**Genetic Variability, Virulence and Epidemiology of Dengue Virus in Africa**

**Abstract**

Dengue Fever is one of the neglected tropical diseases that results in case of approximately 100 million per year with over 5 billion individuals at risk of infection and re-infection. It is now one of the most prominent vector-borne diseases of humans in subtropical and tropical parts of the globe with four dengue virus strains (DEN-1, 2, 3 and 4) being reported based on their genomic variants.Transmission to humans is mainly through theinfective female *Aedes* mosquito bite which can be enhanced due to the climate of the tropic and subtropics.Thevirulence of DENV is function of its genetic variability andthe elevation many cytokines level and chemical mediators, which responsible for capillary leakage and shock. This situation enhances the progression of DF to DHF and DSS in the infected patients. TNF- α and cytokines (IL-1b, IL-6 and IL-8)that are secreted downstream of TNF- α as the inflammatory cascade, contribute to the disease severity. Marked IL-2 and interferon (IFN)-γ are then produced by T cells due to the immune activation that occurs during DENV-infections in the patients with DHF and DSS than the patients with DF. Genetic diversities in the DENV is important in the understanding of viral virulence and mechanisms of its pathogenicity. This will help in the control of the virus especially in vaccine development and preparedness towards any emerging or re-emergence of the virus.

**Keywords:** Dengue virus, Genetic variability, Virulence, Haemorrhagic fever, Africa

**Introduction**

**Dengue Fever (DF).**

Dengue Fever is now one of the most prominent vector-borne disease of humans in tropical and subtropical pats of the globe. The causative agent dengue feveris dengue virus (DENV). It has caused frequent and recurrent epidemics [1,2]. Approximately, over 100 million dengue infections cases occur per year with atleast; an approximately over 5 billion people havingthe possibility of dengue virus infection and 25,000 deaths being recorded annually [1,3]. The four dengue virus serotypes (DEN-1, 2, 3 and 4) have been reported to be transmitted to humans when an infective female *Aedes* mosquito bites which may result in the occurrence of dengue fever (DF). This is a viral infection which is acute and associatedwithsymptoms likeheadache,fever, muscle and joint pain as well as rash[4].

Similarly, dengue fever has been reported constitute a global health issue because of its endemicityoccurring in morethan 100 countries.The DENV infection is mainly affecting tropical and sub-tropical countries [4]. However, Nassar *et al.* [3] has reported occurrence of IgM and IgG in the blood samples of patients with febrile illness. This infection has been occurred and continuously occurring as a major public health problem across the globe; It has been asserted worldwide that 2.5 billion people at risk of dengue infection and 25,000 deaths that are being recorded yearly [5].

Evaluating the progression of DF to a severe DHF/DSS results into a challengingcondition because of non-specificity of signs and symptoms, lack of the detail knowledge of the immuno-physiology and associated molecular mechanisms of the infection. Because DENV infection remains one of the prominent Neglected Tropical Diseases (NTDs) affecting subtropical regions, there is need for collaborated efforts to controlthe spread of dengue virus infection. Some of the control measures involve: public awareness campaign, reliable diagnostictechniques and improvement on vaccine production. There has been recommendation on the requirement for the detailedknowledge on the pathogenesis of dengue infection in order to comprehend the immuno-physiology and inherent molecular mechanisms (DHF/DSS) [4,5].

Although, most of these epidemics occurbecause of the DENV serotypes fluctuations in the epidemiological population of low herdimmunity to a particular serotype and genetic variations in dengue virus which appears to play a distinctive role in epidemic emergence [6]. Several factors which contribute to the genetic changes and virulence of the virus in the disease occurrence is still not well understood. It could be hypothesized that there could be a complex mechanism of host–virus interactions and possible associated environmental factors which may responsible for the spread of specific viral variants compare to others and virulence [7].

**Literature Search**

The information use in this review work was obtained from original and review articles, reports from WHO, CDC and Dengue Virus Net. These documents were downloaded from google scholar, researchgate, semantic scholar, scopus and other research databases.

**Progression in DF and Immunological Markers.**

Occasionally, infections caused by dengue virus majorly dengue fever progresses to dengue haemorrhagic fever (DHF) and dengue shock syndrome (DSS which are illnesses that are threateningto life potentially associated with haemorrhagic manifestations (i.e DHF) and significant loss of plasma from the vascular content therefore, giving rise to shock in severe cases hence dengue shock syndrome (DSS). Pivotal to the pathogenesis of DHF and DSS is the loss of endothelial paradigm that is assumed to be sequel to an abnormal immune elicitation and alteration in immunomodulation. Along with the alteration of immunomodulation, reports of the raised chemical mediators and many cytokines, which can cause leakage of the capillary and subsequently result to shock.These scenarios have been found to be associated with clinical symptoms peculiar to individual suffering from DHF and DSS.

It is fundamental to mention that dengue virus replication of occurs mainly in the mononuclear phagocytes, which are the major origin of tumor necrosis factor alpha (TNF)-α as well as other vasoactive inflammatory mediators. Reports of many studies showed that TNF- α as well as other interleukins(i.eIL-1b, IL-6 and IL-8) which are produced downstream of TNF- α as the inflammatory cascade, contribute to the disease severity [2,5,8]. Other inflammatory cytokines, such asIL-2 and interferon (IFN)-γ, are producedby T cells due to the immune activation that occurs during infections caused by dengue virus. The rate of these cytokines production by the T-lymphocytes are observed to be markedly more in the patients showing DHF and DSS than the patients with DF [7].

