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Review Article:

An Overview of Dengue Fever

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Abstract

Context: Dengue fever has been reported in 129 countries worldwide, including 100 countries in the Mediterranean region, South America, and Southeast Asia. It results in approximately 40,000 deaths each year, and there have been significant outbreaks of dengue fever in these areas in recent years. Approximately 50% of the global population is presently susceptible to acquiring the dengue virus, which is classified as an emerging and re-emerging ailment that is likely to impact several nations in the foreseeable future.

Evidence Acquisition: Despite the significant harm inflicted upon human health and the economic conditions of countries in recent years, dengue continues to be classified as a neglected disease, without the requisite attention and concerted efforts by countries to effectively manage it. Any actions taken in this domain are inherently constrained. Consequently, due to the significance of dengue fever, this study aims to comprehensively examine this matter.

Results: The disease used to be effectively managed in regions like the countries of the American continent and Singapore, but it has made a resurgence. Between 2008 and 2010, the number of cases in the regions of America, Southeast Asia, and the Western Pacific rose from 0.2 million to 2.2 million. These reports exclusively consist of officially documented sick cases. Multiple outbreaks have been documented in Asia, encompassing countries such as China, Pakistan, Taiwan, and Malaysia, as well as in South America, including Brazil and Mexico. Dengue fever cases have been documented in several Middle Eastern nations, including Yemen, Saudi Arabia, and southern Iran. Local transmission of the disease has begun in Europe, with France and Croatia reporting cases of local transmission. Annually, a minimum of 500,000 individuals experience serious illnesses requiring hospitalization. Approximately 2.5% of individuals who contract the condition die from it. Every year, numerous severe cases of dengue fever are documented, resulting in at least 20,000 deaths.

Conclusion: Dengue fever is a complex systemic disease. Assessing the complete range of the disease burden of dengue fever will be crucial to properly comprehend the serious medical and economic repercussions it has on patients and the general public.

Keywords: Dengue fever, Emerging and reemerging diseases, Viral hemorrhagic fever

1. Context

Viral hemorrhagic fevers are a group of syndromes related to hemorrhagic diseases characterized by a decrease in capillary strength, which can result in severe and acute symptoms, sometimes fatal. The clinical syndrome typically includes fever, muscle soreness, weakness, lethargy, and bleeding; in rare instances, hypotension, shock, and mortality are also associated. From an epidemiological perspective, viral hemorrhagic fevers are categorized into four groups: tick-borne (such as Crimean-Congo hemorrhagic fever), mosquito-borne (such as Rift Valley fever and Dengue fever), rodent-borne (such as Hantavirus), and those with transmission methods still unknown (such as Ebola and Marburg viruses).

A significant number of mosquitoes are known to be vectors of significant arboviruses, transmitting diseases like dengue fever through their feeding on human blood. Dengue hemorrhagic fever, also known as Philippine fever, Thai fever, Southeast Asian fever, or Dengue shock syndrome, is a sudden and acute illness. The primary vectors of various serotypes of the dengue virus are mosquitoes belonging to the *Aedes* genus, particularly *Aedes Aegypti*, a member of the Culicidae family. In recent years, this disease has been spreading across South America and Southeast Asia, with occasional localized epidemics occurring in some seasons in these regions. Dengue fever has been reported in 129 countries worldwide, including 100 countries in the Mediterranean region, South America, and Southeast Asia. It results in approximately 40,000 deaths each year, with significant outbreaks occurring in recent years. The global reach of its transmission has also increased, leading the World Health Organization to prioritize it in discussions on disease prevention and control since 1993 [1, 2]. In 2012, it was recognized as the most important viral disease transmitted by arthropods and has emerged as a significant health concern in tropical and subtropical areas worldwide [3].

Approximately 50% of the global population is presently susceptible to acquiring the dengue virus, which is classified as an emerging and re-emerging ailment likely to impact several nations in the foreseeable future. Despite the significant harm inflicted upon human health and the economic conditions of countries in recent years, dengue continues to be classified as a neglected disease, without the requisite attention and concerted efforts by countries to effectively manage it. Any actions taken in this domain are inherently constrained.

Several Iranian health specialists believe that Iran would experience dengue fever epidemics within the coming years [4]. Consequently, due to the significance of dengue fever, this study aims to comprehensively examine this matter from a scientific perspective.

2. Evidence Acquisition

This review article utilized popular search engines such as Google, PubMed, Google Scholar, Scopus, ProQuest, and Web of Science to explore the topics of "dengue fever," "viral hemorrhagic fever," and "bioterrorism". Additionally, valuable information was gathered from reputable library sources. The papers were classified and evaluated based on factors such as etiology, global and Iranian disease history, epidemiology, pathogenesis, clinical manifestations, prevention, management, and treatment.

3. Results

The Cause of Disease (etiological factor)

The Dengue virus is an RNA virus with a single-stranded positive charge. It is enveloped by three structural proteins and seven non-structural proteins that have functional roles. This virus is classified within the flavivirus genus of the Flaviviridae family. The Flaviviridae family consists of various genera, including the *flavivirus genus*. This genus includes viruses like dengue virus (DENV), yellow fever virus (YFV), Japanese encephalitis virus (JEV), tick-borne encephalitis virus (TBEV), West Nile virus (WNV), and Zika virus (ZIKV). Another genus within this family is the *Hepacivirus genus*, which includes the hepatitis-C virus (HCV). There is also the *Pestivirus genus*, and a newly proposed genus composed of G Barker (GBV) virus isolates [5, 6]. Although members of the Flaviviridae family share similarities in morphology, genome organization, and replication, each genus is antigenically and biologically distinct. The Flavivirus genus exhibits distinguishing characteristics, such as most viruses in this genus being present in the genome of vectors (mosquitoes) and being closely related. The genomic organization and sequence similarities result in antigenic cross-reaction across the viruses within this genus [7].

Dengue virus is a nearly spherical virus with a diameter of approximately 50 nm, and based on cross-reaction assay, the virus consists of four serotypes related to independent antigens (DEN1-1, DEN2-2, DEN3-3, DEN4-4). All serotypes except DENV-4, which is genetically distinct, are almost identical in terms of epidemiology, including genetic variation, transmission dynamics, and epidemic potential [8]. Depending on the infection with serotypes 1 to 4,

symptoms can range from asymptomatic or mild to a simple flu to severe and hemorrhagic symptoms, leading to shock and death, especially in children [9].

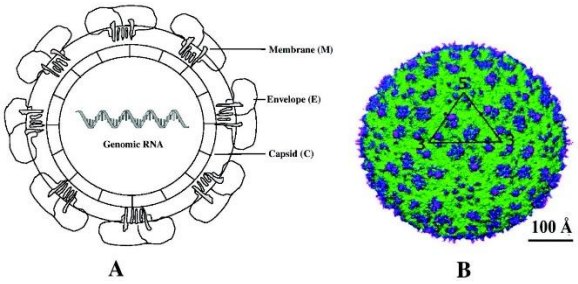

Figure 1. structural components of Dengue Virus (Figure from Dengue virus: epidemiology, biology, and disease aetiology Published in Canadian Journal of Microbiology [10])

The Dengue virus has two unique morphological forms: an intracellular immature virion and a mature virion. The mature virion is characterized by two virus-encoded membranes, which are dependent on E and M proteins, and together they create a relatively smooth surface. (Figure 1). The viral genome contains three structural proteins (capsid C), premembrane proteins (PrM), and coat E, as well as seven non-structural proteins (NS1, NS2A, NS2B, NS3, NS4A, NS4B, and NS5). Structural proteins make up viral particles. Non-structural proteins participate in RNA genome replication, virion assembly and invasion of the innate immune response. Maturation of the immature virion at the surface occurs in an asymmetric and upright manner by undergoing extensive rearrangement of intracellular virus-encoded surface proteins after acidification during maturation in infected cells [11, 12]. (Figure 2).

NS3 and NS5 possess well-documented enzymatic functions, rendering them highly desirable targets for antiviral interventions due to the potential to use these enzymatic activities for the development of high-throughput screening (HTS) assays. RNA replication necessitates additional non-structural proteins, namely NS2A, NS2B, NS4A, and NS4B, which serve as transmembrane proteins that provide structural support for the viral replication complex [9]. (Figure 3).

