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***Review***

# Dengue Fever: Review with insight into pathogenesis and suggested treatment with prevention

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## Abstract

Dengue is a chronic viral infectious disease. The disease has been common and prevalent throughout the world with affecting and having major outbreaks in more than a 100 countries. It is a positive sense, RNA virus. There are number of clinical features which are manifested in patients depending on their age and living circumstances that range from being an asymptomatic illness to a severe symptomatic disease that could prove to be hazardous and life-threatening. Though there are a number of methods which are used for the identification of the virus, but the serological methods are considered to be the most effective and accurate tests for the identification of the infecting serotype and later on for the conformation and diagnosis of the disease. Serological tests used are: Complement Fixation test, Hemagglutination Inhibition test, Neutralization test, and ELISA. Though there are a number of drugs prescribed by the physician for the suppression of symptoms and also a vaccine for dengue has also been licensed.

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**Introduction:**Disregarding the way that there is no undeniable sign for the word dengue yet as demonstrated by specific hypotheses; the word has been gotten from an insignificant articulation "Ka-dingapepo" which generally insinuates an insightful soul (1). Dengue is a viral disease transmitted by four dengue infecting serotypes which range as 1-4 dengue virus serotypes. This disease is primarily caused by mosquitoes (mosquito-borne illness). The disease is transmitted to individuals by the Aedes mosquito (female). This illness is generally progressively inescapable in subtropical and tropical areas, putting about 33% of the human people, far and wide, at risk for infection (2). By and large Aedesaegypti (Ae. aegypti) is the purpose behind dengue fever and rarely Aedesalbopictus. The Ae. aegypti is a day chewing mosquito, was found in tropical and subtropical districts and breeds were viewed as assembled in stale water, Ae. aegypti gets polluted by the dengue tainted individual and can transmit disease to non-defiled individual after an agonizing period which is 8-10 days. Dengue fever addresses extensive extent of clinical signs including smooth fever to cut off structure. DHF which is abbreviated as Dengue Haemorrhagic Fever and dengue shock condition (DSS) are the most extraordinary and veritable kinds of dengue which are responsible for high mortality and inauspiciousness rate on the planet. Extraordinary headache, muscles and joints torture, rash, squeamishness, heaving are the signs of dengue fever while DHF are depicted by high fever, hemorrhagic wonders, hepatomegaly, and consistently circulatory irritation and shock. Dengue is on a very basic level the critical purpose behind hospitalization, and it is assessed that 500 000 people polluted with outrageous dengue require hospitalization in which adolescents are winning while about 2.5% impacted people pass on annually (3). According to statistics, dengue has become such a common disease globally that around three billion people live in dengue-endemic regions and almost a figure of 400 million constitutes of the infections recorded annually, with a demise rate beating 5–20% in some areas.Dengue infection has impacted even the world's most developed countries like United States, various regions of Europe with a prediction of hitting more than 100 countries (USA)(4).

**Molecular Biology:** Dengue virus is a 50nm virion with the genome of dengue virus includes a positive sense RNA of the size 11 kb. This RNA is changed over into a singular polyprotein which encodes for three major structural proteins, explicitly, capsid (C), pre-membrane (prM), envelope (E), and 7 nonstructural proteins; non-structural1, non-structural2A, non-structural2B, non-structural2B, non-structural3, non-structural4A, non-structural4B, non-structural5(2).The 5′ and 3′ completions of each serotype of DENV RNA genome join untranslated territories (UTRs), which are essential for replication and understanding, and possibly help out cell factors related with these functions(5).The viral ribonucleic acid encodes one gigantic open scrutinizing plot flanked by 5′ and 3′ untranslated regions (UTRs) which are required for viral replication. The size of 5′ UTR is usually short (around 100 nucleotides) and has a top structure at the 5′ end, while the 3′ UTR is longer (around 450 nucleotides), doesn't have a poly(A) tail, anyway contains different checked RNA structures(6).

