

CHAPTER 2
LITERATURE REVIEW

2.1 INTRODUCTION

Flaviviruses consists of viruses of positive, single-stranded, enveloped RNA viruses. They are transmitted via arthropods (primarily ticks and mosquitoes) and can occasionally infect humans. These viruses are well known for their ability to cause widespread morbidity and mortality throughout the world. Some of the mosquitoes-transmitted viruses include: Yellow Fever, Dengue Fever, Japanese encephalitis, and West Nile viruses. Other Flaviviruses are transmitted by ticks and are responsible of encephalitis and hemorrhagic diseases: Tick-borne Encephalitis (TBE), Kyasanur Forest Disease (KFD) and Alkhurma disease, and Omsk hemorrhagic fever (CDC, 2014). Flaviviruses are enveloped, spherical, about 50 nm in diameter. The surface proteins are arranged in an icosahedral-like symmetry. Mature virions contain two virus-encoded membrane proteins (M and E), while immature virions contain a membrane protein precursor. Figure 2.1 taken from <http://viralzone.expasy.org> shows the structure flaviviruses virion and its components.

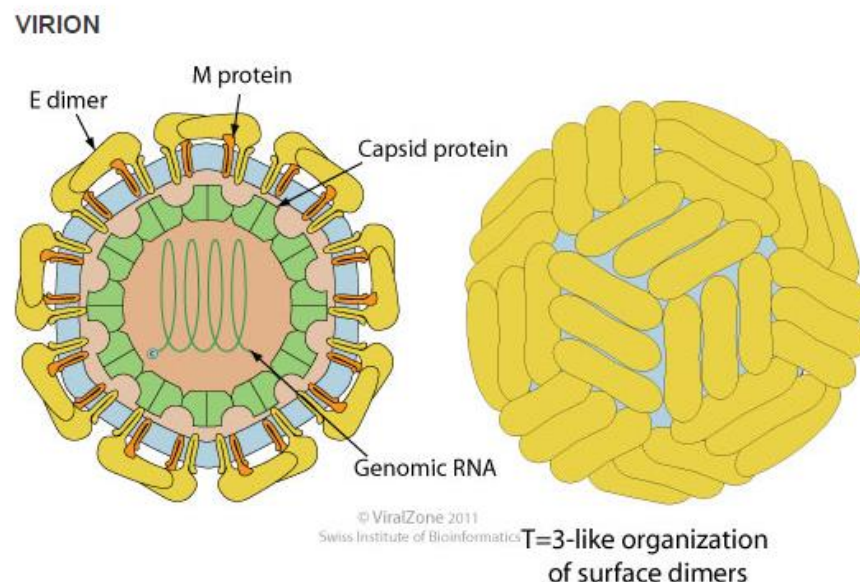


Figure 2.1: Structure of Flavivirus virion and its components

Figure 2.2 from <http://viralzone.expasy.org> shows ssRNA (+) genome of 10-11 kb flaviviruses which is monopartite and linear. The genome 3' terminus is not polyadenylated but forms a loop structure. The 5' end has a methylated nucleotide cap (allows for translation) or a genome-linked protein (VPg).