It is also important to stress the role of the prior dengue virus infection especially those with different serotypes. Many epidemiological findings have reported that prior infection with a different serotype of the viruseswhich constitutes the serious risk factor which results in DHF [9]. Similarly, an *In vitro* study has shown that the impact of antibodies against dengue occurrence at concentrations below neutralization level panacea to the DENV infection of Fcγ receptor positive cells, like monocytes [10]. Considering the epidemiological and laboratory evidences of the roles anti-dengue antibodies in complicating the dengue virus infections, it has been predicted that cross-reaction of anti-dengue proteins may heightened the number of the DENV-infected monocytes which can occur during re-infection.The lysis of the monocytes that is infected by the DENV may result in DHF and DSS. Another hypothesis for the greater inflammatory responses occurring during dengue virus infection is the viral pathogenesis. Report of manyworks aboutdengueshowed that DENV-2 results in illness of greater severity than other dengue serotypes which suggests that the genotype of the virus influences the infection outcome [9,11]. Consequently, the genetic variabilities found in aparticular serotype may also contribute to the differences in the infection severity, however more data is still required to substantiate this assertion [12].

Transmission of multiple serotypes DENV in Haitian population results in Hyperendemic caseswith apparently DHF and DSS absence;frequent occurrence of DHF and DSS among black people compare to the white population.This led to an hypothesis that human genetic variations, such as:polymorphisms and genetic mutations may result to difference in the infection susceptibility[13]. Since genetic polymorphisms is a concept for stable gene variants thereby modulatelittleinfluence on protein functions as well as its. These underlyingprinciples might be responsible for susceptibility of individual to the DENVinfection [14]. Manyworks have reported that genetic polymorphisms may confer protection or predispositionpeople infected with dengue virus to serious cases like DHF and DSS [15]. Adequate knowledgeof the molecular background for DENV infection will provides useful information to the development of DHF and DSS which eventually leads to dengue disease managementand effective vaccine development.

**Genome of the Virus and its Diversity**

Like other flavivirus, the genome of DENVis made up of a single stranded RNA which is approximately 11 kilobases (kb) in size, enclosed by a capsid which together referred to as nucleocapsid.The nucleocapsid isenclosed by envelope which is made up of membrane protein derived from the host cell membrane. Genomic RNA functions as messenger RNA because of its positive polarity translate as a single long strand of open reading frame (ORF) to a large basal polypeptide. Surrounding the ORF are two regions (5’ and 3’ NTR) of about 100 nucleotideswhich are nontranslated. Proteolitic cleavage of the polyprotein whichis Co- and posttranslational modification result in the formation of viral particles, such as membrane (M), capsid (C) and envelope (E) which constitutes the three structural proteins, as well as NS1, NS2a, NS2b, NS3, NS4a, NS4b, and NS5 which are seven non-structural protein, (Figure 1) [16].

Report of the sequencing nucleotide of the entire E gene has been utilized as a molecular tool for the study of the DENV epidemiology which help in determining the source and dissemination of dengue virus. Among the four serotypesof dengue virus, phylogenetic analysis have shown genetic subtypes that is up to 12% nucleotide difference in the envelop of the DENV gene during in sequencing[17]. So far, the phylogenetic analysis of the envelope (E) gene enables the classification dengue virus types into a few E-genotypes whichaligns with geographic sources. DEN-1 is made up of five known subtypes, 1-V while DEN-2 are of six, in addition, DEN-2 subtype II has further been fragmented into sublineages, IIIa and IIIb. DENV-3 and DENV-4 are currently classified into four and two distinct subtypes respectively. However, the genomic differences currently will expand as more serotypes of each dengue virus type being evolved. Within a geographic location, genetic differences in the virus population may be tied to mutation and selection which leads to the appearance of new variants over a certain period[18].

