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# Neurological Manifestations of Perinatal Dengue

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## Abstract

Dengue viruses (DENVs) are single-stranded RNA viruses belonging to the family Flaviviridae. There are four distinct antigenically related serotypes, DENVs types 1, 2, 3, and 4. These are all mosquito-borne human pathogens. Congenital dengue disease occurs when there is mother-to-fetus transmission of the virus and should be suspected in endemic regions in neonates presenting with fever, maculopapular rash, and thrombocytopenia. Although most of the infected infants remain asymptomatic, some can develop clinical manifestations such as sepsis-like illness, gastric bleeding, circulatory failure, and death. Neurological manifestations include intracerebral hemorrhages, neurological malformations, and acute focal/disseminated encephalitis/encephalomyelitis. Dengue NS1Ag, a highly conserved glycoprotein, can help the detection of cases in the viremic stage. We do not have proven specific therapies yet; management is largely supportive and is focused on close monitoring and maintaining adequate intravascular volume.

### Keywords

Antibody-dependent enhancement; Congenital dengue; Dengue encephalitis; IgM:IgG ratio; Neonate; Neurotropism; NS1Ag; CYD-TDV (Dengvaxia); TAK-003; Vertical transmission



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## Introduction

Dengue viruses (DENVs) are members of the family Flaviviridae belonging to the genus *Flavivirus*.[1,2] There are 4 distinct antigenically related DENVs, types 1, 2, 3, and 4,[3] and all are mosquito-borne human pathogens.[4] The first case of a pregnant woman with dengue fever was reported in 1948.[5,6]

## Viral Structure

Dengue viruses are small spherical viral structures that are typically about 50 nm in diameter and contain a single-stranded RNA genome of positive polarity[7] (Fig. 1). The spherical capsid (shell) is surrounded by an envelope containing numerous copies of M and E proteins.[8] During infections, the DENV envelope *E*-glycoprotein binds viral receptors such as heparan sulfate or lectins in cell surface proteins such as DC-SIGN [Dendritic Cell-Specific Intercellular adhesion molecule-3-Grabbing Non-integrin, also known as CD209 (Cluster of Differentiation 209)] and the C-type LEctin domain-Containing 5A (CLEC5A).[9-14] Once the viral and cell membranes fuse in acidified endocytic vesicles, the viral RNA enters the cytoplasm and gets translated into a single polyprotein, which is then cleaved to yield 3 structural (capsid, precursor membrane, and envelope) and 7 non-structural proteins (NS1, N2A, N2B, N3, N4A, N4B, and N5).[7] The non-structural proteins play a role in viral replication and modulation of the cell antiviral response.[15] NS3 encodes a viral protease which helps in the cleavage of viral proteins.[16] NS5 is an RNA-dependent RNA polymerase, which aids in assembling the replication complex and transcribes the RNA to negative-strand RNA.[17] This strand serves as a template for genomic RNA.[18]

## Epidemiology

Dengue virus infection is spread by two Aedes (Ae.) mosquito species, *Ae. aegypti* and *Ae. albopictus*. The DENVs are transmitted in a human-mosquito-human cycle.[6] The incubation period in the mosquito vectors is 8–12 days, after which the virus can be transmitted to humans.[19] In humans, viremia begins after a 4–6-day incubation period and lasts until fever abates.[6,20]

Both *Ae. aegypti* and *Ae. albopictus* are widely distributed in tropical and subtropical areas.[21] *Ae. albopictus* species are more tolerant of cold and have a wider geographic distribution than *Ae. aegypti*.[22,23] *Ae. aegypti* is the most prevalent species in India, Pakistan, and Sri Lanka.[24] A seroprevalence study among children living in India conducted between January 2011 and October 2012 noted 60–80% seropositivity rates.[25,26] The geographical prevalence of these mosquitoes and viruses is depicted in Figure 2.[27-33]

### Patterns of Transmission

The DENV transmission follows the following two general patterns, with different implications for disease risk:

- “Epidemic dengue” occurs when a single DENV strain is introduced into a region as an isolated event with a large population of susceptible mosquitoes

and human hosts.[34] It can lead to infections among 25–50% of susceptible individuals.[35]

- "Hyperendemic dengue" occurs in areas with a year-round presence of vector mosquitoes, continuous circulation of multiple DENV types, and a large population of susceptible individuals. It leads to repeated epidemics.[36] Children are more susceptible than adults to dengue in hyperendemic regions. Dengue hemorrhagic fever (DHF) is also seen in hyperendemic regions.[37]

### Factors influencing Transmission

There has been a steady, worldwide increase in DENV infections. The geographic distribution is expanding with population growth and poor urban planning.[38] Global climate change also has an impact on disease transmission with higher global temperatures increasing the range of *Ae. aegypti* and DENVs.[39,40] DENV transmission has also increased with El Niño/Southern Oscillation events.[41,42]

**Vertical Transmission—**Vertical DENV transmission has been noted in many case series.[43] It should be considered when pregnant women acquire the infection early during pregnancy or at least within 10–15 days prior to delivery. In a prospective study, about 2.5% of women showed a positive immunoglobulin M (IgM) serology. Only 1 (1.6%) of the paired umbilical cord samples was seropositive for dengue although none had evidence of viral RNA by polymerase chain reaction (PCR).

