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Mosquito-Borne Dengue Fever-An Update

AUTHORS DETAIL

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Received: Sept 15, 2022 Accepted: Dec 12, 2022

INTRODUCTION

Globally, dengue fever (DF) is a highly endemic contagious disease and has a significant socioeconomic and health impact on many tropical and subtropical regions. Pakistan is one of the most affected countries for the past two decades with the first outbreak reported in 1994 (Nasir et al. 2022). This mosquito-borne viral infection characterized by nausea, headache, weakness, severe muscular and joint pain, lymphadenitis, and skin rashes. Swollen palms and soles, gingivitis, and intense eye pain are only a few symptoms of dengue fever. Dengue fever has the potential to worsen and develops into a more severe form named dengue shock syndrome (DSS) and dengue hemorrhagic fever (DHF) (Gan et al. 2021; Rajeen and Mayurathan 2022).

Four serotypes of dengue have distinct epidemiological patterns and they can co-circulate within an area and many countries are hyper-endemic to these serotypes. Dengue has huge impact on human health and the world economies. According to an estimate, 390 million people are affected by dengue virus infections (95% credible interval 284–528 million) with over 25,000 deaths/year globally, of which 96 million (67–136 million) manifest clinically. According to WHO, the number of dengue cases increased over 8 times since 2000 from 505,430 cases in 2000, to over 2.4 million in 2010, and 5.2 million in 2019. Moreover, reported deaths augmented from 960 to 4032 within this period, affecting mostly younger age group (Stica et al. 2022; WHO 2022).

Geographic Distribution

The epidemiology of vector-borne diseases is directly influenced by climate change. Scientists agree that dengue viruses first infected monkeys in Africa or Southeast Asia between 100 and 800 years ago before transmission to humans. However, the spread of viruses was greatly due to the global transfer of Aedes mosquitoes that occurred as a result of World War II. Dengue fever (DF) is thewidest spread vector-borne disease worldwide, with the highest disease burden (Kulkarni et al. 2022). The region of Southeast Asia experience recurrent and cyclical epidemics of dengue throughout the year. Geographical location, time and demography also indicate the prevalence of dengue fever. Presently, the clinical worth of deceptive dengue infections remains undetermined, but it is supposed that deceptive dengue plays a vital role in the transmission of dengue in the absence of an epidemic (Gan et al. 2021).

Etiology

The dengue virus is a single strand RNA genome of ~11 kb, and translated into a single poly-protein. It belongs to the flavivirus genus and *Flaviviridae* family. The genome RNA encodes 3 structural protein molecules (Capsid, pre-membrane, Envelope) and 7 nonstructural proteins (NS1, NS2A, NS2B, NS3, NS4A, NS4B, and NS5). The 4 strains of closely related serotypes named DEN-1, DEN-2, DEN-3, and DEN-4 are reported that vary in antigenicity (Kothai and Arul 2020). There are several different types of flaviviruses, including the tick-borne encephalitis virus (TBEV), the Japanese encephalitis virus (JEV), and West Nile virus. DENV, Yellow Fever Virus (YFV), and Zika Virus (ZIKV) are transmitted by arthropods or arboviruses (Higuera and Ramírez 2019).

During DENV replication, virion binds itself with the surface molecules of cells and receptors; still this binding has not been fully identified. Then virus is internalized through receptor mediated endocytosis. Glycoproteins on the virus surface involves in the fusion of viral membrane and cellular membrane at low pH of endosomes. This situation enables the virion to disassemble and release its RNA into the host cell cytoplasm. After that viral RNA is translated into polyprotein with the help of cellular and viral enzymes (proteases). Hence, non-structural proteins of dengue virus are accountable for viral RNA replication (Chan 2021).

The core reason of dengue fever infection is an infected *Aedes* (*A.*) *aegypti* mosquito bite, and in addition to this, vertical transmission may also be acquired accidentally, especially from pregnant women via placenta, blood products (infected), organ transplantation, and also due to needle stick injury (Kothai and Arul 2020).

