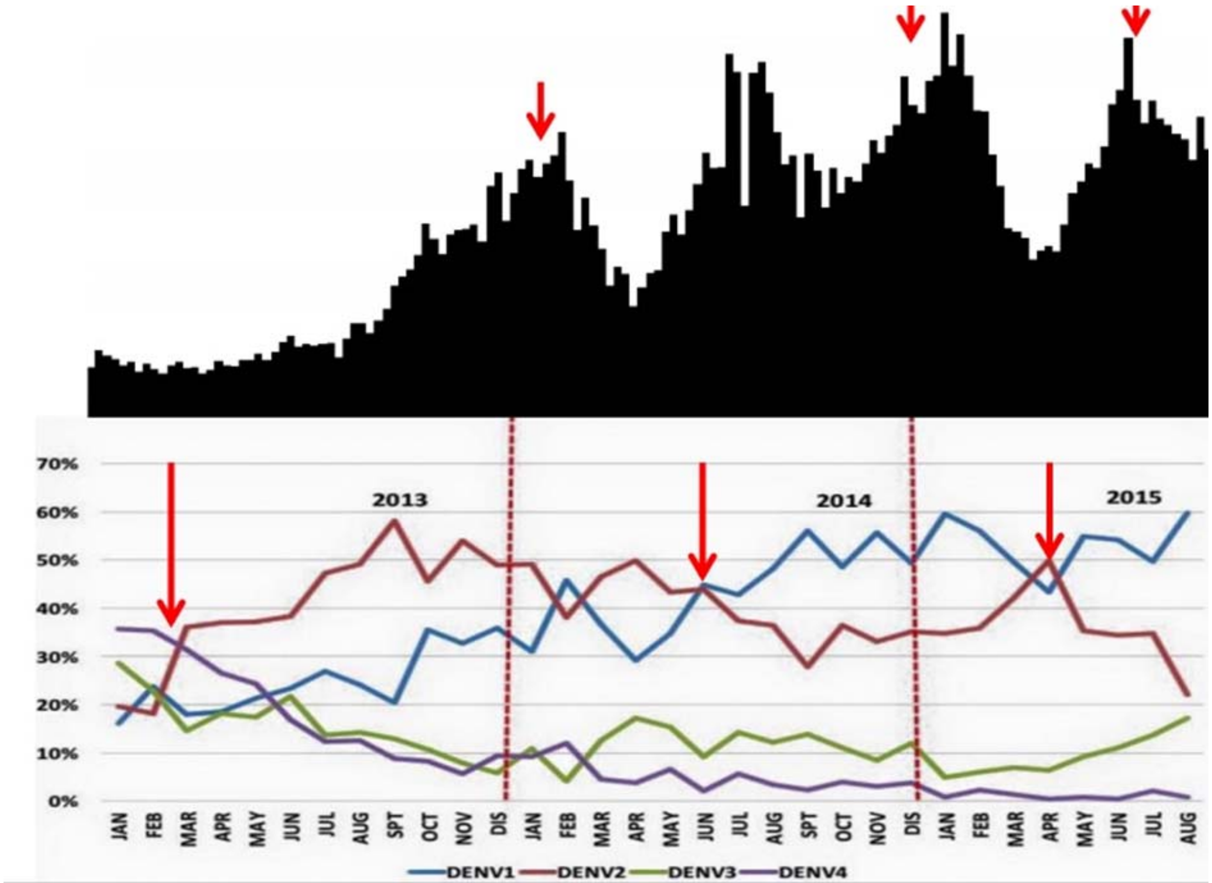

Fig. 2. Circulating dengue-serotypes in Malaysia in relation to Cases 2013 – 2015. [19]

DHF appears commoner in females and those with co-morbids, including diabetes-mellitus and obesity. The case-fatality rate from DHF and DSS also seems much higher in females [20 – 21].

In Malaysia, the disease is endemic since the 1980s [4, 10 – 11, 21 – 22]. Shepard DS et al state that the number of dengue-cases is under-reported here because the country has a passive-surveillance system [22] – 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 [23].

Nur Azila MA et al (2011) studied 1000 people aged 35-74 in Malaysia and found 91.6% to be sero-positive for dengue. 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 [24].

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 [25 – 26].

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, 25 – 26].

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, 25 – 26]. 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 [27].

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 also related with “next-week intervention”, while “conventional intervention” only happened 4 weeks after larvae were found, indicating ample time for dengue transmission [28].

While climate, circulating virus-strain, urban-rural ratio, herd-immunity, population-mobility, community-behaviour, and quality of environmental-sanitation (particularly including dumping of soild-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.

