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Research Article

Evolutionary and Emerging Cosmos of Dengue Infection in India

Himani Prajapati[1], Yogesh Saxena[2*], Vivek Kumar[3], Garima Mittal[4]

[1]Himalayan School of Biosciences, Swami Rama Himalayan University, Dehradun, India
[2]Department of Physiology, Himalayan Institute of Medical Sciences, Swami Rama Himalayan University, Dehradun, India*
[3]Himalayan School of Biosciences, Swami Rama Himalayan University, Dehradun, India
[4]Department of Microbiology, Himalayan Institute of Medical Sciences, Swami Rama Himalayan University, Dehradun, India

Abstract
Dengue is one of the most common vector disease in human which is endemic in more than 125 nations across the globe. It is endemic in most of the Indian states and with all the serotypes existing together. Studies on the nature of the dengue infection and its serotype and genotype has been studied regionally across India . The review attempts to discuss the evolution and emergence of Dengue virus systematically across India till 2022. The observation that DENV1 to DENV4 serotype co- existing make it more likely to mutate and serve as Reservoir for emergence of varied strain in India. Also the genetic modification with emerging of diverse genotype and lineage seems to preludes the severity of the infection. Thus those existing the southern region have extended to the norther region of India despite the difference in environment factors with formation of more resistant and virulent serotype/ genotype mutant Virus.

Key Words: Dengue virus, Serotype of Dengue, Evolution of Dengue

***Author for correspondence: Email:** *yogeshsaxena@srhu.edu.in*

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Introduction

Dengue is the most common human vector borne disease which has spread globally and is causing frequent and repeated epidemic[1]. More than 125 nations are home to this disease, and travellers are targeted for its spread to other places [2] increasing the risk to 40% of population with yearly mortality of severe Dengue as 2.5% [3]. Presently there are 4 known serotypes of Dengue Virus (DENV) world-wide [DENV-1 -DENV-4] all of which result in a self-limiting febrile illness called Dengue fever (DF) with varying percentage developing severe Dengue Infection like dengue haemorrhagic fever (DHF) - characterized by thrombocytopenia , haemorrhage, and dengue shock syndrome (DSS) which is because of excessive leakage of plasma [4] , both of which can be fatal. Pathogenesis of the severe form of disease is the result from hyper immune reaction during host and virus interaction mostly during second infection of same or other serotype.

Epidemic emergence is not only caused by the mutation in prevalent DENV serotype in setting of low herd immunity of specific serotype, but a genetic variation in DENV also seems to play a distinctive role in its occurrence[5].
Complex network of virus host interaction together under varying environmental factors accounts for the transmission of a certain serotype of DENV virus infection over the others [6]. Genetic variations between serotype and genotype and lineages are important determinants of the differential virus virulence, fitness and its epidemic potential [7,8]. Globally such genotype variation and Serotype replacements of DENV have been observed in different regions of world coincides with the severe Dengue prevalence [9,10].

The majority of research has centred on identifying serotypes and genotypes linked to specific epidemics or outbreaks that have occurred in different parts of the world [11-13]. With deceased costs and improved capacity of higher generation sequencing available detailed genome sequence analysis and better understanding of the regional evolutionary trend of the disease is possible.

Review

Materials And Methods:

Literature was searched across PubMed ,Medline ,google scholar and systemic reviews with the keywords and MesH terms of Dengue evolution ; DENV; Dengue Genotype, Dengue Epidemic in India with bullions "and" and "or". The search of articles was filtered up to the year 2022 in human . A total of 170 articles which resulted were screened for the relevance to the topic based on the inclusion criteria of Dengue Virus epidemiology in India ,Dengue virus genomics ,outbreaks with relevant serotyping and genotyping done and articles with Dengue outbreaks across India up to the year 2022. Small study groups of 30 dengue positive subjects were excluded from review.

History of Dengue

Dengue word comes from the Swahili phrase "Ka-dinga pepo" i.e "cramp like seizures". Clinically recognised Dengue epidemic occurred in regions of Asia, Africa and northern America almost simultaneously in the year 1780s. With its first case in 1789 it was given a name of break bone fever due to its symptoms of myalgia and arthralgia[14] and finally the term 'Dengue' came into use only after 1828.

The first significant DHF outbreak appeared in the Philippines in 1953–1954 and was quickly followed by DF/DHF[15] outbreaks all over the world. While all the risk factors being there, DHF did not emerge in India while being prevalent in the neighbouring nations. Although Madras (now Chennai) saw the first pandemic of clinical dengue-like sickness in 1780, and Calcutta [Eastern Coast of India] experienced the country's first dengue fever outbreak in 1963–1964[16,17]. First major epidemic of severe form of Dengue in India occurred during 1996 in areas around Delhi[18] and Lucknow[19] which later extended all over the country [20].

