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The emerging cause and threats of Arboviral diseases and its control measures: A comprehensive review

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Abstract
The recent developments of viral illnesses are vector- borne, such as Chikungunya and dengue fever, and other similar diseases, have raised significant global concern. In this paper, we provide a comprehensive overview of the existing literature pertaining to the transmission, clinical manifestations, diagnostic methods, global impact, and the likelihood of future outbreaks associated with these viral pathogens. Arboviruses are difficult to identify and can cause unexpected clinical consequences. Dengue and chikungunya are the most common arboviruses caused infections worldwide, particularly in tropical and subtropical areas. The transmission of these diseases to human beings is facilitated by the *Aedes aegypti* and *Aedes albopictus* mosquito species. The spread of *Aedes aegypti* is mostly responsible for the rise in dengue and chikungunya cases in India. The expeditious and accurate identification of dengue is of utmost importance in effectively managing and containing epidemics of this disease. In light of the lack of an available vaccine or targeted pharmaceutical intervention for these viruses, the most comprehensive strategy currently available is vector control.

Keywords: Chikungunya, dengue, arboviruses, *Aedes aegypti*, pathogenicity

Introduction
Dengue (DENV) and chikungunya (CHIKV) diseases have caused global interest in the area of human health due to their transmission by mosquitoes. *Aedes aegypti* is commonly found in many tropical and subtropical climates across the globe [1]. *Aedes aegypti* is also associated with spread of the Zika viruses. *Aedes aegypti* has been postulated as a suitable vector for the Venezuelan Equine Encephalitis virus [2], and studies examining its vector competence have suggested that *Aedes aegypti* possesses the ability to transmit the West Nile virus [3]. Dengue fever is a vector-borne illness resulting from infection with the dengue virus (Flaviviridae family) and spread primarily occurs by *Aedes aegypti* and occasionally by *Aedes albopictus*. Infected people may experience subclinical disease or severe flu-like symptoms. Severe dengue infection can lead to several complications, including but not limited to excessive bleeding, organ impairment, and plasma leakage. If severe dengue is not managed appropriately, there is an elevated likelihood of mortality [4]. The classification of dengue by the World Health Organization consists of two distinct types, namely mild dengue, which may or may not exhibit warning indications, and severe dengue [5]. Chikungunya virus (CHIKV), on the other hand, is an alpha virus (family Togaviridae) and a positive-sense single-stranded RNA virus [6]. The first identification of Chikungunya virus as an alpha virus took place in Africa (specifically Tanzania) in 1954.
One of the clinical manifestations observed is the initiation of pyrexia, often accompanied by notable arthralgia. The joint discomfort is frequently incapacitating and typically lasts for few days, although it can last two weeks, months, or even years [7]. The initial comprehensive data on dengue illness was officially released in 1988, wherein it was reported that a total of 80-90 million cases of dengue virus infection had been recorded on a global scale [8]. The WHO has observed a notable increase in the incidence of dengue fever in recent decades. Reported cases of the disease have risen from 505,430 in 2000 to 5.2 million in 2022 [9].

According to estimates, 390 million DENV infections occur worldwide each year, with 96 million resulting in clinical symptoms. Currently, a significant proportion of the global population, approximately 40%, resides in areas these entities exhibit a notable propensity for the transmission of dengue, which is associated with a heightened level of risk. Dengue fever exhibits endemicity over about 100 nations situated in tropical and subtropical regions. The World Health Organization (WHO) has projected has been reported that the annual incidence of dengue infections ranges from 50 to 100 million, leading to around 500,000 cases of dengue hemorrhagic fever and 22,000 deaths. It is worth noting that a significant proportion of these fatalities involve children [10].

