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A Comprehensive Review of Dengue Fever: Epidemiological Trends, Diagnostic Approaches, Novel Therapeutic Strategies, and Challenges in Vaccine Advancement over the Past Five Years in the Context of Globalization and Climatic Change

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ABSTRACT

Dengue fever, which is caused by the dengue virus and primarily disseminated by Aedes mosquitoes, constitutes a significant global health issue, indicating 400 million infections and 22,000 fatalities each year. The clinical presentation of the disease varies widely, encompassing both asymptomatic manifestations and severe forms such as dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS), particularly during secondary infections attributable to antibody-dependent enhancement (ADE). The increasing incidence is influenced by several factors, including climate change, globalization, and urbanization, resulting in recurrent epidemics, particularly in Southeast Asia and the Indian subcontinent. The current diagnostic methodologies encounter difficulties, often intersecting with other medical conditions, thereby necessitating the implementation of advanced techniques for precise identification. Management predominantly entails supportive care and traditional interventions, while substantial deficiencies persist in the realm of effective therapeutic alternatives and vaccine innovation. Notwithstanding advancements with live attenuated vaccines, a universally effective vaccine has yet to be achieved. Ongoing research is imperative to confront these challenges and establish effective preventive measures against dengue fever.

INTRODUCTION

Dengue fever, which is instigated by the dengue virus (DENV), has emerged as a significant public health issue over the past several decades. Significantly, it has been classified as a neglected tropical disease. Each year, an estimated 400 million dengue cases and 22,000 fatalities are reported globally. The infection of humans by dengue is frequently asymptomatic and is universally recognized within both endemic and epidemic transmission cycles [1]. Dengue virus infection has been documented in the Americas, Africa, Southeast Asia, Europe, the Western Pacific, and Eastern Mediterranean territories. Dengue outbreaks are the foremost contributors to the substantial rising burden of morbidity and economics in various global regions, particularly in Southeast Asia and the Indian subcontinent [2]. Dengue is a vector-borne painful viral disease. This disease is also known as Dendy fever or break bone fever due to the immense pain that occurs in humans after they get infected [3]. A single-stranded RNA-enveloped virus belongs to the flavivirus family and is transmitted by the AEDES mosquito [4]. Flaviviridae represent a family of viruses characterized by their positive-sense RNA genome, which is approximately 11

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kilobases in length and contains 10,700 bases. A taxonomic genus that encompasses 53 distinct viral species [5]. The genus Flavivirus encloses various arthropod-borne viruses, including the yellow fever virus, West Nile virus, Zika virus, and tick-borne encephalitis virus. It is estimated to infect approximately 50 to 200 million individuals on an annual basis [6].

Epidemiology

Dengue infection was outbreak in 1944 in India, 1954 in Thailand, in 1962 in Sri Lanka, and 1964 in Bangladesh, where dengue fever is known as Dacca Fever. Moreover, 1965 in Myanmar, and 1968 in Indonesia. Furthermore, outbreaks in Maldives, Nepal, Bhutan and Timor Leste occurred in 2004 [7]. Dengue virus transmission exhibits notable periodicity, with distinct variations observed across different geographical regions. In Southeast Asia, the incidence peaks every three to five years, whereas Brazil experiences a peak approximately every four to five years. Before the year 2010, Guangzhou recognized as the epicenter of dengue outbreaks in China, also demonstrated a peak periodicity of three to five years [8]. I focus on the data of 2017 because of the high fatality rates in comparison with previous years like 2016, 2015, and 2014 (Figure 1).