About Virus

The virus belongs to family of Flavivirus and has four serotype referred as DENV 1, 2, 3, and 4. Virus is a positive stranded encapsulated RNA virus which is composed of three structural proteins genes. These genes encodes for three non-structural protein - (a) nucleocapsid or Core C protein; (b) membrane associated (M) protein ; (c) an envelope E protein glycoprotein and seven non-structural (NS) proteins. The primary mode of transmission of this virus is through the Ades aegypti mosquito. All serotype can cause the variety of diseases from sub clinical infection or mild self-limiting diseases called as Dengue fever to sever diseases that may be fatal, including DHF /DSS. In 1997 WHO classification which is still commonly used divided Dengue fever into three separate types: undifferentiated fever, dengue fever, & dengue haemorrhagic fever. Later the WHO in 2009 classification splits dengue fever into two groups: simple and severe[21]. Four important & common clinical presentation of dengue infection are a continuous high grade fever of 2-7 days; haemorrhagic tendency with petechiae or epistaxis (positive tourniquet test) ;thrombocytopenia (platelet count of <100×109/l); and manifestation of plasma leakage haemoconcentration (a haematocrit 20% above average for age, sex and population), pleural effusion , ascites, etc [22].

Structure of DENV Virus and Virus Proteins :

The mature single stranded RNA virion of DENV exhibits a smooth surface and possesses a diameter of around 50 nanometres (nm). In contrast, the juvenile virion displays a spiky surface and has a diameter of approximately 60 nm[23]. The section of their genome that codes for a single polyprotein is around 10.7 kb in size and is bordered by a short 59 untranslated region (UTR) and a longer 39 UTR, both of which are highly organised and carry components crucial to the viral replication[24]. The single polyprotein is post-translated into 7 non-structural proteins (NS1, NS2A, NS2B, NS3, NS4A, NS4B, and NS5) and three structural proteins (capsid, pre-membrane/membrane (prM/M -75 aa), and envelope -E 495 aa). The DENV virion's structural proteins regulate viral processes of : adhesiont (E), entrance (E and prM/M), assembly (C), and secretion (prM and E). The NS proteins, primarily have enzymatic functions as well as modulating the host immunological response. The C protein is a homodimeric protein consisting of 100 amino acids. It is characterised by the presence of 26 basic amino acid residues and three acidic amino acid residues. During DENV virion assembly, the C protein is essential for nucleocapsid formation[24], whereas the M protein is required for the assembly and maturation of the DENV particle. The E protein consists of three distinct domains, namely domains I, II, and III. Among these domains, domain III plays a crucial role in facilitating receptor binding activity. Virus attachment and fusion to host cell membrane essentially require the E protein [25].

The RNA replication complex necessitates the presence of NS1, a 45 kDa N-linked glycoprotein. Initially synthesised as a monomer, NS1 is subsequently discharged as hexameric lipoprotein particle into the extracellular fluid and circulation[26]. Rapid immune-chromographic assays and enzyme-linked immunosorbent assays (ELISA) have both been utilised as targets for the NS1, which has strong diagnostic value as a screening technique and to confirm DENV infection[27]. The NS5 protein, also referred to as the DENV methyltransferase-polymerase, is a 104 kDa enzyme that exhibits RNA-dependent RNA polymerase activity. This enzyme is characterised by its low fidelity, which consequently results in a heightened likelihood of introducing genetic variation within the viral population[28]. As a result, fresh viral varieties are constantly being produced within a single host, referred to as "intra-host diversity"[29].

Genome of DENV virus

With roughly 103–105 mutations per cycle of replication, the DENV genome exhibits low translational fidelity [30]. The genome of the DENV consists of a positive polarity single-stranded RNA (ssRNA) molecule, which is approximately 11 kilobases long. It is composed of a single open reading frame (ORF) that is lengthy, along with two untranslated sections (UTRs) known as the 5'-UTR (which is 95-101 nucleotides in

length) and the 3'-UTR[28]. The open reading frame (ORF) that is accountable for the synthesis of both structural and non-structural proteins experiences translation within a polyprotein. This polyprotein then undergoes a series of processing events, resulting in the production of a total of 10 mature viral proteins[31]. The N-terminal portion of the open reading frame (ORF) is responsible for encoding three structural proteins, namely C, prM/M, and E. These are then followed by seven non-structural (NS) proteins[31]. The region known as 3'-UTR plays a crucial role in the replication of Dengue virus (DENV) and influences the growth of the virus as well as the synthesis of its RNA in mammalian cells[32]. The 5'-CS is crucial for genome cyclization because it mediates RNA-RNA contact between the viral genome's 5' and 3' ends [33].