The emergence of contemporary illnesses has been influenced by various factors, encompassing human behavior and the ability of microbes to adapt to diverse environmental conditions [11]. In addition, it is worth noting that the majority of these factors contribute to the phenomenon of overcrowding, insufficient sanitation practices, and the escalating human contact with vectors that transmit microorganisms [12]. Understanding the potential linkages between the propagation of Dengue virus (DENV) and Chikungunya virus (CHIKV) in vector-borne mosquitoes that are simultaneously infected is of utmost importance. This understanding is particularly important because the transmission of both DENV and CHIKV by *Aedes aegypti* mosquitoes has been observed in India [13]. This study presents a comprehensive overview of the current knowledge on the pathogenesis, diagnosis, and prevention of Dengue virus (DENV) and Chikungunya virus (CHIKV).

Dengue virus pathogenicity

Dengue virus (DENV) often undergoes replication in many types of mononuclear cell population comprises several cell types, such as hepatocytes, cutaneous dendritic cells, tissue macrophages, and peripheral blood monocytes [14]. The Dengue virus demonstrates the capacity to infect nascent dendritic cells situated in the dermis through the use of a receptor referred to as dendritic cell-specific ICAM3-grabbing non-integrin. In the process of infection, dendritic cells with infectious properties undergo development and migrate to nearby lymph nodes. Within these lymph nodes, T cells come into contact with viral antigens, thereby generating both cellular and humoral immune responses [15]. Dengue viruses indicate replication inside peripheral blood monocytes, hepatocytes, and macrophages, as well as in the liver, spleen, and lymph nodes. Despite their strong serological connections, the DEN viruses differ antigenically. In non-immune individuals, Dengue Fever is usually the outcome of the initial or primary infection [16]. Subsequently, the emergence of a novel serotype of dengue infection has been associated with heightened morbidity, including the manifestation of severe conditions such as dengue hemorrhagic fever (DHF) and dengue shock syndrome. The three key indicators of Dengue Hemorrhagic Fever (DHF) and Dengue Shock Syndrome (DSS) are capillary leakage, abrupt onset of shock, and hemorrhagic diathesis/thrombocytopenia, which coincide with the resolution of fever. According to the literature, initial infection with a primary DENV serotype does not confer immunity against subsequent secondary infection [17]. The antibody-dependent enhancement hypothesis posits that, in the context of an active infection, IgG antibodies present in the bloodstream form complexes with the virus, so enhancing the uptake of the virus by macrophages, leading to its replication. This mechanism leads to an increased viral antigen load, which in turn triggers excessive activation of T cells, ultimately resulting in the manifestation of dengue hemorrhagic fever and dengue shock syndrome.