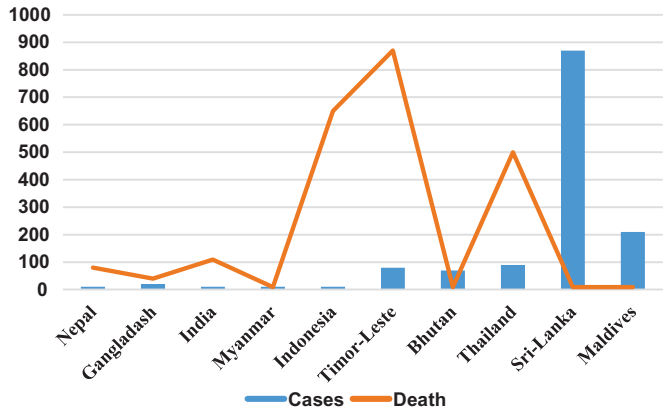

Figure 1: Dengue Incidences and Mortality Rates Among Nations in South East Asia During the Year 2017

Structure and Serotypes

The flavivirus exhibits a spherical morphology with a diameter measuring 50 nm. Mature virions are comprised of virus-encoded, membrane-associated proteins, specifically M and E. Within intracellular immature virions, the precursor protein prM is processed into M during the maturation process [9]. Moreover, Dengue virus (DENV) carries a total of 10 types of proteins of which 3 types are structural and 7 types are non-structural proteins [5, 1]. Furthermore, this virus is classified into 4 different serotypes which show approximately 65% similarity with amino acid sequence [10]. This virus consists of four serotypes. As four serotypes involved in dengue, infection from any one of these (DENV1-4) may elicit a scope of clinical presentations, ranging from mild influenza-like symptoms to potentially fatal severe conditions recognized as dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS) in certain patients [11]. The structural and functional attributes of Dengue virus proteins exhibit considerable variability, with each protein contributing distinctively to the viral life cycle. The C protein (Capsid), consisting of 100 amino acids, forms a homodimer characterized by four α-helical regions and a disordered N-terminal segment. This protein is instrumental in the encapsulation of the viral genetic material. The E protein (Envelope), made up of 493–495 amino acids and possessing a molecular weight of 53 kDa, assembles into a class II N-glycosylated dimer. Ninety E homodimers construct a continuous shell on the surface of the virus, featuring three distinct domains (I, II, III) within each monomer, which facilitate the binding of the virus to the host cell membrane and influence host range, target cell specificity, and the severity of infection. The NS1 protein, which varies from 45 to 560 residues, participates in RNA replication while also inhibiting complement activation, thereby aiding the virus in evading immune system responses. The NS2A protein is composed of 218 amino acids (22 kDa) and facilitates RNA encapsulation and replication while simultaneously antagonizing interferon-mediated responses. The NS2B protein, a membrane-associated component comprising 130 amino acids (14 kDa), functions as a cofactor for the NS3 serine protease and is integral to the formation of the DENV protease complex. The multifunctional NS3 protein, consisting of 618 amino acids (70 kDa), encompasses a protease domain (1–180) and a helicase domain (180–618). This protein exhibits serine protease, RNA helicase, and RNA triphosphate activities, which are essential for the cleavage of the DENV polyprotein and the process of RNA replication. The NS4A and NS4B proteins are hydrophobic membrane-associated entities, with NS4A comprising 150 amino acids (16 kDa) and NS4B consisting of 245–249 amino acids (27 kDa). NS4A is involved in mediating membrane alterations necessary for viral replication, whereas NS4B interacts with NS3 and inhibits interferon signalling, thereby promoting RNA replication. Finally, the NS5 protein, recognized as the most conserved entity within DENV, comprises 900 amino acids (104 kDa). It features a methyl-transferase domain (1–269) and an RNA-dependent RNA polymerase domain (270–900), executing critical enzymatic functions requisite for viral RNA synthesis. Collectively, these proteins orchestrate the intricate processes of viral replication, host cell engagement, and immune evasion.

