Chapter 1

Dengue Fever: A General Perspective

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Abstract

Dengue Fever or commonly known as Dengue, a mosquito-borne arboviral infection has emerged as havoc around the globe. Annually, about 50 million infections are reported, resulting in 22,000 deaths and almost 2.5 billion people are reported living at risk. Dengue infection is caused by Dengue Virus (DENV), which is a member of genus Flavivirus and comprised of ten proteins; three proteins, capsid (C), membrane (M), and envelope (E), play structural role and seven are identified as non-structural that direct DENV replication. Four distinct serotypes: DENV-1, DENV-2, DENV-3 and DENV-4 are transmitted via *Aedes* mosquitoes. Clinically, Dengue patients can be categorized into three groups according to WHO 2009 revised classification. Typical symptoms of dengue include: extreme fatigue; sudden fever (from 3-7 days), headache, joint, muscle, and back pain; vomiting and diarrhea, appetite loss; skin rash along minor bleeding. *Aedes aegypti* is geographically distributed in tropical areas and breeds in artificially filled water containers i.e. drums, tyres, flower vases plastic food containers, tin cans, etc. Due to four viral serotypes and non-availability of the model animal for dengue, producing vaccines is a challenging task. Thus, Dengue can be managed using various vector control strategies through physical, chemical and biological means.

Keywords: dengue fever, dengue hemorrhagic fever, dengue shock syndrome, *Aedes aegypti*, DEN virus

1. Historical background

The word "dengue" is known to be derived from Swahili language "ki denga pepo", which illustrates the meaning as "sudden cramp like seizure". The signs and indications that are suggestive of this viral disease can be tracked back to Chinese Chin Dynasty (265–420 AD) where this infection was believed to be a type of water poison and reported to be linked with insects and water [1]. Some of the historical accounts for dengue fever states that about 500–600 years ago, it appeared from Africa while the first and foremost outbreak of this deadly disease reached other parts of world in 1780s [2]. The detection and isolation of dengue virus date backed to the World War II and it was documented in Japan for the first time in 1942 [3]. Dengue-like symptoms have been reported in early Chinese manuscripts which can be traced back to 992 and to 1600s in the West Indies [4]. In another report, Benjamin Rush observed the first detailed symptoms of dengue shock syndrome (now severe dengue) in 1780 during an outbreak in Philadelphia near Delaware River [5]. Similar disease symptoms were observed in North America along Atlantic coast during eighteenth–nineteenth centuries, on the Caribbean Islands and the Mississippi basin [6]. Bancroft reported for the first time that *Aedes aegypti* mosquito is vector of dengue virus [7]. However, modern research about dengue virus was not started until 1943–1944. For the first time culturing and isolation of this virus was performed from suckling mice brain [8].

2. Geographic distribution

It is scientifically accepted that dengue viruses originated in monkeys and jumped to humans in Africa or Southeast Asia between 100 and 800 years ago. Dengue fever remained geographically