**Alignment of Genetic Difference with Pathogenesis**

Several studies of naive and attenuated dengue viruses have shown genetic variations among strains of four serotypesand this variation is in association with virulence, attenuation and/or epidemic potential. Although a number of nucleotide and amino acid differences were observed throughout the entire RNA genome which comprises of protein coding and nontranslated region (NTR’s), majority of the molecular indicators are found located in the E gene. In spite of the fact thatthere is no specific site(s) could be linked with attenuated or severe disease in human, yet occurrence of DHF and DSS as DENV infections. The evidence of plaque size *in vitro*andmonkey viremia and mouse neurovirulence *in vivo*as indicators are used to evaluate probable virulence determinants; however, it has shown to be an imperfect model of human disease prediction. Although, similar genetic markers of dengue virulence have been investigated by genomic sequencing DENV genome isolated from patients showing diverse disease severities [19,20,21].Several studies have reported structural differences that wereconsistently observed between the two DENV-2 genotype which are associated with distinctive clinical features in human: the Southeast Asian genotype with DF and DHF as well asgenotype associated with American cases of DF only. The differences among six encoded amino acid change were observed in the envelope glycoproteins (E; amino acid 390 Asn→Asp),pre-membrane proteins (prM; amino acid 28 Glu→Lys), and NS5 (amino acid 645 Asn→Asp, 676 Ser→Arg, and 800 Lys→Ser), the nonstructural proteins 4b (NS4b; amino acid 17 Ser→His),while sequence differences were found within the 5’ nontranslated region (NTR) and 3’NTR have been predicted to influencethe secondary structure of RNA at both genomic ends. Suggestions have been made that primary markers of DHF could beassociated with the following molecular factors: amino acid of the E protein, which claimed to alter theability of the virion to bind to the host cells; downstream loop (nucleotidesequence of about 68-80) of the 5’NTR.Thisassertion may be involved initiationof translation; and 300 nucleotide sequences upstream of the 3’NTR, which may modulate replication of the virusthrough the formation of replicative proteins as intermediates. The importance of the differences in the four amino acid of the nonstructural proteins NS4b and NS5, is assumed to be transport protein and RNA polymerase of the virus respectively, however, the main purpose remain unknown[22]. Study has revealed thataddition of American genotype sequences into SE Asian-derived infective clone (chimera) at both 5’- and 3’- terminal alters the replicative efficiency of the clone. This showed that American genotype sequencescould reduce the replicative potential of an SE Asia-derived infective clone and this finding provides insighttowards a fact that American genotype dengue viruses arerarely if not associated with the progression of DFto DHF [22]. Moreover, the comparability of the Thai and The American strains was observed to prevent a possible relationship between the amino acid sequence of the DENV-2subtype and severe clinical manifestation. This is also evident in the serological response of the patients to the DENV disease by the virus serotype [23,24].

Structural protein genes genes

Non-structural protein genes

Dengue Virus Genome: Positive sense single stranded RNA

C

prM

M

NS2B

E

NS3

NS4A

NS5

NS1

NS2A

NS4B

DENV polyprotein

**Figure 1:** The genome of the DENV and its polyproteins.

**Genetic Mutation in the Dengue Fever Virus (DFV)**

Variation in the DENV genome variations associated withgenotypes, serotypes, as well as lineages are vitalmarkers for evaluation of viral pathogenicity, immunoresistance and potential for epidemic [9,10].Replacement of the genotype is a phenomenonthat has been seeninplaces like Sri Lanka, which coincided with severe dengue prevalence. Of notice is that this countryalso has undergone a significant epidemic during 2017 with 186,101 cases of denguewhile decreasing of the intensity of casesassociated with dengue was found during 2018 epidemicwith 51,659 cases.There is a two-fold case rises in dengue occurrence as foundin Sri Lanka occurring in the epidemic during 2019 with 105,049 cases[25]. This fluctuation in the epidemic occurrence in this region suggests a possible genotype/serotype change or clade shift phenomenon.

DENV genotype composition has been on continuous modification, however this depends on the concerned areaswhere the genome is found. Different regions of the genome of DENVthat evolve at different frequencyhowever there could be areas of high mutation magnitudesalongthe genomic location whichis evidentin the E gene or 30 UTR [26]. So far, classification of the genotype found associated with serotype is carried out basically on the sequences of the E gene. Mainly, the composition of the nucleotide in the 30 UTRs is observed to differentiate virulenceone from lessvirulence virus(DENV) strains which is observed in several dengue endemic countries [12,25]. Interestingly, 30 UTR has less been used in characterization of the sequences and phylogenetic analysis [17].The consequences of the structural genome and the impact of the nucleotide variations associated with viral fitness due to genotype replacement phenomenonstill needs to bevalidated by experimental process[15].

Structure of DENV 30 UTR compose of stem loops (SLs), two dumbbell (DB) structures and conserved sequences (CSs) as well as repeat conserved sequences (RCSs). The 30 UTR length varies based on the genotype of the virus, however, it is majorly divided into three domains. Domain I is located directly downstream of the stop codon, consisting of a location with nucleotide sequences and two SL structures.The domain II is averagely conserved with two dumbbell structures through incorporation of conserved locations; repeat conserved sequence2 (RCS2) as well as conserved sequence2 (CS2) regions.However, Domain III is well known to be highly conserved with only an SL structure (Ferede *et al.,* 2018). The biological importance of ensuring two nearly identical RNA structures found within the 30 UTR of flaviviruses is not yet adequately known. Meanwhile, redundant proteins such as replicative enhancers have been suggested for the domain II-30 UTR which comprises of two dumbbell elements [27,28]. Moreover, dumbbell structures are presented as complex RNA segments that accommodate many signals whichregulate viral replication process [29]. However, suggestions of the distinctive folding of DB1 and DB2 suggested that there are possible clear functions [28].

Aninteresting feature of the 30 UTR of flavivirus genomes is the evolutionary conservation of the sequence repeats as well as duplicated RNA structures [30]. The 30 UTR of dengue virus contains two nearly identical SL structures (SLI and SLII).Also, two identical DB elements (DB1 and DB2). These two pairs of duplicated RNA elements possess secondary structures, which can withstand the genome degradation[31]especially during the stages of producing sub-genomic flavivirus RNA (sfRNA). Four different species of sfRNA (sfRNA1-4) have been identified based on the secondary structure [32]. The sfRNA helps the virus to escape the host immune response surveillance[33]resultinginto epidemiological competence [34]. The effectsof lineage replacement has been compare with sfRNA production-related virulence [35,36]. The domain II and domain III regions are predominantly represented regions in the sfRNAs. Having the domain III region being a highly conserved region, the domain II, with considerable difference, is worth studying for the variation in the genome in order to have an insight of the dengue virusin the epidemiological trends.