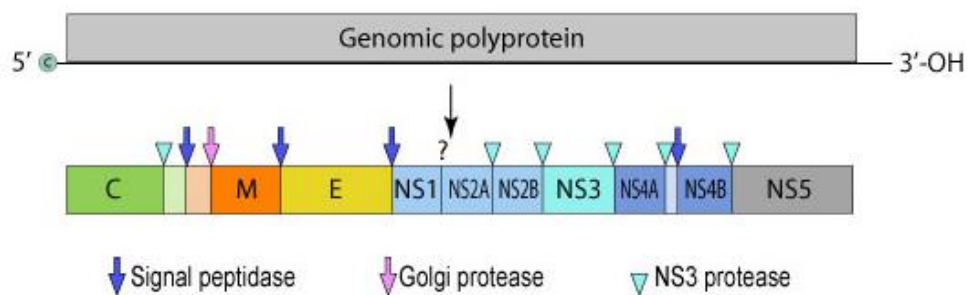


Figure 2.2: The Flavivirus (+) RNA genome and the co-linear polyprotein

The flavivirus NS3 protein plays a key role in the cleavage and processing of the viral polyprotein and also in the synthesis of the viral RNA. Complexes possessing protease and replicase activities through protease and nucleoside triphosphatase/helicase domains are formed via the interaction of NS3 and NS2B. (Prikhod'ko, G. G., et al., 2001). The correct processing of flaviviruses polyprotein by the viral NS3 protease (NS3pro) determines the replication of the viruses (Erbel, P., et al., 2006). For instance, a serine protease that is located within the HCV NS3 protein processes the viral polyprotein at four specific sites which is considered important for the replication of the virus (Kim, J. L., et al., 1996).

2.2 CLASSIFICATION

Flaviviruses is classified under arboviruses in which the viruses are transmitted via arthropod vectors like mosquitoes and ticks. Arbovirus infections are important human and veterinary pathogens and cause serious illness ranging from rash, arthritis, encephalitis and hemorrhagic fever (Hollidge, B. S. et.al, 2010). Flaviviridae (genus *Flavivirus*) is one of the taxonomic families under arboviruses. Figure 2.3 shows arboviruses classification in which *Flavivirus* and *Alphavirus* comprises the single stranded positive- sense RNA (Go, Y. Y., et al., 2014).

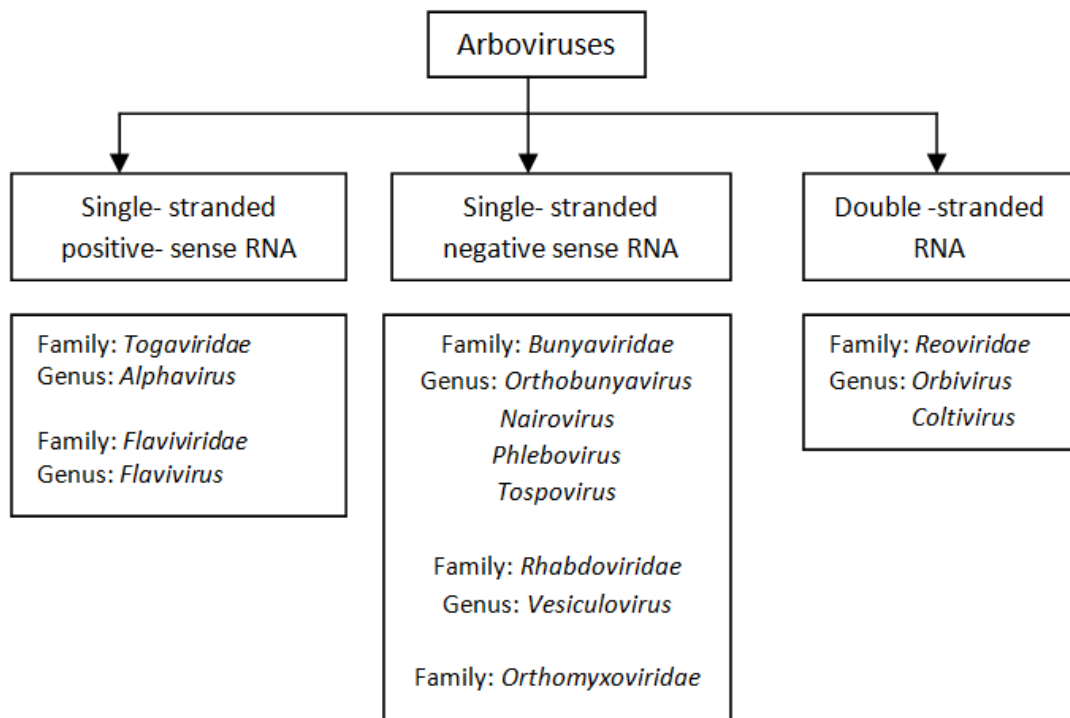


Figure 2.3: Classification of arboviruses. Flaviviruses are one of the six different taxonomic virus families of arboviruses.