(a) As it is indicated in figure 1 that there is string of viral genome which contains 5' and 3' ends that are accompanied by the untranslated regions; also abbreviated as the UTRs. The central region contains an open reading frame which acquires a variety of proteins and those proteins are categorized as structural and non-structural proteins. Structural proteins are the pre membrane, capsid and envelope proteins and the non-structural are classified as NS1, NS2A, NS2B, NS3, NS4A, NS4B, NS5. The exact location of correlative progressions stated as 5'- 3'CS and 5'- 3'UAR are also shown through the addition of straight constant and slashed lines. (b) Also the anticipated structure of the 5' terminal region of the dengue virus genome. Essential segments arranged at the 5' end: stem circle A (SLA), stem circle B (SLB), oligo(U) track spacer, understanding initiator AUG, capsid region fasten (cHP), and the 5'CS part. (c) Schematic depiction: ribonucleic acid parts at the 3'UTR of the DENV genome. The foreseen discretionary structures of the three portrayed regions are appeared: space I (variable locale, VR), zone II (the picture depicts a structure shown drawn as dumbbell shaped, DB1 and DB2), and space III (a conserved sequence CS1 and 3'SL). In addition, the region and gathering of all of the proportioned parts identifying with RCS2, Conserved sequence 2 CS2, 3'CS, and 3'UAR are depicted(7).

**Serotypes: Dengue**

The dengue virus has 4 closely related serotypes which are DENV1, DENV2, DENV3, DENV4. All these serotypes have almost 65% of genetic similarity but they are distinguished by slight genetic variations which further results in their different types of interactions with antibodies in human serum. Even though, there are overall variations in these serotypes but the infection caused by these serotypes present the same disease and almost same range of clinical signs and symptoms(8).

But it is not obligatory for these serotypes to exist in the same region and their prevalence could be divided in different regions of the world e.g. in the 1970s both the serotypes 1 and 2 were found to be present in different regions of America and Africa, though all the four serotypes were found in the regions of South Asia. However, in the early 2000s the distribution of these serotypes became progressively common in different regions of the world. Presently there is circulation of all the four serotypes of the virus in tropical and subtropical regions sharing a common geographical location. However, the question of the origin of the viruses still confused the researchers, but later on according a hypothesis gave by scientists, it is believed that these viruses about 500 to 1000 years ago originated from the non-human primates and were transmitted to the humans through primates in the regions of Africa initially(8).

However, once an individual is infected with a particular dengue serotype, then after recovery the person develops immunity against that particular serotype for life long. But that immunity is believed to effective for only a short

duration of time against the remaining three serotypes which is usually around two to three months(8).

**Classification:**The whole example of dengue diseases construes a collection of clinical signs going from asymptomatic cases to smooth fever and genuine perilous condition inevitably inciting passing. According to such an establishment data; generally, we have three portrayals of dengue ailment: DF (Dengue Fever), DHF (Dengue Haemorrhagic Fever), DSS (Dengue Shock Syndrome) (9). Traditionally this categorization relies upon the WHO data related to the case definitions is still followed in different parts of the world regardless of the new course of action system which is only established on only one parameter (10) and it allows a predominant perception concerning cases (11) yet isn't sensible for confined social protection workplaces in the endemic regions (12).

**DF (Dengue Fever):** DF is a self-confining fever, which by and large prop up for only 5–7 days. The clinical characteristics of the infirmity vary concerning the status of the patient (age, if immunocompromised). The infant kids and little children might have a raised interior warmth level with maculopapular rash portrayed by reddish domains on the skin with the covering of crossing thumps. The signs in progressively settled adolescents and adults join delicate febrile condition or extraordinary disease with high fever, genuine cerebral torment, retroorbital torture, myalgia i.e. muscle pain, joint pain, nausea, regurgitating, and petechial. Low white blood cell count (Leukopenia) and thrombocytopenia are appeared in commonly all age social affairs. There are a couple of cases wherein DF causes depleting multifaceted design, for instance, gingival biting the dust, epistaxis, gastrointestinal passing on, haematuria (a condition referring to the presence of blood in urine), and menorrhagia which occurs in case of woman(9).

**DHF/DSS (Dengue Haemorrhagic Fever/Dengue Shock Syndrome):** The signs of DHF are on a very basic level equivalent to the DF incorporates and is joined by thrombocytopenia, plasma spillage and haemorrhagic appearances. Plasma spillage is also a major factor of severity in DHF. It is moreover the hugest differentiation among DHF and DF. Dependent upon contamination reality and clinical signs, DHF is further disintegrated into four stages I to IV, with grade IV presented as the most outrageous. A couple of patients in like manner have fine petechiae dispersed on the farthest focuses, axillae, face, and sensitive feeling of taste, when in doubt found in the febrile period. The essential stage is by and large coming to around the completion of febrile disorder, set apart by speedy decrease in temperature and normally joined by circulatory agitating impacts including plasma spillage, hemoconcentration, and thrombocytopenia (9).