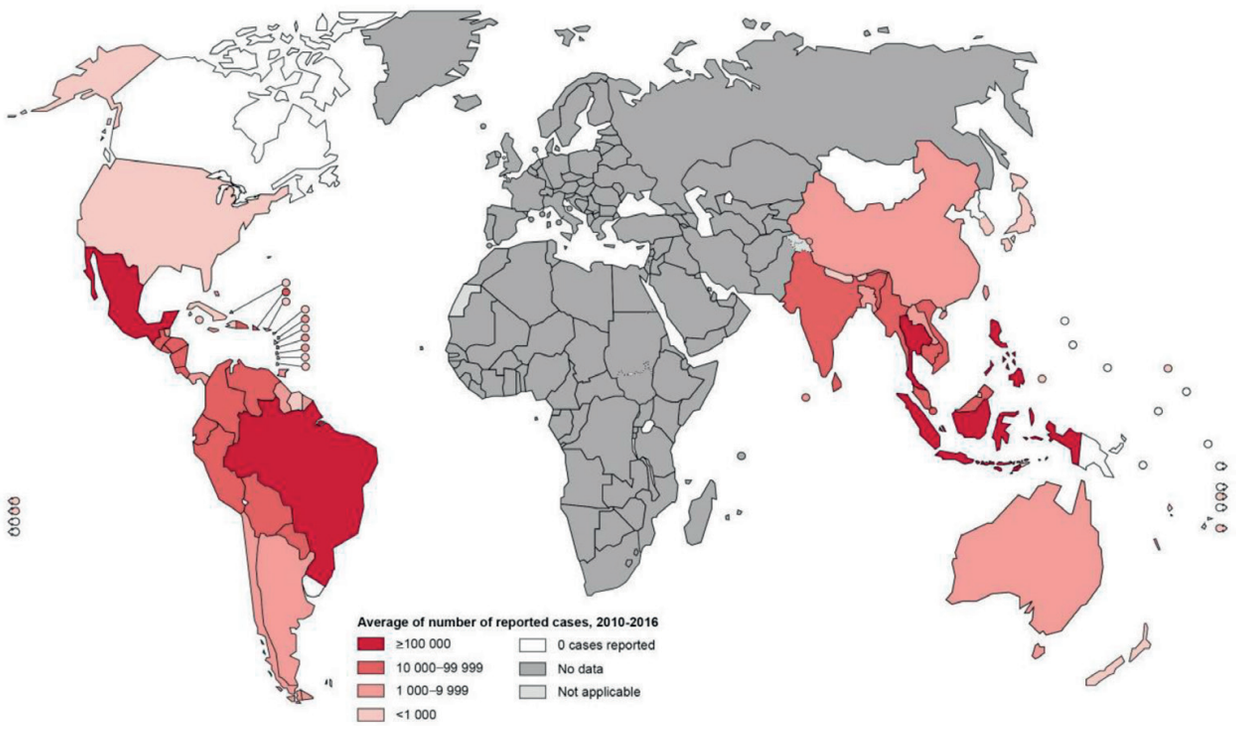

Figure 1. Distribution of dengue worldwide (taken from www.who.int/denguecontrol/ epidemiology/).

restricted till 1950s. But due to the Second World War, transport of *Aedes* mosquitoes happened around the world which played a crucial role in the dissemination of the viruses. Now, approximately 2.5 billion people live in areas where there is a risk of dengue transmission [9–12].

During 1850s, first case of dengue was documented in the Philippines and Thailand. Later, after 1980s large number of cases began to appear in the Caribbean and Latin America. Today, Dengue is endemic in at least 100 countries in Asia, the Pacific, the Americas, Africa, and the Caribbean. Dengue fever is reported to prevail in 26 states [13–15]. DENV-2 was the predominant serotype in dengue outbreaks that occurred before 2000 but DENV-3 was the predominant serotype between 2000 and 2009. After 2010, DENV-1 dominated global dengue outbreaks, and DENV-4 was the least frequently identified serotype [16, 17]. The geographical distribution of dengue with respect to countries has been shown in **Figure 1** which explains the current prevalence of this disease around the world [11].

3. The vector

Dengue virus spreads due to infected females of genus *Aedes*, significantly form *Aedes aegypti* and *Aedes albopictus*. There has been a serious concern amid public health departments. In newly invaded countries, *Aedes albopictus* would cause severe epidemics of arbovirus diseases (it is considered as a competent vector transmitting about 22 arboviruses), especially all four serotypes of dengue; however generally it is transmitted by *Aedes aegypti*. *Aedes albopictus* persists to spread, taking the place of *Aedes aegypti* in some areas. [18] *Aedes albopictus* might serve as a maintenance vector of dengue in non-urban areas of Pacific islands and South-east Asia. *Aedes albopictus* is not considered an imperative urban dengue vector, but in a few countries where *Aedes aegypti* is not present, that is, the Seychelles, parts of China, Japan and Hawaii [18]. The biting females of *Aedes albopictus* were discovered firstly in 1999, in Southern Cameroon; it provoked survey in 2000 and then adults as well as breeding populations were identified in five major cities of the country mainly breeding in old tires imported from Nigeria and USA which were infested with the mosquitoes [19].