2.3 EPIDEMIOLOGY AND PREVALENCE

After decades of research about flaviviruses, although the characteristics of these viruses are well defined, they are still unpredictable with increases in disease severity, unusual clinical manifestations, unexpected methods of transmission, long-term persistence, and the discovery of new species (Gould, E. A., & Solomon, T., 2008). There are two distinct epidemiological groups for the mosquito-borne flaviviruses namely the neurotropic viruses, often associated with encephalitic disease in humans or livestock, correlated with the *Culex* species vector and bird reservoirs and the non-neurotropic viruses, associated with haemorrhagic disease in humans, correlated with the *Aedes* species vector and primate hosts. (Gaunt, M. W., et al., 2001). A combination of constraints showed by the arthropod vector, the vertebrate host, the related ecology, and the influence of human development activities are believed to be the factors that determine the evolution, dispersal patterns and epidemiological characteristics of flaviviruses. This is proven by the the clinical evolution of the tick-borne encephalitis (TBE) complex viruses across the Euro-Asian land mass which reflects the life-cycle and feeding habits of the ixodid tick (Zanotto et al., 1995) combined with suitable climate conditions and the appropriate rodent host species (Randolph et al., 2000). Urbanization and industrialization associated with the increase in human and mosquito population densities resulted in the emergence and expansion of dengue haemorrhagic fever in the tropics (Zanotto et al., 1996).

2.4 TRANSMISSION CYCLE

Arthropods being the transmission vector of flaviviruses get infected by the virus when consume blood meal from a viral infected animal reservoir. The reservoir hosts are normally birds, wild animals and domestic animals. Only a subclinical infection occurs in these animals despite the fact that these reservoir hosts develop a high viremic titer (Weaver, S. C., & Barrett, A. D., 2004). Viral transmission naturally maintained via the cycle between vector and animal reservoir host. Other than that, the virus also can be transmitted through a blood meal to a susceptible host such as human or mammals like horse. These susceptible hosts are considered as dead-end hosts because the viral load in the blood remain low and further transfer from an infected host to another host becomes ineffective. However, Dengue virus is one of the exceptional viruses within the flaviviral group because humans can serve as reservoir host to further spread the virus because of the high viremic load in the blood (Schweitzer, B. K., et al., 2009). Understanding the life cycle and the associated vector-to-disease transmission is useful in predicting epidemics and to help prevent disease spread. Figure 2.4 shows the transmission cycle of flaviviruses involving non human primate/vertebrate hosts and primary arthropod vectors (Go, Y. Y., et al., 2014).

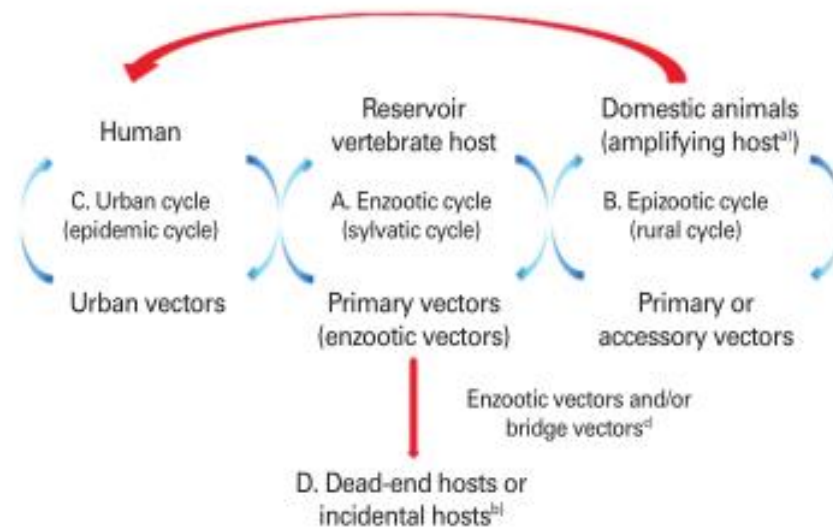


Figure 2.4: Vertebrate host and vector transmission cycle. (A) Enzootic cycle. The natural transmission of virus between wild animals and primary vector that leads to the amplification of the virus in the vector. (B) Epizootic cycle. The virus is transmitted between domestic animals and the primary or accessory insect vectors which can cause to an epidemic outbreak of viral disease. (C) Urban cycle. This virus cycles between humans and insects vectors repeatedly as reinfection occurs with every new bite. (D) Dead-end host. Humans are dead-end hosts in the infection chain and do not develop sufficient viremia thus do not lead to the amplification of the virus.