Citation: Majeed W, Aslam B, Altaf S, Khatoon A, Abbas I and Kanwal HA, 2023. Mosquito-Borne dengue fever-an update. In: Aguilar-Marcelino L, Younus M, Khan A, Saeed NM and Abbas RZ (eds), One Health Triad, Unique Scientific Publishers, Faisalabad, Pakistan, Vol. 3, pp: 1-7. https://doi.org/10.47278/book.oht/2023.70

Pathophysiology

There are still many unknown facts regarding DENV pathogenesis and the host immune response. Dengue fever is an acute serious condition characterized by high-grade fever with frontal headache, myalgia, as well as nausea, vomiting, and rash that affects adults and older children. The main symptoms of the disease include leukopenia, thrombocytopenia with hemorrhagic tendencies, capillary leak syndrome, bleeding in the nose, gastrointestinal tract, and gums (Kathiriya et al. 2020; Kalimuddin et al. 2021). The viral envelope glycoprotein presents in the virus aids in attachment to host cells. Infected cells, such as monocytes, are a primary target of cytokines that drive innate immune responses to DENV via three mechanisms. (a) During localized infection of the skin, the dengue virus triggers degranulation of mast cells and releases inflammatory mediators such as proteases, leukotrienes, and histamine which promote edema at the injection site and increased vascular permeability. (b) During systemic infection, viremia occurs due to elevated levels of mast cell products in serum and the release of TNF, leukotrienes, and vascular epithelium growth factors (VEGF) that enhance vascular leakage from plasma. (c) During secondary infection, antibodies mediated enhanced (ADE) enhanced MC degranulation through crosslinking of FERC. Studies have shown that MCs are activated by endogenous products that lead to the degranulation of mast cells and mosquito saliva co-injected with arboviruses (Imad et al. 2020; Sugianto 2021).

Transmission

All four serotypes of DENV are transmitted to humans by a single bite of infected female mosquitoe, mainly the *A. aegypti* mosquito, and the infected person's blood results in viremia in an early illness that lasts for 2 to 12 days. Approximately 8 to 10 days later, the virus is released into the mosquito's saliva and transmitted to other tissues, including the salivary glands. When it bites another person, the mosquito's saliva spreads the infection to that person (Fig. 1). The mosquito is unaffected by the virus in any way (Gwee et al. 2021). It has also been documented that vertical transmission (from mother to child) of DENV is a considerable risk for adverse pregnancy (Chawla et al. 2014). The various reported cases of DENV infection through different routes has been mentioned in Table 1.

The Virus

Aedes mosquitoes especially *A. aegypti* are primary vector of the dengue virus. The typical range for these mosquitoes is round about 35° N and 35° S while altitude is approximately 3300 ft. They frequently bite in the morning and evening. This virus primarily affects humans but can also elicit primates from another genus. DENV is a positive single strand RNA genome constituting four unique serotypes (DENV-1, DENV-2, DENV-3, and DENV-4). The genome encodes 3 underlying proteins (capsid [C], pre-membrane [prM], and envelope [E] and seven nonstructural proteins [NS]) by viral proteases and the host (Huang et al. 2014). Within every serotype, particular genotype or heredities have been recognized and exhibiting the most hereditary fluctuations in dengue serotypes. Nonetheless, determination keeps on being a prevailing topic in the development of dengue virus. Secondary dengue diseases are frequently connected with European genotype like DENV-2 and DENV-3 (Roy and Bhattacharjee 2021).

The Vectors

Individual serotypes of dengue virus are transmissible through a bite of contaminated female Aedes mosquitoes to people, particularly *A. aegypti*. It generally found in north of 1000 m because of low temperature. The undeveloped stages of *A. aegypti* are found around stagnant water that is closely linked to human dwellings (Tedjou et al. 2019). Research proposes that most of the females may spend their whole life in or around human dwellings where grown-ups arise. *A. albopictus, A. polynesiensis* and a few kinds of *A. scutellaris* are accredited the incidents of the dengue (Ononamadu et al. 2021). Every one of these genera has a particular natural, social, and topographical distribution. *A. albopictus* has taken many years to spread from Asia to Africa, America, and Europe, because their eggs can stay adapted for a long time, without any trace of water (Kothai and Arul 2020).