Aedes is best known vectors of dengue fever and yellow fever. Some species of *Aedes* are also vectors of viral disease and filariasis [20]. Several serotypes of the dengue virus are carried to human beings via the bites of *Aedes* mosquitoes infected with dengue virus. *Aedes aegypti* is considered one of the most crucial vector whereas *Aedes niveus*, *Aedes albopictus* and *Aedes polynesiensis* have been reported as secondary vectors in most of the regions of the world [9]. *Aedes aegypti* and *Aedes albopictus* are known as the two primary vectors for transmitting the dengue in most parts of South Asia, including India. As the distribution of this affliction is concerned in respect to geographically, it is characteristically parallel to that of the principal vector species, *Aedes aegypti* [21]. Dengue mosquito is a subtropical and tropical species having distribution throughout the world [22]. Dengue virus spreads due to infected females of genus Aedes, specifically through *Aedes aegypti* in urban settings and *Aedes albopictus* in sylvatic areas [18]. *Aedes albopictus* (Diptera: *Culicidae*), is basically endemic to Pacific and Indian Oceanic islands, and from South-east Asia, it spread to America, Europe and Africa in recent decades dormant eggs in the tires. Venereal and possibly vertical transmission of dengue virus takes place by infected female of *Aedes aegypti* to its progeny (transovarian) and also from infected male to the female during the process of copulation, respectively [23].

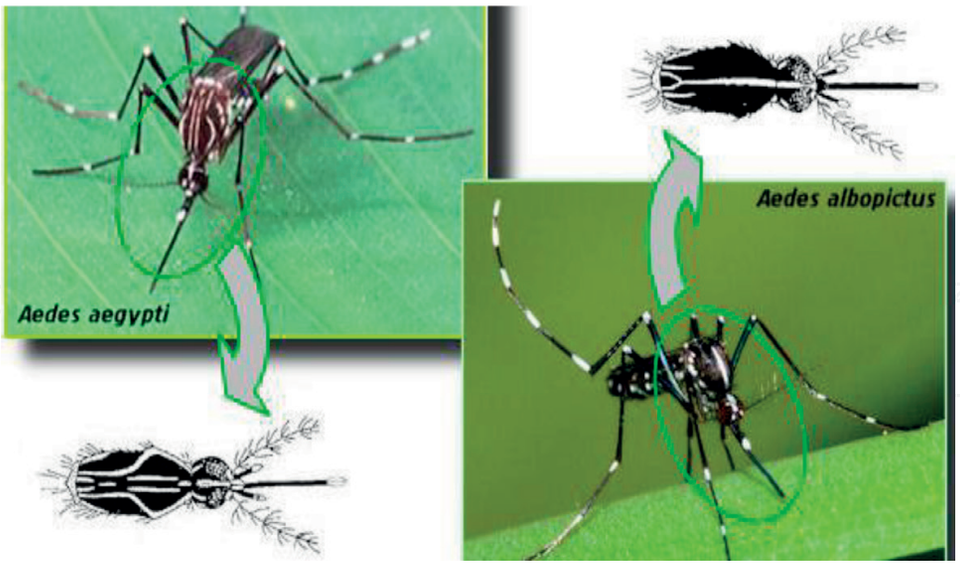

Figure 2. Difference between *Aedes aegypti* and *Aedes albopictus* (Source: http://www.mdsaude.com/wp-content/uploads/2012/04/aedes-aegypti-e-aedes-albopictus.jpg).