The mainorigin of dengue virus genetic diversity is the natural alternation betweeninvertebrate and vertebrate hosts, which enhances different selective pressures on the viral population [5,37]. The origin of this selective pressure and the mechanisms for genetic diversitygive instinct on the positive and negative selection of viral variants during host adaptation is still seriously not yet resolved. It has been shown that sequence differences in the 30 UTR, acquired during host adaptation, are found related to the generation of sfRNAs [32]. The most recent studies on RNA structure duplications are reported by de Borba *et al*. [38], which showed that each of the duplicated DB structures in the DENV-30 UTR is under effects of different selective pressure in the adult mosquitoes. It was also proposed that the maintenance of double copies of RNA structures is a vital strategy for the virus to ensure the functionality of one conserved element while the other is under the influence of different selective pressure in the two hosts [38]. These observations have raised issues regarding the mechanisms by which the viral RNA structures act in thevector and host (humans).The implications of the genetic differences of the 30 UTR in host adaptation, pathogenesis as well as transmission.

DENV as an RNA virus, possesses distinctive genetic variability, majorly because of the inherent high mutation rate peculiar to RNA-dependent RNA polymerase as enzyme necessary for the replication to take place. The occurrence of variation in the dengue virus genome sequence during the transmission from human to invertebrate host which has been reported in most studies andvariability of host adaptation is significance to the virus virulence [38].Mutations occurringon both doublebell(DB) regions of dengue virusgenome sequence increased the frequency ofgenetic variability of an infected *Ae. aegypti* as vector considering the first and second filial generation (F1 to F2). It has also been found that the genetic alterations are highly selected in the vectorwhich alters DB2 structures thereby leading toan enhanced virus replication in the mosquito cells.

Adaptive mutations in the dengue virusgenomes which occur in each host are known to be inherentin wild-type sequences and only occurred once they are dominant in the virus population therefore,well detailed sequencing isexpected to unravel the mutation[39]. However, conservation of the RCS2 and CS2 regions in domain II, 30 UTR has earlier been reported based on the study of human- and vector-derived samples [40]. In recent studies, there was no mutations in the 50 or 30 UTR virus genome except for a single position within the 30 UTR in two out of the twelve DENV1 isolates[41]. The unified changes detected in particular work were found to occur within the UTR betweenDB1 and DB2 of the two isolates. The reason for the genomic conservation in those isolates could be effect of environmental factors on the functionality of the RNA-dependent RNA polymerase.

Evolutionary analyses were carried out in MEGA7 and the evolutionary trend was evaluated using the Maximum Likelihood method based on the Tamura-Nei model[42]. The tree thathas the highest log likelihood (-118.44) was evaluated and initial tree(s) for the heuristic search were obtained automatically by making use of Neighbor-Join and BioNJ algorithms for a matrix of pairwise distances evaluated using the Maximum Composite Likelihood (MCL) approach, and then itemizing the topology with highest log likelihood value. The analysis used 18 nucleotide sequences while thecodon positions were 1st+2nd+3rd+Noncoding. All positions having gaps as well as missing data were nullified. There was a total of 20 positions in the final dataset [43]. Some of the dengue virus isolates with evolutionary value of 0.0000 share similarities with ancestors however it was found in some of the dengue virus isolates that there is gap from the ancestors which shows genomic differences in the evolutionary trends (Figure 2).



**Figure2:** Phylogenetic Concept by Maximum Likelihood method

**Factors affecting genetic diversity in DENV**

DENV are susceptible to changesthereby giving rise to serotypes with differencerates of virulence. On the rise, it is apparently becoming that many cases of DHF epidemic are linked with the circulating viral strains as well aselevated virulence. The driving forces of genetic diversities in DENV is attributed to several factors which possess potential influence observed to associate with genetic diversity in the viruses (DENV)[44].In the first instance, genetic diversity is apparently an inbuilt feature of DENV as presented by the existence of four strains. Being RNA viruses, DENV rely on an error-prone enzyme calledRNA-dependent RNA polymerase (RdRp) which mediates replication process; however, it has been estimated that this replicative enzyme produces at least one error per a round of replication cycle [45]. However, it is observed that the overall spontaneous mutation frequency may be due to functional constraints occurring from the desire of the DENV to replicate in two separate hosts which are, mosquitoes and humans.