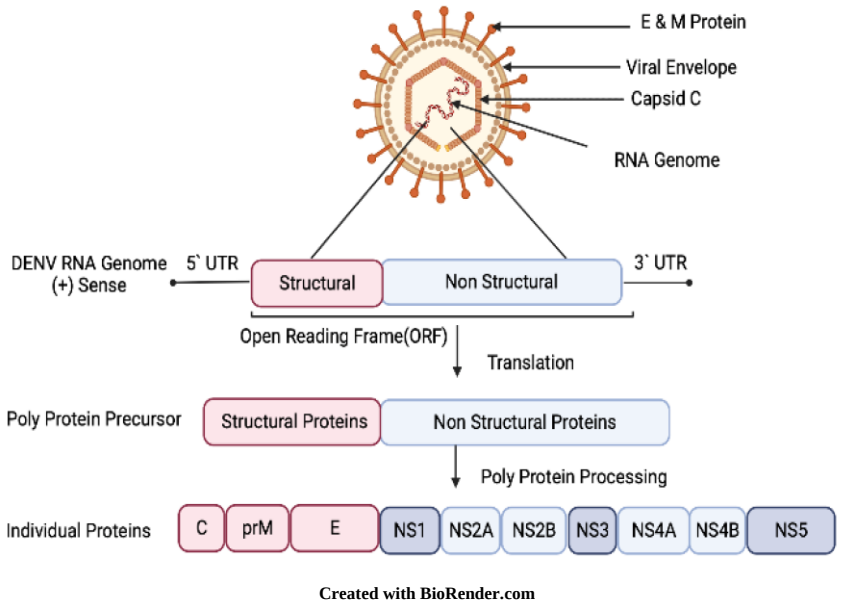

Figure 1. Organization & Genome structure of dengue virus: spherical in shape, enveloped, and contains a positive-sense, single-stranded RNA genome that encodes a precursor polyprotein. Upon viral entry into the host cell, with an open-reading frame translation the polyprotein is divided into structural and non-structural codes of a precursor polyprotein. The precursor polyprotein is cleaved into three structural proteins capsid, pre-membrane. and envelope(pink) , and seven non-structural proteins(blue).

Lifecycle of DENV

With the entry of the Dengue virus in human system, it binds to the cell surface attachment receptor by which it enter the cell by receptor mediated endocytosis. Numerous attachment molecules and receptors including glucosamine glycan, heat shock protein, C type lectins such as dendritic cell and mannose receptors has been identified in mammalian cells [34].

Upon entry into the cell, the DENV encounters a low pH environment within the endosome. This acidic condition induces conformational alterations in the E glycoprotein, leading to the union of the viral and cellular membranes. Consequently, the virion undergoes disintegration. Virion dissolution disintegrates nucleocapsid finally releasing the genome in cytoplasm. This genome undergoes translation into a poly protein which is acted upon by the viral and cellular proteases[34]. The genome with a positive strand functions as messenger RNA (mRNA) for the translation process, resulting in the production of a single polyprotein. Consequently, it functions as a blueprint for the process of RNA production. The polyprotein is transported into the endoplasmic reticulum, where it experiences proteolytic cleavage mediated by the host signalase and viral NS3 protein[28]. This process results in the formation of structural and non-structural proteins. The freshly synthesised RNA can subsequently be utilised for translation and packaging into nascent virions. The RNA intermediate with a negative strand polarity serves as a template for the replication of positive strand viral RNA. Following this, the viral RNA, together with the corresponding proteins, is enclosed within immature progeny virions situated in the membrane of the endoplasmic reticulum[35]. Ultimately, the immature virions are carried via the trans Golgi network, where they undergo morphological maturation, transitioning from a spiky to a smooth morphology[35]. After the process of maturation, the Pr peptide undergoes cleavage from PrM. The M protein persists as a transmembrane protein within the mature particle of SA membrane protein. The maturation process is facilitated by the ghost proteases[36], ultimately leading to the liberation of mature virions from the host cells.

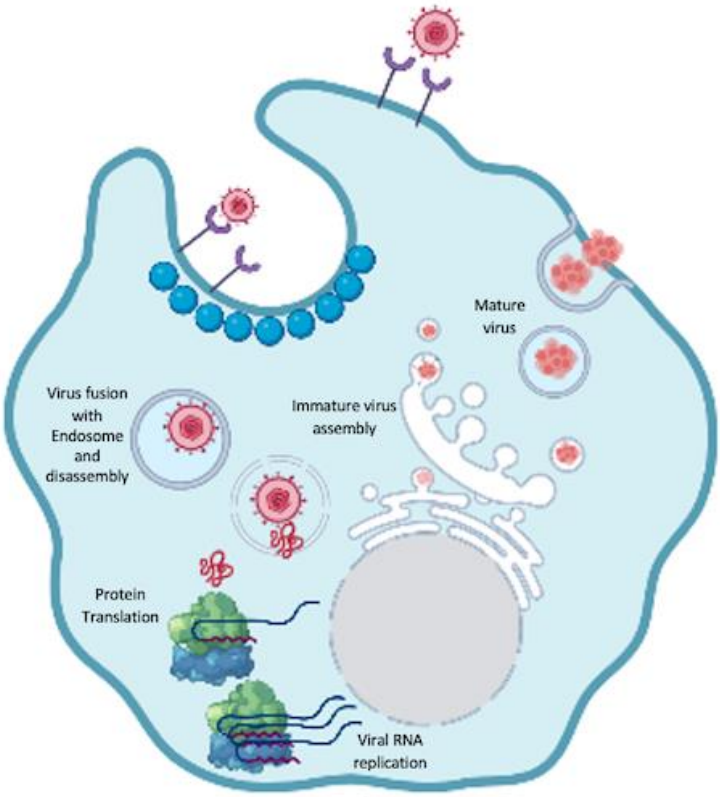

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Figure 2: Lifecycle of Dengue virus in cell: Virus internalization by binding to the receptor as an endosome where it is disassembled by the enzymes . the RA sequence is translated into a Polyprotein that later acts as a template for RNA synthesis. Later the RNA is made use for new translation & for encapsulation into new virions by reassembly in the endoplasmic reticulum and Golgi bodies and finally released from the host cell

