An Elsevier Indexed Journal ISSN-2230-7346

Journal of Global Trends in Pharmaceutical Sciences

CURRENT APPROACHES IN THE MANAGEMENT OF DENGUE: A REVIEW

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ARTICLE INFO

Key Words

Dengue, DENV, Dengue Hemorrhagic fever, mosquito-transmitted disease

ABSTRACT

Dengue is an arthropod-borne infection caused by a flavivirus, also known as break bone fever. Dengue is transmitted by infected Aedes mosquito and is associated with severe manifestations like hemorrhagic fever and hemorrhagic shock. Endemic areas of dengue fever extend over 100 countries. Roughly 2.5 billion people live at risk of dengue infection. Waves of infection occur in epidemics with thousands of individuals affected, creating a huge burden on the limited resources of the country's health care system. As it is caused by a virus, there is no specific drug or antibiotic to treat it, the current approaches are entirely supportive care in the form of judicious fluid replacement and close clinical monitoring during the critical phase of the illness. Different agents are under investigation as potential anti-dengue drugs, which include anti-viral drugs, host modulators, RNA interference drugs, etc. The main objective of this review is to provide an update on current approaches for the treatment and management of dengue fever.

INTRODUCTION

Dengue is an acute mosquito-transmitted disease, caused by a silent, urban mosquito vector including *Ades agepty ,A.polysensis , A.sucutellaries, A.albapictus*. Other modes of transmission are via blood products, organ, and vertical transmission. Nowadays, it has emerged as the most abundant vector- born viral infection [1]. Dengue virus occurs as four serotypes (DV-1, DV-2, DV-3, DV-4). It is a protective standard RNA virus, encoding a polyprotein precursor to generate at least 10 proteins, including three structural proteins those are core, membrane-associated protein, envelop protein and several nonstructural proteins (NS1, NS2a, NS2b, NS3, NS4b, NS5) figure 1[2].

All four serotypes infect man, and infection with one serotype does not confer protection against another serotype. In contrast, infection with second dengue appears to be, in some cases enhanced by pre-existing antibodies generated from primary infection. This phenomenon is said to be an Antibody-Dependent Enhancement or ADE [3]. Southeast Asia, western pacific and America are the endemic regions where incidence and case fatality is observed for dengue hemorrhagic fever [2]. The latest guidelines of 2018 world health organization have outlined several warning signs for dengue such as:

- Abnormal pain or tenderness

- Persistent vomiting
- Clinical fluid accumulation
- Mucosal bleeding
- Restlessness
- Laboratory increase in hematocrit count with a rapid decrease in platelet count [4].

Severe syndrome recently has also been recognized in children infected with the virusthat is characterized by increased vascular permeability and abnormal hemostasis. Replication of dengue virus takes place in cells of mononuclear phagocyte lineage and enhance dengue virus by sub neutralizing the concentrations of dengue antibody [1]. This antibody-dependent enhancement of infection regulates dengue disease in human beings. One of the defining characteristics of severe disease is increased capillary permeability causing plasma leakage, which can lead to intravascular volume depletion and if left untreated, causes shock and death. The disease can be controlled by restricting the growth of viruses in monocytes. Efforts to control this disease are dependent on understanding the pathogenicity of the dengue virus and their transmission dynamics. Currently, there is no specific treatment for DENV, the recent hopeful vaccine has been deemed ineffective and there is no prediction of complete vector control [3].While no therapeutic agents exist for dengue infections, the key to successful management is timely and judicious use of supportive care, including administration of isotonic intravenous fluids, and close monitoring of vital signs and heamodynamic status, fluid balance and hematological parameters[5]. The present review discusses current approaches in the management and treatment of dengue along with an overview of dengue vaccines.

Clinical dengue: Infection with any of the four dengue serotypes can produce the full spectrum of illness and severity. It ranges from a mild, non-specific febrile syndrome to classic dengue fever, to severe form, dengue hemorrhagic fever and dengue shock syndrome. Dengue infected patients are either asymptomatic or symptomatic.

- **Asymptomatic infection:** They have no clinical signs or symptoms of the disease. As many as one-half of all dengue infected individuals are asymptomatic [6].
- **Symptomatic infection:** They have one of three clinical presentations those are
    1. Undifferentiated fever
    2. Dengue fever with or without hemorrhagic fever
    3. Dengue hemorrhagic fever or Dengue shock syndrome [7].