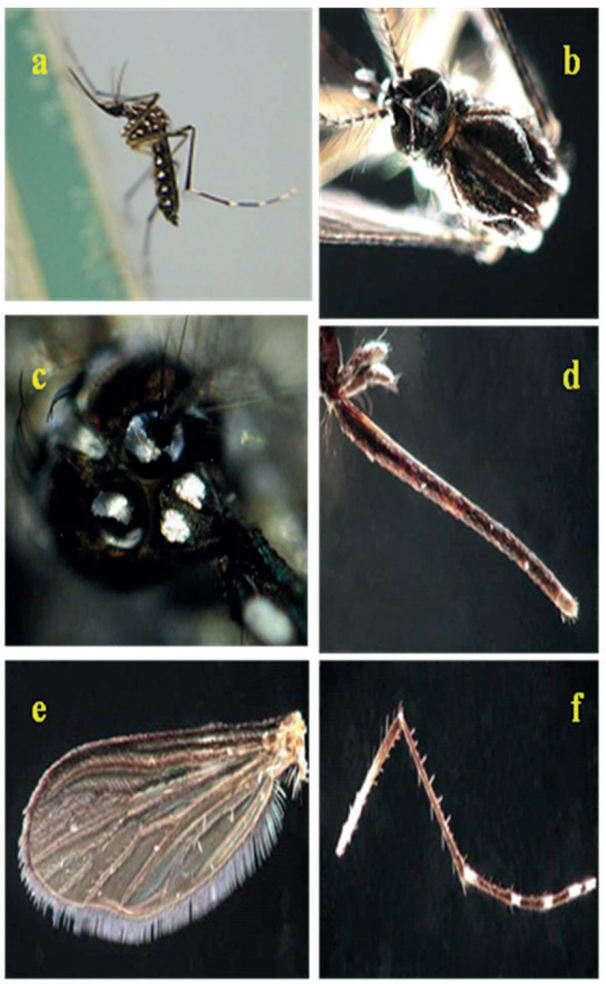

Figure 3. *Aedes aegypti* with its taxonomic characteristics. (a) *Aedes aegypti*; (b) Lyrix at thorax; (c) Clypeus; (d) Proboscis; (e) silvery scales on wing; (f) white stripes on leg.

The adult of yellow fever mosquito have approximately 4–7 mm size and it range from small to medium-sized mosquito. To the human eye, these mosquitoes are similar to the Asian tiger mosquito with a minor dissimilarity in thorax patterns and size. Adults of *Aedes aegypti* have white scales that form the shape of a violin or lyre, on the dorsal side of the thorax while the adults of *Aedes albopictus* is characterized by a white stripe to the middle at the top of the thorax region. Every tarsal portion of the hind legs exhibit white bands, this is what appear to be stripes. Abdomen is usually dark brown to black in color, but also exhibit white scales. Males are smaller than females, and can be discriminated by small palps tipped with white or silver scales. Males are characterized by plumose type of antennae; however, females possess sparse short hairs. Under a microscope, male mouthparts are viewed as modified structure for nectar feeding, and mouthparts of female are modified for feeding f blood. The proboscis from both sexes is darkly colored, and the segment above the proboscis which is known as clypeus has two clusters of white scales. A characteristic feature of all *Aedes* species is the pointed tip of the abdomen (**Figures 2** and **3**) [24].

4. Life cycle of *Aedes aegypti*

Aedes aegypti is geographically distributed in tropical areas and it breeds in artificially filled water containers such as drums, tyres, flower vases such as plastic food containers, tin cans and old motor parts [4]. *Aedes aegypti* is a holometabolous type of insect, going through complete metamorphosis meaning four developmental stages from egg to adult stage. Life span of adult can range from 2 weeks to about 4 weeks but it depends on conditions of environment. A female mosquito lay eggs for about 4–5 times during her entire life span and average number of eggs in single spawn ranges from 10 to 100 eggs. *Aedes aegypti* are found in three different polytypic forms: sylvan, domestic, and peridomestic. The domestic type usually breeds in urban habitats, mostly inside or around houses. The sylvan type is rural form which breeds in tree holes, normally in forests, and the peridomestic form generally lives in environmentally-modified regions as coconut farms and groves (**Figure 4**) [24].

As the spread of mosquitoes is concerned, it occurs by active flight (adult) and passive transportation (immature stages) through international trades. Successive waves of invasion of *Aedes aegypti* and *Culex pipiens* have been aided by commercial passages also from fifteenth century to onward. *Aedes aegypti* substituted *Aedes albopictus* in Asian countries during the twentieth century [25, 26].

5. The virus

Dengue infection is transmitted by dengue virus (DV) which is a member of genus *Flavivirus*. This Arbovirus group of viruses is specifically transmitted via insect vectors. Mature viral particles have diameter of 40–50 nm, spherical shape and 11 kb, having positive single stranded RNA which has a 5′-methyl cap with a single open reading frame. Genus *Flavivirus* has 4 antigenically associated but four distinct serotypes known as DENV-1, DENV-2, DENV-3 and DENV-4 [27, 28]. The serotypes are evolved from a common ancestor and all are considered