Vertical transmission can increase perinatal morbidity and mortality.[44] DENV is transmitted to the fetus during maternal viremia, but these infected mothers may remain asymptomatic.[45,46] Pregnancy itself has also not been shown to increase the incidence or severity of dengue.[47] Infections in early pregnancy have been noted to cause spontaneous abortions or neural tube alterations in some, but most cases do not show any congenital abnormalities.[48-50] The mode of delivery does not alter the rate of transmission. Newborns with lower weight may be at higher risk of severe dengue. In a prospective study of 2,958 pregnant females,[51] a vertical transmission rate of 18.5–22.7% was reported in a study during an epidemic in French Guiana. Fetal infections seem to be more frequent near term.[46] Breastfeeding has also been reported as a mode of vertical transmission during the postnatal period.[52]

The DENV serotype 2 has been the predominant serotype associated with vertical transmission.[53] This may be explained by the high circulation of DENV serotype 2,[54] or the ability of this serotype to cross or disrupt the placental barrier. Sequential fetal growth monitoring should be undertaken in pregnant women with dengue to screen for fetal growth restriction and stillbirths.[55]

## Course of Infection

The course of infection by the DENVs can be subdivided into early events, dissemination, and the immune response and viral clearance:

- Early events refer to the inoculation of DENV into a susceptible host. Dissemination is manifested as viremia, 2–6 days after subcutaneous inoculation, and may last up to 3–6 days.[56]
- Immune response and viral clearance are achieved through innate and adaptive immune responses.[57] Neutralization requires a threshold level of antibodies.[58] Sub-threshold levels may paradoxically increase the uptake of antibody-bound viruses.[59] This phenomenon has been described as antibody-dependent enhancement (ADE) of infection.[46,60]

## Primary vs Secondary Infection

Infection with one of the four serotypes of DENV (primary infection) confers long-lasting specific immunity to viruses of that serotype.[50] There might be some, transient immunity to the other serotypes, and subsequent infections can still occur with the other serotype (secondary infection).[61] In these secondary infections, the concentration of DENV-specific antibodies increases earlier with higher peak titers and lower IgM:IgG ratio, suggestive of an anamnestic response.[62] High levels of DENV-specific antibodies may be seen in later stages of viremia, increasing the formation of immune complexes and activation of complement.[63]

## Neurological Manifestations

Flowchart 1 shows the neurological manifestations. The neurological manifestations of congenital infections may result from (A) direct infection of neurological tissues (encephalitis, meningitis, myositis, myelitis, rhabdomyolysis; (B) systemic or metabolic imbalance (encephalopathy, stroke); and (C) early or late postinfection sequelae (transverse myelitis, acute disseminated encephalomyelitis).[64]

Furthermore, DENVs have strong CNS tropism.[65] These viruses enter the CNS *via* the hematogenous route.[66,67] These viruses activate endothelial cells (ECs), breach the blood–brain barrier (BBB), infect neurons, and induce cytoarchitectural changes.[68] These can reach the brain parenchyma: (A) in infected leukocytes; (B) through axonal transport; (C) *via* infection of the olfactory bulb epithelium; (D) by disrupting the inter-endothelial tight junctions; and (E) *via* endothelial infection and basolateral release.[69,70] The latter two mechanisms and viruses carried in infected monocytes may be the most critical routes.[65] To recapitulate, most DENV strains are neurotropic and neurovirulent, able to evade the immune system and invade the brain efficiently through BBB ECs, leading to replication in the brain parenchyma which induces nervous injury.[68,71]

An EC cross-activation following infection involves the soluble vascular cell adhesion molecule (sVCAM-1) and soluble intercellular adhesion molecules (sICAM-1).[72] The infected endothelium secretes immune mediators; DENV1 is known to induce interleukin-6 (IL-6), tumor necrosis factor (TNF), chemokine (C-X-C motif) ligand 1 (CXCL1), CCL2, CCL5, and CCL20.[73] These molecules have been associated with endothelial hyperpermeability and also with an imbalance in the coagulation pathway leading to microhemorrhages. Many neonates with severe infection can develop disseminated intravascular coagulation.[74,75]

In the eyes, the virus enters through the hematogenous route and infects the endothelium, pericytes, and other cells.[76] Pericytes augment the infection by secreting several immune mediators that modify the barrier physiology. In the CNS, the glia are also infected.[77-79] Activated astrocytes show altered function, morphology, and biochemical reactions.[80] These cells begin to secrete proinflammatory molecules such as IL-6, TNF, and interferon-β.[81,82] Strong, continuous stimuli have been associated with astrogliosis and cellular hypertrophy with longer and thicker astrocytic processes;[83] overexpression of cytoskeletal proteins such as the glial fibrillary acidic protein (GFAP), vimentin, and nestin[84] results in glial cell proliferation and scar formation.[85]