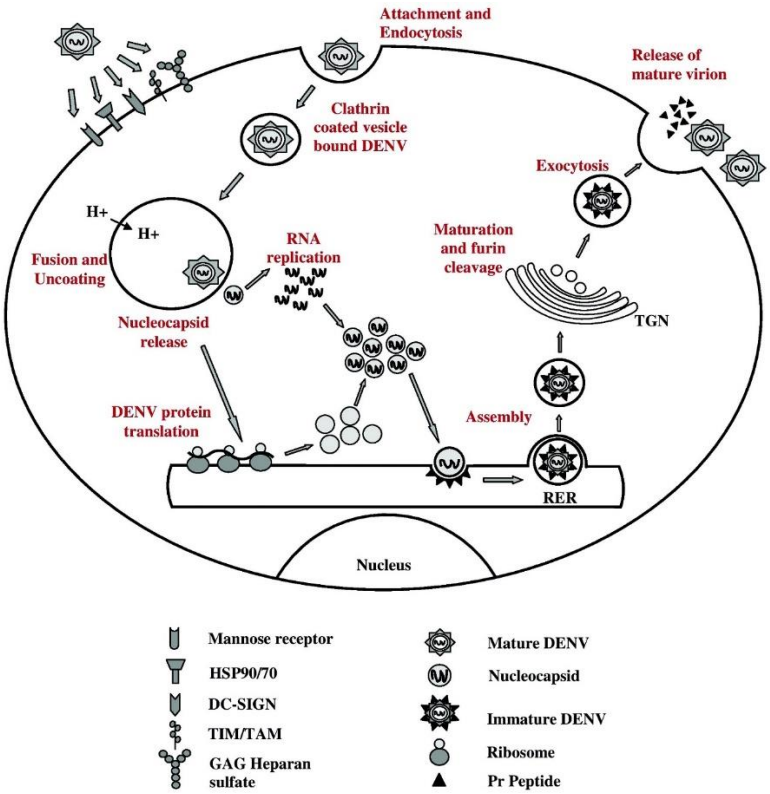

Figure 2. Processes of dengue virus entry in the host cell and its life cycle (Figure from Dengue virus: epidemiology, biology, and disease aetiology Published in Canadian Journal of Microbiology [10])

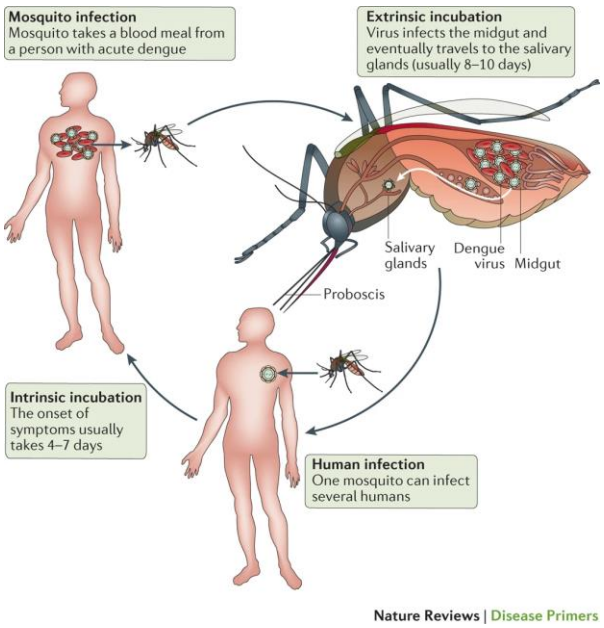

Figure 3. Dengue transmission cycle (Figure from Dengue infection published in Nature Reviews | Disease Primers [18])

Dengue virus serotypes can be classified into several subtypes/lineages or genotypes based on several changes in the viral genome. Dengue viruses have previously been classified into five genotypes (IV) based on the E gene sequence. Of these, genotypes I, IV and V appear dominant, while genotypes II and III appear recessive [13].

The Dengue Virus is composed of six distinct genotypes, namely Asian/American, Asian I, Asian II, Cosmopolitan, American, and sylvatic. Complex DENV-2 genetic structure has fifteen subpopulations/lineages. The Asian/American genotype has seven lineages. Asian I, Cosmopolitan, and sylvatic genotypes each had two lineages. American and Asian II subpopulations were homogeneous. All genes, except for NS4A, showed episodic positive selection. American strains of Asian/American genotype have antigenic and lineage diversity due to positive selection on a few envelope gene codons. Selection on non-structural gene codons affected lineage diversification in Asian I, cosmopolitan, and sylvatic genotypes. Population genetics was used to classify recombinant strains and prove intra/inter-genotype recombination [14].

Transmission Cycle

Medically speaking, there are two significant species of mosquitoes that are linked to the spread of the dengue virus. Mosquitoes belonging to the *Aedes* genus are classified under the Colicidae family. Arboviruses are spread mostly by *Aedes aegypti* mosquitoes, with *Aedes albopictus* mosquitoes serving as a secondary vector in certain regions. Mosquito vectors multiply in diminutive reservoirs of stagnant water, particularly within water storage receptacles located near residential residences. Adult and larval *A. aegypti* mosquitoes are typically more prevalent indoors, particularly in urban regions. *Aedes albopictus* primarily inhabit the exterior of residential buildings and are commonly found in suburban or rural regions [15]. *Aedes aegypti* and *Aedes albopictus* mosquitoes have a black coloration, although they can be readily differentiated based on the distinct arrangement of white stripes on the upper side of their thorax. *Aedes aegypti* displays two straight lines bordered by curved harp-shaped lines, whereas *Aedes albopictus* exhibits a wide stripe consisting of white stripes running along the center of its thorax. Following copulation, mature female mosquitoes receive blood meals, deposit 60 to 100 eggs in both artificial and natural habitats, and typically have a lifespan of 20-30 days. *Aedes* mosquitoes are considered daytime biters because they bite during dawn after sunrise and during the day. Female mosquitoes typically require a blood meal in order to acquire protein and lay eggs. Once the mosquito becomes infected with the virus by bloodsucking, the virus undergoes rapid replication within the mosquito's body and then moves from the midgut to

the salivary glands. It is in the salivary glands that the virus can be transmitted to a new host during the insect's subsequent bite. Prior to sunset, subsequent to acquiring the dengue virus from an individual who is infected, the virus persists and replicates in the mosquito's salivary gland for a duration of 4 to 12 days (known as the incubation period) before being transmitted to another individual. (Figure 4) The peak flight of mosquitoes is relatively short, they fly in the range of 50 to 200 meters from their breeding places, so it is expected that they will be seen less in high and mountainous areas [16, 17].

Aedes mosquitoes can be identified by their distinctive dark and white stripes and spots on their body and legs, as well as their tendency to feed on blood during daylight hours, particularly in the early morning and evening before sunset. Contrary to the malaria mosquito, this particular mosquito exhibits diurnal feeding behavior by biting humans during daylight hours. The infected female mosquito has the ability to transmit the virus to its eggs and spread the disease-causing agent throughout its entire lifespan. The dengue virus undergoes replication within the human body, and infected individuals serve as the primary means of transmitting the virus to uninfected mosquitoes. An individual who has contracted the virus can transmit the virus to mosquitoes within a timeframe of 4 to 5 days, and this transmission can continue for up to 20 days following the initial appearance of symptoms [19].

The *Aedes aegypti* mosquito thrives and reproduces in urban households, particularly in the residences of impoverished and marginalized communities within cities. The Albopictus mosquito, a different species of *Aedes*, has emerged as the secondary vector of dengue disease in Asia. Its range has shifted from Southeast Asia to northern regions like China and Japan, and it has even spread to North America and Europe [20].

Based on the most recent checklist by Azari-Hamidian (2007), there are a total of 64 species of mosquitoes belonging to the Colicidae family in Iran. Among these, 10 species are from the Aedini tribe and are classified under two genera: *Aedes* (6 species) and *Ochloratatus* (1 species). It is worth noting that sometimes all these species are grouped together under the genus *Aedes* [21].

Research has been conducted on the species diversity of Colicidae mosquitoes in the Iranian islands located in the Persian Gulf. The study focused on the distribution of *caspius Ochlerotatus* and *Aedes vitatus*, which are known to have a high capacity for maintaining and transmitting flaviviruses. These species were found along the southern coasts of Iran, as well as on Qeshm and Abu Musi islands. Additionally, these mosquitoes are also found in various other regions, including the Azerbaijan region of Iran. The animal reservoir for the dengue fever virus in Iran remains unidentified, while in Malaysia, the virus is transmitted between monkeys by *Aedes niveus* (*Ae. neveus*) [22].The scarce records of *Aedes aegypti* sightings in Iran, specifically in the districts of Khuzestan, Bushehr, and Hormozgan, pertain to previous years and have not been documented in the past 65 years. There is currently no officially recorded documentation regarding the observation of *Aedes aegypti*. Additionally, an unpublicized report exists documenting the capture of Aedes albopictus in the province of Sistan and Baluchistan. Currently, the *Aedes* species present in Iran are *Aedes vittatus (Ae. vittatus)* and *Aedes vexans (Ae. vexans)*, which have the potential to transmit some flaviviruses [23].

The dengue outbreak results in a significant number of morbidity and mortality within a brief timeframe. Furthermore, it has the potential to induce widespread alarm among individuals who anticipate prompt intervention from the authorities. Several researchers on the Arabian Peninsula have conducted studies on the distribution of adult mosquitoes belonging to the family Culicidae Diptera, as well as their larvae. They have documented a total of 51 species and subspecies [24]. During the 1990s, there were outbreaks of the disease in West Asia, which included a significant outbreak in Jeddah, Saudi Arabia. Having knowledge of the prevalence and variety of mosquitoes and assessing an efficient mosquito control program in a specific region is crucial [25]. In the study conducted by M Abbas et al. (2022) regarding the prevalence of arbovirus-carrying mosquitoes, it was shown that the population of immature A. aegypti mosquitoes experiences a large increase throughout the months of March, April, May, and December in the Arabian Peninsula. The peak levels of adult mosquito population occur in April, January, October, and December [26]. *Aedes aegypti* is a species that is well-suited to living in cities and is found in many tropical and subtropical regions, as well as some areas beyond the Arctic. Collecting adult vectors by sampling can be valuable for a targeted study, as it can yield data on factors such as the risk of transmission, the patterns of transmission, the seasonal variations in population, and the effectiveness of treatments aimed at controlling adult vectors. Efficiently studying vector species and their infections is crucial for evaluating disease risk and implementing suitable strategies to avoid transmission and reduce mosquito populations [27].