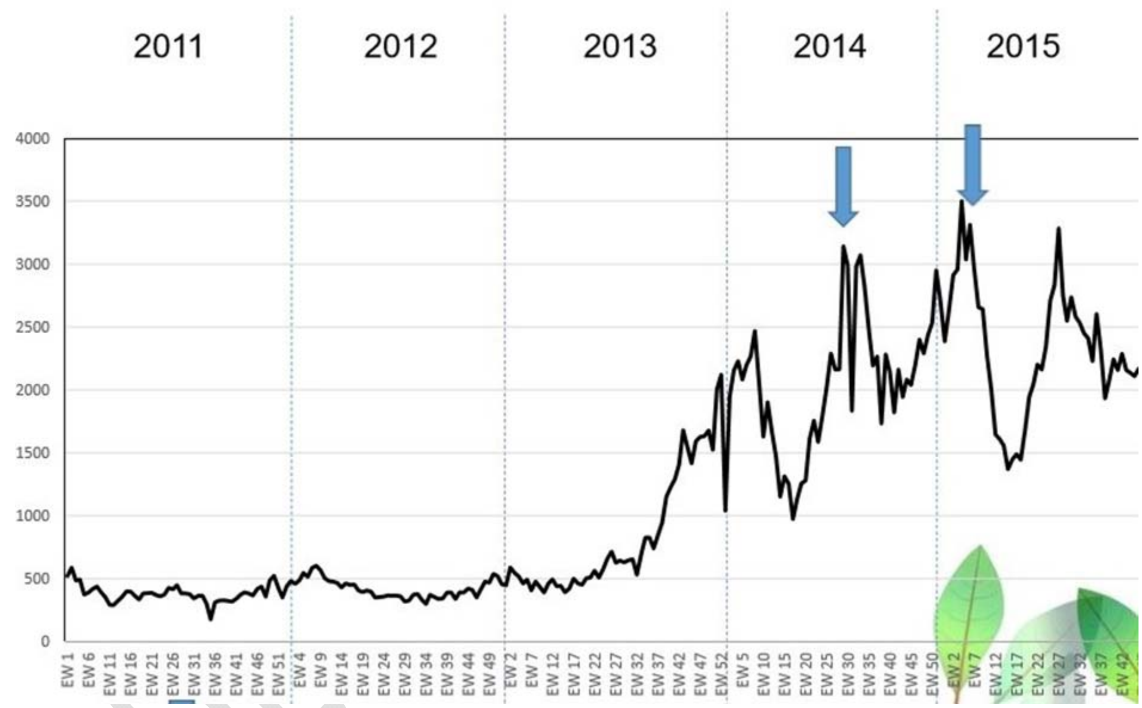

Fig. 3. Weekly-trend in number of Dengue-cases in Malaysia, 2011 – 2015. [18]

	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 [29].

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 [22].

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 [30].

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, 31].

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 [32].

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) [11 – 12,18, 33] .

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 – 11,18, 33]

b. Communication through Mass-media and Social-media [4, 10 – 11, 18, 33]

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, 33]

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 [10-11, 18, 33, 36]

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 [10-11, 18, 33, 37]

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 [36 - 38].

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 [36 - 38].

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, [36 - 38].

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 [36 - 38]

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 [36 - 38].

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 [36 - 38].

4. In view of difficulties with insecticides, **innovative new-strategies** have been developed specifically to outsmart the vector. These are described in Table 1 [36 - 38].

5. **Release of genetically-modified Aedes or Wolbacchia-infected Aedes** [10-11, 34 – 40]:

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.

But, the strain of Wolbacchia shown to be effective in this method is not able to survive ambient-temperatures in the tropics - although this claim is still controversial. 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. [33, 35, 37 – 38, 42 - 43]:

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, 33, 35 - 38]. Besides, diagnosis is usually made on 3rd to 5th day [1 – 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 [36 – 38]	a. Attracts all the hungry and dehydrated adult-mosquitoes (male & female) when they emerge from pupae (especially first two days) b. Since nectar-meals are scarce indoors, the bait is the most readily-available and attractive choice. c. Only needs placement in strategic-locations indoor d. Safe because no chemicals extruding into air or environment e. Mostly used as supplement in control
2.	Attractive Lethal Ovi-position Traps [36 – 38]	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. 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.

	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. 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. [35, 39 – 41, 47]. 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, 35, 39 – 41].

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 [48 – 52].

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 [53].

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 [48, 53].

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 [53].

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 [53]

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 [54 – 56].

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 [54 - 56].

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.

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