Transmission and Vector

In the year 2010, it was approximated that the global

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incidence of dengue infections reached 390 million, of which 96 million cases presented clinically, with severe expression of dengue contributing to approximately 21,000 fatalities on a worldwide scale [12]. The proliferation of dengue fever can be ascribed to a multitude of factors, including contemporary climatic fluctuations, globalization, increased mobility, international commerce, socioeconomic variables, urbanization, and the evolutionary adaptations of the virus [13]. Non-structural genes help in the replication of viruses. The prevalence of Dengue infections varies between 2.5 and 30 percent, elevating to 40-50 in specific regions characterized by dengue hyper-endemicity [14]. Transmission of DENV virus occurred in both urban and forested areas but the transmission cycle is different because of the change in environment and evolutionary history. At 30 C transmission of the virus requires 8-10 days from the gut to the salivary gland. The temperature fluctuation between summer and winter is the main cause of seasonal transmission of the dengue virus. Moreover, the main vectors are also different in urban areas main vector is Aedes. Aegypti and Ae. Albopictus mosquito whereas in forested areas the main vector is Ae. Luteocephalus, Ae. Furcifier, Ae. Taylori [10]. Furthermore, rapid travel and trade are also the main factors in the expansion of the dengue virus. Indonesia has become the continuous hub of DENV transmission. Congenital dengue may manifest when there exists an inadequate duration for the transference of maternal protective antibodies to the fetus. A pregnant female has the potential to transmit the dengue virus to the fetus if she experiences a febrile condition from 10 days before delivery up until 10 hours post-delivery [15].

Pathogenesis

The pathogenesis of dengue is significantly shaped by the characteristics of the virus as well as the factors associated with the host, which are not yet fully explained. Severe manifestations of dengue may arise in individuals undergoing a secondary infection with a heterotypic strain of DENV, as well as in neonates born to mothers possessing dengue immunity characterized by primary anti-DENV antibody responses. This phenomenon, known as Antibody-Dependent Enhancement (ADE), can be explained through two simultaneous mechanisms. Initially, during the primary infection, antibodies that are cross-reactive to the serotype and exhibit sub-neutralizing properties are generated [10]. The majority of primary infections are typically asymptomatic or present as mild febrile syndrome; however, they may also lead to hemorrhagic fever in certain individuals, particularly in neonates born to mothers with pre-existing immunity to DENV [16]. Subsequently, during a secondary infection involving a heterologous serotype, the sub-neutralizing antibodies generated from the initial infection interact with the novel Dengue virus, leading to the formation of antibody-virus complexes that are internalized into target cells through Fc gamma receptors (FcγR), thereby facilitating an augmentation of the infection [10].

Symptoms of Dengue Fever

Three phases of the dengue are recognized in the patients when they get infected with Dengue infection. Evident infections emerge as clinical cases after an incubation period of 3–15 days, succeeded by an acute onset of symptoms. It is imperative to differentiate mild illness from influenza, the common cold, and other acute febrile conditions. Classical dengue presentations generally manifest as a sudden febrile response (≥38.5 °C), accompanied by headache, rash, myalgia, arthralgia, thrombocytopenia, and leukopenia, which correlates with a heightened propensity for individuals to seek medical attention. These cases unfold through three distinct natural phases: febrile, critical, and recovery [17].