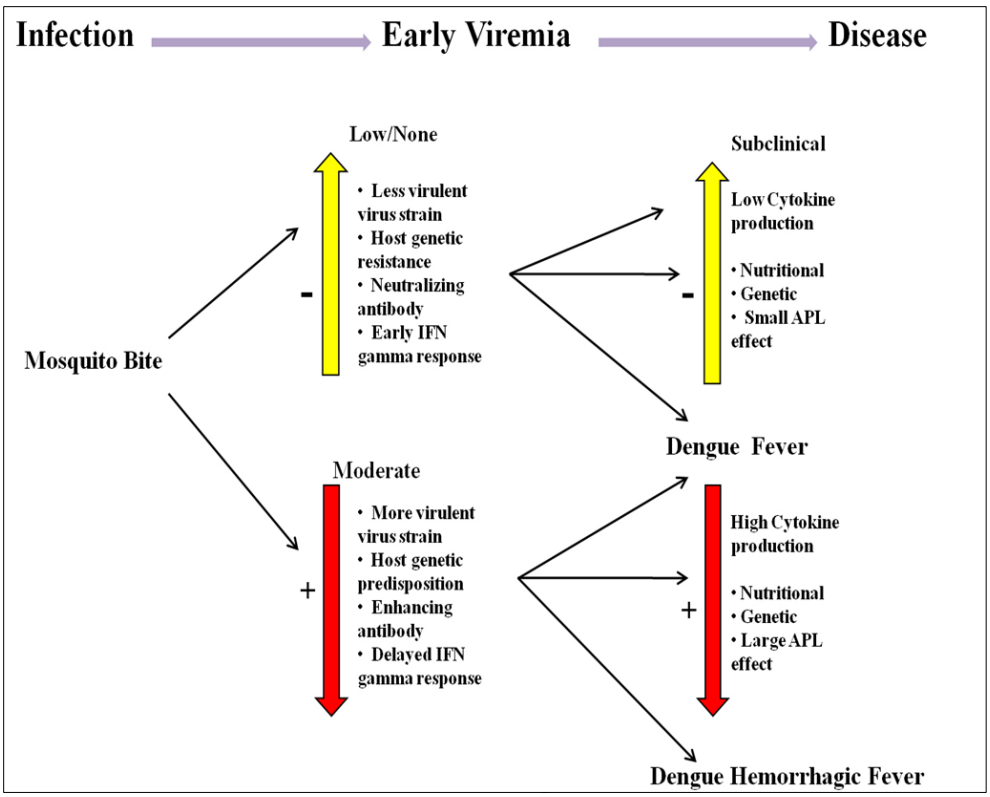

Fig 1: Factors affecting the severity of dengue infection

The syndrome is characterised by a reduced IgM antibody response, subsequently leading to the secretion of cytokines and vasoactive mediators that augment vascular permeability and hemorrhaging (Figure 1). The occurrence of disseminated intravascular coagulation (DIC) is anticipated, subsequently leading to vascular collapse, potentially culminating in fatality of the individual [18].

Clinical manifestations of dengue

Dengue Fever

Dengue fever is caused by primary and secondary infections that are more commonly seen in adults and children. The onset of symptoms is accompanied by a biphasic, high-grade fever that endures for a period of three to seven days [19]. Severe headaches (usually retrobulbar), muscular cramps, joint discomfort, diarrhea, vomiting, and skin rash are frequently reported. Dengue virus (DENV) exhibits an incubation period that typically spans from four to seven days, with a potential range of three to fourteen days. The prevalence of the Dengue fever stage is highest during the primary infection, however it can also manifest subsequent to the initial secondary infection. Clinically, distinguishing DF from other viral illnesses is difficult; thus, it frequently goes untreated [20].

Dengue Hemorrhagic Fever

In babies, Dengue hemorrhagic fever manifests during an initial infection resulting from the transmission of dengue antibodies from the mother, while in adult individuals, it commonly ensues after a subsequent infection. Dengue hemorrhagic fever is defined by hemorrhagic episodes that include at least one of the following symptoms: purpura, petechiae, mucosal bleeding ecchymosis, nose/gum hemorrhage, melena and hematemesis [21]. Dengue hemorrhagic fever hemorrhage is associated with a number of variables, including platelet shortage. The presence of irregularities in the blood coagulation pathways, as well as the occurrence of vasculopathy, might be observed. Thrombocytopenia arises from a combination of reduced platelet production, heightened platelet dysfunction, and enhanced platelet destruction. These defective platelets weaken blood vessels, resulting in bleeding [22]. Dengue hemorrhagic fever progresses via three stages: fever, convalescent phase and plasma leak [23]. The patient gets a rash and hemorrhages during the initial stage. The feverish period lasts two to seven days [24].

Dengue Shock Syndrome

Dengue shock syndrome (DSS) is characterized by the manifestation of dengue hemorrhagic fever (DHF) together with symptoms such as an irregular pulse, reduced pulse pressure, hypothermic skin, agitation, and discoloration around the oral region. Dengue shock syndrome has a significant death rate due to hypovolemic shock, multi-organ destruction, and consumption coagulopathy. In general, the duration of shock is brief, since patients tend to recuperate through the administration of supportive interventions [25].