On the second instance, co-infection of a host cell by two serotypes of the virus can stimulate genetic recombination in which RdRp switches from one serotype to another as replicative enzyme. This possibility is similar to the report from the work of Worobey *et al*.[46] who performed a diversity analysis of 71 published dengue virus sequences and observedmany hybrid sequences which were mosaics comprising gene regions with conflicting evolutionary trends. This work showed that dengue viruses manifested widespread recombination within, but not between, strainswithin the natural populations. This study supports the significance of recombination as anessential factor in modifying the genetic variation of dengue viruses. As the third driving force, it has been suggested that genetic diversities can be introduced through migration, or gene flow, based on the fact that human hosts as well as vectors can move over a long distance which enables wide geographical distribution of viral serotypes[47]. This, in turn, could result into a major mixing of viral strains and the production of molecular diversity through genetic recombination[44]. Lastly, the source of diversity in dengue viruses could simply be the consequence of an enhanced opportunities for transmission which isstimulated from the size and density of the human host population[48]. Thus, it appears that genetic variation that is evidence in dengue viruses may be a function of the effects of the multiple factors [44].

**Epidemiology of DF, DHF and DSS**

Epidemiology of dengue fever (DF) is weakly characterized in Africa, even though the vector (mosquitoes) present a greater burden in the Middle East as well as Sub-Saharan Africa.This is in addition to all serotypes of DENV that are circulating in nineteen (19) countries ofAfrica[49]. In the area of the Sub-Saharan Africa, dengueappears to be a significant infection burden for public health, with an infection burden of about 25% (21–29%) through evaluation of IgG, 10% (9–11%) by evaluating IgM while infection burden was 14% (12–16%) through evaluation of viral nucleic acid[36] as shown as Table 1. Also, in many parts of the Africa countries, there have been report of outbreaks dengue feversuch as Burkina Faso investigated during 2016 and 2017, Côte d’Ivoire during 2017, Cape Verde during 2009, as well as Egypt during 2015[37] (Table 2).

The dengue is endemic in many Africa countries, the Eastern Mediterranean,the Americas, Asia, Australia and the Western Pacific which aremostly within the WHO regions [29,30,50], although the Americas, South–East Asia and Western Pacific regions are the most seriously affected regions, with Asia representing 70% of the global burden dengue fever [44]. The lack of concerted and coordinated effort at the regional levels to start an intervention programme that is population-based epidemiological surveillance with distinct operational goals leads to the reduction of the infection burden acrosshigh-risk zones[31]. Since 1940, the risk of contracting the dengue virus infection has risen by over 30-fold and widely spread spontaneously as population movements occurred during World War II [49]. In the late 1990s, dengue fever(DF) was found to be the second most significant mosquito-borne disease after malaria, with almost 40 million dengue fever cases and hundreds of thousands of dengue haemorrhagic fever (DHF) cases yearly[49]. About half of the world populations are continuously at risk of contracting DF infection. Yearly, there have been an estimated value of 390 million DF infections, where about 100 million of the total cases manifesting clinical features however,about a thousand of the cases develop fatal conditions called DHF/DSS, predominantly in the tropical and subtropical parts of the globe including America, Australia, Asia as well as Africa [35,50].

The transmission and distribution of the cases of dengue fevercould be attributed to the essential factors such as population growth pattern, globalization as well as urbanization, climate changepoor sanitary conditions, ineffective vector control, and neglection ofdengue virus surveillances and adequate review of dengue virus case reports. These factors may account for the incrementof vector (mosquitoes) populations and susceptibility of the host to the circulating strains. Climate shift may create favourable precipitation, humidity and temperature which enhances the breeding and feeding patterns of the mosquito and subsequentlyenables the completion of the incubation periodof the DENV [3]. Moreover, in fewdecades, the losses of enzootic amplification and the adaptation for viral replication at higher temperatures in the mosquitoes have made dengue virusresultsinto the enormous and extensive epidemic in tropical urban areas[36]. Endemic and epidemic of dengue fever transmission cycles are sometime augmented with prominent morbidity, mortality, as well as economic implications in developing countries [51,52].

Since 2000, a significant rise in thedengue fever incidence, the spread of DENV cases to new countries, and the urban-to-rural transmission risk have resulted in almost half of the world’s population risk[3]. The virus limit of infectivity has recently reached 129 countries with distinct evidence of dengue fever cases and subsequently result in outbreaks in many regions, including 36 countries that have previously been classified to be dengue-free regions by WHO and/or the US CDC [52]. The tendency of theoutbreak increase may be due to globalization, population growth pattern, urbanization and climate change, poor sanitary conditions, ineffective mosquito control methods and inadequate DENV surveillances as well asdeficient virus case reports [3].

In thelast two decades, there is progression that is more than eightfold and fourfold in the number of dengue fever cases as well asmortality raterespectively in the data available in WHO repository. The reported cases of DF haverisen from 505,430 cases in 2000 to a value greater than 2.4 million in 2010, case rises was also recorded in 2019 with value of 5.2 million cases.Similarly, reported mortality rate has alsorisen from 960 deathsduring 2000 outbreaks to 4032 deathsduring 2015 outbreaks [3]. Also, the cases of dengue fever have changed from majorly affecting peoplewithin the age of 40–50 years old to situation of affecting all age groups [31]. During the year 2020–2021, the entire reported DF cases and deaths contrarily seemed to decline. However, the data were not yet completed due to the COVID-19 pandemic that affected case reporting in many countries (WHO, 2022). Even though, the dengue fever and mortality reports have been increasing over wide geographical locations as well asacross all age group within the population, It worthy of note that the current global distribution dengue fever remains seriously uncertain [52].