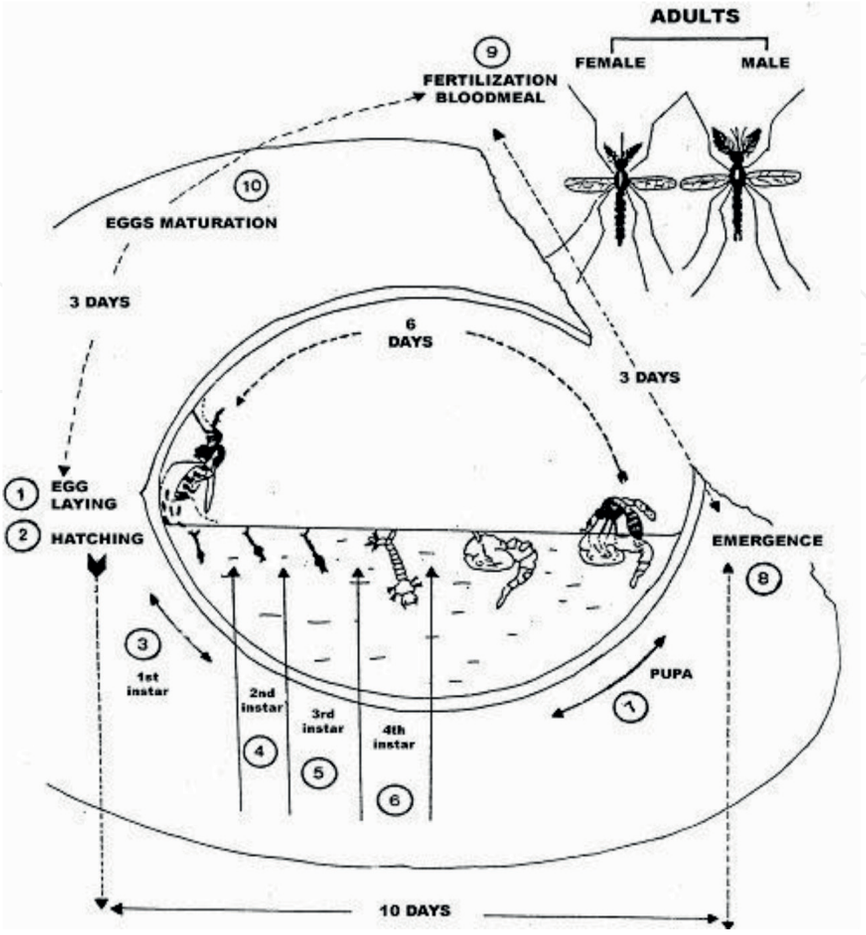

Figure 4. Lifecycle of *Aedes aegypti* (http:/www.ipnc.nc/FCKeditorFiles/Image/entomo_20.jpg).

causative agent of broadly analogous disease spectrum in humans [29–31]. It consists of ten proteins, out of which three proteins, capsid (C), membrane (M), and envelope (E), play structural role and seven (NS1, NS2A, NS2B, NS3, NS4A, NS4B and NS5) are identified as non-structural that direct DENV replication. Approximately 17% of these virions are lipid by weight which forms a lipid bilayer between E/M outer shell and the nucleocapsid core [32, 33].

Binding of dengue virus like most of the other viruses to its receptor is regulated by envelop protein (E). In mammalian cells, all the serotypes binds with nLc4Cer, DC-SIGN/L-SIGN, Heparan sulfate as well as Mannose receptors. Additionally DENV-2 serotype also show binding trend with HSP70/HSP90, CD14-associated protein, GRP78 and two other unknown protein receptors. On the other hand DENV 1–3 serotypes can also attach with Laminin receptor while DENV 2–4 serotypes are also found to bind with protein receptor which is unknown [34]. After binding with particular receptors through receptor-mediated endocytosis, virion fuses with acidic lysosomes. Then, the viral particle releases its RNA in the cytoplasm of host cell for the synthesis of viral proteins. After the synthesis of all the required proteins, viral RNA starts generating a minus strand, and then transcription of new plus stranded molecule occurs. Hundreds of copies of viral particles are generated from a single virus particle leading towards cellular damage and even death. RNA-dependent RNA polymerases (RdRps) encoded by the virus itself and other cellular factors catalyze the infection cycle of this virus

[35]. However the exact mechanism of vascular permeability and hemorrhagic fever is not clear. Studies are being oriented to understand these mechanisms specially focusing on the role played by T-cell immune response. High levels of interferon alpha were reported during secondary infection after 1–2 days of fever onset [36] while high concentration of soluble interleukin 2 receptor, interferon γ, soluble CD8 and soluble CD4 interleukin 2 were also described by researchers during the outset of vascular permeability [36, 37].

