Editorial

Challenges in controlling the dengue epidemic in Brazil

Dengue is an acute febrile disease caused by 4 genetically related but antigenically different viruses (DENV 1-4) and transmitted by arthropod vectors, which characterizes an arbovirus. In Brazil, the dengue vector is the female Aedes aegypti mosquito and, in some regions of Africa and Asia can be transmitted by Aedes albopictus, family Flaviviridae and genus Flavivirus. The dengue virus (DENV) is single-stranded RNA with positive polarity.\(^{(1,2)}\)

Dengue epidemics with a historic increase in cases, hospitalizations and deaths in year 2024 is an important challenge for the Unified Health System (SUS) and the Brazilian economy.

Evidence suggests that the transmitting mosquito came on ships leaving Africa with slaves. In Brazil, the first documented epidemic occurred in 1981-1982 in Boa Vista (state of Roraima - RR), caused by serotypes 1 and 4. After four years, in 1986, epidemics reached the state of Rio de Janeiro and some capitals in the Northeast region. Since then, dengue has been occurring endemically, interspersed with the occurrence of epidemics, often associated with the introduction of new serotypes in areas without transmission or change in the predominant serotype, accompanying the expansion of the mosquito vector.\(^{(3,4)}\) Dengue epidemics have an important impact on the health system, both by the overload of care and the economy.\(^{(5)}\)

Uncontrolled urbanization with the accumulation of non-biodegradable containers such as bottles and tires, accumulation of garbage, potted plants in open areas in homes and around living areas provided the aquatic environment necessary for the development of mosquitoes. Allied to this, the lack of basic sanitation, especially on the outskirts of large urban centers, and climatic factors such as increased temperature and rainfall maintain favorable conditions for the mosquito’s expansion. Therefore, the role of the State in dengue epidemics stands out, as they must provide decent housing conditions and guarantee basic sanitation for the entire population.

Dengue has a seasonal pattern with a risk of epidemics, mainly between the months of October of a year to May of the following year and is distributed mainly in the Eastern Mediterranean, Southeast Asia, Africa, Western Pacific and South America. Worldwide, around 2.5 billion people are at risk of contracting dengue, and reported cases exceed 100 million per year. Up to 500,000 people develop severe, potentially fatal forms of the infection.\(^{(5,6)}\) In the last decade, dengue epidemics have increased in frequency and importance in Brazil and in different parts of the world,
with an increasing number of severe disease, chikungunya and Zika, also transmitted by the *Aedes aegypti* mosquito.

In the first quarter of 2024, Brazil registered more than 2.5 million cases, a historic record for the period, with more than 1,000 deaths. The dengue virus has four different serotypes: DENV-1, DENV-2, DENV-3 and DENV-4, all of which can cause disease. The four serotypes circulate simultaneously in the national territory, although serotype 1 is the most prevalent.\(^{(3,4)}\)

The immunological response with the production of antibodies generated after primary infection by a given serotype also induces a heterotypic response (infection with another serotype) in the short term for a few months after the primary infection. However, immunological memory can neutralize a homologous serotype (same serotype as the previous infection) of dengue, that is, immunity specific to the serotype persists throughout life. A new infection with a different serotype (heterologous) can worsen the clinical picture, leading to severe and potentially fatal dengue. During the second infection, antibodies produced in the first infection may cross-react, although they are not fully neutralizing. This immune response can be overreactive, dependent on a second infection, and result in serious illness and death.\(^{(7-9)}\)

The clinical picture of dengue is a consequence of an immune response, involves leukocytes, mainly macrophages and monocytes, and the production of cytokines and immune complexes, determining a generalized endothelial inflammatory process, causing increased permeability due to poor vascular endothelial function, interstitial plasma leakage, drop in blood pressure and hemorrhagic manifestations associated with thrombocytopenia and damage to hepatocytes (acute hepatitis). The non-structural protein of the dengue virus (NS1) can also alter vascular permeability by direct interaction with the vascular endothelium and the release of vasoactive cytokines from immune system cells.\(^{(7)}\) Increased vascular permeability leads to shock and consequent organ hypoperfusion, resulting in progressive organ impairment, metabolic acidosis, disseminated intravascular coagulation (DIC) and acute renal failure. There are variations in pathogenicity between strains and serotypes, and viral titer correlates with disease severity. Host factors are also important for greater severity, such as extremes of age, comorbidities and genetic factors.\(^{(4,7,10)}\)

The clinical diagnosis of dengue can be difficult, depending on where the patient is and the symptoms develop. The clinical picture can be mimicked by a series of pathogens such as the Zika virus, chikungunya, among others. The incubation period for dengue is 3-14 days, average of 5-6 days.\(^{(4-19)}\)