2.5 GEOGRAPHICAL DISTRIBUTION

The members of Flavivirus genus have a world- wide distribution but individual species are restricted to specific endemic or epidemic areas (King, A. M., et al., 2012). These viruses are also known as ‘emerging viruses’ because of the current increases in prevalence and geographic distribution with the signs of continued increases in incidence in the future (Morse, 1994). For instance, dengue virus caused a dramatic increase of morbidity and mortality globally in recent decades (WHO, 2001). Likewise, the geographical distribution of Japanese Encephalitis Virus (JEV) has an annual incidence of approximately 50000 and a case fatality rate of 33% (Solomon et al., 2000).

2.6 DISEASES

Flaviviruses infections such as yellow fever, dengue, West Nile, St Louis encephalitis, Japanese encephalitis, and tick-borne encephalitis can cause typical manifestations of diseases like haemorrhagic disease, encephalitis, biphasic fever, flaccid paralysis, and jaundice (Gould, E.A., & Solomon, T., 2008). Population growth, environmental changes like urbanization and agricultural, animal husbandry and land use changes are key factors of the increased transmission of flaviviruses diseases (Gubler, 2002). Currently, flaviviruses are considered as the most important emergent tropical diseases that leading to tens of millions of cases and thousands of death annually (Shi, 2012). This scenario is well portrayed in the emergence of dengue fever in the annual number of cases reported by World Health Organization (WHO) has increased nearly tenfold in forty years (Figure 2.5). Figure 2.5 shows the global emergence of dengue or dengue haemorrhagic fever reported to WHO from year 1955 to 2007.

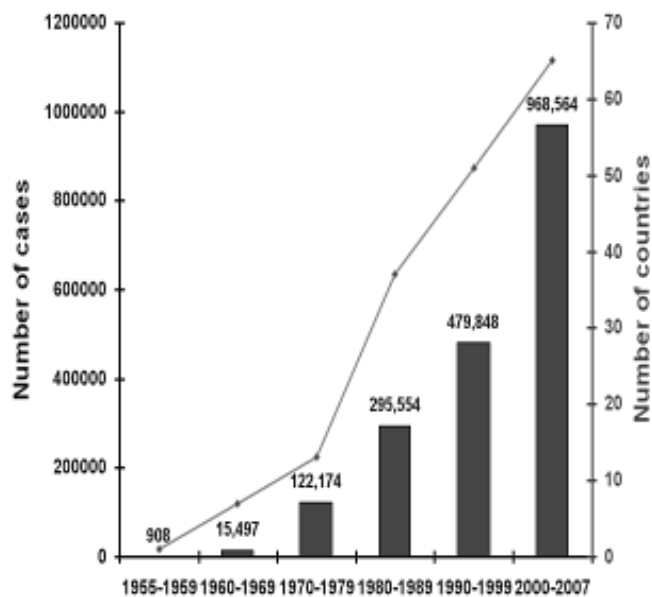


Figure 2.5: The global emergence of dengue or dengue haemorrhagic fever

Currently there are vaccines for three flaviviruses namely yellow fever, Japanese Encephalitis and tick- borne encephalitis which varies depending on the country (Gubler et. al., 2007). Although the yellow fever 17-D live vaccine is affordable, long lasting and safe to use; it is still not suitable to be used as a preventive purpose. Meanwhile, there are still no antiviral drugs for the other flaviviruses and prevention is mostly dependent on the vector control (Shi, 2012).