**Table 1: Confirmation of DENV infection in Africa**

|  |  |  |
| --- | --- | --- |
| **S/N** | **Diagnostic Techniques** | **Confirmed DENV Infection** |
| 1 | IgG | 21 – 29 % |
| 2 | IgM | 9 – 11 % |
| 3 | Viral RNA Detection | 12 – 16 % |

**Table 2: Occurrence of DF Outbreaks some African Countries.**

|  |  |  |
| --- | --- | --- |
| **S/N** | **Country** | **Year of Outbreak** |
| 1 | Burkina Faso | 2016, 2017 |
| 2 | Côte d’Ivoire | 2017 |
| 3 | Cape Verde | 2009 |
| 4 | Egypt | 2015 |

**Conclusions**

Dengue virus infection has continuously emerged and re-emerged as a global health challenge of the world. The pathogenesis of dengue fever which eventually result in severe casesstill needs detailed investigation, as appropriate *in vitro* and *in vivo* models for the progression of mild DF to severe DHF/DSS are rarely or not available. Frommany proposedepidemiological and experimental evidence,dengue fever associated with heterotypic dengue virus strains have been reported in many countries of the world. Occurrence of severe cases of DF which are DHF and DSS are the major causes of deaths during outbreaks.

Molecular findingsavailable in the recent years is rapidly pointing attention to the involvement of viral factors in the development of DHF/DSS during viral pathogenesis. Viral pathogenicity evaluation have shown that viral genes modulate the level of virulence, and hence, disease severity. Also, not all cases of DHF are caused by viral virulence but other factors such as climate change are involved. In fact, many other host-related factors have also been linkedto the disease pathogenesis. Therefore, it is most likely thatpathogenesis of DHF may be multifactorial based.

Furthermore, it has been difficult to narrow the contribution of viral genetics to the occurrence of dengue disease in humans. This assertion is mainly due to theinadequate models for the disease occurrence. Availability of advances in molecular techniques especially rDNA technology and sequencing has helped to monitor DENV pathogenesis through the cloning of the infectious particles of dengue viral RNA.The application of quantitative real-time PCR to determine viral RNA in the human immunological cells have recently contributed to significant understanding of dengue replication and patient prognosis.

As we depend on the advances in the molecular biology to comprehend the mechanisms of the virus replication, there is still need for the advances in dengue molecular virology further understand virus virulent factors that exacerbate its pathogenesis. This novel knowledge will help the existing findings on the virulence factors such as human immune and genetic factors..

**Ethical Approval**

Not applicable

**Conflicts of Interest**

All authors declare no conflict of interests whatsoever

References

1. Holmes, E.C.; Twiddy, S.S. (2003). The origin, emergence and evolutionary genetics of dengue virus. Infect. Genet. Evol. 2003, 3, 19–28.

2. Stanaway, J.D.; Shepard, D.S.; Undurraga, E.A.; Halasa, Y.A.; Coffeng, L.E.; Brady, O.J.; Hay, S.I.; Bedi, N.; Bensenor, I.M.; Castañeda-Orjuela, C.A. (2013). The global burden of dengue: An analysis from the Global Burden of Disease Study 2013. Lancet Infect. Dis. 2016, 16, 712–723.

3. Nassar AS, Olayiwola JO, Ogunsanya YG (2018). Prevalence of dengue virus antigenemia in the malaria endemic area of the southwest Nigeria. Acad. J. Microbiol. Res. 6 (2): 019 – 022.

4. Olayiwola J. O. (2019). Dengue fever: A neglected infectious arbo-viral disease. EC Microbiology RCO. 01 (2019): 01 – 02.

5. WHO (2022). Dengue and severe dengue. Fact Sheet [Internet]. World Health Organization. 2022 [cited 2024 Jun 13]. Available from: https://www.who.int/news-room/fact-sheets/detail/dengue-and-severe-dengue.

6. OhAinle, M.; Balmaseda, A.; Macalalad, A.; Tellez, Y.; Zody, M.; Saborío, S.; Nuñez, A.; Lennon, N.; Birren, B.; Gordon, A (2011). Dynamics of dengue disease severity determined by the interplay between viral genetics and serotype-specific immunity. Sci. Transl. Med. 2011, 3, 114ra128.

7. Filomatori, C.V.; Carballeda, J.M.; Villordo, S.M.; Aguirre, S.; Pallarés, H.M.; Maestre, A.M.; Sánchez-Vargas, I.; Blair, C.D.; Fabri, C.; Morales, M.A (2017). Dengue virus genomic variation associated with mosquito adaptation defines the pattern of viral non-coding RNAs and fitness in human cells. PLoS Pathog. 2017, 13, e1006265.

8. James, S.; Abate, D.; Abate, K.; Abay, S.; Abbafati, C.; Abbasi, N.; Abbastabar, H.; Abd-Allah, F.; Abdela, J.; Abdelalim, A (2017). Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990–2017: A systematic analysis for the Global Burden of Disease Study 2017. Lancet 2018, 392, 1789–1858.

9. Bennett, S.; Drummond, A.; Kapan, D.; Suchard, M.; Munoz-Jordan, J.; Pybus, O.; Holmes, E.; Gubler, D. (2010). Epidemic dynamics revealed in dengue evolution. Mol. Biol. Evol. 2010, 27, 811–818.

