International Journal of Bioinformatics and Biomedical Engineering
Vol. 4, No. 3, 2021, pp. 31-36
http://www.aiscience.org/journal/ijbbe
ISSN: 2381-7399 (Print); ISSN: 2381-7402 (Online)

Future Directions of Diagnosis and Treatment of Dengue Virus

Milton Kumar Debnath[1], Ishita Rani Das[1], Rozina Akter[1], Anita Jackson[2], Md. Zakir Hossain[1, *]

[1]Department of Biomedical Engineering, Medical Center, Jessore University of Science and Technology, Jessore, Bangladesh
[2]Eshelman School of Pharmacy, University of North Carolina, Chapel Hill, USA

Abstract

Dengue fever is a hot topic now-a-days which is caused by dengue virus. This virus belongs to the *Flavivirus* genus and *Flaviviridae* family, affects mainly coastal and sub-costal region. It takes away millions of human lives every year and that's why scientists are working day and nights for a solution of this prevailing problem. A lot of articles have been reviewed about dengue till date and tried to find out present modalities and advancement regarding this problem. The focused has given on the future direction of prevention and treatment of this virus including vaccine invention, modern diagnostics and therapeutic modalities use for this purpose. So, a lot of emphasis is needed in this arena for fruitful control of this life threatening devastating virus.

Keywords

Dengue Virus, Diagnosis, Treatment, Prevention

Received: May 28, 2018 / Accepted: July 6, 2018 / Published online: November 26, 2018

1. Introduction

Dengue virus (DENV) is the reason for dengue fever. Dengue virus is the member of genus *Flavivirus* and family *Flaviviridae* [1]. DENV belongs to this family with other viruses that are *Yellow fever* virus, *Zika* virus and *West Nile* virus. All the viruses of this family are single stranded and the viral RNA is positive polarity (+) which has envelope and icosahedral protein capsid [1-3]. In 1780, this disease was first defined and in 1944 DENV was isolated by Sabin [4]. Complex natures for dengue fever include dengue shock syndrome (DSS) and dengue hemorrhagic fever (DHF). DHF is a disease complicated by dengue fever and DSS is a fatal consequence of dengue fever [5]. Dengue is also called Arbovirus as it is an arthropod borne disease and its vector is *Aedes aegypti* mosquito [2, 6].

2. Structural Analysis

The DENV genome consist of nearly 11000 bases which is positive sense single stranded RNA (ssRNA). These genetic sequences code for various proteins of the virus [3-4]. DENV has seven nonstructural (NS) proteins and three structural proteins. The NS proteins are named as NS1, NS2a, NS2b, NS3, NS4a, NS4b and NS5. Structural proteins are named as envelope protein E, membrane protein M and capsid protein C [7].

DENV has known five serotypes of which four is commonly infectious to human. These serotypes are commonly recognized as DENV1, DENV2, DENV3 and DENV4 [8].

* Corresponding author
E-mail address: mzh.bme@gmail.com (Md. Z. Hossain)