Encephalopathy is a recognized complication of dengue,[86,87] and is usually ascribed to the neurotropism of these viruses and consequent invasion of the brain parenchyma (dengue encephalitis). Multisystem involvement from hepatic derangement, cellular fluid leak, hypotension, and altered hemostasis worsens the illness. In a case–control evaluation of the cytokine response in patients with DENV, elevated levels of IL-6 and IL-8 were associated with severe neurological manifestations and poor outcomes.[88] In an *in vitro* study using BV2 microglial cells,[89] various DENV serotypes induced different responses. DENV1 induced a cytokine profile that altered vascular permeability, whereas DENV2 altered the oxidative stress-mediated apoptotic response.[90] Also, DENV3 established a distinct response with anti-inflammatory and antiviral mediators. DENV4 altered the BBB by inducing matrix metalloproteins.[89]

## Clinical Presentations

Congenital dengue occurs when there is insufficient time for the induction/transplacental passage of protective antibodies postmaternal infection.[91] It should be suspected in neonates presenting with fever, maculopapular rash, and thrombocytopenia in endemic regions (Figs 3A and B). Both the mother and baby should be simultaneously evaluated by tests for DENV antigens and serology.[91]

Maternal DENV infections have been shown to increase the incidence of prematurity.[44,57,92] This association can be explained by inflammatory changes triggered by maternal infection, which stimulate uterine contractions (Flowchart 2). There is increased production of pro-inflammatory cytokines such as IL-6, −8, and TNF, which stimulate the uterus, leading to preterm labor.[5,6,20,93] There is conflicting evidence regarding the correlation between the severity of neonatal and maternal dengue, factors affecting vertical transmission, and disease onset.[5,57,94] The longer the time from the onset of maternal fever to giving birth, the sooner the occurrence of fever in the neonate with an incubation period of 5–6 days.[95] Petechiae in neonatal dengue are seen more frequently as compared to older infants and children.[96] Hemoconcentration is not a reliable parameter in neonatal dengue because of an increased red blood cell mass with a higher hematocrit compared to older children and adults.[97,98] Investigations such as chest X-ray, renal and liver function tests, and ultrasonography of the chest and abdomen may be done as clinically indicated.[99]

Mild-moderate maternal DENV infections have not been clearly associated with intra-uterine growth restriction/low birth weight.[5] However, in severely afflicted cases, hypovolemia resulting from plasma leakage and hemorrhages could result in uteroplacental

insufficiency leading to fetal growth restriction and even demise.[100] In a study of 44 pregnancies from India,[55] there were miscarriages in 2 (4.5%), stillbirths in 4 (9%), and neonatal deaths in 2 (4.5%). There was preterm delivery in 15 (34.1%) and the infants were born with low birth weight in 13 (29.5%).[101,102]

Population studies do not show *in utero* DENV infections as consistently increasing the rates of cesarean sections in infected women or as a cause of congenital anomalies in affected neonates.[51,55] In some of these studies, the small number of infants with clearly evident clinical features may have resulted in the lack of statistically significant differences. A small number of infants with early onset *in utero* infections show neurological manifestations such as microcephaly (Figs 3C and D), anencephaly, and hydrocephalus.[60,103] Most of the infants with later-onset infections that likely occurred during the perinatal period, developed encephalopathy and had an uneventful recovery.

Peripartum maternal dengue makes newborns susceptible to complications because most of the transplacentally delivered antibodies lack a protective effect[47] and instead, enhance the entry of virus into the host cells.[104,105] Postnatal dengue infections are usually asymptomatic, although some infants may manifest with undifferentiated fever, upper respiratory tract symptoms, vomiting, and diarrhea. Liver involvement is more frequent in infants compared to older children.[106] The higher frequency of DENV hepatitis can be explained by the tropism of these viruses for liver cells.[107] Many studies show that the diagnosis of neonatal dengue requires a high index of suspicion.[43,44,46,108] Infants with cutaneous manifestations and/or fever frequently show hepatomegaly.[98] It is seen more frequently in epidemic-region countries where pregnant women could get infected near the time of delivery.[5,44,93]

Neonatal dengue can be a difficult diagnosis.[109,21] In one study, 12 out of 32 cases were classified as neonatal sepsis or neonatal immune thrombocytopenia.[110] Neonates who are diagnosed with dengue should be monitored for warning signs of shock or severe hemorrhages. The hemorrhagic manifestations are usually mild and are usually limited to petechiae.[110] Total leukocyte counts can drop during the febrile phase but then normalizes in the critical phase.[110] Some infants may show gall bladder wall thickening.[20,26,49,111-113] Monitoring for complications should continue for 24–48 hours after defervescence.

Pregnant women should avoid travel to *Aedes* spp. endemic regions. Post-travel laboratory testing should be reserved for symptomatic patients.[114]

## Laboratory Diagnosis

The diagnosis of congenital DENV infections is based on the history of maternal fever and the presence of either dengue nonstructural 1 (NS1) antigen or dengue antibodies.