- **Undifferentiated fever:** The patient experiences fever with mild non-specific symptoms that can mimic other acute febrile illnesses. The diagnosis will remain unknown.
- **Dengue fever with or without hemorrhage:**Clinical presentation of dengue fever and early phase dengue hemorrhagic fever are similar. It occurs when a patient develops dengue fever. These patients are typically older children and adults and are with 2 to 7 days of high fever with other symptoms like severe headache, retro-orbital eye pain, myalgias, mild hemorrhagic manifestation. The development of dengue hemorrhagic fever can be detected at the time of defervescence so that appropriate therapy can be initiated[6].
- **Dengue hemorrhagic fever or dengue shock syndrome:** The third clinical presentation results in the development of dengue hemorrhagic fever, which some patients progress to dengue shock syndrome. It occurs asthe Febrile phase, the critical phase(plasma leak phase) or the Convalescent phase(reabsorption) [7].

All patients with dengue hemorrhagic fever recover rapidly with timely initiation of

judicious fluid management and careful monitoring[5]. This is due to the period of increased vascular permeability is time-limited [lasting 24 to 48 hours] and the functional change in the vascular endothelium appears to be entirely reversible with no known permanent structural defect.

DRUGS USED IN THE TREATMENT OF DENGUE: There are multiple anti-DENV agents in various stages of development which are discussed below and summarized in table 1.

I. NS3-protease inhibitors:

a) BP13944:
BP13944 is an effective small molecule that targets DENV NS3 protease, developed via high-throughput screening (HTS) of 60,000 compounds using a stable cell line harboring. BP13944 reduced the expression of the DENV Replicon reporter in cells. It inhibits the synthesis of viral RNA in all four serotypes of DENV [8].

b) Bowman-Brik inhibitors: These are protein molecules, mainly acting on NS3 protease, contains two inhibitory domains for enzymes similar to trypsin and chymotrypsin.Its structure provides a starting point for the design of site-specific mutations to probe the mechanism of catalysis by the catalytic domain, its activation by the regulatory domain and for the design of specific inhibitors of enzymatic activity [9].

II. NS5-Methyltransferase inhibitors:

a) Ivermectin: It is an anti-helminthic, anti-viral drug. Ivermectin can inhibit NS5 methyl transferase, NS3-Helicase and NS5 polymerase. It can directly or indirectly inhibit DENV-2 multiplication [10]. Ivermectin is being effectively used in blocking the transmission of dengue.

b) Ribavarin: Ribavarin is a synthetic guanosine analogue, inhibits inosine monophosphate dehydrogenase with resulting GTP pool depletion. Ribavarin is a broad-acting inhibitor of RNA and DNA viruses. Ribavirin has been used limitedly due to its toxicity of both aerosolized and oral formulations. Ribavirin has been shown to have anti-DENV properties in several cell lines and primary cells and is often used as a positive control in cell culture assays of anti-DENV compounds [11]. Recent studies have shown evidence of the potentiation of a sub-effective dose of α glucosidase inhibitor CM-10-18 by ribavirin.

III. NS5 polymerase inhibitors:

a) Balapiravir [RG1626]: It is a recent nucleoside monophosphate prodrug with better potency. It represents the largest class of antiviral agents and has been actively pursued potential therapy of anti-dengue viruses. It mainly targets inhibition of NS5 polymerase. Unpredictable toxicities remain one of the main reasons for clinical failure [11]. Combination therapies minimize resistance and improve therapeutic index. Balapiravir failed to be effective for patients with DENV. No efficacy was found in phase II clinical trials [12].

b) N-sulfonylanthralnic acid derivatives: These are allostearic inhibitors of DENV RNA dependent RNA polymerase [RdRp]. The inhibitor was identified through the screening of one million compounds using a primer extension based RNA dependent RNA polymerase assay. The compound potency was affected by the order of addition of RNA template and inhibitor during the assembly of RdRp reaction. It indicates that the compound inhibits RdRp through blocking the RNA tunnel [13].

IV. Capsid inhibitors:

a) ST-148: It is a potent inhibitor of all four serotypes of DENV *in vitro*. It significantly reduces viral load and viremia in vital organs and tends to lower cytokine levels in the plasma in

a nonlethal model of DENV infection in AG129 mice. ST-148 appears to interact with the DENV C protein and inhibits a distinct step(s) of the viral replication cycle [14].