Chikungunya pathogenicity

Chikungunya (CHIKV) is classified as an alphavirus belonging to the Togaviridae family. The virus in concern is a positive-strand RNA virus that is encapsulated. The creation of four nonstructural proteins (nsP1–nsP4) and five structural proteins (C–E3–E2–6K–E1) is attributed to the genetic material of the virus. Chikungunya viruses are found in connective tissue, skin fibroblasts, muscle, joints and the central nervous system [26]. The transmission of the Chikungunya virus is characterized by two distinct cycles, namely the urban cycle involving human-to-human transmission, and the sylvatic cycle involving animal-to-human transmission [27]. In the case of human infection, the route of viral transmission exhibits variations compared to other arboviruses, wherein certain cell type's display heightened vulnerability to infection. The specimens being examined display a biological makeup consisting of the cell types under consideration are human epithelial and endothelial cells, fibroblasts, and macrophages, which have been obtained through the differentiation of monocytes. Never less, it has been observed Primary lymphocytes, dendritic cells generated from monocytes, and monocytes do not exhibit any detectable evidence of Chikungunya virus replication [28]. The current understanding of the immune response to Chikungunya virus infection is incomplete, with many aspects of the response yet to be fully elucidated.

Clinical manifestations of chikungunya

Acute Stage

The acute stages occur within 10 days of infection following the commencement of the sickness. High-grade fever, arthralgia, back discomfort, and headache are the most typical symptoms. During this stage, individuals may experience symptoms such as fatigue, anorexia, myalgia, nausea, and vomiting. Interphalangeal joints, wrist joints, and ankle joints are frequently affected [29]. The affected areas exhibit signs of inflammation, characterized by swelling and discomfort, which can be alleviated with the administration of no steroidal anti-inflammatory drugs. The avoidance of aspirin is recommended due to its potential to produce bleeding. The symptoms go away after around 10-15 days [30].

Chronic Stage

In Chikungunya virus patients, inflammatory symptoms persist after the acute stage. Long-term rheumatism may occur, particularly when the viral load of the Chikungunya virus is elevated during the acute phase. Within 3 months, patients experience a return of proximal joint pain and tendon inflammation. It is possible that a considerable number of individuals are experiencing symptoms indicative of carpal or tarsal tunnel syndrome [31].

Diagnosis of Dengue Virus and Chikungunya Virus Infection

Because of the vast range of non-specific symptoms that occur during febrile illness, relying just on clinical symptoms to diagnose DENV and CHIKV is unreliable. There are specific and sensitive diagnostic techniques available for use throughout specific stages of disease. Methods such as virus isolation, nucleic acid amplification tests (NAAT) for RNA detection, or antigen identification, specifically NS1, can be employed for the early diagnosis of infection within a span of five days. The detection of DENV and CHIKV RNA and antigens may no longer be feasible beyond a certain time frame, specifically beyond five days following infection. This is due to the cessation of viremia and the subsequent development of antibody responses. At this juncture, it is suitable to employ serological methods for the particular

detection of antibodies, either IgM or IgG. According to a study by reference [32], the presence of NS1 (nonstructural protein 1) antigen in certain patients can persist for several days following the resolution of fever.

Virus Isolation

The process of isolating viruses is highly specific and can provide confirmation for diagnosis of dengue virus (DENV) or Chikungunya virus (CHIKV). DENV can be obtained by inoculating clinical specimens onto mosquito cell lines such as C6/36 (Aedes albopictus) or mammalian cell lines such as Vero (African green monkey kidney), LLCMK2 (Monkey Rhesus kidney), and BHK21 (baby hamster kidney) [33]. Whole blood, serum, plasma, or homogenized tissues (most commonly in fatal instances) are clinical specimens utilized for virus isolation [34]. Following the stages of inoculation and incubation, it becomes imperative to execute a validation procedure, such as immunofluorescence or reverse transcriptase polymerase chain reaction (RT-PCR) are employed to validate the obtained findings. Virus isolation is subject to several practical limitations: The process of incubation and conformational testing is a time-consuming endeavor that necessitates a minimum of seven days. Additionally, it necessitates the utilization of well-established laboratory facilities staffed by highly qualified individuals. Furthermore, this method is only applicable during the acute phase of infection and is not suited for culturing the DENV virus when viremia levels are low [35].