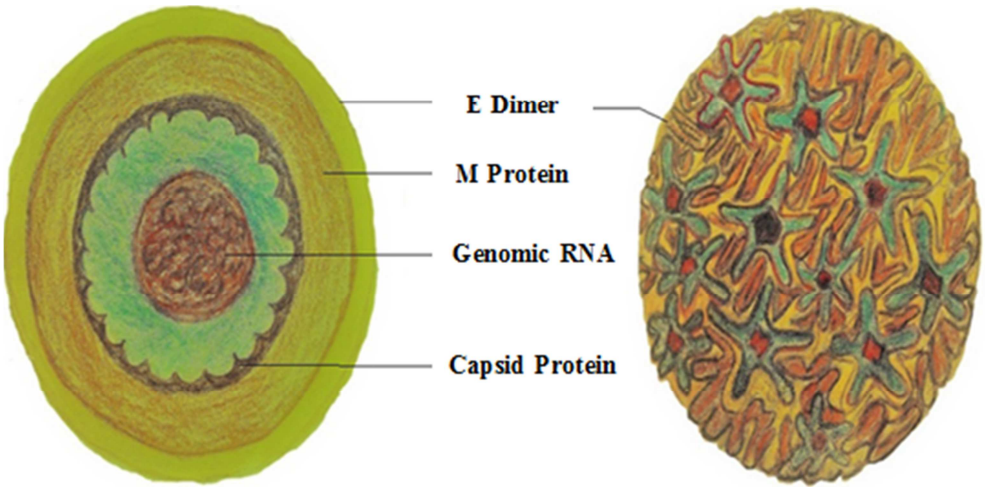

Figure 1. Dengue virus structure.

3. Transmission

This virus has a life cycle in both human and *Aedes aegypti*. The female mosquito bites the DENV affected human or reservoir when they need blood for breeding [6-8]. Then the virus is taken up within the mosquito and multiplies into the mosquito cell. Then come to saliva of the mosquito and again spread to healthy human after being bitten again [6, 8-11].

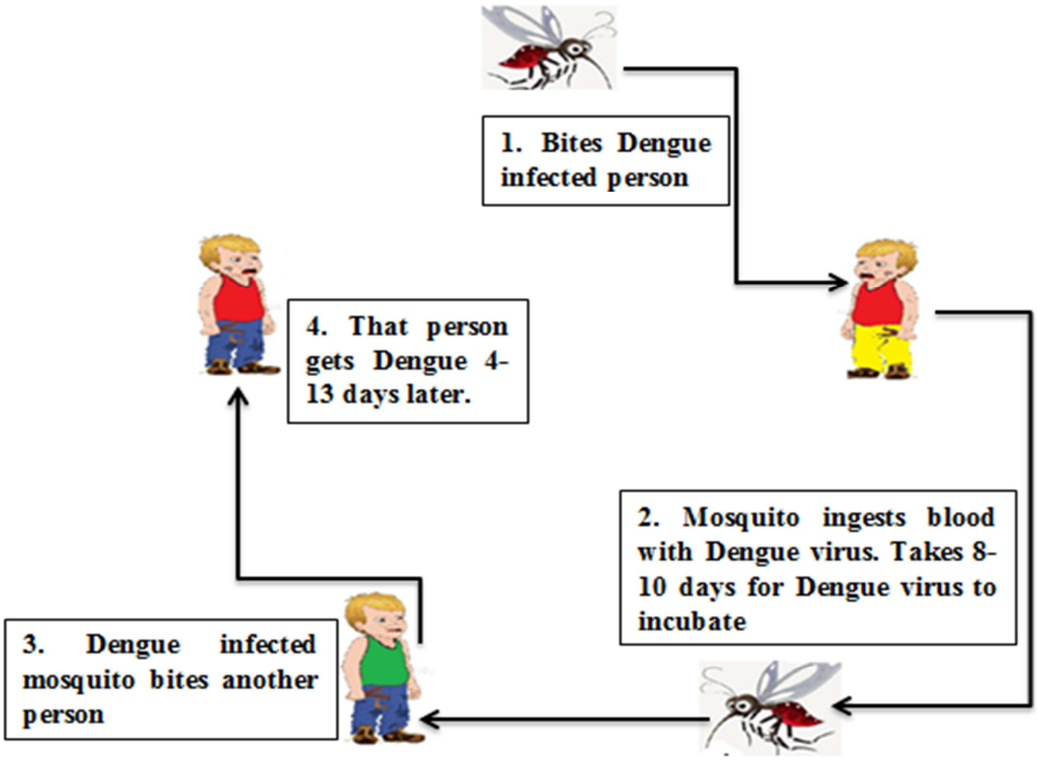

Figure 2. Dengue virus transmission flowchart.

4. Symptoms of Dengue Fever

Symptoms of dengue fever largely vary from person to person. Symptoms range from classical high fever, bone and joint pains, maculopapular rash, headache, myalgia, lymphadenopathy to severe hemorrhagic fever and shock. DHF or DSS causes mortality rate of 5-10% [12].