History of Dengue Fever in The World

Dengue is believed to have been initially

documented in China several years ago. An individual with symptoms consistent with dengue fever is mentioned in a medical encyclopedia from the Jin Dynasty, a Chinese dynasty that existed from 265 to 420. This book discusses the phenomenon of "blue poison" and its correlation with flying insects. Additionally, there exist written records from the 17th century that detail a potential occurrence of dengue. The period between 1779 and 1780 is the most probable timeframe for the occurrence of dengue epidemics. These tales describe a pandemic that rapidly spread across Asia, Africa, and North America. Subsequent to that time, there have been no other occurrences of epidemics until the year 1940 [28].

The term "break-bone fever" was initially coined by Benjamin Rush, a prominent figure in the founding of the United States of America. In 1789, Rush employed the term "bone-breaking fever" in a report documenting a dengue outbreak that occurred in Philadelphia in 1780. The report frequently employed the alternative term "biliary transmission fever"[29]. The term "dengue fever" was not commonly used until after 1828. Before that, different people used different names for this disease; For example, dengue was also called “break heart fever" and "la dengue"[30]. Terms used for referring to severe cases were "infectious thrombocytopenic purpura" or "Philippine", "Thai", or "Singapore hemorrhagic fever" [31].

In 1906, scientists demonstrated the transmission of diseases by the *Aedes* mosquito genus. In 1907, researchers demonstrated the etiological role of a virus in the occurrence of dengue fever. This sickness was the second to be definitively attributed to a viral etiology. Prior to this, scientists had already shown that yellow fever was also caused by a virus. John Burton Cleland and Joseph Franklin Siler conducted a study on the dengue virus, focusing on its transmission mechanisms [32]. The transmission of dengue significantly accelerated during and following World War II. War is believed to induce environmental alterations through multiple mechanisms and create circumstances that facilitate the transfer of diseases by vectors. Furthermore, various strains of dengue disease have extended their reach to formerly uninfected regions. Individuals were experiencing dengue hemorrhagic fever for the first time. The initial occurrence of dengue hemorrhagic fever, a severe form of the disease, was documented in the Philippines in 1953. During the 1970s, dengue hemorrhagic fever emerged as the primary cause of mortality among children. The virus also began to propagate throughout Oceania and America [28].

The first documented instance of dengue 1 generating a broad epidemic of dengue fever occurred in 1977. The disease spread from Jamaica to Cuba, Puerto Rico, and Venezuela. Subsequently, the virus disseminated to the remaining Caribbean nations, Mexico, Central America, and northern Asia. By 1978, the phenomenon had a significant impact on Colombia, Guyana, Surinam, French Guyana, El Salvador, Guatemala, and Belize. Approximately 702,000 cases were documented throughout the period spanning from 1977 to 1980. In 1981, the initial outbreak of dengue hemorrhagic fever (DHF) in the area occurred in Cuba. This outbreak resulted in over 300,000 cases of dengue, with 10,000 cases specifically caused by DHF. Additionally, there were 158 deaths, including 101 children.The 1980s witnessed the emergence of dengue hemorrhagic fever (DHF) epidemics and the simultaneous circulation of many serotypes, including dengue 1, 2, and 4 [33].

Status of Dengue in The World

The Dengue virus is transmitted to humans in over 100 countries annually, posing a threat to around 3.6 billion individuals. Over the past five decades, there has been a significant 30-fold rise in the prevalence of dengue. DENV epidemics have yearly occurrences throughout the Americas, Asia, Africa, and Australia, and they also impact those traveling from countries where the disease is prevalent. In addition to their implications for public health, these epidemics exert a substantial economic burden on the impacted nations. In 2016, the United States experienced the most extensive dengue outbreak, with over 2.38 million recorded cases. Brazil had the most significant contribution to this outbreak, with a total of 1.5 million reported cases. The prevalence of dengue outbreaks in Southeast Asian countries increased significantly following World War II, primarily as a result of urbanization [34].

Approximately 50 million cases of dengue are reported each year, and almost 2.5 billion individuals reside in areas where dengue is prevalent. Approximately 1.8 billion individuals, accounting for over 70% of the global population susceptible to dengue, reside in member states of the World Health Organization's South-East Asia Region and Western Pacific Region. These regions collectively bear approximately 75% of the existing global disease burden attributed to dengue [35].

The disease was previously successfully controlled in parts of the world such as the countries of the American continent and Singapore, but now it has returned again. In the region of America, Southeast Asia and the Western Pacific, the number of cases has increased from 0.2 million to 2.2 million from 2008 to

2010. These only include official reports of disease cases. Several epidemics of it have been recorded in Asia, including China, Pakistan, Taiwan, Malaysia, and in South America, including Brazil and Mexico. Cases of dengue fever have been reported in some Middle Eastern countries such as Yemen, Saudi Arabia, and southern Iran. Local transmission of the disease has also started in Europe and France and Croatia have reported cases of local transmission. Every year, at least 500,000 people suffer from severe diseases and need hospitalization. And about 2.5% of those infected with the disease die. Hundreds and thousands of severe dengue fever cases occur every year and at least 20,000 deaths are reported [3]. Dengue epidemics usually occur in rainy and hot seasons. Before the 1970s, this disease was reported only in 9 countries, now this disease has become endemic in more than one hundred countries of the world, and based on the studies, it is possible that the disease will spread again in the future in areas that have been free of this disease [19, 36].

Dengue virus is the predominant flavivirus in both rural and urban areas of Vietnam. According to statistics from the World Health Organization (WHO), the virus primarily spreads in urban areas where vectors may readily locate appropriate water sources for breeding. The number of dengue infections in Vietnam rose from 105,370 cases in 2009 to 184,000 cases in 2017 [37]. Hanoi, situated in northern Vietnam, has a subtropical climate characterized by four distinct seasons. Prior to 2008, Hanoi was comprised of nine urban districts and five suburban districts. Subsequently, the city increased its jurisdiction by merging certain regions from neighboring provinces. As a result, the new Hanoi now encompasses twenty-nine districts and one city. This is a highly populated metropolis with approximately eight million inhabitants. Historically, Hanoi had a low incidence of dengue infection. However, as its territory expanded, the incidence of dengue has risen in recent decades, with a higher prevalence observed in recurrent cycles. The onset of the dengue season in Hanoi commences in June. The highest point is reached in October and gradually decreases starting from December. Due to its ideal environment, high population density, and fast urbanization, Hanoi is currently considered an endemic region for dengue fever [38, 39].

Due to its predominantly desert terrain, Saudi Arabia features sand dunes, sandy plains, lakes, and streams. Consequently, the climate is extremely dry, with infrequent rainfall in most regions. On average, the country receives about 100 millimeters of rainfall per year, primarily during the rainy season in March and April. However, when dengue fever started spreading in Saudi Arabia, certain researchers contended that the country's limited rainfall hindered the disease's transmission [40]. However, the country is now struggling to control the increasing number of dengue cases reported each year. Both mosquito vector species are present in Saudi Arabia and their reproduction increases with dengue fever transmission, especially after the rainy season [41]. *Aedes aegypti* is recognized as the primary vector, but *Aedes albopictus* is acknowledged as a secondary agent in the transmission of the disease. The geographical range of *A. aegypti* has expanded in Saudi Arabia, and it can now be found in the cities of Jeddah, Mecca, Jizan, and Asir. *Aedes aegypti* mosquitoes have lately been observed in the city of Medina [42]. The presence of numerous migrant workers and religious pilgrims from dengue endemic areas in the Middle East and Asia, along with other factors, contribute to the complexity of dengue fever in Saudi Arabia. These factors are associated with the emergence and persistence of the disease in the country. Jeddah, specifically, experiences a moderate average temperature, high levels of humidity, and serves as the main entry point for religious and international pilgrims. This location is particularly conducive to the introduction and spread of the dengue virus, and it has a high prevalence of dengue fever. Understanding the full spectrum of disease vectors in Saudi Arabia might provide valuable insights for directing future research and prevention initiatives, as well as enhancing the readiness of the healthcare system [43].

The *Aedes aegypti* mosquito, which is a vector of diseases, initially emerged in Africa as a natural vector that inhabits and breeds in cavities within tree trunks. This mosquito species is considered domesticated, meaning it lives in close contact to people, in tropical and subtropical regions outside of Africa. It is hypothesized that the proliferation of global trade has facilitated the dissemination of this species, which has adapted to human environments, to both the New World and Asia. *Aedes albopictus* is native to Bengal, India, and has subsequently expanded its range to encompass Southeast Asia, Africa, the Middle East, Europe, North America, and the South Pacific Islands. Currently, both kinds of vectors have a global distribution, encompassing Southeast Asia as well [44, 45]. Bhatt et al. (2013) claimed that there were almost 390 million cases of dengue worldwide in 2010, out of which 96 million were diagnosed with clinical dengue fever, including dengue hemorrhagic fever or dengue shock syndrome. Asia represented 67% (47 to 94 million infections) of the total global burden of disease [46].

Dengue epidemics are common and recurring throughout the year in most Southeast Asian nations. The prevalence of dengue fever in non-clinical settings is also significantly elevated and exhibits geographical, temporal, and demographic variations. The seroprevalence of dengue fever in Malaysia has been documented to range from 28% to 92% [47].

The majority of deaths are attributed to the viral infection of dengue fever, which causes hemorrhagic fever and dengue shock syndrome. The first outbreaks of dengue-like epidemics were reported in the city of Aden, Yemen, between 1870 and 1873. In 1954, 98% of dengue fever cases were recorded in the Al Hudaydah province. Subsequently, dengue fever became an epidemic in the coastal areas of Ta'izz (Hudaydah). Since 2005, the disease has continued to spread and affect new provinces [3].