The acute phase of dengue occurs within the first 5 days of symptoms. During this period, the virus can be identified in the blood. Molecular tests such as reverse transcription polymerase chain reaction (RT-PCR) can detect DENV RNA. The non-structural protein NS1 can also be detected in the first 5 days of symptoms by immunochromatographic tests. A negative
molecular or NS1 test result is not conclusive, depending on how long the disease has been developing. The IgM antibody capture enzyme-linked immunosorbent assay (MAC-ELISA) can be used for the qualitative detection of IgM antibodies occurring after the 6th day of symptom onset. The IgM may persist for 90 days or more, while IgG antibodies begin to be detected from the 7th day after the onset of symptoms in primary infection. However, in heterologous infection (second infection) they can be detected from the 1st day after the onset of symptoms.\(^{(4,9,10)}\)

Around 80% of primary DENV infections do not present symptoms and the infection can go unnoticed. The first clinical manifestation of dengue is sudden fever, generally high (39°C to 40°C), lasting 2-7 days, associated with headache, adynamia, myalgias, arthralgias and retro-orbital pain. Anorexia, nausea and vomiting may be present, as well as diarrhea. The rash occurs in approximately 50% cases, is predominantly of the maculopapular type, affecting the face, trunk and limbs, including the soles of the feet and the palms of the hands. In most cases, symptoms improve from the 7th day onwards and clinical recovery takes around 2-3 weeks.\(^{(4,7,18)}\)

Around 10% of symptomatic cases may progress to severe disease. Warning signs must be valued and patients advised to seek medical assistance in case they occur. Most warning signs result from increased vascular permeability, which marks the beginning of the patient’s clinical worsening and its possible progression to shock due to plasma extravasation. Thrombocytopenia and DIC can lead to serious bleeding. The main warning signs of dengue are: intense (reported or on palpation) and continuous abdominal pain; persistent vomiting; fluid accumulation (swelling, ascites, pleural effusion, pericardial effusion); postural hypotension or lipothymia; hepatomegaly; mucosal bleeding; lethargy and irritability.\(^{(4,7,18)}\)

To date, we do not have antiviral medications for dengue. Treatment is supportive with hydration and symptom management. Anti-inflammatories and acetyl salicylic acid (aspirin) are contraindicated, as they alter platelet aggregation and increase the risk of bleeding. Several works have studied monoclonal antibodies specific to DENV1 that demonstrate strong neutralizing potency, but do not show cross-reactivity with other serotypes.\(^{(9,10)}\)

Current strategies for dengue control are limited to efforts to suppress the number of immature and adult mosquitoes through insecticide spraying, media campaigns to reduce domestic and per-domestic breeding sites and guidance on the use of repellents. Even where considerable resources are invested in these activities, sustained suppression of mosquito densities has been difficult and seasonal outbreaks continue to occur, particularly in locations lacking basic sanitation. Another promising area for dengue control is the use of modified mosquitoes: since the discovery that mosquitoes infected by Wolbachia bacteria have a limited ability to transmit arboviruses. Pioneering programs to introduce Wolbachia-infected mosquitoes have been initiated in Brazil, Indonesia, Colombia and Singapore, although still with no conclusive results.\(^{(11-13)}\)
The ideal dengue vaccine should produce a long-term response against the four serotypes. Currently, there are two vaccines licensed in Brazil: Dengvaxia (Sanofi-Pasteur) and QDenga® (Takeda Pharma), both made of live attenuated viruses. The two vaccines use recombinant DNA technology in which genes from different serotypes of the dengue virus are inserted into the genetic structure of an attenuated virus. The difference between the vaccines lies in the attenuated virus used as the genetic structure: Dengvaxia uses the yellow fever vaccine virus, and QDenga® uses the attenuated DENV-2 itself.(14,15)

In Brazil, Dengvaxia® is recommended from 6 years of age to 45 years and the complete regimen consists of three doses. The phase 3 trial showed that children who were originally seronegative for DENV and received the vaccine were at greater risk of developing severe dengue after acquiring infection due to the exacerbated immune response. Therefore, the vaccine is only approved for individuals with previous laboratory-confirmed dengue infection and who live in endemic areas. QDenga® is indicated from 4 years of age to 60 years with two doses with a three-month interval between doses. Individuals who are both seronegative and seropositive for dengue can take the vaccine. Vaccines have proven to be effective in preventing dengue and reducing hospitalizations.(16) Dengvaxia® is rarely used in endemic areas due to the need to pre-screen for antibodies against dengue.

A single-dose vaccine called recombinant Butantan-DV with live attenuated virus is being evaluated by the Butantan Institute (São Paulo, Brazil). A recently published study showed 84% overall efficacy in 2 years among individuals aged 2-60 years.(17)

Controlling dengue continues to be a major challenge for Brazil. In the coming years, we will not have changes in weather conditions, on the contrary, excessive heat and intense rains with flooding are expected. Brazil is the first country in the world to offer the vaccine in the SUS. Dengue vaccines bring relief, but their impact has not yet been fully elucidated on large populations, in addition to being limited in immunocompromised people and older adults, and contraindicated in pregnant women. Although there is an important individual role of the population in eliminating mosquito breeding sites, the State has a fundamental role in establishing a national policy of promoting basic sanitation and improving infrastructure on the outskirts of large urban centers, in addition to training multidisciplinary health services in the rapid recognition of severe cases and appropriate treatment to reduce mortality.

References


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