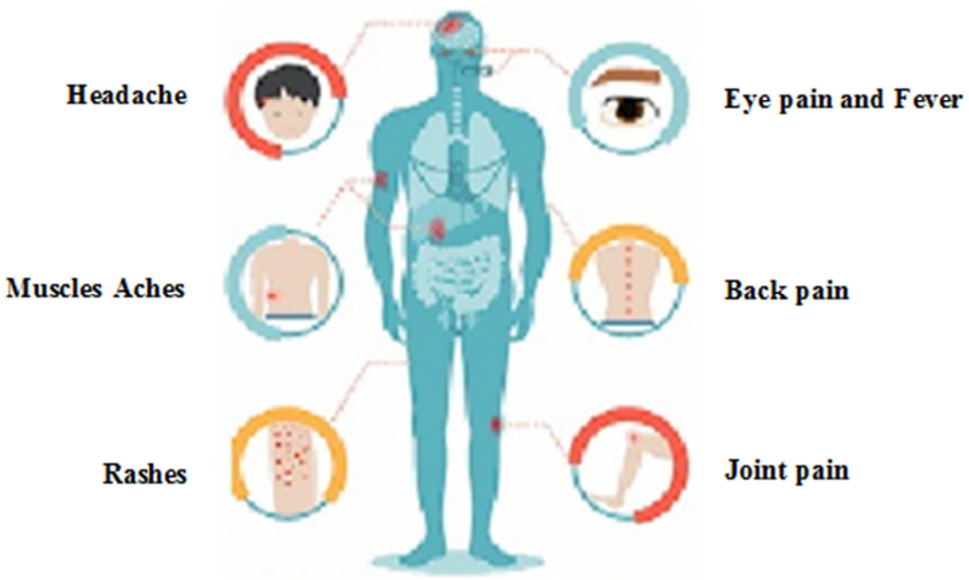

Figure 3. Symptoms of dengue infection.

5. Diagnosis

The present diagnostic modalities of Dengue are based on serological tests, isolation of virus, and molecular methods [13-14]. Isolation of virus from autopsy tissue specimen or serum confirms acute infection caused by DENV. By utilizing reverse transcription polymerase chain reaction (RT–PCR), the exact dengue virus genome can be identified from autopsy tissue specimens, plasma or serum and cerebrospinal fluid at any point of critical febrile illness [13]. Another way of confirming acute infection in autopsy tissue specimens is detection of viral RNA or antigen by immunohistochemical or immunofluorescence analysis [14]. Seroconversion of negative immunoglobulin M (IgM) antibody to positive IgM is also helpful for identification of acute illness. Determination of fourfold or greater rise in immunoglobulin G (IgG) antibody titer in coupled serum can be done for identifying acute and convalescent stage. [13-14].

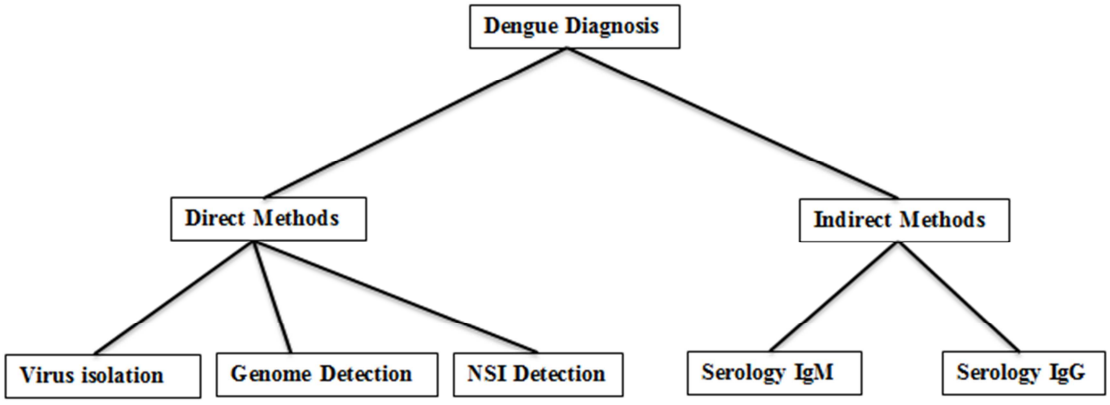

Figure 4. Diagnosis of dengue.