V. Protein E inhibitors:

a) **Castanospermine:** It is a natural alkaloid derived from black bean, it acts as an ER α-glucosidase inhibitor and reduces infection of a subset of enveloped RNA and DNA viruses. Its mechanism of action is to disrupt the folding of some viral proteins by preventing the removal of the terminal glucose residue on N-linked glycans. It was found to inhibit all four DENV serotypes [15].

b) Celgosivir: It is a prodrug of castanospermine that inhibits α-glucosidase with broad antiviral activity. It can strongly inhibit all four DENV serotypes. Its mechanism of action is the prevention of glycosylation of viral proteins by the host. Although it is a safe and well-tolerated compound, it does not seem to reduce the fever burden in patients with dengue fever [16].

VI. Host Modulators:

a) Mycophenolic acid (MPA**):** It is a drug currently used as an immunosuppressive agent, to inhibit dengue virus antigen expression, RNA replication, and virus production. Pharmacological concentrations of MPA effectively blocked DV infection [17]. Mycophenolic acid did not block the initial phase of viral translation but did interfere with viral protein synthesis in the amplification phase. Quantitative RT-PCR demonstrated that MPA reproduced in hematoma cell lines by preventing synthesis and accumulation of viral positive and negative-strand RNA as the infection proceed.

VII. Agents that target host-mediated post-translational modification:

a) Lovastatin: Statins are 3-hydroxy-3-methylglutaryl coenzyme A inhibitors, used for lipid-lowering and mortality reduction in cardiovascular disease [18,19]. Dengue reflects the inflammatory process affecting the vascular endothelium, which is important in dengue pathogenesis. In addition to lipid-lowering, statins have pleiotropic effect including stabilizing and anti-inflammatory effect on the endothelium.

b) Vitamin D:

Vitamin D is known to play an essential role in the immune system, and vitamin D deficiency has long been associated with autoimmune disease as well as increased susceptibility to viral infection. Treatment of both monocytic (U937) and hepatic cells (Hug cells) with 1,25-dihydroxy-vitamin D3 significantly reduces the number of infected cells and lowers the production of proinflammatory cytokines (IL-6, TNF-α, IL-12p70, AND IL-1β). In monocytic cells, vitamin D3 interferes with the activation of several host cell signaling pathways that are essential for DENV survival and replication [20]. It has been shown that vitamin D3 regulates the Toll-like receptors, that activates the nuclear factor-kB (NF-kB) or RelA pathway, which reduces the phosphorylation of mitogen-activated protein kinases, p38, and p42/44, as well as the production of TNF-alpha and IL-6. The activation of MAPKs c-junN-terminal kinase and p38 pathways is very necessary for the virus to successfully replicate and infect macrophages. Therefore, the down-regulation of this pathway by vitamin D3 would result in the reduction of infected cells.

c) Heparin and Heparan sulfate: Heparin is an analogue of heparan sulfate, can compete for heparan sulfate on cell membrane for virus

binding and subsequently inhibit the replication of the dengue-2 and Japanese encephalitis viruses in hematoma and BHK-21 cells respectively. The binding of these viruses with HS is an important process for their invasion. Moreover, the inhibitory effect of heparin correlates with the infectivity of the virus in the cells [21]. All together, HS is an important host component of dengue virus replication, which can be blocked by heparin.

d) D4 dopamine receptor antagonists: Smith *et al* have identified a class of tricyclic small molecule compounds, the dihydrobenzodiazapines. Recent researches say that these drugs have a high potent inhibitory activity against DENV serotype 2. A highly active DHTB, inhibited all 4 serotypes of DENV *in vitro* at an early event in the DENV lifecycle, and the mechanism of activity is inhibition of host D4 dopamine receptor [22]. Antagonism of DRD4 and subsequent downstream phosphorylation of epidermal growth factor receptor-related kinase (ERK) were found to impact DENV infection negatively, and blockade of signaling through this network was confirmed as the mechanism of anti-DENV activity for this D4 dopamine receptor antagonists.