10. Gubler, D.; Clark, G. (1995). Dengue/dengue hemorrhagic fever: The emergence of a global health problem. Emerg. Infect. Dis. 1995, 1, 55.

11. Yamanaka, A.; Mulyatno, K.C.; Susilowati, H.; Hendrianto, E.; Ginting, A.P.; Sary, D.D.; Rantam, F.A.; Soegijanto, S.; Konishi, E. (2010). Displacement of the Predominant Dengue Virus from Type 2 to Type 1 with a Subsequent Genotype Shift from IV to I in Surabaya, Indonesia 2008–2010. PLoS ONE 2011, 6, e27322.

12. Silva, R.; de Silva, A.; Harris, E.; MacDonald, G. (2008). Genetic analysis of Dengue 3 virus subtype III 50 and 30 non-coding regions. Virus Res. 2008, 135, 320–325.

13. Kanakaratne, N.; Wahala, W.M.; Messer, W.B.; Tissera, H.A.; Shahani, A.; Abeysinghe, N.; De Silva, A.M.; Gunasekera, M. (2009). Severe Dengue Epidemics in Sri Lanka, 2003–2006. Emerg. Infect. Dis. 2009, 15, 192–199.

14. Thu, H.M.; Lowry, K.; Jiang, L.; Hlaing, T.; Holmes, E.C.; Aaskov, J. (2005). Lineage extinction and replacement in dengue type 1 virus populations are due to stochastic events rather than to natural selection. Virology 2005, 336, 163–172.

15. Finol, E.; Ooi, E. (2019). Evolution of subgenomic RNA shapes dengue virus adaptation and epidemiological fitness. iScience 2019, 16, 94–105.

16. Chambers TJ, Hahn CS, Galler R, Rice M. (1990). Flavivirus genome organization, expression, and replication. Annu Rev Microbiol. 1990; 44:649-88.

17. Rico-Hesse R. (1990). Molecular evolution and distribution of dengue viruses type 1 and 2 in nature. Virology. 1990; 174:479-93.

18. Lanciotti RS, Lewis JG, Gubler DJ, Trent DW. (1994). Molecular evolution and epidemiology of dengue-3 viruses. J Gen Virol. 1994; 75: 65-75.

19. Pandey BD, Iragashi A. (2000). Severity related molecular differences among nineteen strains of dengue type 2 viruses. Microbiol Immunol 2000; 44(3) : 179-88. 5.

20. Leitmeyer KC, Vaughn DW, Watt DM, Salas R, De Chacon IV, Ramos C (1999). Dengue Virus Structural Differences That Correlate with Pathogenesis. J Virol 1999; 73(6): 4738-47.

21. Igarashi A. (1998). Molecular and in vitro analysis of eight dengue type 2 viruses isolated from patients exhibiting different disease seveties. Virology. 1998; 244 : 458-66.

22. Cologna R, Rico-Hesse R. (2003). American genotype structures decrease dengue virus output from human monocytes and dendritic cells. J Virol.; 77(7):3929-38.

23. Blok J, Gibbs AJ, McWilliam SM, Vitarana UT. (1991). NS1 gene suquences from eight dengue-2 viruses ang their evolutionary relationships with other dengue-2 viruses. Arc Virol. 1991; 118: 209-23. 24.

24. Kinney RM, Butrapet S, Chang GJ, Tsuchiya KR, Roehrig JT, Bhamarapravati N, Gubler DJ. (1997). Construction of infectious cDNA clones for dengue 2 virus; strain 16681 and its attenuated vaccine derivative, strain PDK53. Virology. 1997; 230:300.

25. Dash, P.K.; Sharma, S.; Soni, M.; Agarwal, A.; Sahni, A.K.; Parida, M. (2015). Complete genome sequencing and evolutionary phylogeography analysis of Indian isolates of Dengue virus type 1. Virus Res. 2015, 195, 124–134.

26. Villordo, S.M.; Alvarez, D.E.; Gamarnik, A.V. (2010). A balance between circular and linear forms of the dengue virus genome is crucial for viral replication. RNA 2010, 16, 2325–2335.

27. Endale A, Michlmayr D, Abegaz WE, Asebe G, Larrick JW, Medhin G, (2020). Community-based sero-prevalence of chikungunya and yellow fever in the South Omo Valley of Southern Ethiopia. PLoSNegl Trop Dis [Internet]. 2020;14(9):e0008549. https://doi.org/10.1371/journal.pntd.0008549.

28. Mohan A, Fakhor H, Nimavat N, Wara UU, Lal PM, Costa ACDS, (2021). Dengue and COVID-19: a risk of coepidemic in Ethiopia. J Med Virol. 2021;93(10):5680–1.

29. Guzman MG, Halstead SB, Artsob H, Buchy P, Farrar J, Gubler DJ, (2010). Dengue: a continuing global threat. Nat Rev Microbiol. 2010;8(12 Suppl):S7-16.

30. Kalayanarooj S. (2011). Clinical manifestations and management of dengue/DHF/DSS. Trop Med Health. 2011;39(4 Suppl):83–7.

31. Guha-Sapir D, Schimmer B. (2005). Dengue fever: new paradigms for a changing epidemiology. Emerg Themes Epidemiol [Internet]. 2005;2:1. https://doi.org/10.1186/1742-7622-2-1.