The first outbreak of dengue virus infection in Ethiopia took place in 2013, coinciding with a dengue-related outbreak in the Deira Daweh city administration in eastern Ethiopia. During this outbreak, a total of 12,000 suspected cases connected to dengue were documented in that region. Out of them, a total of 88 cases were verified using the ELISA and RT-PCR techniques. There were 50 cases that tested positive for a viral infection, specifically the DENV-2 subtype. In the subsequent year, numerous further instances of illness epidemics transpired throughout the year [48, 49].

In the Somali region, the same months of three consecutive years (January, February, and March of 2014 2015, and 2016) were observed. A cumulative total of 440 cases have been documented in this outbreak [50]. Kebridhaar, a city in Somalia, experienced an epidemic of the disease in May 2017. A total of 101 patients were reported, with 5 cases classified as serious and 1 resulting in death. From 2017 to 2021, there have been documented outbreaks of dengue fever in the Somalia region and Deira Diwa urban management, as indicated by epidemiological evidence [48]. In addition, Ethiopian health authorities documented an epidemic of 160 confirmed cases of dengue infection in Woreda Warder of Dolo District and 47 suspected cases of dengue fever in Dolo between January 1 and February 4, 2021. The Ado Woreda Dolo in the Lebanon area of Somalia has been one of the regions affected by a dengue virus outbreak in the years 2017 and 2018 [51].

Europe is currently experiencing local transmission of the disease, with confirmed cases identified in France and Croatia. Annually, a minimum of 500,000 individuals experiences debilitating illnesses that necessitate hospitalization. Approximately 2.5% of individuals who contract the condition succumb to it. Annually, a substantial number of severe dengue fever cases are documented, with a minimum of 20,000 recorded fatalities [3]. A summary of global cases of Dengue fever in 2022 from is demonstrated in Figure 4.

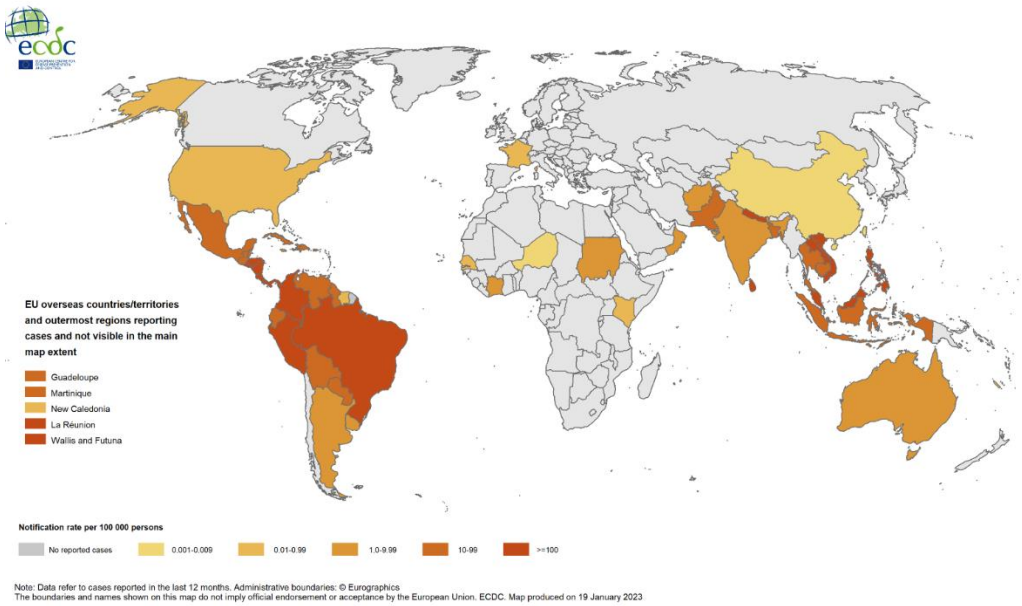

Figure 4. Cases of DF in 2023 around the world (Figure from European Centre for Disease Prevention and Control [52])

The primary contributing factor to the rise in dengue cases is the rapid growth of the global urban population. This population has surged from 0.7 billion to 1.5 billion people and is projected to reach 4.9 billion people by 2030. Unfortunately, a significant portion of this increase is concentrated in large cities across Asia, where access to adequate healthcare and social services is limited. *Aedes aegypti* and *Aedes albopictus*, which are the primary vectors of dengue fever, have been observed in Italy and certain southern European nations. Nevertheless, not only has there been a rise in the incidence of the disease, but the geographic range of dengue fever is also expanding, with frequent and widespread outbreaks of the disease. The occurrence of dengue epidemics exerts significant strain on the healthcare infrastructure of the countries engaged in conflict. The second aspect contributing to the issue is the surge in travel, particularly international travel, which has resulted in a notable impact on a considerable number of individuals visiting their home regions. Studies on molecular epidemiology conducted in Cuba and Brazil have demonstrated that viruses with higher pathogenicity have exhibited a greater extent of dissemination. The outbreak of dengue fever in 2014 and 2015 in Guangzhou, China, Taiwan, India and Pakistan [53-55] and its recent epidemic in Tokyo, Japan (introduced by athletes from the Asian Games in Guangzhou, China), which has been unprecedented in the past 70 years [6]. Each of them demonstrates the alterations and expansion of the geographic distribution, as well as the shifts in the disease's epidemiological characteristics and the ecology of its vectors. Floods and tsunamis, along with the proliferation of *Aedes* mosquito breeding grounds, contribute to the dissemination of dengue fever and its vectors. Expansion into the Eastern and Central European regions is anticipated in the future. Based on these predictions, the Middle East region, including Iran, will fall within the future geographical coverage area of these carriers [55].

Dengue fever is known in various metropolitan regions of developing tropical countries in Asia, including Afghanistan, Pakistan, India, and Iran, where the spread of vectors is facilitated. The geographical spread of dengue fever in Afghanistan is likely influenced by several factors, including heightened international travel, inadequate control measures, and limited access to vaccines. This is evident through the occurrence and transmission of the disease in neighboring countries of Afghanistan, as well as the movement of millions of Afghans to destinations such as Pakistan, India, Iran, and other nations. The tropics exhibit a significant incidence of dengue owing to various factors, including education, treatment, tourism, and trade. Furthermore, it is crucial to take into account environmental alterations, particularly in the regions neighboring Pakistan's borders. Dengue fever may be growing in the Afghan districts that share a border with Pakistan. However, the lack of awareness or knowledge about this disease sometimes leads to its misdiagnosis as other similar diseases. Furthermore, factors such as temperature variations, global warming, limited availability of potable water, inadequate sanitation, insufficient infrastructure for rainwater collection, and a lack of knowledge regarding dengue fever contribute to the spread of the disease [56]. A Projection of Dengue fever distribution in 2050 is demonstrated in Figure 5.

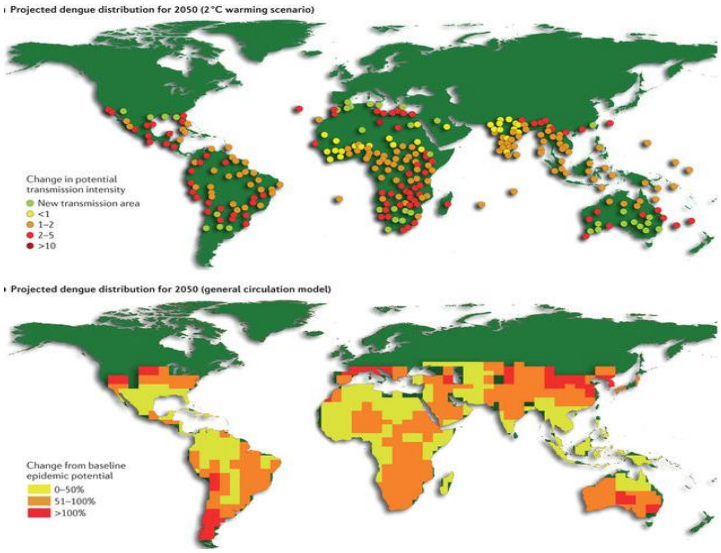

Figure 5. Projected DF distribution for 2050. (Figure from the many projected futures of dengue Published in Nature Reviews | Microbiology [57])

Dengue Fever in Iran

Iran is susceptible to the dengue virus from two adjacent geographical directions. There is a potential risk of disease carriers entering Sistan and Baluchistan province in Iran from Pakistan, as well as from the Persian Gulf and the Oman Sea in the south. This could lead to contamination of the islands and coastal strip of Iran. The region of Iran and its coastal strip are classified as part of the eastern region (oriental) in terms of animal geography (zoogeography), similar to South Asia, India, and Pakistan. Additionally, this area is considered a subtropical region in terms of weather and climate conditions. The meteorological characteristics of this region differ from other areas of Iran due to its location inside the Arctic Plateau geogeographical zone. From a theoretical and scientific standpoint, it is always possible for the main vector of the dengue virus, namely *Aedes aegypti* and the secondary vector *Aedes albopictus*, to spread from the mentioned areas to the oriental regions of Iran. The initial conditions for the establishment of these species' populations are consistently present. The geographical regions of the Arctic Plate are unlikely to facilitate the spread of *Aedes* populations unless there are permanent changes in their climatic and biological circumstances that encourage the growth of *Aedes* mosquito populations. As of now, Iran has not recorded any instances of dengue transmission. All reported cases of this disease have been individuals who have traveled and brought it into the country from the Pakistan border. Despite the warnings from healthcare specialists in Iran about the imminent arrival of a dengue fever outbreak in recent years, and the predicted maps indicating the presence of two varieties of *Aedes* mosquitoes that transmit dengue in Iran, there is presently no outbreak. At the moment, the epidemiological and entomological data do not provide compelling evidence that the dengue virus transmission cycle can be established in the islands and coasts of Iran, including the southeastern regions, in the foreseeable future. This is due to the absence of a significant population of the primary *Aedes* vectors in Iran, which is necessary for the virus to spread. Therefore, it is unlikely that Iran will be included in the global dengue fever pandemic map in the near future. If the necessary conditions for the reproduction, growth, and spread of the Aeds vector population are present in southern Iran, there is a potential risk of dengue fever spreading in the country, as it has already occurred in neighboring countries like Pakistan [58].