Evolutionary dynamics of DENV

Four antigenically different DENV serotypes (DENV-1, DENV-2, DENV-3, and DENV-4) are still maintained and are co-existing in endemic demographic areas over the globe. [37]. All four DENV serotypes are now hyperendemic (the circulation of several serotypes) globally and have expanded throughout tropical and subtropical areas of the world [38]. In addition, each DENV serotype is made up of a number of genotypes, which are generally characterised with strains having divergence at the E/NS1 intersection is less than 6% [39]. Based on empirical findings, it has been observed that during a span of 7 to 10 years, lineages of the Dengue virus (DENV) tend to diminish and give way to novel genetic variants. These newly emerged variants frequently contribute to the occurrence of epidemics. [40].

Overall, a wide range of human parameters, such as population, immunity, virus fitness, and seasonal fluctuations [41,42,43], contribute to the evolution of DENV. Also, the virus error-prone RNA-dependent RNA polymerase (RdRp)[44], causes it to acquire an average of one mutation every complete genome replication cycle within a vertebrate host, leading to diversification of gene within the infected host, also known as variations [45]. Events of Recombination are uncommon in both intra and inter serotype infections, despite the well-documented coinfection by numerous DENV serotypes[46]. Most studies on the evolution of DENV have concentrated on single gene dynamics , usually the E gene. Positive selection pressure has a less significant impact on DENV evolution than strong negative selection pressure [47]. The rate of DENV E gene nucleotide substitution varies depending on the serotype, but all four evolve at a rate of about 7.6 X 10^4 substitutions/site/year, which is slower than that of other RNA viruses [48,].

Virus Epidemic across India

Very lately in 2017 India had a major epidemic (1.8 lakhs cases) which was followed by a significant reduction of dengue cases was observed in year 2020 (50 thousand cases). Later in year 2021 a two times increase in dengue cases was observed (1.9 lakhs cases)[49], and up to 80000 cases of Dengue have been reported till date with most cases of the DENV 2 serotype. Moreover, contrary to the last year, the death number in 2022 is more in the adults rather than the children that suggest a strain/genotype shift or a genotype/clade replacement event.