## Enzyme-linked Immunosorbent Assay-based NS1 Antigen Tests

Dengue NS1Ag is a highly conserved glycoprotein, which is produced in both membrane associated and secreted forms and is abundant in the serum of patients during the early stage of dengue infection. It helps in the detection of cases early in the viremic stage.[5,57,94] Other diagnostic options are dengue virus isolation or detection of antibodies.

## Serologic Assay for DENV

**Enzyme-linked Immunosorbent Assay—**It is a simple test based on detecting the dengue-specific IgM antibodies in the test serum by capturing them using antihuman IgM bound to the solid phase.[115] After adding dengue antigen, if anti-dengue IgM is present, it will bind and give a color reaction with the enzyme substrate. Antidengue IgM is detectable by day 5 of the illness.[116] For single serum, enzyme-linked immunosorbent assay (ELISA) IgM titer more than or equal to 1 or an IgG titer above 3 is considered evidence of acute and/or recent DENV infection. An ELISA IgM:IgG ratio of above 1.8:1 is considered a primary infection. Acute DENV infections are typically associated with a 4-fold or higher rise in antibody titers.[117]

**Hemagglutination (HI)—**Seroconversion or high titers (≥1:2560) are suggestive of recent infection. Moreover, WHO recommended using HI titers of convalescent sera as the criteria to distinguish between primary and secondary infection. The infection is diagnosed as primary if the titer in a week or more after the onset of illness is above 1:1280 or as secondary if antibody titers are more than or equal to 1:1280.[118] Also, HI antibody is used in laboratories and is believed to assess seroprotection; Ig-G ELISA compares well to the HI test.[118]

## Dengue Viral Isolation

**Tissue Culture—**Serum samples are inoculated into tissue culture flasks containing *Ae. albopictus* mosquito cell monolayers.[119] After 90 minutes of adsorption of the inocula on cells at 28°C, cell cultures are incubated for 7 days at 28°C. Cells are harvested for the identification of viruses by indirect immunofluorescence staining. Virus isolation and nucleic acid tests have high specificity but are expensive and labor intensive and are used for early detection in the first week of illness.[120] Virus isolation takes around 7–10 days.

**Mosquito Inoculation—**Dengue viral isolation has been attempted with laboratory-reared mosquitoes (*Toxoshynchites splendors*) by an intrathoracic inoculation technique.[121] Identification of DENV serotypes is performed by indirect fluorescence antibody staining using serotype-specific monoclonal antibodies.[122]

**Reverse Transcription Polymerase Chain Reaction—**The reverse transcription polymerase chain reaction (RT-PCR) can be used to detect DENV RNA. Nested RT-PCR, real-time RT-PCR, or nucleic acid sequence-based amplification (NASBA) can be used.

Pauci-symptomatic dengue cases may be underdiagnosed during the neonatal period because DENV infections during pregnancy are not identified.[46]

The “diagnosis of vertical transmission” of dengue can be made if a sample of the umbilical cord, placenta, or newborn peripheral blood collected immediately postpartum reveals a positive result in a dengue diagnostic test.[46] Umbilical cord blood and placenta should be tested if there is a history of dengue during pregnancy or fever within 15 days before the term in dengue-endemic regions. Positive results indicate a need for close clinical

monitoring of the newborn; peripheral blood samples should be tested if the infant becomes symptomatic.

The “diagnosis of neurological manifestations” may require an ultrasound of the skull or a magnetic resonance imaging (MRI) brain.[123] The cerebrospinal fluid (CSF) studies are required to diagnose dengue encephalitis. Tests for CSF IgM, IgG, and NS1 antigen should be performed if neurological manifestations are present.[124] Carod–Artal et al.[125] defined dengue encephalitis if each of the following criteria were fulfilled: (A) Dengue CNS involvement; (B) Presence of dengue virus RNA, IgM, or NS1 antigen in CSF; and (C) CSF pleocytosis without other neuroinvasive pathogens.

Pleocytosis in CSF may not be seen in 5% of encephalitis cases, especially early in the course of dengue.[126,127] Furthermore, IgM antibodies in CSF have high specificity but low sensitivity; these appear only by the seventh day following infection.[128] Hence, the absence of antibodies does not exclude the neurological manifestations associated with dengue.