6. Clinical aspects

The most commonly occurring DENV infection transits through an asymptomatic or mildly symptomatic course [38]. Symptomatic dengue fever is usually accompanied by headache, malaise, retroorbital pain, arthralgia, and myalgia with a severity that honors "break-bone" fever alternative name of this disease. It lasts from three to 7 days. A small fraction of these patients evolve to the life-threatening clinical form of severe dengue, usually preceded by the appearance of warning signs (see below). All the four viral serotypes cause resembling disease symptoms.

In comparison to the previous 1997 version, the WHO revised classification of 2009. This makes more precision towards sensitivity and specificity of dengue cases. While being reported having changed dengue features with the passage of time during treatment; the dengue affected patients are categorized in Group A or Group B. More concern is recommended if symptoms becoming serious for next step of necessary hospitalization [39, 40]. As WHO 1997 version already includes plasma leakage and bleeding; but, however, the WHO 2009 classification entails target monitoring and organ impairment exhibiting the situation more clearly towards future dengue disease cure. Group C category of dengue patients has been explained in a better way in revised classification of WHO version 2009. This version, indeed is a practical guidance and very much helpful in dengue endemic areas especially where medical facilities are lacking. It is worth mentioning that WHO 2009 classification also highlights the other co-existing factors such as pregnancy, child and old age, diseases like diabetes and various social circumstances [41].

The WHO 2009 revised dengue classification stratifies disease into the following:

1. Without warning signs of dengue,
2. With warning signs of dengue (i.e., abdominal pain, vomiting, fluid accumulation, mucosal bleed, lethargic condition, liver enlargement >2 cm, and rapid decrease in platelet count), and
3. Severe symptoms of dengue.

Furthermore, three categories have been described in 2 WHO scheme of dengue-affected patients:

i. Group A includes patients without warnings signs,
ii. Group B includes patients with more than one warning sign, and annotated with certain coexisting conditions such as pregnancy, infancy, old age, obesity, diabetes, renal failure, and chronic hemolytic diseases), and with certain social circumstances,

iii. Group C includes patients with severe plasma leakage, severe bleeding leading towards extreme condition of organ impairment [41].

The classification is meant to make it realized that the group is clearly identified so that patients are going to be treated keeping in view the relevant category.

7. Diagnosis of dengue fever

Dengue infection symptoms are the major tool for its diagnosis. However, this is not a reliable method for the confirmation of dengue infection but laboratory studies are needed [42, 43]. Dengue virus in the initial stages may cause fever to dengue fever or later on more it can result in severe dengue. Common tools for the detection of dengue infection in laboratory tests include; an identification of the particular viral serotype, genomic sequences, viral antigen, genomic sequence, and/or antibodies. Major advances in the diagnosis of this infection include IgM captured ELISA, dengue specific monoclonal antibodies, viral RNA detection by nucleic acid amplification tests (NAAT), and viral isolation from mosquito cell lines and also live mosquitoes, all these are reported to have major advances in dengue diagnosis. Diagnosis involves two levels of detection. At level one, the patient is in acute febrile phase, where NS1 antigens and viral RNA can be detected, and at level two is the stage in which IgG and IgM antibodies are abundant in blood with the post febrile period [44]. Acute stages of dengue may be represented by flu like fever in which diagnosis is made possible by identifying viral RNA/proteins in the patient's blood. Dengue viral RNA can also be identified in early stage of infection using RT-PCR. This technique is quite reliable but unaffordable for the poor people [45, 46]. ELISA test is also being utilized to identify primary as well as secondary infection by utilizing dengue-specific monoclonal NS1 antibody to identify NS1 in victim's blood [47–49]. MACELISA assays in combination with NS1 Ag can be utilized for the detection of dengue viruses in earlier stages of infection [50]. Commonly used laboratory methods include immune-fluorescence tests, capture ELISAs, and hemagglutination assays [51]. Nonetheless, it is important to consider that serological tests can be misleading due to cross-reactivity while there is more that flavivirus circulating in the region.