e) Viral sensor [RIG, MDA5, and TLR3] agonists: The innate immune system includes the detection of viral RNA by the helicase domain of RIG-1. A synthetic 5' triphosphate RNA was designed to stimulate this host's innate immune response as an antiviral agent and was found to have anti DENV effects when transfected into A549 cells as well as primary human monocytes before DENV infection. RIG-1, MDA5, and TLR3 knockout macrophages were highly susceptible to DV infection. When cells were silenced for only RIG-1, MDA5 but not TLR3, substantial production of INF-β was observed upon virus infection and vice versa. High susceptibility to virus infection led to ER-stress induced apoptosis in HUH-7 cells [23]. Recent researches demonstrated that the intracellular RNA virus sensors (RIG-1, MDA5, and TLR3) were activated upon DV infection and are essential for host defense against the virus.

f) Chloroquine: It is 9-aminoquinoline, has a long history of use as an anti-malarial agent. The antiviral effect of chloroquine could be related to the impairment of viral replication by raising intracellular pH in acidic organelles, including endosomes, lysosomes, golgi vesicles, leading to unwanted changes in the post-translation modifications of newly synthesized proteins, particularly inhibition of glycosylation [24]. Chloroquine acts as an anti-inflammatory agent as it inhibits TNF-α whose serum levels are high in dengue. Chloroquine promoted a reduction in the intensity of pain and improvement in the well-being of patients with dengue infection but did not alter the duration of the disease or the intensity and days of fever.

g) Amodiaquine: It is a known antimalarial drug, is a 4-aminoquinoline derivative. Amodiaquine hasshown to inhibit flavivirus' NS2B-NS3 protease, it can be measured by plaque assay. Both p-hydroxyanilino and diethylaminomethyl moieties are important for amodiaquine to inhibit DENV2 replication and infectivity [25].

VIII. Other compounds used to treat dengue: Agents suggested to treat dengue fever include genticin - an aminoglycoside, antibiotics like chloromphenicol, ciprofloxacin and acetaminophen for the prevention of fever. Patients with dengue fever can recover by the initiation of judicious

fluids and careful monitoring. It is due to increased vascular permeability [12].

IX. **Medicinal plant derivatives which are useful for dengue treatment:** There is a significant amount of research dedicated to hypothesis-driven and practice-based identification of naturally occurring compounds with anti-dengue activity [1,26].The WHO and Ayurveda suggested the use of medicinal plant extracts and their derivatives for anti-dengue activity. They suggested that ayurvedic medicines which are isolated from the plant extracts are more effective and non-toxic than synthetic medicines. Medicinal plants with therapeutic potential in anti-dengue activity are*Andrographispaniculata, Cymbopogus citrus, Carica papaya, Momardica charantia, Meristiella gelidium, Myrtopsiscorymbosa, Ocimumsantum, Pelargonium citrosum.*etc [5].

CURRENT VACCINE DEVELOPMENT

The development of the Dengue vaccine against the disease is challenging with four different serotypes of the dengue virus that can cause the disease. The vaccine must immunize against all four types to be effective [33]. Vaccination against only one serotype could possibly lead to severe DHS when injected with another serotype due to Antibody-dependent enhancement. There are some dengue vaccines like CYD-TDV, DEN-Vax, TetraVax-DV, TDEN PIV.

a) **CYD-TDV:** It is a live attenuated tetravalent chimeric vaccine made using recombinant DNA technology by replacing the pre-membrane and envelope structural genes of the yellow fever attenuated 17D strain vaccine. WHO recommends that countries should consider vaccination with the dengue vaccine CYD-TDV only if the risk of severe dengue in seronegative individuals can be minimized either through pre-vaccination screening or recent documentation of high seroprevalence rates in the area (at least 80% by age 9 years) [26]. Ongoing phase 3 trials in Latin America and Asia involve over 31,000 children between the age of 2 and 14 years. An analysis of both Latin America and Asian studies at the 3rd year of follow up showed that the efficacy of the vaccine was 65.6% in preventing hospitalization in children older than 9 years of age. The vaccine series consists of three injections at 0, 6, and 12 months. Trade-named Dengvaxia, approved for use for those aged 9 and older and can prevent all four serotypes.

b) **DEN-Vax:** It is a recombinant vaccine with DENV1, DENV3 and DENV4 components on a dengue virus type 2 backbone originally developed at Mahidol University in Bangkok and now funded by DENVax and TAK-00. phase 1 and phase 2 trials are ongoing in the united states, Colombia, Puetro Rico, Singapore, and Thailand. Based on the latest 18-month data TAK-003 produced sustained antibody responses against all four viral strains [33].

c) **TetraVax-DV:** It is a tetravalent admixture of monovalent vaccines that were tested separately for safety and immunogenicity [26]. The vaccine passed the phase 1 trial and being tested in phase 2 studies in Thailand and Brazil.

d) **TDENV PIV:** It is an inactivated tetravalent vaccine undergoing phase 1 trials as part of a collaboration between GSK and Walter reed army institute. A synergistic formulation with another live attenuated candidate vaccine is also being evaluated in a phase 2 study [33].

e) **DNA vaccines:** The naval medical research center attempted to develop a monovalent DNA plasmid vaccine [26].