In view of these limitations, another definition was suggested for dengue encephalitis: (A) presence of fever; (B) acute signs of cerebral involvement such as altered consciousness or seizures and/or focal neurological signs; (C) reactive IgM dengue antibody, NS1 antigen, or positive dengue PCR on serum and/or CSF; (D) exclusion of other causes of viral encephalitis and encephalopathy.[129] This definition will reduce the number of missed cases of dengue encephalitis. Brain-evoked response auditory (BERA), visual-evoked potential (VEP), and follow-up MRI should be considered. These infants need follow-up for neurocognitive outcomes.[130]

Congenital DENV infections can show notable CNS lesions on imaging (Fig. 4). However, many of these findings are not characteristic of *in utero* infections and can also be seen in infants who acquire the virus after birth. In a retrospective study of 36 patients with serologically proven DENV infections with neurological symptoms,[131] The MRI did not show any abnormalities in 11, showed an encephalitic pattern in 12, encephalopathic (seizure related/metabolic) findings in 4, acute disseminated encephalomyelitis (ADEM) in 3, and isolated micro- or macro-hemorrhages in 6. Such a pattern-recognition approach may help in identifying the pathology, differential diagnosis, and in making treatment decisions. In another study,[132] the basal ganglia, thalamus, brainstem, cerebellum, cortical white matter, periventricular white matter, and cortical gray matter were most frequently involved and appeared hyperintense on T2-weighted images, and the fluid-attenuated inversion recovery (FLAIR) protocol. These lesions appeared iso- or hypo-intense on T1-weighted images. “Blooming” micro-hemorrhages were seen on susceptibility-weighted MRI (Figs 5 and 6). Children who are infected or manifest at later ages typically show less severe imaging changes (Fig. 7).

## Clinical Management

**Treatment—**No credible anti-DENV therapy is currently available.[133] Management is supportive with close monitoring and is focused on maintaining adequate intravascular volumes (Flowchart 3). In mild cases, oral rehydration by breastfeeds or formula feeds is sufficient. Acetaminophen (maximum 60 mg/kg/day) can be used for the management of

fever. Aspirin or nonsteroidal anti-inflammatory agents should be avoided because of the risk of bleeding complications and potentially of Reye's syndrome in infants.

Plasma leakage should be managed with intravascular volume repletion to prevent hypovolemic shock. Infants with established intravascular volume depletion may require intravenous fluids. Blood transfusions may be needed in patients with significant bleeding and anemia, and inadequate response to fluid resuscitation.[134-136] Acidosis, hypoglycemia, and hypocalcemia should be investigated and corrected as needed. Prophylactic platelet transfusion is not recommended.[137] Fresh frozen plasma may be used in cases with coagulopathy with bleeding.

**Breastfeeding—**The secretion of DENV in human milk is uncertain and likely very rare, even though there are some positive reports.[52] Breastfeeding is encouraged in infants of infected mothers.[138] Human milk contains antiviral antibodies that may provide protection.[139] Neonates may be discharged once afebrile for 24–48 hours, hemodynamically stable with good urine output, and accepting feeds well.

There is no role for corticosteroids,[140-142] intravenous immunoglobulins, pentoxifylline, or activated factor VII.[143-145] Direct viral inhibitors and modifiers of virus-host interactions are under investigation.[146,147] Chloroquine, lovastatin, balapiravir (a polymerase inhibitor), and celgosivir (an α-glucosidase inhibitor) have not been shown to have any benefit in randomized controlled trials.[148-150]

## Outcomes

The DENV infections during pregnancy can increase the overall risk of neurologic anomalies by 50% and of congenital malformations of the brain by 4-fold.[102] The biological mechanism(s) for this teratogenicity are unclear, but there is evidence for the DENV virus crossing the placental and blood–brain barriers[102,151,152] and for its neurotropism.[125,153] The DENV antigen and antibody testing in CSF has procedural inconsistencies, limited availability, and variable sensitivity and specificity.[154] An MRI of the brain may reveal hyperintensities in globus pallidus known as the "double doughnut sign".[155] Dengue encephalitis should be considered as a possibility in an infant with dengue fever with altered sensorium.

Unlike fetal dengue, the outcomes of postnatal infections seem more encouraging but still need further study. One study from Thailand showed normal growth and development in all infants with neonatal dengue at 1-year follow-up.[53] Some neonates can recover even from ADEM following vertically transmitted infections. The mothers had a history of febrile illness before delivery; the infants developed fever, lethargy, poor feeding, and seizures that lasted for up to a week. The MRI scans showed multiple areas of restricted diffusion of the white matter in the frontoparietal and temporal lobes and internal capsules. However, even though the severity of ADEM can vary between patients, many recover over time probably because the immune response differs from that in adults and does not augment tissue damage.[4,151] In one case reported from India, the neonate fulfilled all criteria for dengue encephalitis; there was fever, lethargy, and seizures, positive serology for NS1 antigen, and detectable titers of DENV IgM antibody in serum and CSF. Management

includes supportive measures and phenobarbitone.[156] There was gradual recovery without any sequelae.