The Host

After incubation period of 4-10 days, contamination due to any of the four viruses serotype can cause a large numbers of diseases, mostly asymptomatic or subclinical (Krishnamoorthy et al. 2022). Primary infection is responsible for long term defensive behavior of a body's immune system against serotype infections. From 2 to 3 months after primary infection, without any long term cross-defensive resistance, people experiencing contamination are sheltered from clinical illness with a particular serotype (Wei Xiang et al. 2022). In the course of primary infection in infants and secondary infection, antibody-dependent enhancement (ADE) of the infection has been assumed as a mechanism of action to define the severity of dengue (WHO 2022). According to this model, cross-reactive and non-neutralizing antibodies are composed that bind with epitopes present on the surface of heterologous infective virus during primary infection and facilitate the entry of the virus in the Fc-bearing cells. Viral load increases with expanding infected cells and activate the host immune response like mediators which results in the capillary leakage. During secondary infection, memory T cells (cross-reactive) are triggered and further proliferate to release cytokines and correlate the

Table 1: Reported healthcare-associated transmission of dengue virus

Virus	Routes of transmission	Comment	References
Dengue	Blood transfusion	Donated blood, from which RBC's transfused recipients; fever and myalgia developed after 3 days of transfusion and was detected with DENV-2.	(Perera et al. 2020)
	Bone marrow transplant	A bone marrow donation caused the death of a 6-year-old Puerto Rican who infected with DENV-4.	(Bhat et al. 2018)
	Needle-stick	Several medical professionals became infected after needle-stick injuries during care of returned travelers diagnosed with dengue.	(Grobusch et al. 2020)
	Renal transplant	Dengue hemorrhagic fever developed in renal transplant recipients.	(Delfino and Mazzali 2022)
	Mucocutaneous	A medical professional became infected with DENV-3 after being splattered in face by blood from a febrile traveler return from Peru diagnosed with dengue.	(Ullah et al. 2019)

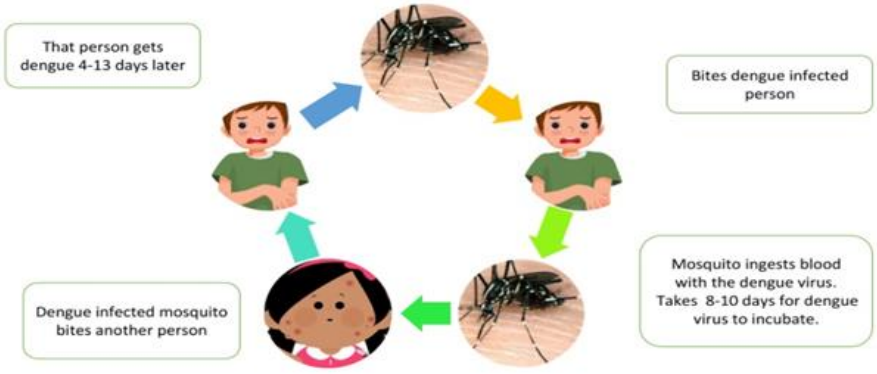

Fig. 1: Transmission of dengue fever

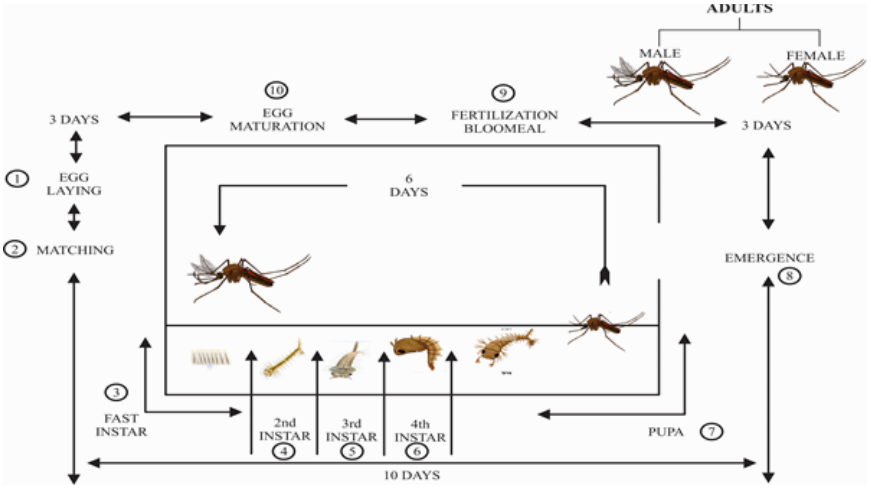

Fig. 2: Life cycle of *A. aegypti*: Female *A. aegypti* lays eggs on the inner walls of artificial containers. As the containers fill with water, mosquito larvae hatch from the eggs. The larva metamorphose into pupa after four larval stages which are named as four instars

severity of the disease. Research studies show that dysfunction of endothelial cells can mediate plasma leakage and can also be linked with the augmentation of infected T cells, monocytes, monokines, cytokines, complement system and generation of mediators (Uno and Ross 2018).