Nucleic Acid Amplification Tests

Nucleic acid amplification tests have the capability to detect the presence of DENV and CHIKV RNA in clinical specimens within a timeframe of 24-48 hours following infection. These tests can be effectively employed for the diagnosis of dengue during the acute phase of infection, which typically spans duration of 5 days. RT-PCR, real-time RT-PCR, and isothermal amplification processes are illustrative instances of molecular biology techniques. The nested (RT-PCR) approach [36], the one-step multiplex (RT-PCR) technique, which utilizes four serotype-specific oligonucleotides primers in a single reaction tube, has been described in a study [37]. Furthermore, there have been reports on the utilization of the one-step pan-flaviviruses quantitative (RT-PCR) assay [38, 39] can be employed for RT-PCR analysis. The sensitivity of RT-PCR techniques might vary between 80% and 100%, depending on factors such as the specific genome region targeted by primers, the amplification or detection method employed for PCR products, and the serotyping technique utilized. The technique employed in this study is a multiplex real-time reverse transcription polymerase chain reaction (RT-PCR) assay is characterized by its enhanced speed and ability to identify viral titers in clinical specimens [40]. Nevertheless, the implementation of this test requires the use of expensive apparatus and chemicals, in addition to the requirement of proficient experts [39]. In comparison to RT-PCR tests that are specific to individual species, one-step pan-flavivirus quantitative RT-PCR assays have similar characteristics [41].

Detection of antigens

Enzyme-linked immune sorbent assay (ELISA) and rapid immune chromographic (IC) assays have demonstrated the capability to identify primary and secondary Dengue virus (DENV) infection within a period of nine days following the commencement of symptoms. A comprehensive meta-analysis comprising 30 studies conducted in various countries revealed that the Panbio NS1 Enzyme-linked immune sorbent assay kit exhibited a sensitivity of 66% and specificity of 99%, while the Platelia NS1 Enzyme-linked immune sorbent assay kit had a sensitivity of 74% and specificity of 99% [42]. Another meta-analysis revealed that the NS1 antigen detection immune chromatographic (IC) test had somewhat greater sensitivity compared to the enzyme-linked immunosorbent assay (ELISA) [43]. In general, tests based on NS1 demonstrate favorable diagnostic efficacy for both the screening and confirmation of Dengue virus (DENV) infection. Nevertheless, there exist certain challenges associated with this test. Tests that rely on the NS1 antigen demonstrate reduced sensitivity when used to detect secondary infections. Furthermore, sensitivity is reduced for DENV-4 and DENV-2 (relative to DENV-1) and marginally lowers in Southeast Asian and Oceanian samples [44].

Serological Tests

Serological assays, such as the hemagglutination inhibition (HI) assay and the enzyme-linked immune sorbent assay (ELISA), are commonly utilised in developing nations for the diagnosis of dengue. This is mostly owing to their ease of use, cost-effectiveness, and the ability to maintain specimen stability at ambient temperatures. The hemagglutination inhibition assay relies on the ability of the E protein to cause agglutination of red blood cells. The hemagglutination inhibition assay quantifies the degree to which the presence of anti-DENV antibodies in serum inhibits agglutination [45]. The hemagglutination inhibition assay possesses certain limitations that render it impractical. First and foremost, it is important to note that each serotype has a certain ideal pH level for the red blood cells. Consequently, the use of several pH buffers becomes necessary in order to accommodate these variations. Furthermore, the diagnostic method under consideration has a deficiency in its capacity to distinguish between infections induced by the Dengue virus and other closely related Flaviviruses. Additionally, it is unable to discern between various immunoglobulin isotypes. Finally, it can be necessary to employ pre-treatment techniques such as chemical and thermal approaches in order to remove non-specific inhibitors that are present in the clinical sample [46]. Consequently, the predominant substitution of this specific assay has been the use of ELISA-based techniques for the identification of dengue-specific IgM and IgG antibodies. The sensitivity and specificity of IgM detection using the enzyme-linked immunosorbent assay are approximately 90% and 98%, respectively. According to a recent study [47], the accuracy of IgM-based assays is significantly impacted by the variability in the quality of the antigen utilised may exhibit significant differences across commercially accessible kits.