Azizi et al. (2017) conducted a study using the RT-PCR method to investigate the COI genes (DNA barcode) at a molecular level. The role of *Aedes* mosquitoes in the transmission of dengue fever in Hormozgan province was assessed in 2017. A combined total of 447 adult mosquito samples and 852 larvae samples were gathered and chosen from four cities in Hormozgan province. These samples were then recognized as five distinct species of the *Aedes* genus. The RT-PCR analysis of *Aedes* mosquitoes revealed the detection of Ae. caspius (80 larvae and 100 adults), Ae. vexans (120 larvae and 240 adults), and Ae. vittatus (30 larvae and 7 adults). The most recent instances *of Aedes aegypti* mosquito detection in Hormozgan province occurred in Bandar Lange city in February 2018, Bandar Abbas city in December 2018, and Sirik city in March 2019. As of now, there have been no documented cases of viral infection in the collected mosquitoes [59].

The predominant demographic affected by dengue fever in Iran is the male population. The primary factor contributing to the elevated prevalence of dengue fever among men in Iran may be attributed to their occupational engagements, which entail a greater frequency of business travel to endemic regions compared to women. Based on the study findings, 53.3% of the 15 confirmed cases have visited foreign regions such as Malaysia, India, and Thailand. Given the substantial number of Iranians who go overseas for educational and business purposes, particularly to countries like Malaysia, further investigation is required for individuals suspected of having dengue fever. This includes those with a travel history to regions where dengue is prevalent, as well as presenting clinical symptoms such as bleeding and fever. Travelers play a significant role in the spread of dengue infections in Iran. Therefore, it is advisable for them to receive pre-travel guidance on applying insecticides to protect themselves from mosquito bites in locations where the disease is common. Additionally, choosing accommodations with screened windows or air conditioning can help minimize the risk of infection [60].

Pathogenesis

The etiology of dengue virus infection is intricate and not completely comprehended, although the fact that the spectrum of pathogenicity of all serotypes ranges from a moderate manifestation to a severe manifestation and dengue shock syndrome. The development of the disease is caused by the intricate interplay between the virus, the genes of the host, the reactions of the host, and the immune system [61].

The clinical features and severity of dengue fever (DF) can be influenced by various factors, including age (particularly in infants and young children), gender, body weight, high body mass index, genetic variations, and previous infection with dengue virus

serotype 1 (DENV-1). Additionally, the presence of underlying conditions such as diabetes and asthma can further complicate the disease course if the patient is subsequently infected with DENV-2 or DENV-3 [62]. In extreme instances of the disease, the dengue virus induces hemostatic abnormalities and plasma leakage, heightening the vulnerability of blood vessels and resulting in bleeding. Furthermore, the virus enhances the permeability of capillaries. Therefore, the pathophysiological characteristics of the severe form of the disease may result from atypical plasma leaks and disrupted homeostasis. The phenomenon of plasma loss in dengue fever and its subsequent consequences have been recognized for the past decade, however the precise mechanism by which the virus induces this remains unknown [63].

Conversely, the infection's severity reaches its highest point after the host's immune system has eliminated the virus, rather than during the period of highest viral load [64]. It is necessary to verify the significance of the host immune response in the development of DENV infection. The primary factors influencing the development of DENV infection are the specific organs and tissues that the virus targets. Nevertheless, the limited availability of suitable orientation assays and animal models has impeded the comprehension of replication tropism in tissue cells for disease [65]. The presence of negative charge in dengue virus RNA or NS3/NS5 proteins within specific cells may serve as an indication of DENV replication, as these antigens are only present during active DENV infection. Conversely, the detection of other antigens (E, prM, C, (+)-sense RNA) may suggest the absence of active DENV replication in cells, as they do not support the replication process. DENV cells can indiscriminately take in viral RNA and other antigens from their immediate surroundings. Following a mosquito bite, infected skin cells transport the DENV virus to the draining lymph nodes via the lymphatic system in both in vitro and necropsy experiments. Within the lymph nodes, resident macrophages and other unidentifiable cells get infected. The virus spreads to the lymphatic and vascular system, resulting in infection of the bone marrow and spleen. Subsequently, Peyer's plaques and lymph nodes become infected, and the virus can be transferred either directly after the lymph has been drained from the nodes or through the bone marrow and spleen, as well as many non-lymphoid organs including the stomach, thymus, lungs, brain, digestive system, liver, and kidney. and acquire hearts that are likely contaminated. The involvement of immune system cells and endothelial cells (EC) that line blood vessels in DENV tropism and severe pathogenesis is evident [66].

On the other hand, the hematopoietic process is inhibited, resulting in reduced blood thrombogenicity, depending on the extent of infection in the stromal cells of the bone marrow and the levels of IL6, IL8, IL10, and IL18. Elevated viral load in the blood, viral preference for endothelial cells, and impaired platelet function due to severe thrombocytopenia result in increased susceptibility of capillaries to damage and the onset of dengue hemorrhagic fever (DHF). Medically, it manifests as petechiae, accelerated bruising, and bleeding of the gastrointestinal mucosa [67].

DENV infection elicits the generation of targeted antibodies and cellular immunological responses, even in the presence of pre-existing immunity. Research indicates that IgM antibodies generated in response to DENV can interact with EC, platelets, and plasmin to intensify the process of increased vascular permeability and coagulation. This, in turn, leads to the production of more effective IgG antibodies that can attach to other viruses during subsequent infections. T-cell cross-reactivity can lead to both underestimation and overestimation of viral load. T lymphocytes impede the timely elimination of the virus by the immune system and generate substantial quantities of pro-inflammatory cytokines and other signaling molecules. Elevated concentrations of soluble substances induce alterations in endothelial cells, resulting in the activation of coagulation and subsequent depletion of plasma and disseminated intravascular coagulation (DIC) [68].

Clinical Signs and Symptoms

A female mosquito transmits pathogens to a human through its bite. The virus undergoes replication within the human body, and infected individuals serve as the primary reservoir for transmitting the virus to uninfected mosquitoes. Dengue hemorrhagic fever can manifest across a wide range of clinical presentations (Figure 6), ranging from asymptomatic infection (with seroconversion as the only indication) to symptomatic infectious disease with fever, and from mild cases without fever to severe cases characterized by bleeding and shock. The disease has an incubation period of 4-12 days. Most initial infections often manifest as either an asymptomatic or moderate febrile sickness. However, certain patients, particularly newborns born to mothers with immunity to DENV, may develop hemorrhagic fever and infection. The latter, characterized by distinct serotypes, can result in severe clinical presentations such as Dengue Hemorrhagic Fever (DHF) and Dengue Shock Syndrome (DSS) [69].

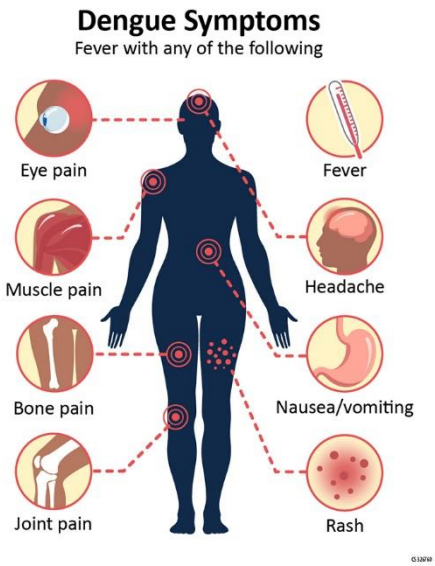

Figure 6. Dengue fever Symptoms (Figure from the CDC [70])

The clinical symptoms might persist for 2-7 days and may include an asymptomatic phase. or symptomatic, which can result in undifferentiated fever, dengue fever (DF) or dengue hemorrhagic fever (DHF), and leakage of plasma and dengue shock syndrome (DSS), which can lead to hypovolemic shock. Dengue virus infections with symptoms were categorized as Dengue Fever (DF), Dengue Hemorrhagic Fever (DHF), and Dengue Shock Syndrome (DSS) based on the World Health Organization's categorization recommendations between 1997 and 2009 [8].

Nevertheless, during the 2000s, expert groups specializing in DF reached a consensus that DF is a fundamental ailment characterized by diverse clinical presentations and frequently unforeseeable clinical characteristics and results. The reclassification of DF cases is contingent upon the levels of severity. In 2009, the World Health Organization (WHO) categorized DF into two classifications: moderate DF and severe DF, using a specific set of clinical and/or laboratory characteristics. An individual who contracts DENV can acquire lifelong immunity solely against the specific serotype that caused the infection. However, this this immunity offers only transitory and incomplete immune responses against other serotypes [20, 71].