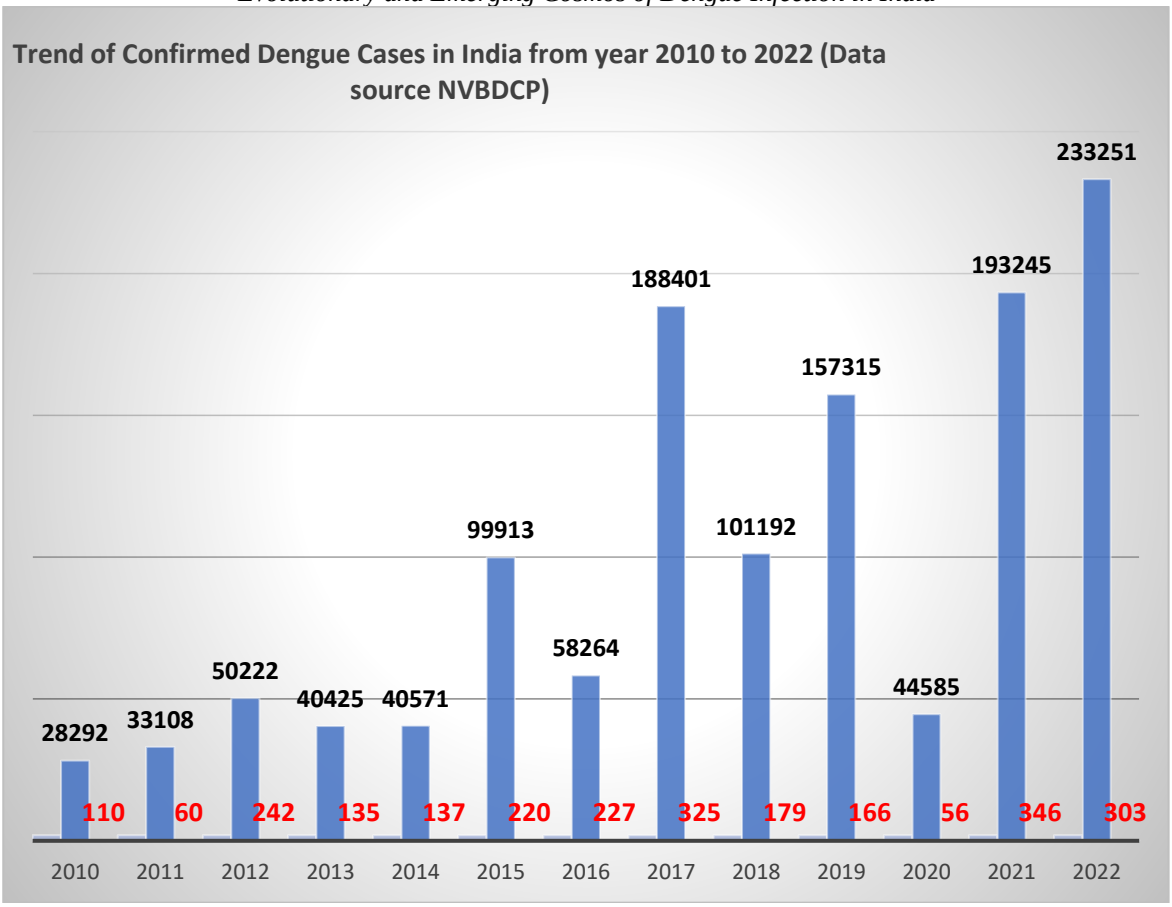

Figure 3. Viral Epidemic across India: Trends of the absolute confirmed cases of the Dengue In India from the year 2010 to 2021 with the mortality (figure in Red) as per the NBVDCP data source.

The epidemiology of dengue infection in India is characterised by a high level of complexity and has seen significant changes over the past six decades in terms of the prevailing strains, their geographical distribution, and the severity of the disease. With the first reported epidemic in 1963 in east coast the DENV 4 was reported in Kanpur in 1968 , with the coexistence of both DENV 4 and 2 in the subsequent year [50]. In 1970, the nearby area of Hardoi observed a completely replacement of DENV4 by DENV 2[50]. In Southern India of Vellore, Myers et al reported an epidemic of DENV3 [51] during the year 1966 in both patients and Ae. aegypti which during later epidemic of 1968, was related with all four types of DENV and their isolation from both vector and patient[52].

Western India state of Gujrat reported an epidemic of DENV 2[53] in both urban and rural area during 1988 and 89 with the nearby state of Rajasthan had an outbreak of DENV1 and DENV3[54,55]. The virus DENV 2 was predominantly circulating in northern India including Delhi, Haryana, Lucknow and Gwalior[56-58]. Meanwhile, DENV1 serotype was isolated in the epidemic of 1997 at Delhi[59]. Studies on molecular epidemiology may reveal DENV genotype and lineage turnover (extinction and/or replacement). An individual genotype or lineage may appear in a specific geographic area, survive for a while, then go wiped out and be substituted by an altogether new genotype.

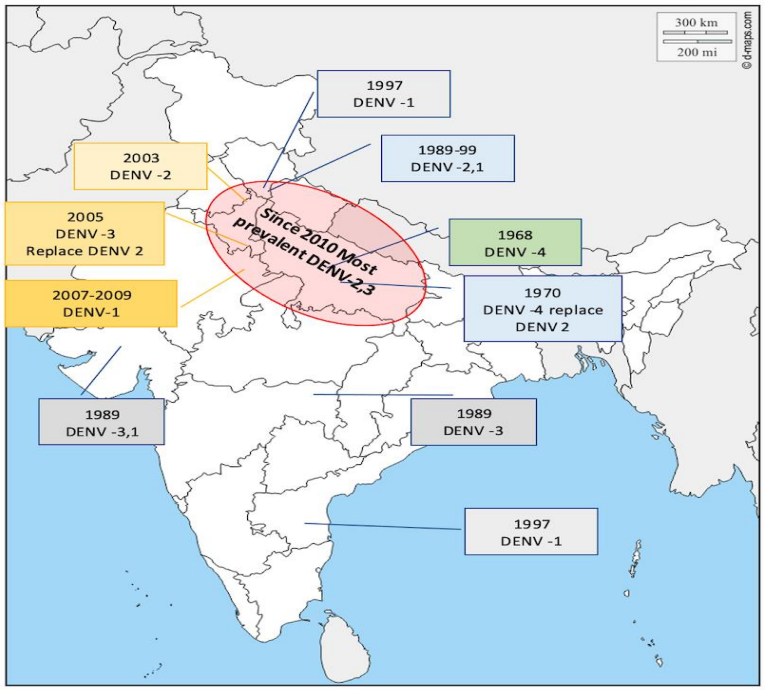

Figure 4: Epidemiology of Dengue Outbreaks in India : from its first appearance to the changing sequence of different serotypes of Dengue virus over substantially over the last decade in terms of the prevalent strains and their location.

Serotype and Genotype Studies

According to genetic and antigenic characteristics, the dengue virus (DENV) can be divided into 4 antigenically defined serotypes, with each of them has a variety of genotypes and their lineages/clades based on phylogenetic study of the envelope (E) or entire genome sequences. Host and viral variables have both been implicated in the development of spectrum of dengue infection. The significance of virus genetics has been demonstrated by connections between specific DENV genotypes and extensive and severe outbreaks.