**Steps of life cycle of Dengue Virus:**

**Step 1:** The dengue infection has distinctive primary structures and it exists in various varieties which at last relies upon the cleavage of pre-membrane protein (prM). However, the viruses' particles of dengue which are completely immature acquires a complete complement of membranousproteins, such particles of virus are completely non-infectious. However, the complete set of membrane proteins is cleaved incase of fully mature viral particles. Also there is a frequency of partially mature or intermediate viral particles in which there are some membrane proteins which are completely cleaved while others remain solely intact(13).

**Step 2:**In the very next stage, there is replication of the dengue virus particles which occurs as a result of the interaction of the virus particles with a variety of receptors on the host cells which is a direct interaction or when the immune complex region that is the Fc portion of the virus binds to the Fc receptor on susceptible host cells(13).

**Step 3:** Also, consequently there would be the passage of the infection molecule into the host cell by means of receptor-interceded endocytosis(13).

**Step 4:** In very next stage, there is change in shape of proteins and such conformational changes of the envelope proteins of virus leads to the trimerization of proteins (irreversible) by the process of acidification in endosomal vesicles. It uncovers the combination peptide and intercedes combination of the viral and the endosomal layers, permitting arrival of nucleocapsid in the cytoplasm. The RNA is discharged in the cytoplasm with its transportation in endoplasmic reticulum (ER)(13).

**Step 5:** In ER, ribonucleic acid is transformedin a singular polyprotein as a result of translation which is controlled by virus and hostenzymes which cleave the proteins and are known as proteases(13).

**Step 6:** Right after the complex of viral replication is synthesized, translation of viral genome i.e. RNA turns off, and there runs the process of transcription of antisense RNA together with the amplification of ribonucleic acid synthesizes RNA(13).

**Step 7:** Recently produced ribonucleic acid is further accordingly combines and packages by the proteins of the capsid (C), framing a nucleocapsid(13).

**Step 8:** Congregation of viral particles occur on Endoplasmic Reticulum (the outer surface) during the budding of virion into the ER lumen, which results in the synthesis of completely immature and non-invasive viruses(13).

**Step 9:** The newly synthesized completely immature viruses are further carried and passed from the region of Golgi apparatus to the trans-Golgi complex, where the process of acidification initiates some changes in the shape and ultimately there are alterations in the conformation of the virion and hence the cleavage sites of Furin are exposed (enzyme involved in activating the proteins)(13).

**Pathogenesis:** Though primary infection presents strong if not deep rooted security (inferring a long term protection) from again acquiring an infection via a serotype of homologous Dengue Virus, while in case of a secondary disease, a heterologous DENV serotype happens much frequently and commonly in regions which are endemic and is the mostdefinite and significant lethal factor contributing to a serious disease. Even during the phase of secondary disease, serious dengue infection is mostly very rare and highly unlikeable, with a mere probability of 0.5 to 1% of infections progressing towards the DHF (Dengue Haemorrhagic Fever) and DSS (Dengue Shock Syndrome). On the contrary, in babies

destined to dengue-resistant moms, primary infection may cause extreme sickness (also named as "baby DHF") (14). The actual mechanism through which the body's immune response fights against the virus is still ambiguous. However, the antibodies killsthe infectivity when bound to the viral particles in adequately enormous numbers. Moreover, at a concentration that is actually below the edge for balance, antibodies then propagate the entry of dengue virus into cells communicating Fcγ receptors (FcγR) through a mechanism which is known as "antibody dependent enhancement". Thus the less affinity of the antibodies against the virus proteins which were synthesized in the phase of primary infection can promote the process of ADE in vivo during the phase of secondary infection bringing about expanded viral load. Though in non-human primates the administration of monoclonal and polyclonal antibodies can enhance the viral load. However, in mice the increasing concentration of the antibodies perpetuates a cytokine storm which results in the vascular leakage. Nevertheless, in case of infants Dengue Haemorrhagic Fever, it is seen that specific dengue virus IgG antibodies of the mother are carried across the placenta to such a level that there are high chances of acquiring primary DENV disease. Along these lines, the quantity and nature of the cross-receptive counter acting agent reaction that either is previous in serum or quickly initiated by the memory B cell pool is accepted to impact the seriousness of Dengue virus infection(14).Aside from ADE, the ligation of FcγR receptors on myeloid or pole cells by DENV immune complexes may exert a controlling influence suppression on the host cell immunity and sickness pathogenesis by enhancing the production of the interleukin-10 (IL-10), with an enhancing degranulation of vasoactive particles and a sudden change in direction of the CD4+ T cell reactions, that upgrade hairlike spillage. Though in historical perspective, it is believed that high levels of vasoactive cytokines produced by theseT cells and no quick clearance of dengue virus infecting cells are verifiably have been involved in sickness pathogenesis during secondary infection, ongoing investigations recommend that cross-responsive CD8+ T cells ensure against serious DENV disease(14).