Treatment

Dengue has no particular treatments or cures at the moment. Current treatment options are supportive, with the goal of limiting complications and symptoms severity. One such critical therapy in dengue care is fluid therapy. Oral fluid replacement is suitable enough for managing dengue fever (DF), however intravenous fluid replacement is recommended for the purpose of preventing shock in cases of severe dengue [48]. The most recent WHO recommendations [39] include

specific instructions for the management of various dengue severities. Currently, the US Food and Drug Administration (FDA) have not approved any specific drugs for the treatment of dengue. Numerous potential therapeutic agents for combating dengue fever, which aim to target either viral or host components, have undergone evaluation in clinical trials. For instance, carbazochrome sodium sulfonate has been investigated for its efficacy in preventing capillary leakage. In addition, researchers have conducted investigations into the effectiveness of oral prednisolone as a pharmacological agent with anti-inflammatory properties [49]. In a similar vein, the efficacy of lovastatin, a type of statin, has been assessed in its dual role as an agent against dengue virus (DENV) and as an anti-inflammatory agent that specifically targets the endothelium. Previous studies have conducted limited trials to assess the effectiveness of single platelet donations and recombinant human (rh) IL-1 in the reduction of severe bleeding or acceleration of bleeding cessation. Chloroquine, balapiravir (a nucleoside analogue and polymerase inhibitor), and celgosivir (a glucosidase I inhibitor) have been evaluated in clinical trials as prospective treatment candidates for combating Dengue virus (DENV) [50].

Future Perspectives

Dengue fever is the major viral infection that is transmitted to humans by mosquito vectors. The prevalence of this issue poses a significant public health risk in developing nations across Asia and Latin America. There is a need for more comprehensive molecular epidemiology data, especially in regions where there is a lack of available data on circulating Dengue virus (DENV) strains. This information is critical not just for predicting dengue epidemics, but also for vaccine formulation and composition. Performing molecular epidemiological research, which involve the utilization of whole genome sequencing (WGS), is of utmost importance in order to obtain data regarding the viruses that are now prevalent, as well as to enhance our understanding of the transmission and epidemiology of the Dengue virus (DENV) within a particular geographical area [50, 51]. Prospective cohort studies examining the previously mentioned viruses will yield valuable insights into the transmission patterns of these arboviruses in regions where DENV coexists with other arboviruses, namely CHIKV and ZIKV. In order to effectively prevent and manage CHIKV infection, it is imperative to enhance existing diagnostic procedures for CHIKV. These improvements should focus on early and accurate detection of low levels of CHIKV antigens, as well as the ability to differentiate CHIKV infections from those caused by other medically significant alpha viruses, notably other febrile illnesses. There is a need for greater investigation into the path physiology of dengue, as well as a need to explore the potential impact of previous Zika virus (ZIKV) infection on clinical outcomes [52].

Conclusion

In the paper, we studied two significant arboviral illnesses, dengue and chikungunya. All two illnesses have afflicted a considerable portion of the world's population, particularly those living in resource-limited areas. Therefore, it is imperative for doctors and healthcare professionals worldwide to possess comprehensive knowledge regarding the pathogenicity, clinical manifestations, diagnostic methods, and therapeutic approaches for these highly lethal viral diseases. The papers underscore the importance of implementing efficient strategies for the prevention and mitigation of arboviral illnesses. In addition to the current implementation of preventative measures based on insect behavior, there is potential for future initiatives to be explored. These strategies include research on vaccines, creation of antiviral treatment regimens, and the exploration of innovative vector control technologies.

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