Life Cycle of *Aedes aegypti*

A. aegypti is a primary vector of viruses that cause dengue fever. It is geologically distributed in tropical and subtropical areas and utilizes an abundance of artificial containers for breeding (Tedjou et al. 2019). *A. aegypti* is a polymorphic type of arthropods that undergoes complete metamorphosis. An adult's life span ranges from 2-4 weeks depending on the environmental temperature and climate. During entire life, a female member lays ova about 4-5 times (Fig. 2). There are three polytypic forms of *A. aegypti* that have been found including (a) sylvan type which is a rural form that reproduces in forests, especially in tree holes, (b) domestic in urban habitats, and (c) peridomestic form that breeds in ecologically modified areas (Calma and Medina 2020).

Manifestations

Three clinical forms have been found such as dengue fever, dengue shock syndrome and dengue hemorrhagic fever in individuals infected with dengue (Kothai and Arul 2020).
Most dengue virus infections are not symptomatic which means that when a patient with fever has only mild symptoms, DENV is not yet recognized as the infection's primary cause. With the influenza-like dengue fever and dengue shock syndrom, each of three clinical presentations has a different level of symptom severity. In many cases, dengue virus infections may sometimes be fatal or life-threatening and develop to dengue hemorrhagic fever (DHF) or dengue shock syndrome (DSS) while mild febrile DF is often not lethal (Umakanth and Suganthan 2020).
Typically, symptoms start to manifest within 3-10 days during the incubation period. The clinical manifestations for DHF and DSS range in intensity from minor symptoms to severe life-threatening symptoms. Due to the ambiguous clinical presentation and lack of knowledge on the pathophysiology and molecular pathways underlying the disease, predicting the transition from mild symptoms to severe DHF/DSS is still challenging (Kothai and Arul 2020). According to the WHO, febrile episodes that are about 40°C for 2-7 days are characteristic of DF and are frequently accompanied by rash, nausea, vomiting, and headache. The severity of the preceding symptoms may increase after 3 to 7 days, along with the appearance of new symptoms such as abdominal pain, nasal bleeding, insomnia, and restlessness. Leukocyte counts are often increased and hepatic aminotransferase activity is mildly enhanced in instances of mild dengue fever, according to laboratory testing. If no therapeutic measures are adopted when these symptoms first appear, the disease will proceed to a severe form (DHF/DSS). Clinical interventions at this stage and ongoing monitoring are required, especially in the endemic area, to stop vascular leakage (Ahmad et al. 2020).
Any of the four identified DENV 1-4 serotypes causes severe dengue infection. Individuals having a history of dengue infection with a heterogeneous serotype are more likely to develop DHF/DSS. Severe DHF/DSS may affect 5–10% of the patients, and if left untreated, it can be fatal. Significant bleeding especially from the digestive system is another feature in addition to thrombocytopenia (50,000/mm^3), which may affect up to 50% of DHF cases. Remarkably, the quantity of platelets in the blood and the incidence of DHF are negatively correlated. Further, the precise mechanism responsible for this correlation is still being investigated. Vascular fragility is a result of decreased platelet numbers, loss of function and other factors and it may increase the possibility of bleeding and plasma leaks (Umakanth and Suganthan 2020). The DENV induces thrombocytopenia by direct contacting with megakaryocytes and platelets which in turn inhibit or activate platelet counts. Deep shock, also known as dengue shock syndrome, can be brought on by hypotension and systolic pressure that persist. DSS that lasts a long time can increase the risk of developing further issues such excessive bleeding, diffuse intravascular coagulopathy (DIC), respiratory arrest, multi-organ failure, and rarely meningitis and encephalopathy that results in death (Madi et al. 2014).
Along with the normal symptoms, dengue can also have an impact on a number of other bodily functions like dengue encephalopathy is earlier considered to be exclusively linked with dengue hemorrhagic fever and dengue shock syndrome (Trivedi and Chakravarty 2022). The Guillian Barre Syndrome (GBS) and transverse myelitis are two more neurological diseases that resemble with the dengue. The course of dengue infection is further divided in to three phases such as febrile, serious and recovery as mentioned in Table 2 (Kothai and Arul 2020).