In neonatal and adult murine models infected by intranasal inoculation, DENV serotype 2 showed brain tropism with encephalitis.[157] After invading the upper respiratory tract mucosa, it likely entered the brain through the olfactory nerve with massive viral replication. There were neurological symptoms.[69] Affected areas showed considerable leukocyte recruitment, but paradoxically, these cells may have increased the severity of encephalitis owing to the Trojan horse effect.[158,159]

**Prevention—**Approaches for the prevention of DENV infection in endemic areas may include vaccination, mosquito control, and personal protective measures.[160]

**Vaccine Development:** Infection with one DENV type provides long-term protection against reinfection with that same type and a short-lived cross-protection against the other DENV types.[161]

The vaccine CYD-TDV (Dengvaxia) has been licensed in many countries in Latin America and Southeast Asia. It is a formulation of four chimeric yellow fever 17D-dengue vaccine viruses.[162,163] The vaccine shows 75% efficacy against DENV-3 and DENV-4, 50% for DENV-1 and 35–42% for DENV-2. According to the WHO, the vaccine is protective against severe dengue for individuals with dengue seropositivity at the time of first vaccination. Vaccine efficacy is lower (34–36%) in children 2–5 years of age and in children who do not have detectable dengue-neutralizing antibodies prior to vaccination.[164-166] Two vaccines are in clinical development, the TAK-003 and a tetravalent, live-virus vaccine attenuated by directed mutagenesis with a DENV-2/-4chimeric strain.[109,111,112] TAK-003 is tetravalent vaccine based on an attenuated laboratory-derived DENV-2 virus.[167-170] Further studies are required to evaluate efficacy and safety, especially for DENV-3 and DENV-4.

**Mosquito Control:** The methods that are most efficacious involve reducing breeding sites and larva control. Seeding water vessels with copepods (these are small crustaceans found in most freshwater and saltwater habitats) that feed on mosquito larvae can eliminate *Ae. aegypti* and dengue transmission. Endosymbiotic control can be achieved by releasing mosquitoes infected with *Wolbachia*, an obligate intracellular bacterium, which lowers the susceptibility to infection by DENVs.[171-174]

**Protective Measures against Mosquito Bites:** This include careful use of insect repellents, wearing long-sleeved shirts and long pants, and control of mosquitoes inside and outside the home. Repellents containing DEET (name derived from DET in *N,N*-diethyl-meta-toluamide) are generally considered safe if used in only necessary amounts. These should not be applied on the face and around the eyes.

Detailed information for some of the viral components is listed in Table 1.

## Future Directions

Future efforts should be directed toward the development of antiviral agents for the management of dengue. In addition, there should be an emphasis on planned urbanization with the escalation of efforts toward mosquito control and vaccine development.

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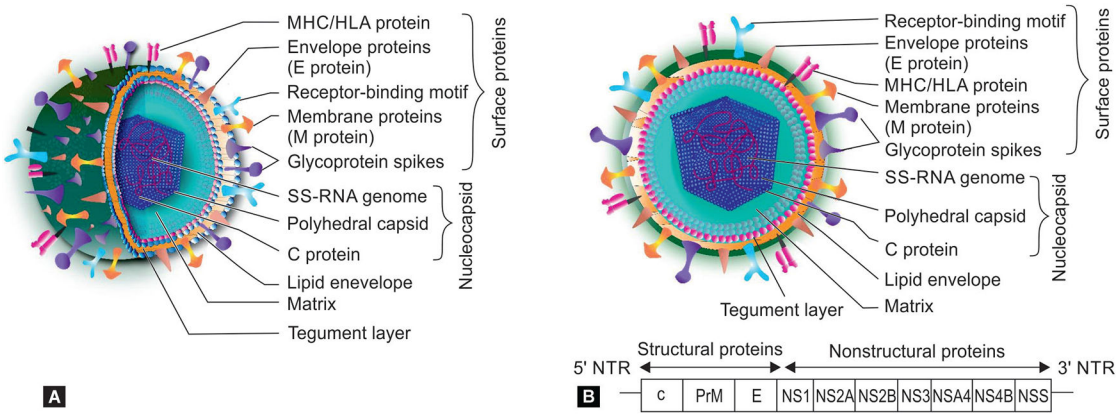
## Highlights

- There are four known antigenically related dengue serotypes, named dengue viruses (DENV-1, –2, –3, and –4). The mosquito species *Aedes (Ae.) aegypti* and *Ae. Albopictus*, are widely distributed in tropical and subtropical areas and serve as vectors for transmission of these viruses.
- Vertical transmission of DENV can be diagnosed if a sample of the umbilical cord, placenta, or newborn peripheral blood tests positive for a DENV diagnostic test in cases with a history of dengue during pregnancy or fever within 10–15 days before delivery in dengue-endemic regions.
- Most infants remain asymptomatic, although some can develop multi-organ system failure. Neurological manifestations can include malformations of the nervous system, acute focal/disseminated encephalitis/encephalomyelitis, and sometimes as a part of the systemic illness, intraventricular hemorrhages.
- Elevated serum levels of interleukin (IL)-6 and IL-8 are associated with neurological involvement and poor outcome.
- Management is largely supportive, and focused on maintaining adequate intravascular volume, breastfeeding, and close monitoring.
- The vaccine CYD-TDV (Dengvaxia) is recommended for persons who are 9–45 years in age, live in endemic areas, and have a confirmed history of dengue infection(s) in the past.