As like other viruses, serological tests for dengue are also available. One of them is microsphere-based immunoassay (MIA). This may be a future test option. [13, 15-16]. The principle for MIA is covalent bonding between antigen and microspheres or antibody and microspheres. The test is superior upon MAC-ELISA (Avidin Biotin Complex IgM Antibody capture Enzyme Linked Immunosorbent Assay) because it is faster [14]. Main technique for MIA is using lasers to elicit fluorescence. This fluorescence has multiple wavelengths. [15]. MIA can also be used to differentiate various viruses through the antibody which is created by its antigenic response. [13-16].

The biosensor technology has come to use in modern days. Mass spectrometry (MS) is another technology that can produce tangible molecular profile of a given virus or bacteria [17]. Biosensor and MS if used together can develop a unique system. It can separate rapidly biological components from complex mixtures [14]. This system will work by comparing the desirable virus or bacteria with the database of known pathogen. For this comparison, a powerful

software system is needed. This software will be used in biosensor to sense the resultant virus or bacteria. Thus, within a very short time, a thousand of pathogens can be identified which will be more time saving [17-18]. The system will be helpful to identify not only the known pathogen but also the unknown pathogen which is unavailable by comparing it to the available bioinformations in the database. MS will help to identify the serotype along with its genetic sequence [14, 17-18].

Another one is microarray technology. This technology makes it possible to identify various nucleic acid fragments of various viruses in parallel [3, 19]. In this technique hybridization of genetic material is necessary. Then amplification of target conserved sequence together with random based one is done [19-20]. Small oligonucleotides which are connected with the microarray slide provide comparatively correct sequence of identification. In the meantime, larger DNA fragments show more tolerance for mismatches. It ensures the ability to detect dispersed strains [3, 13, 20]. To identify amplified fragments, a scanner which is based on laser is used. This scanner is acts as a reader and it is labeled by fluorescent dyes [12-13]. So, to say, microarray technology will be very much useful to detect dengue virus as well as other arboviruses in a region [3, 12-13, 19-20].

6. Treatment

Treatment modalities of present DENV infection is totally symptomatic and no definitive treatment is available till now [2, 14]. Now clinicians use acetaminophen for pain reliever and avoid medicines with aspirin, which could worsen bleeding [2]. Supportive care which may include followings: hospitalization, intravenous fluid replacement, respiratory support if respiratory distress present and prevention of secondary infections. DHF needs to be treated with appropriate fluid replacement [2, 14].

Figure 5. Treatment of Dengue.

Dengue fever decreases the platelet number [2-4]. The carica leaf juice proves its efficacy that it can boost up the platelet counts [21]. This can be a treatment option for dengue fever [21]. The future treatment modalities may include interferon treatment as like other flavivirus (hepatitis C), which may inhibit the envelop protein that help replication [3].

7. Prevention

Currently the preventive measures for dengue include being safe from mosquito bite and destroying the breeding place of *Aedes aegypti*. Therefore, it plays a little value when DENV spread in densely populated costal area rapidly [2].

Preventive treatment includes the invention of vaccine. Still progress is very poor because of having multiple serotypes that is the main hindrance for vaccine. Re-infection with another serotype of DENV may complicate the disease and may cause DHF or DSS due to cross-interaction with antibody that was produced before [8]. The scientists are trying and at present one vaccine is on clinical trial at phase 3. The first dengue vaccine is CYD-TDV. Mexico is the country to make license this first [22]. It was certified to be used among human aged 9 to 45 years who reside in endemic area. CYD-TDV is a tetravalent live recombinant vaccine. Sanofi Pasteur has designed this vaccine. It has 3 dose schedules at 0, 6, and 12 months apart. The vaccine is similar to *Yellow fever* virus vaccine though it has huge limitations [22-23].