The nucleotide diversity between serotypes is 30% (60% amino-acid similarity)[60]. Each serotype has a genotype subgroup based on genetics. Worldwide, DENV-1-4 can be split into five genotypes (I - V), six genotypes (Asian I, Asian II, Cosmopolitan, American, American/Asian, and Sylvatic), four genotypes (I, II, III, and V), and four genotypes (I, II, III, and Sylvatic), respectively [61-65]. The presence of diverse genotypes within a single serotype might elicit distinct immune responses [66], resulting in variations in their capacity to infect different target cells and consequently, differences in their ability to induce severe manifestations of dengue[60]. Each genotype can be further separated into numerous lineages according to phylogenetic study of E gene sequences. Variable adaptability is conferred by different genotypes along with genetic mutation in DENV, which increases the transmission of the virus and its potential for epidemics in various regions [67] .

Phylogenetic analysis suggested dengue isolates from year 1967 from India were similar to the 1957 isolates and were of DENV 2 serotype with Genotype V. In 1996 Delhi and Gwalior isolate of DENV2 was identified as Genotype IV indicating that previous DENV 2 isolate of genotype V was substituted by Genotype IV [68] . The Genotype IV DENV 2 strain has been persistently and inconspicuously circulating in northern India, with the capacity to resurface and trigger a significant epidemic of dengue fever (DF) and dengue hemorrhagic fever (DHF) [69] . In 2003 for the first time all four serotypes of DENV virus co circulated[70] in northern Region which was completely dominated by the DENV 3 serotype by 2005 which reflected a shift and dominance of a DENV 3 serotype which replaced the earlier circulating serotype 2 genotype IV [71,72]. In 2006 epidemic in the northern region observed a combination of viral serotypes with serotype 1 and 3 (44%), followed by 1 and 4 (22%).[73] Over a period of three years (2007-2009), The serotype DENV-1 emerged as the prevailing strain in Delhi, effectively supplanting the previously prevalent serotypes DENV-2 and DENV-3. [74]. In southern India out breaks due to DENV3 isolates was involved in epidemics at Vellore in 1966 [51] , which was similar to outbreaks at Kolkata in 1983[75] & 1990 [76] , in 1985 at Rajasthan town[55.] and in Gwalior in 2003 & 2004[69,77] and in southern India state of Tamil Naidu in 2010 [78].· Major outbreak by DENV-2 has also been reported from southern India ,Kerala along with DENV-3 in the Ernakulum outbreak of 2006 [79] . While the type 2 strain were related to Gwalior strain 2001 epidemic.the Type 3 strain did not exhibit a distinct correlation with any prior isolates from India. DENV type 1 strain during the same outbreak were similar to strain from Delhi -2001 and Gwalior 2002 outbreaks.[79,] The emergence of DENV-4 was documented in Andhra Pradesh in 2007 [80] and Pune, Maharashtra in the years 2009-10 [81], resulting in heightened disease severity.

Both DENV 1 and DENV 2 are the predominant viral types involved with documented outbreaks.[82] Empirical evidence indicates that DENV-2 outbreaks[83] have been linked to the greatest aggregated fatality rates, as they tend to induce more severe secondary infections compared to other serotypes[84]. DENV-4 is not the most common kind in India, but there are occasionally reports of its circulation[70,]. Among the four

serotypes of Dengue virus currently in circulation within the country [85], it has been shown that DENV-2 and DENV-3 are primarily responsible for causing significant outbreaks of Dengue Haemorrhagic Fever (DHF) in India[86,69]. These two serotypes exhibit the highest prevalence and possess the greatest capacity for transmission.

Small genomic region investigations of dengue strains in India[81] using specific gene segments are utilised to characterise the dengue virus strains on a molecular level. Whole-genome analysis is taking the role of this method in order to better understand the dynamics of the dengue illness[87] . The significance of virus genetics has been demonstrated by links between specific DENV genotypes and outbreaks that are especially extensive or severe[88]. The examination of the E gene sequence of DENV suggests that the process of in situ evolution has the potential to enhance the fitness of the virus and result in the switching of clad within the genotype.

Genotype in India

Each and every isolate of DENV-1 from India from 1962 to 2005 is of the American African (AM/AF)[90 Cecelia 2017] genotype. The Cosmopolitan genotype of DENV-2 eventually took the place of the American genotype, which predominately distributed in India before 1971. Indian isolates from after 1971 established a distinct subclade within the Cosmopolitan genotype. An epidemic causing strain of DENV -3 returned to Delhi in 2003, and its survival in future years signalled a shift in the pattern of DENV circulation in this region of India[91] . For DENV2 the cosmopolitan genotype[92],the Genotype III for DENV 3[93] and genotype II for DENV 4 is most prevalent of the genotype in India[94].