**Clinical Manifestations:** It has been confirmed through a consensus made by the experts that dengue is a mere single entity with various clinical features that vary accordingly considering the age and severity of the infection. Clinical features of dengue viral infection range from condition of no symptoms (asymptomatic) to serious symptomatic illness that may prompt death of the individual if not appropriately treated. However, the cases which are symptomatic are classified as undifferentiated febrile illness (UF) which is not possible for diagnosis clinically and has to be studied using serological techniques, dengue fever (DF) which is characterized by myalgia severe headaches and malaise, dengue hemorrhagic fever (DHF) which is quite similar to the normal dengue fever but with some distinguishing features, dengue shock syndrome and unusual dengue also known as the expanded dengue syndrome (EDS)(15).

• The undifferentiated febrile illness cannot be identified clinically; so the analysis is made by the serological tests(15).

• Dengue Fever is viewed as a gentle ailment since demise is once in a while revealed, yet enormous draining might be related with Dengue Fever(15).

• DHF – the initial features are very much similar to that of the dengue fever in the febrile stage. Although the differentiating factor is the vascular permeability. Process of plasma leaking is the leakage (selective) into the pleural (space filled with fluid between the two pulmonary pleurae) and peritoneal cavities which causes the pleural effusion(15).

• DSS – The features in this type are very much similar to that of the DHF but there is plasma leakage to such a severe extent that the patient may die of shock(15).

• UD – most of the unconventional cases are the DHF cases with shock and Dengue Haemorrhagic Fever manifesting altogether along other infections(15).

UF and DF comprise the majority cases while DHF/DSS constitutes about 10% of the indicative cases(15).

**Suspected dengue disease: Case definition**

Initially, in the first few period of dengue illness, most of the patients develop symptoms of febrile illness with general symptoms of severe headache, abdominal pain, itching, rashes and malaise.Muscle pain that is myalgia and arthralgia are mostly manifested in DF patients, though some DHF/DSS patients also develop these manifestations(15).

**Research facility Diagnosis:**

Outline: Efficient and accurate conclusion of dengue is an important process for a suitable and appropriate clinical treatment (for instance, early diagnosis of extreme cases, case affirmation and differential conclusion with various irresistible illnesses), flare-up control, pathogenesis, research, antibody improvement, and clinical preliminaries (16). Researchers and diagnostic labs carry out some principle methods for the diagnosis and confirmation of infection which takes into account a number of parameters including the identification of antibodies or antigens, viral genetic material (nucleic acid), or a blend of these methods. After the onset of disease, usually in around four to five days the infection can be recognized in serum, plasma, blood cells and different tissues. During the beginning phases of the ailment, viral isolation, nucleic acid or antigen recognition can be utilized to analyze the infection. Towards the end of the acute phase of infection, serology is the strategy for decision for diagnosis (16).

**Specific Diagnostic Test:**The most accurate and definitive diagnostic test of dengue is only performed in the lab, which is contingent and corresponds to the isolation of virus, analysis of the viral antigens or more specifically their genetic material i.e. RNA in tissue or serum sample(17).

**Serologic Tests:**Various types of serological tests have been utilized to determine the dengue contamination: hemagglutinationinhibition (HI), Complement Fixation test (CF), Neutralization test (NT), and ELISA(17).

**Complement Fixation Test:**The Complement Fixation is generally a test not performed very often as a routine

dengue finding, since it is difficult and troublesome to perform, and moreover it requires exceptionally qualified and prepared staff to accomplish great outcomes. The test is contingent to the rule for the consumption of the complement during the antigenantibody reaction. Though limitation of this test is that the antibodies detected for CF are generally indicated later as compared to the antibodies shown in the hemagglutination-inhibition and thus are shown for a short span which is ultimately of less importance and limited value for theseepidemiological studies. This test is quite certain in the primary infection, confirming the detection of the serotype, as observed throughthe monotypic reactions in case of primary infections (17).