8. Conclusion

Thus, the future of DENV diagnosis and treatment will be based on identification of its total genetic sequence, targeting its structural and non-structural proteins that can help to invent its curative and preventive treatment. Diagnostic methods based on direct isolation of virus and its genetic sequence, indirect identification of anti-dengue antibody by various methods including microsphere-based immunoassay (MIA), mass spectrometry (MS), microarray technology etc. Therapeutic modalities are supportive care of the affected person including platelets transfuse or platelets booster ingredient supplement. But in case of preventive measures which will eradicate dengue one day as like other viral diseases i.e. small pox, is still very poor.

Conflict of Interest

The authors declare that they have no conflict of interest.

Ethical Approval

This article does not contain any studies with animals performed by any of the authors.

Acknowledgements

The author has acknowledged the contribution of the University Grants Commission (UGC) of Bangladesh for funding the research work.

References

[1] Izabela A. Rodenhuis-Zybert, Jan Wilschut, Jolanda M. Smit; "Dengue virus life cycle: viral and host factors modulating infectivity." J Cellular and Molecular Life Sciences; August 2010, Volume 67, Issue 16, pp 2773–2786. doi: 10.1007/s00018-010-0357-z.

[2] *WHO (2009).* Dengue Guidelines for Diagnosis, Treatment, Prevention and Control. *World Health Organization.* ISBN 92-4-154787-1.

[3] Botting C, Kuhn RJ. "Novel approaches to flavivirus drug discovery." J Expert Opinion Drug Discovery. 2012 May; 7 (5): 417-28. doi: 10.1517/17460441.2012.673579. Epub 2012 Mar 22.

[4] SILER, J. F.; HALL, M. W.; HITCHENS, A. P. "Dengue: Its History, Epidemiology, Mechanism of Transmission, Etiology, Clinical Manifestations, Immunity, and Prevention. Philipp." J. Sci 1926 Vol. 29 No. 1-2 pp. 1-304 pp.

[5] Wiatrek, Melissa. "Dengue Fever." http://www.austincc.edu/microbio/2993p/df.htm. Accessed [23.12.2017]

[6] Haddow, AD; Guzman, H; Popov, VL; Wood, TG; Widen, SG; Haddow, AD; Tesh, RB; Weaver, SC (Jun 5, 2013). "First isolation of Aedes flavivirus in the Western Hemisphere and evidence of vertical transmission in the mosquito Aedes (Stegomyia) albopictus (Diptera: Culicidae)". J Virology. 440 (2): 134–9. doi: 10.1016/j.virol.2012.12.008. PMID 23582303

[7] Vivek Dhar Dwivedi, Indra Prasad Tripathi, Ramesh Chandra Tripathi, Shiv Bharadwaj, Sarad Kumar Mishra; "Genomics, proteomics and evolution of dengue virus." J Oxford Academic. 10 January 2017. Briefings in Functional Genomics, Volume 16, Issue 4, 1 July 2017, Pages 217–227. https://doi.org/10.1093/bfgp/elw040

[8] Dennis Normile. "Surprising New Dengue Virus Throws a Spanner in Disease Control Efforts." J Tropical Medicine. 25 October 2013. Vol. 342, Issue 6157, pp. 415. DOI: 10.1126/science.342.6157.415

[9] "Dengue virus". *Pathogen Information (PathInfo). Virginia Bioinformatics Institute, Virginia Tech. Archived from* the original *on 2010-08-30.*

[10] Holmes, EC; Twiddy, SS (May 2003). "The origin, emergence and evolutionary genetics of dengue virus". J Infection, Genetics and Evolution. 3 (1): 19–28. doi: 10.1016/s1567-1348(03)00004-2. PMID 12797969.