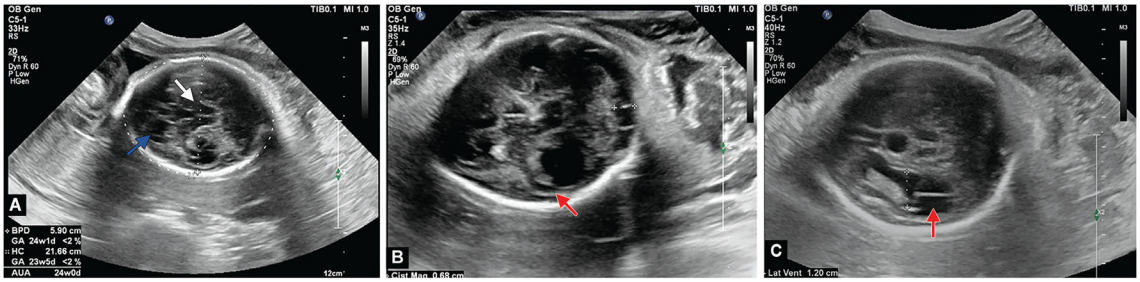

**Figs 1A and B:**

Schematic diagrams showing (A) surface and side dissection and (B) cross-section of the dengue virus

**Fig. 2:**

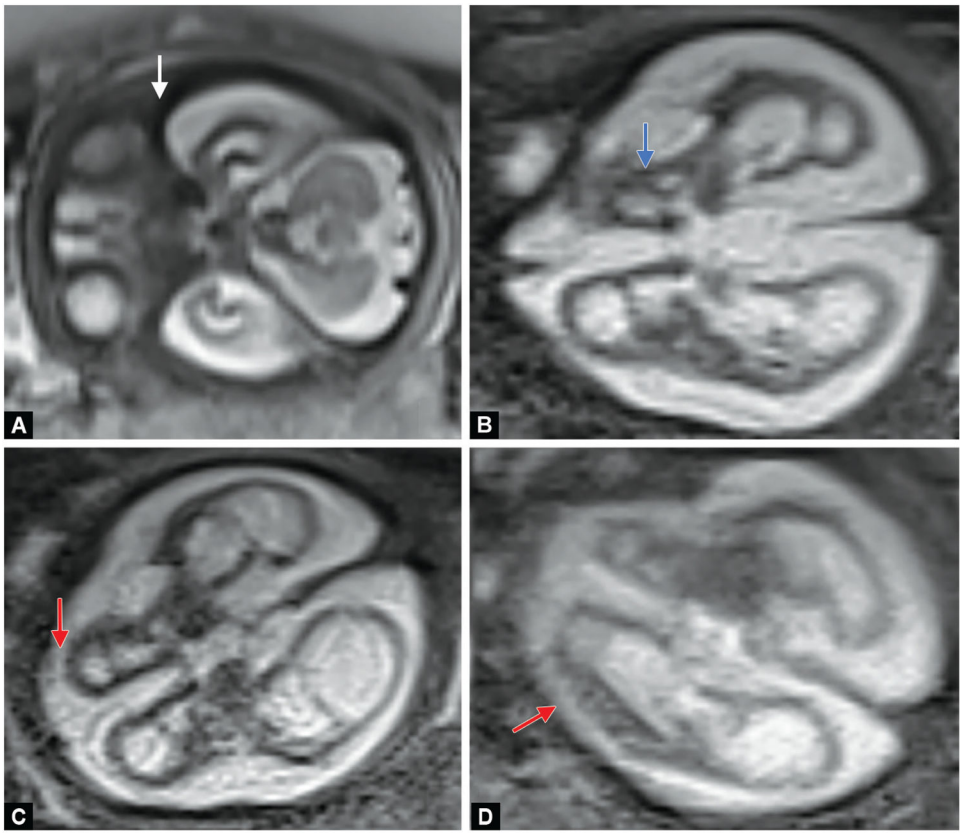
Global distribution of dengue (regions highlighted with purple color). The disease is frequently seen in Southeast Asia, the Northeastern corner of Australia, sub-Saharan Africa, Eastern Mediterranean regions, Southern Europe, the Middle East, Western Pacific Islands, Mexico, the Southern United States, the Caribbean, and all South American countries except Chile


**Figs 3A to D:**
Clinical manifestations of congenital dengue in neonates. (A and B) Images of infants showing maculopapular rash; (C and D) Images of infants showing microcephaly due to congenital dengue