Diagnosis

The possibility of a prompt and accurate diagnosis is occasionally exacerbated by the fact that the manifestations of DF are identical to several other diseases such as typhoid fever or malaria. Diagnosis of dengue initiates with a clinical sign of febrile phases of illness, dengue patients often have fever accompanied by nausea, body pain, maculopapular rashes, bleeding nose, and gums (WHO 2022).
In order to effectively combat the disease, it is crucial to make an early and accurate diagnosis of dengue infection in the laboratory. According to estimates, up to 50% of dengue cases could go undiagnosed. This is particularly for those who reside in or travel to locations where tropical infectious diseases are widespread, the signs and symptoms of dengue differ vary greatly from those of other viral infections. Avoiding severe instances and reducing the financial burden of the illness until an availability of anti-viral vaccine, is crucial for diagnosis in early and accurate manner (Kothai and Arul 2020).
The major advance laboratory tools used for detecting dengue infection involve; (a) nucleic acid amplification tests (NAAT) to identify the specific virus serotype; (b) genomic sequences and viral isolation from mosquito cell lines and (c) ELISA to detect antigen and antibodies (Huang et al. 2014). For early detection of dengue infection, two screening methods; direct and indirect approaches have been used. The former is used for detection of NS1 antigens and viral RNA from patient's blood infected with viremia in case of acute febrile phase. The latter is used in post febrile phase where IgG and IgM antibodies are detected by Mac-ELISA. The rapid and reliable method used for diagnosis of dengue virus is the extraction of RNA from blood, serum, tissues, saliva, and urine and perform reverse transcriptase PCR (RT-PCR) (District 2019).
For the first time, the neutralizing antibodies measured by neutralizing test was developed by Russell named as Plaque Reduction neutralizing tests (PRNT). The neutralizing antibodies inhibit dengue virus infection and offer greater specificity in separating DENV- specific antibodies from those that are cross reactive *flavivirus* antibodies. Since PRNT requires a lot of labor, takes a long time and has a low throughput, it is not frequently employed in dengue diagnosis

Table 2: Phases of dengue infection

Phases	Symptoms	Duration
Febrile	High grade fever, headache, vomiting, rash	2-7 days
Serious	Organ dysfunction, fever, severe bleeding from GIT, DSS and DHF	1-2 days
Recovery	Serious pruritus, bradycardia, maculopapular rash,	2-3 days

Table 3: Laboratory diagnostics for dengue with specimen and sensitivity.

Diagnostic methods	Technique	Specimen	Sensitivity
Antibody detection	IgM detection	Serum, plasma, whole blood	61.5-100
	IgG detection		46.3-99
	Rapid IgM detection		20.5-97.7
Antigen detection	Viral antigen detection (NS1)	Serum, plasma	54.2-93.4
Antigen-antibody combined detection	NS1 and IgM	Serum, whole blood	89.9-92.9
	NS1 and IgG/IgM		93.0
Viral detection	Virus isolation (cell culture)	Whole blood, serum, tissues	40.5
	Viral RNA RT-PCR		58.9-100
	Viral RNA (NASBA) RT-PCR		98.5

Table 4: Natural sources activity against *A. aegypti*

Plant	Common Name	Part Used	Reference
Boesenbergia rotunda	Temukunci	Roots used to make paste	(Akram et al. 2021)
Kaempferiaparviflora	Thai ginseng	Leaves and stem	(Balaji et al. 2022)
Carica papaya	Papaw	Leaves	(Teh et al. 2022)
Solanumvillosum	Red nightshade	Berry	(Siam et al. 2022)
Combretumcollinum	Weeping bushwillow	Shoots	(Schultz et al. 2021)
Azadirectaindica	Neem	Leaves	(Dwivedi et al. 2021)
Citrus limetta	Sweet lemon	Peel extract	(Bailão et al. 2022)
Acalyphaalnifolia	Copper leaf	Leaf	(Subbiah 2021)
Delonixelata	White gulmohur	Leaf	(Suresh et al. 2020)

even though it is still the assay for immunity studies that is most frequently utilized (Lima et al. 2022). In order to get around the limitations of PRNT, newer tests have been created such as the ELISA-based spot and microneutralization test, the fluorescent antibody cell sorter that based on dentritic cell specific intercellular adhesion of molecule-3-grab-bing Non-integrin expressor DC assay. Immune fluorescence test, capture ELISA and hemagglutination assays are used for the diagnosis of DENV infection in early stage by using hematological and biochemical indicators (Limkittikul et al. 2022). Laboratory diagnostics for dengue with specimen and sensitivity has been mentioned in Table 3 (Lima et al. 2021; Alidjinou et al. 2022).