8. Control of dengue fever

Vaccines against dengue are difficult to develop. Nonetheless, as for December of 2015, CYD-TDV vaccine was approved for human use, and to date it remains as the sole vaccine with this status. As for specific treatments none is available, however various anti-viral natural entities are being evaluated for the elimination of dengue virus [32, 47, 48, 52–54].

There are several methods used to control dengue infection. The first and most important preventive measure is the prevention of contact with infected mosquitoes. *Aedes* mosquitoes usually have biting preferences during daytime and its contact can be minimized in various ways, for example, proper management of stored water and wastes, use of insecticides to eradicate the mosquitoes, use of mosquito nets and coils as well as repellents, use of wearing which minimize the exposed body surface. Insecticide treated nets (ITNs) are also available

in the market for the protection of people including young children, pregnant women, old people [55].

9. Control of vector *Aedes*

The best way to control dengue is to improve capabilities of mosquito abatement especially in the most populated areas where vector densities are high due to availability of hosts [18].

10. Public awareness

Public awareness counts in integrated pest management at a significant level, various examples can be sited from the literature when community efforts played a role for the eradication of disease agents. As *Aedes aegypti* was eliminated from countries various regions of the USA during the 1960s when relatively well funded eradication campaign supported by a high degree of political and community were involved. The effective collaboration of a well-educated society with the assistance of mosquito control well-trained staff will be the most compelling and economically reliable method for the removal of *Aedes albopictus* populations in rural and suburban regions [18].

11. Chemical control

The vector borne diseases are controlled worldwide, simply via controlling the vector. This thumb rule equally implies on dengue vector *Aedes* mosquitoes as well. Integrated Vector Management (IVM) mostly focuses on chemical control using insecticides; most frequently used are reported organophosphates and pyrethroids by WHO against dengue, malaria as well as yellow fever. These insecticides are affective against larvae, pupae and adults as well [25, 56, 57]. No new public health insecticides have been developed for mainstream vector control in disease-endemic countries (DECs) for the last three decades. Narrow range of public health insecticides necessitates new, safe, less expensive, environment friendly insecticides to replace those already being commercially used and mostly have been reported to develop resistance. Pyrethroid insecticides such as Permethrin, Deltamethrin, Cypermethrin, Cyhalothrin, etc. and DDVP organophosphate insecticides have been frequently used against mosquitoes and flies at household level. However, pyrethroid insecticides are reported to develop resistance. Hence, synergistic use of organophosphae and pyrethroid insecticides is being used now-a-days in order to combat this resistance menace [58]. New insecticides which are safe for health and environment as well demand investment. It is estimated that about US$70 million amount is required to develop a new insecticide. Public health insecticide market encompasses about US$151.2 million worldwide, hereby, shows the overall small size market. It is a dire need of time to engage commercial partners in the development of new insecticides. It has been suggested that both commercial and academic partners must collaborate and work together. In addition, community level health workers must be stimulated

to locate and target the investment so that safe, cost-effective, user-friendly vector control insecticides can be developed.

12. Biological control

Although, chemical use in the form of synthetic insecticides remains promising factor for the control of insect vectors; however, indiscriminate and overuse pose insecticide resistance issues [58]. Moreover, various health and environmental concerns make the use of insecticide questionable. Thus, it is imagined that in future only those techniques will be accepted which may overcome the problems related to chemical insecticides. Recently, non-chemical methods have been summed-up into "biopesticides"; meaning thereby simply to kill the pest using material originated from living things [59]. Hence, it necessitates to explore biological control agents like various predators and parasites, that is, viruses, fungi, bacteria, etc. to look for a potent agent for the development of safe control program. Various pathogens and predators have been reported to use against mosquitoes as biological control agents. Recently, in Vietnam, copepods were used to control larvae of *A. aegypti*. At local level, the control program was launched very successfully and showed good results [61, 62]. In addition, a bacterium *Wolbachia pipientis* which is an obligate intracellular bacterium and vertically transmitted from mother to their offsprings and causes cytoplasmic incompatibility. It has been reported to present in 60% populations of insects in field conditions. Wolbachia infects the gonads and ensures transmission to the next host generation and orchestrates various reproductive manipulations in host. The symbiont can also cause feminization of genetic males, parthenogenesis and male killing, depending on the host species [63]. Thus, via females the Wolbachia spreads in the host populations and ultimately hinders its increase in number in future. It is reported that Wolbachia infections spread upto 100 km per annum. The Wolbachia strains were manifested and manipulated successfully in 1967 in Burma against filariasis vectors, where Wolbachia infected male *Culex quinquefasciatus* were released in wild populations. In principle, Wolbachia infection affects the sperm and prevents the further reproduction as a measure of local mosquito population control [65].