The occurrence of dengue hemorrhagic fever (DHF) outbreaks in India during the late 1980s coincided with a simultaneous alteration in the genotypes/lineages of all four serotypes[95]. Over the past two decades in India, there have been observed shifts in the genotypes of DENV-2 from American to Cosmopolitan[96], changes in the genotype of DENV-3 from lineage 3 to 4 between 2008 and 2011 in Kerala[93], alterations in the genotype of DENV-4 from IV to I[74], and lineage changes in the AM/AF genotype of DENV-1 during the 2006 outbreak in Delhi[97]. Alterations in lineages have been observed in the AM/AF genotype of DENV-1[98], the Cosmopolitan genotype of DENV-2[91], and genotype III of DENV-3[96]. However, these alterations have not been found to be linked to virulence. Based on the application of reverse-transcription polymerase chain reaction (RT-PCR) and nucleotide sequencing methodologies, it can be deduced that there is a simultaneous occurrence of multiple serotypes of the dengue virus. Additionally, there are instances of co-infections involving Genotype III of DENV-1, Genotype IV of DENV-2, and Genotype III of DENV-3, which are prevalent[98].

Genotype evolutionary analysis

Results of the whole genome coding sequences suggest that the dengue genotype are relatively geographically distributed with very few intermixing of the genotype occurring across continents. The Asian sequences exhibit a prevalence of two prominent genotypes across all serotypes, while the Indian sequences typically display only one genotype across all serotypes, except for the DENV-1 serotype. Over the course of the last two decades, the prevailing genotypes in India have been genotype III of DENV-1, the cosmopolitan genotype of DENV-2, genotype III of DENV-3, and genotype I of DENV-4. The genotypes exhibit a clear co-circulation of lineages that is both temporal and geographical in nature.

Changes in DENV1

For knowing the dynamics of DENV-1 in India, the envelope (E) gene were sequenced and analysed with the available global representative isolates. The DENV-1 isolates from India are classified into four distinct lineages, namely India I, India II, India III, and the Africa lineage. Among these lineages, India III is considered the oldest and no longer in existence. The Afro-India lineage, on the other hand, is considered temporary. India I is believed to have been imported from Singapore, while India II is said to have evolved locally and is now circulating[97].

First isolated Indian DENV-1 in 1956 at Vellore had all the isolates belonging to the American African (AM/AF) genotype [97] .Post epidemic sero-epidemiological survey of the 1997 epidemic of DENV-1 at Delhi also reported that the virus belonged to the genotype of AM/AF [59,99]. Sequencing of CprM gene junction from isolates from Delhi and Gwalior between 2001 to 2007 outbreak of Dengue infection and compared2001 to 2007 with the 70 global reference sequences from NCBI observed the outbreak to be of Genotype III with the phylogenetic studies revealing existence of multiple lineage of Genotype III [99]. Appearence of a distinct lineage of DENV-1, having similarity with Delhi 1982 strains was observed during outbreak in 2006 at Delhi following the CprM gene junction nucleotide sequencing [91] . The molecular phylogeny following complete genome sequencing reported the Indian DENV-1 of genotype III which remain most prevalent genotype from 2009 to 2011 which was similar to that of southern India but of a different clade [100]. Until the year 2012, the DENV-1 AM/AF genotype was the sole genotype observed in circulation in India. However, in the period between 2012 and 2013[101], the appearance of the DENV-1 Asian genotype was documented in the southern region of India. Notably, the isolates from this period were found to belong to both genotypes G III and GI. In the outbreak in 2014-2015 the pattern was reversed as 80% of the isolates belonged to the G I [Asian]. This change in the predominant genotype replaced the DENV2/DENV3 by the DENV1 in 2014-2015. With the Genotype I strain having 99% nucleotide identity with the Kerala strain of 2013 whereas the Genotype III isolates closely relate to the Indian lineage II strain from Delhi 2006-07 [102].

Till 2015 both Asian and the AM/AF genotype were observed to be co-circulating in southern India[102] but in North India was dominated by American African genotype that included the 2014 outbreak of DENV-1 in Delhi [46]. In the late months of 2017, a significant development occurred in western India, specifically in Pune, with the detection of the Asian genotype for the first time.[103] This finding indicates a shift in the genotype of DENV-1, as the Asian genotype has replaced the previously dominant American/African genotype in this region[88]. However, it is noteworthy that by the years 2011 and 2018, both

genotypes were shown to be co-circulating in western India[8,104]. Phylogenetic analysis using the CprM gene sequencing revealed that the Eastern Uttar Pradesh experienced an outbreak of the DENV -1 of genotype III during the 2018-2019[105,106] .And since then the genotype Asian[GI] and Genotype AM/AF[GI] are co circulating based on the E gene sequencing . Among DENV -1 genotype (I & III) G III has been the dominant across India based on the CprM gene sequencing.