**Neutralization Test:** The Neutralization Test is considered to be the most delicate and accurate serological technique for dengue infection conclusion, and it is distinguished for a significant duration. Because a general monotypic reaction is seen in the patient's serum during the phase of convalescence, so this test could be performed in order to detect the serotype in primary dengue infection. On the contrary, neutralization test does not prove to be a reliable and valid test in the case of a secondary or tertiary dengue infections. The major setbacks of this technique are its significant expense, the long duration of time required to carry out the procedure, and the related specialized difficulties (17).

**Enzyme Linked immunosorbent assays (ELISAs):**Presently, ELISA has been viewed as one of the most reliable, best and accurate test for dengue determination, because of its high affectability and the convenience. ELISA has been used for the identification of acute stage (IgM) and convalescent stage (IgG) antibodies, just like in the identification of antigens (Ag). Since it is anything but difficult to perform and there is no requirement for complex system and equipment, ELISA has been generally used in serological technique for the dengue infection analysis (17).

**Treatment:**

There is no specific treatment of dengue suggested, though your primary care physician might suggest you to intake a lot of fluids to suppress high fever (18). While recouping from dengue fever, watch for signs and side effects of drying out. Keep updating your p physician right in the event that you build up any of the accompanying:

- Decreased pee
- Few or no tears
- Dry mouth or lips
- Lethargy or disarray
- Cold or sticky extremities

If it is a case of serious dengue fever, one may require:

- Supportive consideration in a medical clinic
- Intravenous (IV) liquid and electrolyte substitution
- Blood pressure check
- Transfusion to compensate for the blood loss (18)

**Paracetamol:** which is also known as Acetaminophen is a drug of choice (Tylenol, others) can ease the torment and diminish fever. However, it is also advised to avoid using pain killers which can contribute to expand bleeding complications, for example, anti-inflammatory medicine like naproxen sodium and ibuprofen (18).

**Platelet Transfusion:** In severe cases of dengue fever where there is significant bleeding or dangerously low platelet counts, platelet transfusion may be necessary to prevent or manage bleeding complications.

**Intravenous Fluid Replacement:** In addition to fluid and electrolyte replacement, intravenous fluids may also include colloids or blood products to stabilize blood volume and pressure. This is crucial in cases of severe dehydration or shock.

**Oxygen Therapy:** For patients experiencing respiratory distress or severe complications such as acute respiratory distress syndrome (ARDS), supplemental oxygen therapy may be administered to ensure adequate oxygenation of tissues.

**Critical Care Monitoring:** Patients with severe dengue fever may require close monitoring in an intensive care unit (ICU) setting. This allows for continuous assessment of vital signs, organ function, and response to treatment.

**Medications for Complications:** Depending on the specific complications arising from dengue fever, additional medications may be prescribed. For example, antibiotics may be needed if there is a concurrent bacterial infection, or medications to manage symptoms such as nausea, vomiting, or diarrhoea.

**Blood Pressure Management:** In cases of severe dengue fever complicated by shock, medications to support blood pressure and improve perfusion to vital organs may be necessary.

**Respiratory Support:** In rare cases where severe dengue fever leads to respiratory failure, mechanical ventilation may be required to assist breathing and maintain adequate oxygen levels.

**Hemodynamic Support:** In cases of severe shock, vasopressor medications may be administered to support blood pressure and prevent organ damage.

**Dialysis:** In cases where severe dengue fever leads to acute kidney injury and significant impairment of kidney function, dialysis may be necessary to remove waste products and maintain electrolyte balance

**Prevention**

- Wear shirts with long sleeves and trousers with legs covered that covers your whole body.
- Treat garments with anti-agents like permethrin.
- It is essential to use the EPA-enrolled mosquito repellent like DEET.
- Considering the condition of your living place, it would be beneficial to sleep in a mosquito net.
- It is important to make sure that any entry or gateway to your home specially windows should be closed to hinder the passage to mosquitoes.
- It is highly important to keep your surroundings from standing water, more specifically during the evening(18).

**Other preventive and Control measures**

**Mosquito Control Programs:** Implementing measures to reduce mosquito populations, particularly Aedesaegypti, which is the primary vector for dengue virus transmission, is essential. This can include larval source reduction

through environmental management, such as removing or covering stagnant water sources where mosquitoes breed, and adult mosquito control through insecticide spraying or fogging.

**Community Engagement and Education:** Educating communities about dengue fever transmission, symptoms, and prevention measures empowers individuals to take proactive steps to protect themselves and their communities. This can involve door-to-door awareness campaigns, community meetings, school programs, and the dissemination of educational materials through various media channels.

**Water Management:** Promoting proper water storage practices, such as covering water containers and regularly cleaning and emptying them to prevent mosquito breeding, is crucial. Additionally, advocating for improved water supply and sanitation infrastructure can help reduce the availability of breeding sites.