In the classical form of the disease, when the virus enters the human body after a mosquito bite, it creates a primary viremia, and after the incubation period, the symptoms of the disease appear in three stages: the fever period, the critical period, and the recovery period.

- **The first period (febrile)**: patients suddenly experience a high temperature of 19 to 41 degrees for 2 to 7 days. These symptoms include severe headache, facial flushing, skin redness, diffuse body pain, photophobia, rubella-like skin lesions, joint and bone discomfort, lack of appetite, and stomach pain, especially on the right side below the ribs. Nausea and vomiting are typical. Early fever makes it hard to distinguish dengue from other febrile disorders. A positive tourniquet test means a higher probability of dengue fever [1,4]. Although the clinical symptoms are present, it is not possible to accurately forecast the severity of the condition. Thus, it is crucial at this point to thoroughly examine warning indicators and other clinical criteria to promptly implement appropriate interventions if the disease advances to a severe stage.

Warning signs manifest following a shock, predominantly during the latter phases of the fever period and within the first seven days of the disease. The initial indicators of plasma leakage are persistent vomiting and intense stomach pain, which get more severe as the patient's condition deteriorates towards shock. The patient is experiencing growing bewilderment, characterized by lethargy, while maintaining neurological consciousness. During the initial stage of shock, individuals may experience a combination of muscle weakness and mental disorientation because of a sudden decrease in blood pressure after changing positions. Spontaneous mucosal bleeding, also known as bleeding in previously venipunctured areas, is a significant and indicative symptom. An increase in size of the liver and its sensitivity are observed usually. Extravascular fluid buildup can only be diagnosed when there is a substantial loss of plasma or when it happens following serum therapy. The initial indications of plasma leakage may manifest as a fast and gradual decline in platelet count to 100/000 cells/mm3, accompanied by a concurrent rise in hematocrit. In addition, leukopenia frequently manifests, characterized by a white blood cell count of 5000 cells/mm3 or less [20].

- **The second period (critical)**: it occurs when the fever subsides and typically lasts from the third to eighth day of the illness. During this period, the body temperature rapidly drops within 24 hours and ranges from around 17.5 to 12 degrees. Alternatively, if the condition persists, the plasma may escape from the bloodstream, causing a decrease in blood pressure. The patient exhibits symptoms of restlessness and weakness, with cool and somewhat damp skin, accompanied by an accelerated pulse. Progressive leukopenia develops after a significant reduction in

platelet count, which is then accompanied by the leakage of plasma. As platelet levels decrease, there is a possibility of experiencing gastrointestinal bleeding. In more severe cases, this might lead to circulatory failure. Following the development of clinical symptoms, one may observe the presence of pleural effusion and ascites, as well as the emergence of free fluid in sonography of the chest, abdominal area, or gallbladder edema. Furthermore, alongside plasma leakage, one frequently observes bleeding symptoms such as fast bruising or bleeding at the site of vein extraction. If there is a shock resulting from the loss of a significant amount of plasma owing to leakage, it is likely that warning signals will also manifest. During the state of shock, it is common for body temperature to be below the normal range [72].

Dengue Shock Syndrome (D.S.S)

Dengue shock syndrome is a form of hypovolemic shock caused by heightened vascular permeability and loss of plasma. It primarily manifests during the intermediate phases of the disease, typically occurring between the third and eighth days, and frequently follows the onset of preliminary symptoms. The progression of dengue shock is a physiological sequence that initiates with the asymptomatic phase of capillary leakage, followed by compensated shock, then hypotensive shock, and ultimately culminates in cardiac arrest. Tachycardia occurring in the absence of fever throughout the fever period and the critical period is seen as an initial cardiac reaction to hypovolemia. The significance of this matter lies in the fact that tachycardia is not typically observed in adolescents and adults experiencing shock [73].

During the early phase of shock, the body's compensatory response aims to maintain normal systolic pressure. This response includes increased heart rate (tachycardia), rapid breathing without symptoms (silent tachycardia), heightened effort in breathing, and constriction of blood vessels in the extremities. As a result, there is reduced blood flow to the skin and slower capillary filling, which can cause the nails to appear normal in color. Following the application of pressure, the affected area has a loss of color, turning white. This leads to a decrease in temperature within the organs and a delay in capillary refilling, lasting for a duration of more than 2 seconds. Additionally, the peripheral pulse volume becomes feeble. Dengue patients experiencing compensatory shock phase typically maintain consciousness [73].

Severe Hypovolemic Shock

It manifests as an elevated heart rate and constriction of blood vessels in the extremities. In this scenario, the occurrence of coolness and cyanosis in the end organs is accompanied by the presence of cyanotic patches, as well as coldness and dampness in the organs. During this phase, respiration accelerates and intensifies. During this phase, peripheral pulses cease to be detectable while core (femoral) pulses exhibit reduced strength. Hypotension occurs when the body's attempt to regulate blood supply and systolic blood pressure within the normal range is unsuccessful. One crucial diagnostic indicator in this scenario is the alteration in both the state and level of awareness resulting from a problem in cerebral blood flow. The patient experiences restlessness, impaired consciousness, and confusion. Additionally, the patient may experience convulsions, sporadic agitation, and compromised cognitive function. Children and young people may maintain a normal degree of consciousness even after experiencing deep shock. Conversely, people may continue in their activities until they experience a deep shock. The ability of infants and children to recognize and maintain eye contact with their parents is disrupted, as well as their ability to communicate. Additionally, the sensation of pain experienced after a venipuncture may also be affected. These symptoms can be seen as the initial indication of the deterioration of the disease, which is caused by a reduction in blood flow to the cerebral cortex [74, 75] .

- **The third period (recovery):** it occurs after the critical period, following successful therapeutic intervention. During this stage, the extravascular fluid is gradually absorbed over a period of 42 to 72 hours. The patient's overall health is improved, with the return of appetite and resolution of gastrointestinal complaints. Additionally, there will be an improvement in the patient's hemodynamic status and a rise in urine volume [76].

Laboratory Findings

Dengue fever (DF) should be considered as a possibility in patients who exhibit a sudden onset of fever, headache, pain, and occasionally a rash that originates from the trunk. This consideration also applies to individuals residing in an area where the disease is endemic or those who have recently visited such a region within two weeks prior to the manifestation of symptoms [77]. Diagnosis can be achieved through the identification of the virus, viral nucleic acids, antigens, anti-DENV antibodies, or a combination of these methods. During the initial phase of the disease (within seven days of its onset), the presence of DENV infection can be identified in serum, plasma, circulating blood cells, or other tissues using viral detection. The presence of RNA can be detected by nucleic acid amplification tests, while the NS1 protein can be recognized using certain

commercial tests. Additionally, the virus can be isolated and studied in human or mosquito cell culture to ascertain its genotype and lineage. The dengue virus is susceptible to heat. The preservation of samples plays a crucial role in the precise detection of RNA and isolation of the virus, ultimately leading to accurate diagnosis of the results [35].

The samples must be stored in either a refrigerator or freezer until they are dispatched to the laboratory. In order to preserve samples for a maximum of 24 hours, it is recommended to store them in a temperature range of 4-8°C. For extended storage, it is advisable to freeze the samples either in a refrigerator set at -70°C or in a container filled with liquid nitrogen [78]. In suspected cases of DF disease, blood samples should be obtained during the acute phase (within 7 days of disease onset) and analyzed using reverse transcription polymerase chain reaction (RT-PCR) or NS1 protein and/or antibody detection methods to identify viral RNA sequences. DENV, particularly IgM and IgG levels, can be identified by enzyme-linked immunosorbent assays (ELISA) or rapid point-of-care tests [79].

Possible cases of dengue are diagnosed in the laboratory with high biological care and special equipment. On the sixth day, it may be possible to isolate IgG and IgM antibodies in the serum using the ELISA method. It is possible to measure antibody by different methods within 5 to 41 days from the onset of the disease and during clinical recovery. Some other methods of laboratory diagnosis are as follows [78]:

- Molecular method through identification of the relevant virus gene (PCR)
- Various serological methods, including ELISA method to detect the IgM antibody of the relevant virus.
- Virus isolation method

Furthermore, the recent advancement of ELISA and dot blot techniques, which specifically detect E/M and NS1 antigens, has revealed the presence of substantial amounts of these antigens in the form of immune complexes in patients affected by both primary and secondary dengue infections. The diagnosis is typically made within 9 days of the disease's beginning. The NS1 glycoprotein is excreted by all flaviviruses and synthesized by mammary cells. resulting in a robust humoral immune response. Thus, the identification of NS1 enables the prompt detection of dengue, leading to early diagnosis [78].

After the decline of the acute phase of infection or after 7 days from the onset of fever, IgM antibody detection is the preferred diagnostic method, using ELISA and hemagglutination inhibition (HI). Although NS1 is reported positive up to 12 days after the onset of fever [78].

If DENV infection has occurred in a person with no prior flavivirus infection or vaccination against flaviviruses, such as ZIKV, YFV, JEV, and TBE; Patients develop an initial antibody response that builds up slowly over a limited period [6].