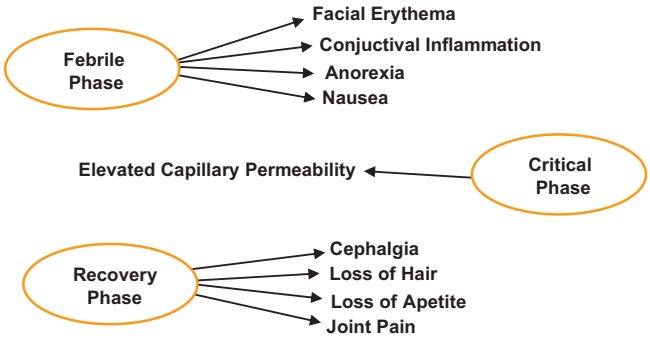

Figure 2: Three phases of Dengue

Severe Dengue and Diagnosis

Due to the fact that infection by a singular serotype confers minimal immunity against the remaining serotypes, recurrent infections involving various serotypes could play a significant role in the escalation of cases of Dengue Hemorrhagic Fever (DHF) and Dengue Shock Syndrome (DSS). For instance, preliminary investigations conducted in Thailand indicated that the incidence rates of Dengue Hemorrhagic Fever/Dengue Shock Syndrome (DHF/DSS) in the pediatric population escalated by 12.5%, with an odds ratio of 6.5 observed in individuals with a prior Dengue Virus (DENV) infection [18]. Physicians have articulated that there exists a vital impetus for the advancement of point-of-care (POC) diagnostic way specifically targeting severe dengue. The implementation of POC diagnostics is anticipated to be profoundly beneficial in rural locales characterized by inadequate laboratory infrastructure for the execution of critical serological assessments necessary for the diagnosis of severe dengue [19]. Electrochemical, optical, and piezoelectric biosensors are used in the diagnosis of dengue [20]. The specialists further articulated the perspective that the introduction of

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a diagnostic assay for severe dengue would serve to mitigate expenses, given that the prevailing methodologies employed for the clinical identification of severe dengue namely, recurrent clinical evaluations, platelet quantification, and ferritin assays are characterized by both prolonged durations and substantial costs[21].

Supportive Care

Traditional medicinal practices, including the utilization of papaya leaf, guava juice, and crabmeat soup, were frequently employed by patients; notably, papaya leaf emerged as the most prevalent remedy cited. Our group of patients ingested papaya leaf predominantly in the form of juice (achieved through the infusion of boiling water with papaya leaf) or consumed tablets derived from its extract. Patients did not perceive any detrimental effects associated with the consumption of these remedies. Papaya leaf could enhance immunological responses in cases of dengue [22]. Dengue patients typically receive supportive management that encompasses bed rest, fluid rehydration therapy, analgesic medications, and antipyretic agents to reduce febrile symptoms[23].

Serological Test

Serological assays are frequently employed to identify dengue fever due to their relative cost-effectiveness and simplicity compared to molecular or culture-dependent techniques. Medical practitioners generally analyze serum (a component of blood) and cerebrospinal fluid for the presence of IgM and neutralizing antibodies; however, they may also assess plasma or whole blood in certain instances. The presence of another antibody, IgG, persists in the organism following the initial dengue infection and serves as an indicator for viral detection. Nonetheless, the presence of IgG may occasionally yield ambiguous results in cases of secondary infections or produce false positives if the individual has previously been infected or vaccinated against related viruses such as the West Nile virus, yellow fever virus, or Zika virus[24].

IgM Based Test

IgM antibodies are proteins produced by the immune system to fight infections, typically appearing five days after symptoms begin and lasting 2-3 months or longer. Due to its capacity to provoke an immune response, it is synthesized in reaction to a foreign entity referred to as an immunogenic. A particular antibody is designed to recognize exclusively one specific compound, known as an antigen [23]. The main challenge for dengue antibody detection devices is the five-day window before IgM antibodies appear. The MAC-ELISA test, developed by the Armed Forces Research Institute of Medical Sciences, is employed for the detection of IgM antibodies in dengue [24].

Plaque Reduction Neutralization Test

The Plaque Reduction Neutralization Test (PRNT) detects specific neutralizing antibodies to identify the exact origin of infection in IgM-positive individuals and is considered the gold standard for testing WHO's vaccine immunogenicity. PRNT is used to confirm cases or when detailed serological information is needed. The test involves coating cells with semi-solid media in test tubes or microtiter plates, mixing diluted serum with the virus, and counting plaques formed over a few days. It can be done at the CDC or designated labs, but lacks a global standard, making result comparisons difficult. Despite its effectiveness in identifying asymptomatic dengue infections, PRNT is time-consuming and labor-intensive [24].