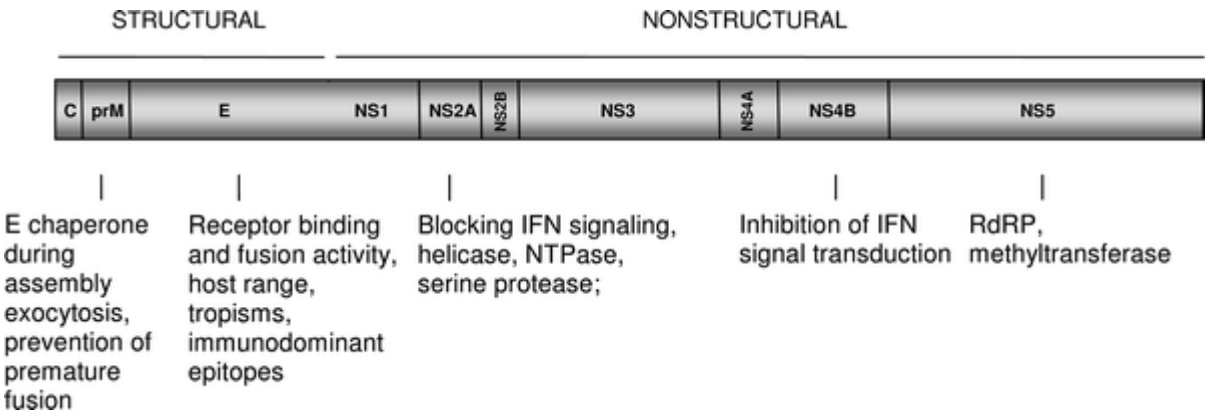

Figure 1: schematic of the dengue virus protein [3].

Table 1: DRUGS USED IN THE MANAGEMENT OF DENGUE:

S.No	Drug Name	Brand Names	Dose	Mechanism	Use
1.	Ribavarin	Copegus, Rebetol, Ribasphere, Virazole	An initial loading dose of 30 mg/kg (maximum 2 g), followed by 16 mg/kg (maximum 1 g) every 6 hrs for 4 days and then 8 mg/kg (maximum 500 mg) every 8 hrs for 6 days.	NS5-methyl-transferase inhibitor.	It is an antiviral agent used to treat viral hemorrhagic fever [12].
2.	Lovastatin	Altoprev	80mg	3-hydroxy-3-methylglutaryl coenzyme A inhibitor	It may have an anti-viral effect in dengue by reducing virion assembly [12].
3.	Balapiravir	R-1626, Ro4588161	100mg orally	It is a nucleoside analogue and direct antiviral inhibitor.	It was used for potential dengue therapy [12,27].
4.	Chloroquine	Aralen®	600mg orally initial dose, followed by 500mg after 6 to 8 hours once a day.	Interfere with the acidic pH of endosomal, lysosomal compartments and the trans-Golgi network in which the virus undergoes fusion and	It is an antimalarial drug and it also exerts anti-dengue activity [12].