The IgM isotype of the antibody is the first to appear, and the speed of detection in the serum increases as follows: it is detected in 50% of patients in 3-5 days after the onset of the disease. On the 5th day, it is detected in80% of the patients and on the 10th day in 99% of the patients [78]. During secondary DENV infection or after vaccination or infection with a non-dengue flavivirus, IgG isotype antibody titers increase rapidly. The predominant isotype antibody is detected in secondary infection with high levels [6]. During the recovery period, IgM antibodies can be consistently identified, but viral RNA or NS1 testing yields negative results. The levels of IgM during the initial recovery phase are markedly lower than those observed during the main infection, but higher than those seen during a secondary infection. Consequently, the presence of an infection may go undetected depending on the IgM levels. Therefore, the identification of IgM is a dependable serological test and serves as the primary objective of diagnostic testing for early infections. The IgM/IgG antibody ratio and HI tests are employed to distinguish between primary and subsequent dengue infections [80]. Detecting IgM and IgG antibodies against DENV is valuable for confirming recent or previous infection. IgM antibodies can be produced approximately one week after infection and reach their highest levels 2 to 4 weeks after the disease begins. The generation of IgG antibodies takes longer than that of IgM. However, IgG persists in the body for extended periods of time [6]. IgM presence signifies a recent infection. IgG presence signifies a past infection with DENV. Furthermore, the IgG/IgM ratio is crucial in differentiating DENV infection throughout the clinical course. A threshold of 1.10 or higher is the ideal value at which to distinguish between secondary infection and initial DENV [27].

Differential Diagnosis

Many infectious and non-infectious diseases have symptoms similar to dengue and severe dengue. In patients presenting with fever with sudden acute onset and no known cause, the presence of clinical symptoms and epidemiological findings and examination of virological tests are helpful in diagnosing the disease. Diseases with flu-like symptoms such as measles,

chikungunya, influenza, mononucleosis infection and human immunodeficiency virus (HIV) may mimic the febrile phase of dengue disease. With the difference that in influenza, in addition to fever, headache and body pain which are commonly seen in dengue disease, the symptoms of upper respiratory disease such as runny nose and cough are always seen [53]. The symptoms of fever, arthralgia, rash, fatigue and leukopenia are seen in both chikungunya and dengue, but arthritis of the small joints is an important symptom of chikungunya, and also the tendency to cause bleeding and thrombocytopenia is more common in dengue [36, 75].

Primary infection with HIV may mimic dengue in the presence of high fever, bruising, rash, and generalized adenopathy [53]. If an individual presents with an enlarged spleen and a prolonged fever, it is advisable to consider the possibility of both malaria and typhoid fever. The presence of symptoms such as fever, bruising, vomiting, liver enlargement, and elevated liver enzymes in cases of viral hepatitis and dengue can potentially result in misdiagnosis. The rash associated with measles and rubella exhibits a distinct pattern of dissemination, primarily extending from the head to the trunk and subsequently to the limbs. In contrast, the rash in dengue initially manifests on the trunk and subsequently spreads to the face and limbs [81].

Immediate administration of antibiotics is warranted in patients experiencing shock and exhibiting potential signs of sepsis and meningococcal disease. Typical manifestations of dengue consist of fever, skin rash, small red or purple spots caused by bleeding, and a sudden drop in white blood cell count leading to shock. These symptoms are also observed in cases of severe gram-negative sepsis and meningococcal sickness, both of which have a poor prognosis. Additionally, thrombocytopenia is a common feature. Septic shock typically presents with elevated body temperature, however in advanced stages, hypothermia may occur. In the early stages of shock, there is a bounding pulse and warmth at the extremities of the organs. In dengue patients, shock typically occurs during the temperature decrease stage. As a result, the body temperature is frequently normal or below normal, and the pulse volume is low while the pulse pressure is narrow. Additionally, the extremities of these patients often feel cold [20].

Clinical differentiation between leptospirosis and dengue can be challenging, especially when both occur in epidemics at the same time [53]. High mortality rates are associated with a delay in initiating antibiotic treatment for leptospirosis. Jaundice is a common symptom in cases of leptospirosis, although this disease may also present with eye pain, arthralgia, and diarrhea. Leptospirosis is primarily associated with occupational activities, particularly those related to agriculture, or with a history of contact, such as walking in water or engaging in water sports. Pulmonary hemorrhage is a notable clinical indication of leptospirosis in the absence of jaundice. Some of its symptoms closely resemble those of severe dengue, such as fever, thrombocytopenia, shock, and profound pulmonary hemorrhage. Pulmonary hemorrhage is infrequent in cases of dengue, and the manifestation of plasma leakage, such as pleural effusion or ascites, is the main symptoms of dengue in patients [82].

Yellow fever, currently emerging as a disease in Africa and America, shares common symptoms with dengue. This disease typically manifests in two distinct phases: the febrile phase and the toxic phase. During the toxic phase, hepatic injury results in the appearance of jaundice, renal failure, and central nervous system disorders posing a significant risk to the patient's life. In adults, this disease is correlated with a significant fatality rate, a relatively short duration, and symptoms including headache, back pain, fever, nausea and vomiting, jaundice, bleeding, and loss of consciousness [56].

Treatment and Management

There is no specific treatment for dengue fever [35]. Individuals require tailored treatments based on their specific symptoms. During the initial stage of the disease, known as the febrile period, it is advisable to provide oral fluids and administer antipyretic treatment with paracetamol if necessary. Avoid other non-steroidal anti-inflammatory drugs. If the patient has readily available healthcare and treatment facilities for daily CBC (complete blood count) testing, they are eligible to receive effective treatment at home. Excessive vomiting and diarrhea result in dehydration. Indications for admission and hospitalization include bleeding manifestations and acute warning signs. Some individuals require administration of intravenous fluids and transfusion of blood. Typically, individuals require intravenous fluids for a duration of approximately one to two days [82]. The healthcare practitioner gradually increases the prescribed fluid volume until the individual achieves a specific urine output of 0.5-1 mL per kilogram of body weight per hour. Furthermore, the volume of fluid increases until the individual's hematocrit and vital signs are restored to their usual levels [83].

Health professionals aim to minimize the use of invasive medical procedures, such as oral and nasal intubation, intramuscular injections, and arterial punctures, due to the reduced vascular strength and the

risk of bleeding they also refrain from puncturing an artery with a needle [83]. Acetaminophen (Tylenol) can be prescribed for fever and pain. Nonsteroidal anti-inflammatory drugs (NSAIDs) (such as ibuprofen and aspirin) should not be used because they increase the risk of bleeding [82].Immediate initiation of blood transfusions is warranted in the event of vital sign fluctuations or abnormalities, as well as in cases of decreased red blood cell count. When a transfusion is required, either whole blood (blood that has not been fractionated into its constituent parts) or packed red blood cells should be administered. generally, (separated from whole blood) and fresh frozen plasma are generally not advised [84].

During the critical period of dengue fever, there is no specific and efficacious treatment available. Prudent fluid management remains the cornerstone of treatment. The primary concern at hand revolves around the act of forecasting and recognizing. The onset of the critical period, characterized by the clinical detection of effusion or ascites, signifies that the critical period commenced a few hours prior. Obtaining a lateral chest radiograph or an ultrasound scan can provide valuable assistance. However, it may not be technically feasible to detect early indications of fluid buildup in serous cavities for every disease and at all times [84].

Typically, the critical period can be anticipated when there is an increase in the hematocrit level from its initial value. (It should be noted that numerous patients are admitted to the hospital with a hematocrit level considered within the normal range, yet they have progressed to a critical stage, presenting a challenging situation in their case.) If the number of platelets drops below 100,000/μL, it indicates that the patient is at risk and will enter the critical period within the next 24 hours. The next step in management involves precise monitoring of vital signs, parameters, hemodynamic parameters (such as blood pressure fluctuations, tachycardia), clinical evidence of hypovolemic shock, and manifestations of bleeding. Careful attention must be paid to monitoring charts (those that graphically represent key parameters such as hematocrit and platelet count). Regular assessments (at least every four hours) by physicians and nurses are essential in the critical phase. A key management strategy in the critical phase is the rational prescription of fluids [82].

During the treatment of dengue fever, additional intravenous fluids are typically withheld so the individual does not reach a state of fluid overload. If the medical professional has prescribed extra fluids and the patient's vital signs are stable, discontinuing the administration of additional fluids may be sufficient. If the individual is not in a vulnerable phase of the disease, they may be administered a diuretic medication that impacts the Henle's loop, such as furosemide (Lasix). This can facilitate the elimination of excess fluids within the bloodstream [85].

In general, the World Health Organization and health authorities in countries where the disease is endemic provide specific recommendations and guidelines. The principles of fluid therapy can be succinctly summarized as follows [82, 86]:

- Oral administration of fluids should be prioritized whenever feasible. Intravenous supplementation is required in cases where the patient is unable to consume fluids orally due to severe vomiting, fainting, or being in a state of shock.
- The fundamental concept of fluid management is to ensure sufficient fluid volume within the vascular system during the leakage phase, to prevent hypovolemia, while simultaneously avoiding the administration of excessive fluids to the patient.
- The recommended first line is intravenous crystalloids (0.9% saline).
- During the critical period, it is imperative to carefully adjust the dosage of intravenous fluid administration, gradually increasing or decreasing it as necessary. Additionally, it is crucial to closely monitor the patient's hematocrit levels for a duration of 4-6 hours.
- However, in the setting of shock, immediate resuscitation with boluses of 20 mL/kg is recommended until blood pressure can be recorded.
- Several guidelines suggest calculating the fluid requirement for the entire critical period. This computation encompasses the determination and retention of the necessary fluid for a duration of 24 hours, in addition to 50 ml per kilogram (up to 50 kg) of the corrective shortfall, and the amplification of this cumulative quantity for a period exceeding 48 hours. This quantity encompasses the entire volume of fluid administered over a period of 48 hours during the critical phase, whether through intravenous infusion or oral administration in a concentrated dose.
- Colloids (eg, dextran) are recommended as second-line therapy when hypotension does not respond to bolus intravenous crystalloids.
- An elevation in hematocrit levels signifies an

increased blood concentration caused by leakage, necessitating an increased fluid intake. Conversely, a reduction in hematocrit levels may arise from either recovery periods (reabsorption of expelled fluid) or internal bleeding. If the patient remains in a debilitated condition and is in a critical state with low number of platelets, it is important to consider the possibility of bleeding. Occasionally, there might be no apparent external signs of bleeding.