32. WHO (2009). Dengue guidelines for diagnosis, treatment, prevention and control: new edition [Internet]. World Health Organization. 2009 [cited 2024 Jun 13]. Available from: https://apps.who.int/iris/handle/10665/44188.

33. Ferede G, Tiruneh M, Abate E, Wondimeneh Y, Damtie D, Gadisa E, (2018). A serologic study of dengue in northwest Ethiopia: suggesting preventive and control measures. PLoSNegl Trop Dis. 2018;12(5): e0006430.

34. Stanaway JD, Shepard DS, Undurraga EA, Halasa YA, Coffeng LE, Brady OJ, (2016) The global burden of dengue: an analysis from the Global Burden of Disease Study 2013. Lancet Infect Dis. 2016;16(6):712–23.

35. Weaver SC, Reisen WK. (2010). Present and future arboviral threats. Antiviral Res. 2010;85(2):328–45.

36. Eltom K, Enan K, El Hussein ARM, Elkhidir IM. (2021). Dengue virus infection in Sub-Saharan Africa between 2010 and 2020: a systematic review and meta-analysis. Front Cell Infect Microbiol. 2021;11: 678945.

37. CDC Africa (2021). Dengue Fever [Internet]. Africa Centres for Disease Control and Prevention. 2022 [cited 2021 Oct 3]. Available from: https://africacdc.org/disease/dengue-fever/.

38. De Borba, L.; Villordo, S.M.; Marsico, F.L.; Carballeda, J.M.; Filomatori, C.V.; Gebhard, L.G.; Pallarés, H.M.; Lequime, S.; Lambrechts, L.; Vargas, I.S.; et al. (2019). RNA Structure Duplication in the Dengue Virus 30 UTR: Redundancy or Host Specificity? mBio 2019, 10, e02506-18.

39. Gloria-Soria A, Ayala D, Bheecarry A, Calderon-Arguedas O, Chadee DD, Chiappero M, (2016). Global genetic diversity of Aedes aegypti. Mol Ecol. 2016;25(21):5377–95.

40. de Castro, M.; de Nogueira, F.; Nogueira, R.; Lourenço-de-Oliveira, R.; dos Santos, F. (2013). Genetic variation in the 30untranslated region of dengue virus serotype 3 strains isolated from mosquitoes and humans in Brazil. Virol. J. 2013, 10, 3.

41. Manokaran, G.; Finol, E.; Wang, C.; Gunaratne, J.; Bahl, J.; Ong, E.Z.; Tan, H.C.; Sessions, O.M.; Ward, A.M.; Gubler, D.J. (2015). Dengue subgenomic RNA binds TRIM25 to inhibit interferon expression for epidemiological fitness. Science 2015, 350, 217–221.

42. Tamura K. and Nei M. (1993). Estimation of the number of nucleotide substitutions in the control region of mitochondrial DNA in humans and chimpanzees. Molecular Biology and Evolution 10:512-526.

43. Kumar S., Stecher G., and Tamura K. (2016). MEGA7: Molecular Evolutionary Genetics Analysis version 7.0 for bigger datasets.Molecular Biology and Evolution 33:1870-1874.

44. Lambrechts, L.; Fansiri, T.; Pongsiri, A.; Thaisomboonsuk, B.; Klungthong, C.; Richardson, J.H.; Ponlawat, A.; Jarman, R.G.; Scott, T.W. (2011). Dengue-1 Virus Clade Replacement in Thailand Associated with Enhanced Mosquito Transmission. J. Virol. 2011, 86, 1853–1861.

45. Drake JW. (1993). Rates of spontaneous mutation among RNA viruses. Proc Natl Acad Sci U S A 1993 May 1;90(9):4171-5.

46. Worobey M, Rambaut A, Holmes EC. (1999). Widespread intra-serotype recombination in natural populations of dengue virus. Proc Natl Acad Sci U S A 1999 Jun 22;96(13):7352-7.

47. Rico-Hesse, R. (2003). Microevolution and virulence of dengue viruses. Adv. Appl. Microbiol. 2003, 59, 315–341.

48. Zanotto PM, Gould EA, Gao GF, Harvey PH, Holmes EC. (1996). Population dynamics of flaviviruses revealed by molecular phylogenies. Proc Natl Acad Sci U S A 1996 Jan 23;93(2):548-53.

49. Dengue Virus Net (2022). Dengue Epidemiology [Internet]. Dengue Virus Net. 2022 [cited 2022 Sep 5]. Available from: http://www.denguevirusnet.com/epidemiology.html.

50. Bhatt S, Gething PW, Brady OJ, Messina JP, Farlow AW, Moyes CL, et al. (2013). The global distribution and burden of dengue. Nature. 2013;496(7446):504–7.

51. Harapan H, Michie A, Sasmono RT, Imrie A. (2020). Dengue: a minireview. Viruses. 2020;12(8):E829.

52. Degife LH, Worku Y, Belay D, Bekele A, Hailemariam Z. (2019). Factors associated with dengue fever outbreak in Dire Dawa administration city, October 2015, Ethiopia—case control study. BMC Public Health [Internet]. 2019;19(1):650. https://doi.org/10.1186/s12889-019-7015-7.