				maturation.	
5.	Celgosivir	Celgosivir hydrochloride	50 mg Q6H for 5 days [9].	Inhibits DENV replication, disrupting folding of DENV structural proteins prM and E, as well as NS1.	α-glucosidase inhibitor, used in the treatment of acute dengue fever [12,28].
6.	Eupatorium Perfoliatum	Boneset	The dosage should be 2 drops in one tablespoonful of water two times a day and subsequently at least 2 doses a weak, at the interval of 3-4 days until the epidemic subsides.	It Inhibits the dengue virus.	Eupatorium Perfoliatum is an effective homeopathic medicine for dengue prevention. It develops higher resistance and immunity to dengue fever. It is a herbal anti-viral medicine [12].
7.	Castanospermine	_	250mg/kg of body weight per day.	Inhibit DENV replication, disrupting folding of DENV structural proteins prM and E, as well as NS1.	It is α-glucosidase inhibitor, used in the treatment of acute dengue fever[12].
8.	Aprotinin	Trasylol	Loading dose: 280 mg Pump prime dose: 280 mg Continuous infusion dose: 70 mg/hr.	Aprotinin envelops the enzyme and prevents the substrate from accessing the protease active site.	Aprotinin is NS3 protease inhibitor, used for the treatment of dengue [12].
9.	Ivermectin	Stromectol	0.2 mg/kg orally once	Inhibits NS3 HelicasE	A Promising compound as the first specific therapy against flaviviruses [12].
10.	Suramin	309 F; Antrypol; Bayer 205; Belganyl; Fourneau 309; Germanin; Moranyl; Naganin; Naganol; Naphuride.	Intravenous, 100 to 200 mg	Suramin acted as a potent NS3 helicase inhibitor of dengue virus by a non-competitive mode of inhibition.	Sumarin is mainly used to treat Trypanosomiasis.it also has anti-dengue activity [12].

11.	Sinefungin	A 9145; Antibiotic 32232RP; Antibiotic A 9145; RP 32232	1 mg	Sinefungin inhibits NS5 methyl transferase, which leads to an inhibition of DNA synthesis.	It is an analog of the methyl donor S-adenosyl-L-methionine. It has anti DENV activity [12].
12.	Lycorine	Amarylline Galanthidine Licorine Narcissine	500 mg	No specific action.	Lycorine potently inhibited flaviviruses in cell culture, it was reported to reduce viral titers of WNV, DENV, and YFV mainly through suppression of viral RNA replication [12].
13.	Amodiaquine	Camoquine and Flavoquine	10 mg/kg of amodiaquine base once daily for 3 days, usually in combination with other drugs.	No specific action.	Amodiaquine inhibited DENV2 infectivity [12].
14.	Favipiravir	T-705 or Avigan	120 mg/kg/day and 200 mg/kg/day	No specific action.	It is an anti-viral drug used for inhibiting DENV at higher concentrations [12].
15.	Carica papaya	Caripill	One tablet of Caripill (1100 mg) should be taken three times a day, for five days.	It helps to increase the platelet levels in patients with dengue fever.	It is used to treat thrombocytopenia in dengue patients [30].
16.	Chloramphenicol	Chloromycetin Kapseals, Daclor 500, Cafcol - 500, Welmycin, Elichlor, Colfen, Fencol, Decol, Enteromycetin, Aglomycetin	500 mg per day	Antibiotic, inhibits RNA polymerase.	Chloramphenicol is an antibiotic, prescribed for certain types of bacterial infection [31].
17.	Ciprofloxacin	Orpic, Wyserin, Penquin, Quinotab, Ciprind, Ciprocure, Strox, Ciprotum, Ciprocore	250 to 750 mg/day in divided doses.	It inhibits DENV infection.	Ciprofloxacin is a fluoroquinolone antibiotic used to treat certain bacterial infections [31].

18.	Acetaminop-hen	Actamin, Anacin AF, Apra, Bromo Seltzer, Children's Tylenol, Elixsure.	Do not take more than 1000 mg at one time.	It is a nonsteroidal anti-inflammatory drug, reduces the prostaglandin level.	Acetaminophen is an Analgesic and Antipyretic [32].

CONCLUSION:

In the last two decades, dengue emerged as a serious health problem worldwide. Roughly 2.5 billion people live at risk of dengue infection. The pharmaceutical industries and government have been taking initiatives to develop new strategies for the diagnosis and treatment of dengue. The major challenges ahead include the identification of compounds with a favorable safety profile for dengue treatment. Dengue vector control is still considered the most effective way of controlling and preventing the transmission of the dengue virus. Researchers also aim to improve diagnostics for patients with dengue so that they can receive effective treatments sooner.Future strategies should consist of a fast reacted anti-dengue team, either under government or not, for designing the control program, tracking the dengue cases and communicate with the residents from the hot spot area. Targets such as the DENV protease and polymerase are being captured in the act of carrying out their essential enzymatic activities, and these can contribute enormously to the development of designer compounds that could be potent inhibitors. The goal of finding a cure for dengue in the next decade is highly feasible, judging from the success of potent directly acting antivirals against the *Flaviviridae* family virus.

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