[11] Halstead, SB (1988). "Pathogenesis of dengue: challenges to molecular biology". Science. 239 (4839): 476–481. Bibcode: 1988Sci...239..476H. doi: 10.1126/science.3277268. PMID 3277268

[12] Centers for Disease Control and Prevention. Dengue. https://wwwnc.cdc.gov/travel/yellowbook/2016/infectious-diseases-related-to-travel/dengue Accessed [20.01.2018]

[13] Centers for Disease Control and Prevention. Laboratory Guidance and Diagnostic Testing. Dengue; Clinical/Laboratory Guidance. https://www.cdc.gov/dengue/clinicallab/laboratory.html Accessed [20.01.2018]

[14] World Health Organization; 2009. Dengue: Guidelines for Diagnosis, Treatment, Prevention and Control: New Edition. https://www.ncbi.nlm.nih.gov/books/NBK143156/ Accessed [27.01.2018]

[15] Alison J. Johnson, Ronald C. Cheshier, Giorgio Cosentino, Heather P. Masri, Valerie Mock, Rebecca Oesterle, Robert S. Lanciotti (2007). "Validation of a Microsphere-Based Immunoassay for Detection of Anti-West Nile Virus and Anti-St. Louis Encephalitis Virus Immunoglobulin M Antibodies". J Clinical and Vaccine Immunology 2007 Sep; 14 (9): 1084–1093. Published online 2007 Jul 3. doi: 10.1128/CVI.00115-07.

[16] Alison J. Johnson, Amanda J. Noga, Olga Kosoy, Robert S. Lanciotti, Alicia A. Johnson and Brad J. Biggerstaff (2005). " Duplex Microsphere-Based Immunoassay for Detection of Anti-West Nile Virus and Anti-St. Louis Encephalitis Virus Immunoglobulin M Antibodies." J Clinical and Diagnostic Laboratory Immunology 2005 May; 12 (5): 566-574. doi: 10.1128/CDLI.12.5.566-574.2005

[17] Hui-Yee Chee, Sazaly Abu Bakar (2004). "Identification of a 48 kDa tubulin or tubulin-like C6/36 mosquito cells protein that binds dengue virus 2 using mass spectrometry". J Biochemical and Biophysical Research Communications 16 July 2004; Volume 320 (1). https://doi.org/10.1016/j.bbrc.2004.05.124

[18] Rangarajan Sampath, Thomas A. Hall, Christian Massire, Lawrence B. Blyn (2007). "Rapid Identification of Emerging Infectious Agents Using PCR and Electrospray Ionization Mass Spectrometry". J The New York Academy of Science 23 April 2007; https://doi.org/10.1196/annals.1408.008

[19] Fink J, Gu F, Ling L, Tolfvenstam T, Olfat F, Chin KC, et al. (2007) "Host Gene Expression Profiling of Dengue Virus Infection in Cell Lines and Patients." PLoS Negl Trop Dis 1 (2): e86. https://doi.org/10.1371/journal.pntd.0000086

[20] A. M. A. Nasirudeen, Ding Xiang Liu, et al. (2009) "Gene expression profiling by microarray analysis reveals an important role for caspase-1 in dengue virus induced p53 mediated apoptosis." J Medical virology Jun 2009. Vol: 81 (6): 1069-1081. https://doi.org/10.1002/jmv.21486

[21] Sinhalagoda Lekamlage Chandi Asoka Dharmarathna, Susiji Wickramasinghe, Roshitha Nilmini Waduge. "Does Carica papaya leaf-extract increase the platelet count? An experimental study in a murine model." Asian Pac J Trop Biomed 2013; 3 (9): 720-724. doi: 10.1016/S2221-1691(13)60145-8

[22] Schmaljohn, Alan L.; McClain, David (1996). "Ch. 54: Alphaviruses (Togaviridae) and Flaviviruses (Flaviviridae)". *In Baron S.* Medical Microbiology (4th ed.). University of Texas Medical Branch at Galveston. ISBN 0-9631172-1-1. *NBK7633.*

[23] Torresi J, Tapia-Conyer R, Margolis H (2013). "Preparing for dengue vaccine introduction: recommendations from the 1st dengue v2V International Meeting". PLoS Negl Trop Dis. 7 (9): e2261. doi: 10.1371/journal.pntd.0002261. PMC 3784468. PMID 24086776.