- In cases of suspected bleeding, the management strategy is transfusion of fresh whole blood.
- Fluid administration should be managed by monitoring and assessing intravascular volume status during the critical period, and fluids should never be administered at a fixed rate without supervision.

Vaccine Development

As mentioned, dengue virus has four serologically distinct types (DV-1, DV-2, DV-3 and DV-4). The virus has a positive-sense RNA strand that codes for three structural proteins (C-capsid, E-velope, and M-membrane) and non-structural proteins (NS1, NS2a, NS2b, NS3, NS4a, NS4b, and NS5) [87]. The initial optimism about the successful development of a dengue vaccine is largely due to the focus on the simple structure of the virus and the successful development of a yellow fever virus vaccine that has structural similarities to the dengue virus. However, several problems have prevented the development of a successful dengue vaccine [85].

First, unlike the yellow fever vaccine, dengue virus has four distinct serotypes. All of them are fatal to humans in a severe infection. Therefore, the ideal vaccine should be immunogenic against all four serotypes. Infection with one serotype has been shown to confer long-term protection against that serotype, but possibly short-term protection against other serotypes [30]. Indeed, individuals who experience a subsequent infection with a different serotype may encounter a more intense form of the disease [88]. One significant issue pertaining to dengue vaccines revolves around the possibility of heightened susceptibility to exacerbated disease in those who exhibit an inadequate or poor immune response, or when their originally protective levels of antibodies diminish to potentially enhancing levels. These concerns stem from epidemiological studies that have demonstrated a heightened risk of serious disease in 6- to 12-month-old newborns of DENV-immune mothers who have a second infection with a different serotype or a spontaneous infection [89]. At now, the most advanced dengue vaccines are exclusively tetravalent in nature and rely on recombinant live attenuated viruses [90].

Another important point is that our understanding of the pathophysiology of dengue fever is not yet complete. One theory, as mentioned above, is that a secondary heterotypic virus (a different serotype of dengue virus) causes disease by activating previously sensitized T and B cells and by interacting with circulating neutralizing antibodies to the former serotype. The infection becomes more severe. This process is hypothesized to activate an immune cascade and cytokine storm in which clearance of the infecting virus serotype is ineffective but highly damaging to the host [91].

However, some observations suggest that barrier is the only mechanism responsible (severe infection can occur as a first infection in individuals with no prior infection, previously circulating antibodies, and infants without any preexisting cellular immune antibodies can have severe infection [92, 93].

Furthermore, there is currently no animal model available to accurately replicate the disease and its progression in humans. This poses a significant impediment to the progress of vaccine development as the results of experimental studies cannot be easily and definitively understood in relation to both safety and effectiveness. Several mammalian species, such as mice, dogs, guinea pigs, and goats, when exposed to the virus, do not exhibit viral growth or manifest dengue-like symptoms in humans [94]. Mammals such as rhesus and cynomolgus monkeys (Macaca mulatta, Macaca fasicularis) develop viremia and antibody response when inoculated subcutaneously, but not clinically. However, most of the animal studies conducted to date on dengue vaccines have been based on these primates [95, 96].

Additionally, it is crucial to assess the antibody titer's neutralization ability following vaccination, as it serves as a significant factor in determining the vaccine's effectiveness and potentially its safety. An important issue in accurately measuring these titers using current assay methods is a lack of uniformity in the assay [48]. The World Health Organization has recently made efforts to establish standardized protocols for evaluating dengue vaccine trials. Additionally, there is a challenge in discerning between distinct neutralizing antibodies specific to each serotype. Indeed, in regions where a disease is commonly found, the presence of individuals who already possess antibodies that can neutralize one strain can complicate the immune response to multiple strains of the vaccine, thereby making it challenging to

distinguish between them [30].

Dengue virus (DENV) poses a substantial health risk, necessitating the urgent development of an optimal vaccine to mitigate the societal impact of this disease. Dengue is a complex and demanding virus due to its four distinct serotypes. To create a successful dengue vaccine, it is necessary to generate neutralizing antibodies with a strong affinity for all four serotypes at the same time, in order to prevent Antibody Dependent Enhancement. The sole dengue vaccine now in use is Dengvaxia (CYD-TDV), which has been produced by Sanofi Pasteur [97].

Prevention and Control

At present, the most important way to deal with dengue fever is to control its vectors, i.e. *Aedes* mosquitoes. In China, which has suffered from a dengue fever epidemic in recent years, the government's comprehensive plans to control dengue fever are focused on rapid detection and control of *Aedes* vector populations. The World Health Organization has suggested that to prevent disease in humans, the mosquito population should be monitored, and humans should be protected from mosquito bites. To prevent dengue fever, the World Health Organization has presented a program (called the "Integrated Vector Management" program). The Framework lists the following five components as essential to an effective IVM implementation:

- Public health advocacy, social mobilization, regulatory control, and community empowerment.
- Cooperation through the best possible use of resources, planning, monitoring, and decision-making both within the health sector and with other sectors.
- Combination of chemical and non-chemical vector control techniques with other disease management strategies.
- Scientific research, entomological and epidemiological surveillance, and evaluation all serve as a basis for evidence-based decision making.
- Creation of sufficient career paths, training programs, and human resources at the local and national levels to support capacity building and oversee IVM initiatives.

To ensure the effectiveness of every dengue prevention measure, decisions should be based on the available evidence. Dengue-affected areas ought to receive assistance until they are able to combat the disease on their own [98].

Based on the suggestions of reliable sources, the control policy for dengue fever in Iran can be summarized as follows:

- Advancement of fundamental, practical, and groundbreaking research.
- Enhancement of human resources, infrastructure, and healthcare systems in all pertinent fields for the purpose of monitoring, controlling, overseeing, and assessing.
- Reinforcement of coordination and collaboration between different departments and within the same department.
- Community participation and mobilization.
- Scaling functions and tool integration.

The Infectious Disease Control Center of the Ministry of Health, Medicine and Medical Education of Iran developed dengue disease control recommendations in 2013. In 2014, a strategic plan was developed to manage the disease, and a network of entomological surveillance laboratories was formed. Provision was made for the acquisition of equipment for entomology laboratories. The national dengue prevention and control plan was established in 2015 in a collaborative effort with the World Health Organization, with the document being written in English. Additional initiatives, such as creating informative health communications regarding dengue, were implemented and distributed to medical universities. Additional measures and essential approaches encompass acquiring political endorsement, enhancing healthcare personnel and doctors' awareness in both public and private sectors, securing support from within and outside the sector, enhancing the proficiency and capacity of human resources, procurement and assistance, and enhancing measures. The objective is to combine human care with entomology and vector control strategies, enhance awareness and engage public engagement, support and promote applied research, and secure financial resources for program monitoring and evaluation [99].

A strategy that receives ongoing assistance and involvement from all relevant parties, including local, national, and regional stakeholders is suggested. The World Health Organization explores strategies for mosquito control, including measures to prevent mosquito bites and eliminate the *Aedes aegypti* mosquito by eradicating its habitats of reproduction. It is advisable for individuals to drain exposed water reservoirs to prevent mosquitoes from depositing their eggs in them. Additionally, insecticides and biological control agents can be employed to manage mosquito

populations in these regions. Scientists posit that organophosphate and pyrethroid sprays exhibit no impact. It is necessary to eradicate stagnant waterways, which lack movement and flow, as they attract mosquitoes. Also, the accumulation of pesticides in these waters might pose a risk to human health [100].

Overall, the management of dengue fever predominantly depends on the utilization of insect repellents. Applying insect repellants to both the body and clothes, ensuring that regions vulnerable to mosquito bites are covered by wearing gloves, tucking pants into socks, and buttoning cuffs, routinely inspecting clothes and skin for the presence of mosquitoes after returning from walks in the desert, and avoiding mosquito-prone locations. Avoiding Squashing mosquitoes on the skin is a crucial step in prevention [101].

4. Conclusion

DENV infection is a complex systemic disease. Assessing the complete range of the disease burden of dengue fever will be crucial in order to properly comprehend the serious medical and economic repercussions it has on patients and the general public. The rise of globalization, population growth, urbanization, inadequate sanitary facilities, climate change, and environmental variables have all contributed to the ineffectiveness of mosquito control. Surveillance of dengue fever worldwide is not adequate, which is one of the reasons for the increase of dengue fever. In addition, major risk factors for the development of dengue fever include poor nutrition, persistent drought, population displacement, poor water management, living with the sick, and lack of formal education. It is recommended that the risk of dengue virus infection be minimized by taking appropriate precautions. Efforts are being made to expand surveillance coverage, yet achieving the goal of dengue virus elimination by 2030 requires ensuring prevention and control measures in all sectors of healthcare organizations. However, global health still has a long way to go. In the meantime, humans are trying to achieve this goal without preventive vaccines, and efforts should be made to use the effective prevention of vaccines.

Ethical Considerations

Compliance with ethical guidelines

This article is a review with no human or animal sample.

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