Challenges in Treatment

Almost all the physicians noted that diagnosis and treatment were a great challenge. It was not feasible to discover which specific patient among the cohort may progress to severe dengue; therefore, as a precautionary measure, clinicians typically opt to admit patients to the hospital initially, primarily guided by the platelet count. In Malaysia, as well as in numerous Southeast Asian nations, there exists a variety of infectious diseases wherein the initial symptoms closely resemble those of dengue fever, including but not limited to Leptospirosis, Chikungunya, and Zika virus infections; therefore, it was essential to implement prompt diagnostic procedures. Frequently, employ the NS1 antigen assay for the diagnosis of dengue fever. An additional significant consideration highlighted by the doctors was that individuals diagnosed with DF could exhibit diminished levels of NS1, thereby presenting a risk for the occurrence of false negative results. Moreover, the concentrations of NS1 may vary among distinct patients, and it was proposed that further investigations be conducted to identify additional more indicative biomarkers, particularly for patients experiencing severe dengue, which could result in fatality if not appropriately managed [25]. In addition to that, developing drug for DF also face several challenges. Trials for dengue drugs mainly measure how quickly fever goes away and how much the virus or a specific protein (NS1) is reduced. However, these trials haven't shown significant differences between treated and untreated groups. Moreover, most of the drugs are rejected because of the toxic effects on organs like liver, kidney, heart and brain[26].

Vector Control Strategies

Its objective is to diminish or eliminate human interaction with these vectors through the implementation of chemical and non-chemical interventions. For the immature stages of vectors, such as mosquito larvae, control strategies encompass the eradication of larvae

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utilizing both chemical and biological larvicides, along with the elimination of their breeding habitats. In the case of adult vectors, control methodologies comprise the lethal application of indoor residual spraying (IRS) or space spraying, as well as the minimization of human and animal exposure through the use of topical repellents, architectural barriers, insecticide-treated bed nets (ITNs), and insecticide-impregnated collars for dogs. Examples of novel vector control strategies [27].

Vaccine Development

As research showed many vaccines were developed to treat the dengue infection. There are different types of vaccines were invented like live attenuated vaccines, inactivated virus vaccines, DNA vaccines, recombinant subunit vaccines and viral vector vaccines. If we talk about live attenuated vaccine, three vaccines were developed CYD-TDV, TAK-003 and TV003/TV005. TAK-003 and TV003/TV005 are the most effective vaccines as compared to CYD-TDV [28]. In the inactivated vaccine S16803, PDK-50, R80E, and TPIV were developed and TLAV as a booster. PDK-50 and booster showed a stable response [28]. The protein is used in recombinant subunit vaccines. One monkey is immunized with E protein to boost the immune response. A vaccine called V180 was developed [28]. In the viral vector vaccine, MVA-DENV was stable because it produced good antibody levels whereas, VRP showed an effect and was not stable in comparison to MVA-DENV [29].

Research Gaps

Currently, there exists no licensed vaccine for dengue fever, and clinical trials connected to potential novel vaccines for this disease are actively underway [30]. A significant body of research has been conducted regarding this medical condition; however, there remains an absence of efficacious therapeutic drugs for this disease [31, 32]. The complex nature of the human immune response is the main cause of ineffective therapeutics because there is still a lack of research regarding the dengue mechanism interacting with the complex immune response of humans. Vector control strategies are not useful because they are ineffective and expensive [33-35].

CONCLUSIONS

It was concluded that clinical manifestations encompass a spectrum that ranges from mild clinical presentations to severe conditions such as dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS), particularly during instances of secondary infections attributable to antibody-dependent enhancement (ADE). The escalating incidence of these manifestations is influenced by factors such as climate change, globalization, and urbanization, with Southeast Asia and the Indian subcontinent being the region's most adversely impacted. The diagnostic process presents considerable challenges, often exhibiting overlap with other medical conditions, thereby necessitating the application of advanced diagnostic methodologies. The approach to treatment is predominantly supportive, yet there are significant deficiencies in the availability of effective therapeutic interventions and vaccines. Notwithstanding advancements made with live attenuated vaccines, the pursuit of a universally effective vaccine continues to be an elusive goal. Ongoing research is imperative for the formulation of effective preventive strategies against dengue fever.

Authors Contribution

Conceptualization: NY
Methodology: NY, AR, NB, AS
Formal analysis: NY
Writing review and editing: FB, AA

All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest

All the authors declare no conflict of interest.

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