**Integrated Vector Management (IVM):** Adopting an integrated approach that combines various vector control measures, including biological control methods (e.g., introducing mosquito predators like fish or bacteria that target mosquito larvae), environmental modifications, and chemical control when necessary, can enhance the effectiveness and sustainability of vector control efforts.

**Community-Based Surveillance:** Establishing systems for community-based surveillance enables early detection of dengue fever cases and outbreaks. This involves training community members, healthcare workers, and local authorities to recognize and report suspected cases promptly. Timely reporting allows for rapid response interventions, such as targeted vector control measures and healthcare provision.

**Behavioural Change Interventions:** Promoting behaviour change to encourage individuals to adopt protective measures against mosquito bites, such as wearing long sleeves and pants, using insect repellents, and sleeping under mosquito nets, is essential. These interventions can be tailored to specific demographic groups and cultural contexts to maximize their effectiveness.

**Community Mobilization and Participation**: Engaging communities in the planning, implementation, and evaluation of dengue prevention and control programs fosters ownership and sustainability. This can involve forming community task forces or committees dedicated to vector control, organizing clean-up campaigns, and incentivizing community participation through rewards or recognition.

**Partnerships and Collaboration:** Building partnerships between government agencies, non-governmental organizations, community-based organizations, academia, and other stakeholders enhances the coordination and effectiveness of dengue prevention and control efforts. Collaborative initiatives can leverage resources, expertise, and networks to implement comprehensive and sustainable interventions.

**Conclusion:**Dengue is a chronic infectious disease which has become a very common and life threatening disease throughout the world. Dengue presents a number of varying clinical manifestations, thus the clinical physicians need to be aware of these features to start the treatment of patient in appropriate time. Future prospects on fighting with this cursing disease aims to target the most appropriate and accurate methods, mode of prevention and vaccines.

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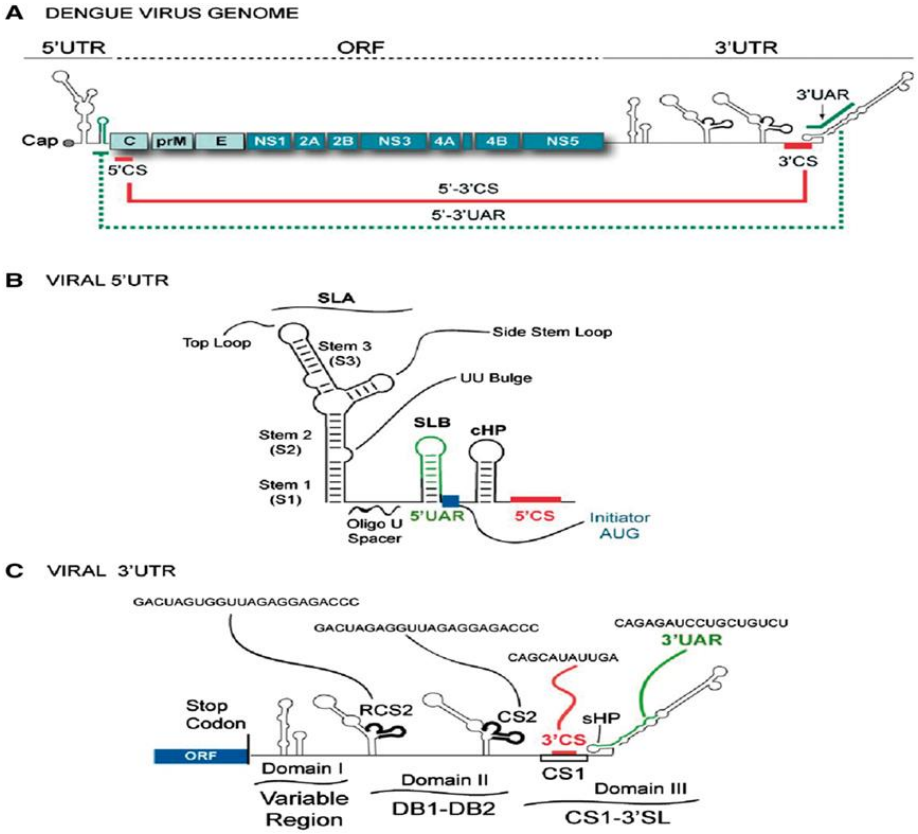


**Figure 1.** The hierarchical presentation of the Dengue virus (DENV) genome