The sterile insect technique (SIT) is widely tested strategy in insects; wherein, males are treated with either sterilizing chemicals or exposed to γ-irradiation producing random dominant lethal mutations; means only one locus containing the DNA damage can cause dominant effect in the form of lethality. The SIT males when mate with normal females results non-viable offsprings leading to elimination of the populations in successive generations [65]. Another approach is RIDL (release of insects carrying a dominant lethal mutation) which is an improved version of SIT using transgenic technique and specifically focuses on female-killing. For instance, gene specifically expressing in the flight muscles were made transgenically expressed low and the resulting females in the offsprings would not be able to fly properly which causes its non-feeding on human blood meal which ultimately leads towards low fecundity [67]. Specific transgenic approaches have been proved successful also in pupae and adults [68, 69]. This RIDL techniques is being exploited and deployed by Oxitec® in Brazil and Malaysia and reproduced appreciable results [70]. Subsequently, *Bacillus thuringiensis*

israelensis (*Bti*), methoprene and the insect growth hormone are also proven to be quite effective against *Aedes albopictus* in the laboratory as well as in the field [57, 71–75].

13. Botanical control

Plants as a whole and/or their certain parts plus various products originated from different plants have been incorporated in the control programs from long time ago. However, plant oils have been annotated with potentially good insecticidal properties [76, 77]. Plant extracts are reported as fumigant and caused ovicidal, larvicidal, and overall insecticidal activity against various insects. The plants derived insecticides; mostly mentioned as biopesticides are non-hazardous to the environment, cheap, and are considered safe to human as well as other animals. Black pepper extracts have been shown with significant potential as adulticide against *Aedes aegypti* and *Anopheles stephensi* [78].

It is thus, suggested that plant extracts have promising capability to control the mosquitoes. Being safe to human health and to the environment; these can be successfully incorporated in mosquito control programs [79]. In addition, a few plants extracts have been successfully tested against some viral diseases. Aforementioned wherein the life cycle of dengue virus; DENV makes an attachment with host via host receptors and envelope proteins; suggesting thereby that DENV infection can be controlled via inhibition of host-viral interactions using plants extracts. Moreover, NS2-NS3 protease and NS5 have also been reported as significant antiviral drug targets due to their impact on viral replication and other cellular processes as well [80, 81]. Several medicinal plants such as *Momordica charantia* and *Andrographis paniculata* have been reported in inhibiting the replication cycle of DENV. Few of the weed plants have been shown to cause insecticidal and enzyme inhibitory activities in insects [83, 84]. Further investigations are needed to develop potential dengue treatment [85].

14. Conclusion and future perspectives

Dengue viral disease is an emerging health concern in many regions of the world and has become a serious threat in many areas of the world including Southeast Asia and Pakistan. The control of the dengue is difficult as there is no vaccine available so far. Vaccine preparation against dengue requires a tetravalent vaccine but no such licensed compound has been prepared so far. However dengue viral envelope proteins can be targeted to make an effective drug against dengue as these proteins are involved in the entry of the virus into the host cell. Several medicinal plants have been identified so far which show significant inhibitory results against dengue but still there is a need of proper medicine which can show promising results. In future, exploration of interaction of *Aedes albopictus* and other mosquito species is required. *Toxorhynchites* mosquitoes should be searched out for their predatory role against *Aedes albopictus* and *Aedes aegypti*. Vectoral role of *Aedes albopictus* and *Aedes aegypti* must be regulated in and between countries. In addition, the predominant serotype in dengue outbreaks can be managed through respective vaccine especially against the documented serotype.

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