Changes in DENV2

The initial documentation of the DENV-2 outbreak occurred in 1969 in Kanpur,[57] India. This particular strain exhibited similarities to the isolate discovered in 1957 inside the same country, leading to its classification as genotype V, also known as the American genotype[106]. The prevalence of the American genotype in India prior to 1971 was subsequently supplanted by the cosmopolitan genotype [genotype IV] during the epidemic in Delhi in 1996[86,107]. Since then the Genotype IV was the dominant virus strain that was prevalent in India and it continued till 2002 dengue epidemic in northern India at Gwalior [58]. A comprehensive examination of the whole envelope (E) gene sequences of 37 strains of DENV-2 originating from India revealed that the Cosmopolitan genotype exhibited dominance, whereas a limited number of Asian I and Asian II strains were found till 2012[106] The phylogenetic tree, constructed using aligned sequence data, revealed that the strains of the epidemic at Delhi in 2013 were grouped together in the Cosmopolitan genotype within three distinct lineages, namely Lineage I, Lineage II, and Lineage III. Notably, Lineage III replaced Lineage I during the outbreak of dengue fever in this particular instance[91]. By 2015 the Asian II and Cosmopolitan genotypes co-circulated with former more prevalent in Sub continent India[108]. Subsequently, the Asian II genotype continued to exhibit dominance. However, during the 2018 epidemics in northeast India, two unique genotypes of DENV-2, specifically genotype IVb (Cosmopolitan) and Asian-I genotype, were observed to be circulating[109].

Changes in DENV3

Several outbreaks of DENV 3 was reported from West Bengal in 1990 [75], and from Maharashtra in 1994[10] . But since then no outbreak of DENV 3 was reported till, in 2003 when North India including National Capital Delhi and Gwalior in Madhya Pradesh observed an outbreak. Resurgence of the DENV 3 outbreak occurred after gap of 9 years where the phylogenetic sequencing of CPrM gene junction revealed that the genotype III of DENV 3 have replaced DENV 2 (Gen II) in this region[76,111]. The observed transition in dominance is a matter of significant concern and can potentially be linked to the rising prevalence of Dengue Hemorrhagic Fever (DHF) and Dengue Shock Syndrome (DSS) in India. [69,] . From year 2009 to 2013 molecular characterization of Dengue virus -3 circulating in Uttar Pradesh belonged to G III and some G I both type co circulating [112].

The investigation of the C-prM gene junction using phylogenetic analysis unveiled the presence of a novel lineage of DENV-3 (genotype III) actively circulating in the northern part of India during the outbreak that occurred in Lucknow in 2012[113]. Outbreak in southern part of India during 2012 for the first time reported the presence of lineage IV strains of the DENV 3 (Gen III) in the India and with a change from the existing lineage III strains to lineage IV [92].

The Indian DENV3 genotype III sequences can be classified into two distinct geographical groups, namely lineages IIIA (Asian) and IIIB (American). All DENV 3 isolates sequenced in the studies from 2003 to 2013 belonged to the GIII. 2013 epidemic of Delhi observed that the GIII and GI co-circulated in northern India, with GIII being the more dominant genotype[114] . Phylogenetic study revealed G III remained dominant genotype in Delhi during 2016 [115] .Since than GIII remained the dominant genotype throughout the period up to 2018, with sporadic detections of GI [116]. During the epidemic of 2018-2019 in eastern Uttar Pradesh of India there was co circulation of all the 4 serotype of dengue virus but the DENV -3 was observed to be of a different lineage [lineage III] and of genotype III [105]. Outbreak in Bengal in 2022 [117] and North India during 2017-18 [118] exhibited circulating genotype III of Indian clade of the DENV 3 .

Changes in DENV 4

The emergence of DENV 4- (Genotype I) cases in India was initially documented in 1945. Since 2015, there has been a notable surge in the incidence of these cases, particularly in the southern region of the country[119]. Earlier the genotypes I and II were predominant & responsible for outbreaks in northern and western India [80,] with Andhra Pradesh reporting the genotype II as well.[120] The analysis of CprM sequences from strains of DENV4 - genotype I, observed during the epidemic from 2012 to 2015, revealed that the DENV 4 isolates belonged to lineage C of Genotype I[119]. This lineage further diverged into two distinct clades, namely Ia and Ib. Clade Ia exhibited a 99% nucleotide identity with the Indian strain from Kerala in 2010 and Madhya Pradesh in 2016. [104] .Later outbreaks during 2017-18 in Theni [121] and in Tamil Nādu in 2017 observed DENV 4 genotype I Indian strain having 90% sequences of DENV 4 Gen I grouped in clade Id [119]. Two lineages in Indian DENV4 sequences (Ic and Id) were identified and are presently endemic with outbreak of Dengue in Pune in 2016 [122] observing replacement of DENV4-Ic with DENV4-Id lineage. First report of DENV-4 Gen I detection from Eastern U.P.in 2019 was observed which were distributed between lineage Ic & lineage Ib but the Ic predominated[100] .

Conclusion

The article discusses about epidemiology of DENV virus with their different serotype. This article shows how DENV virus effect the India with their different serotype. All serotypes have their own fulfil capacity to effect the people. Affecting people get severe if that serotype have genetically modified genes. The observation of DENV1 to DENV4 serotype co-existing in India make it very likely for the virus to undergo mutations and may serve as reservoir for emergence of diverse strain. It can be concluded that population diversity is observed to influence intergenotype admixture and adaptive evolution with the diversity in CprM gene coding the amino acid in both structural and non-structural proteins causing variations in antigenicity of DENV. Such variations can cause outbreak in children , adults, or may be in old aged peoples. Such emerging Cosmos of

Dengue virus in India will help us to know the trend of different variations across country which can help us to develop definite vaccine of dengue virus.

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