Treatment of Dengue Fever

Currently, to cure the dengue fever no specific treatment is available. Typically, the fluid replacement along with the use of analgesics and proper rest is satisfactory. Acetaminophen can be used for the treatment of fever. The use of drugs like corticosteroids, aspirin, and NSAIDs should be evaded (Kellstein and Fernandes 2019). Research studies have been carried out by Novartis Institute for Tropical Diseases (NITD), Singapore to find out the inhibitors of target proteins of dengue virus to decrease the load of virus in active infection. The acute form of dengue fever necessitates fluid therapy and treatment of hemorrhage. The patients with dengue shock should be admitted to an intensive care unit. Ringer lactate which is an isotonic solution could be used in patients who are deficient in intravascular volume (Yokokawa 2020).

A hemostatic drug such as carbazochrome sodium sulfonate (AC-17) (due to capillary stabilizing activity) reduces the high permeability of blood vessels. This vascular hyper-permeability may be induced by vasoactive components via an agonist induced inhibition of phosphoinositide hydrolysis. Fluid therapy is used in the critical phase. There is inadequate evidence regarding the quantity and fluid selection. Fluids which could be used to increase the volume are 5% albumin, normal saline, plasma or plasma substitutes, ringer lactate and 5% glucose diluted in ratio 1:2 or 1:1 in normal saline (Hasan et al. 2016).

The fluid therapy is based on the principles comprising oral as well as intravenous fluid intake depending upon the condition of the patient. The purpose of this fluid therapy is to prevent hypovolemia. However, the excessive fluid therapy is prohibited. Crystalloids like 0.9% saline are recommended as first line I/V fluids (Kajimoto and Kitajima 2020). The intake of I/V fluids in patients can be increased gradually to minimize the risks. The use of acetaminophen prevents the use of NSAIDs such as acetylsalicylic acid and ibuprofen because of their increased risk of bleeding. The patients with reduced hematocrit should be transfused with blood (van Bergen et al. 2022).

The drugs obtained from natural sources have larvicidal and mosquitocidal activity against *A. aegypti*. The important natural cures are mentioned in Table 4.

Prevention and Control

In December 2015, Sanofi Pasteur was licensed to develop the first dengue vaccine Dengvaxia® (CYD-TDV) which is now approved by regulatory authorities in almost 20 countries. Additional analysis was performed in November 2017 to find out the serostatus at the time of vaccination release. The results of the study showed that the group of volunteers (without prior dengue virus infection) who participated in the trial study were deduced to be seronegative at their first vaccination and had a great risk of severe dengue and hospitalization in comparison to unvaccinated participants. Therefore, use of CYD-TDV vaccine is allowed for 9-45 years old people with laboratory established prior dengue virus infection (WHO 2022). The risk of dengue infection is increased in seronegative vaccinated individuals because they are exposed to natural dengue infection for the first time as the live-attenuated Dengvaxia® triggers an initial immune response to dengue. Strategic Advisory Group of Experts from World Health Organization (WHO) updated its recommendations from April 2018 assuming that pre-vaccination screening method must be recommended for nations contemplating CYD-TDV immunization, in which only people who are seropositive for dengue can be immunized. In 2019, Food and Drug Administration also approved Dengvaxia® as dengue vaccine (Biswal et al. 2022).

Currently, avoiding the bite of vector mosquito is the only way to avert dengue virus. This could be done by avoiding traveling to the areas where dengue is endemic. Mosquito netting is also used but its use is not much beneficial because *Aedes* bites during daytime. The mosquito indoor sprays can also be used for elimination of mosquito (Wang et al. 2020). Recently, non-chemical techniques have been categorized as "biopesticides," which simply refers to eradicating the pathogen with substances derived from living creatures. To find a powerful agent, it is necessary to investigate biological control agents such as diverse predators and parasites, i.e., viruses, fungus, bacteria, etc. The use of different viruses and predators as biological mosquito control agents has been documented. Wolbachia is an intriguing prospective new dengue biocontrol method against Wolbachia infection uses inherited endosymbiotic bacteria to make mosquito populations resistant to arboviruses and exhibit low significance against vector (Ritchie 2018).

Conclusion

Dengue fever is a rising public health issue throughout the world. For disease prevention, all dengue-endemic countries require more effective surveillance systems. A vaccination is urgently needed to reduce dengue fever-related morbidity and mortality. Several medicinal plants have been identified that have significantly inhibited response towards dengue but still effective and proper treatment needs to show positive and therapeutic outcomes. In addition, distinct serotypes in dengue endemic can be managed with the help of respective vaccine.

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