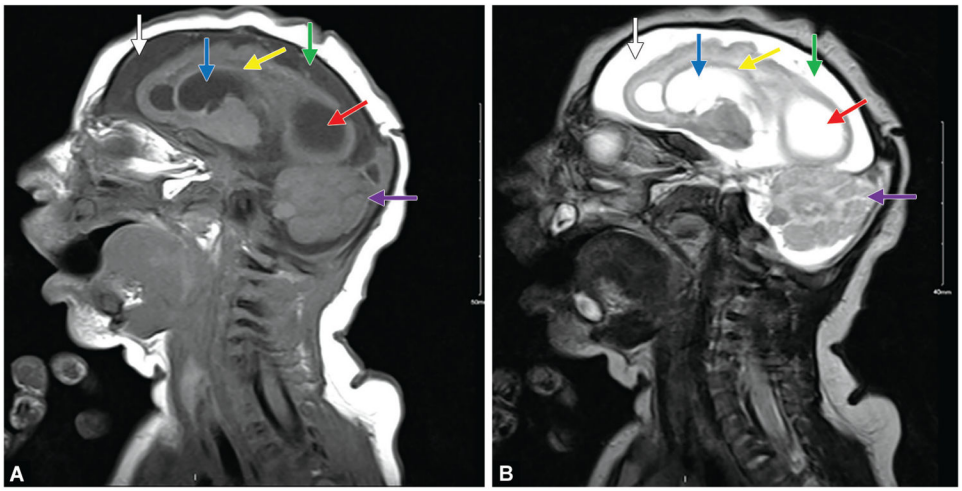



**Figs 4A to C:**

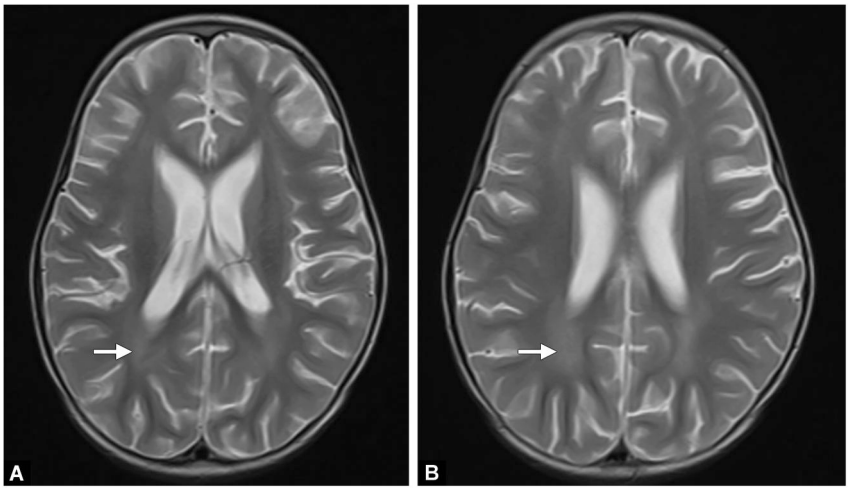
Antenatal scan of a mother at 29 weeks, 3 days gestation. (A) Enlarged extra-axial CSF spaces with ventricular dilatation (white arrow) and cystic changes (blue arrow); (B) Thinning of parenchyma (red arrow); and (C) Ventricular dilatation (red arrow)



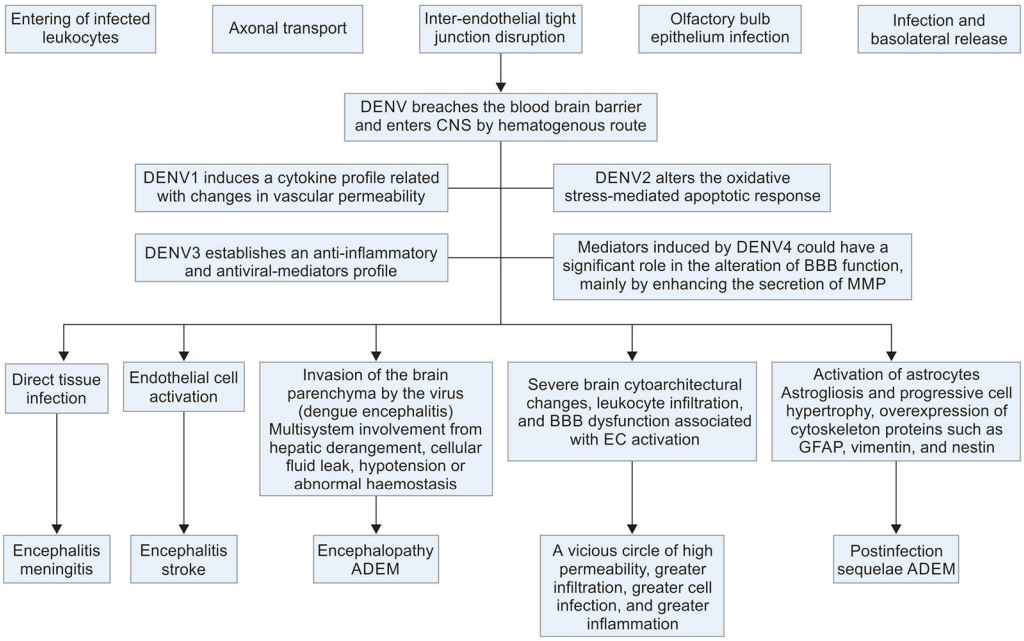

**Figs 5A to D:**
Fetal MRI at 29 weeks, 6 days. (A) Enlarged extra-axial CSF spaces with ventricular dilatation (white arrow); (B) Cystic changes of the bilateral frontal lobes and left parietal area (blue arrow); (C) and (D) Images showing thinning of the parenchyma (red arrows), which resulted in the loss of volume and architecture of the cerebral parenchyma



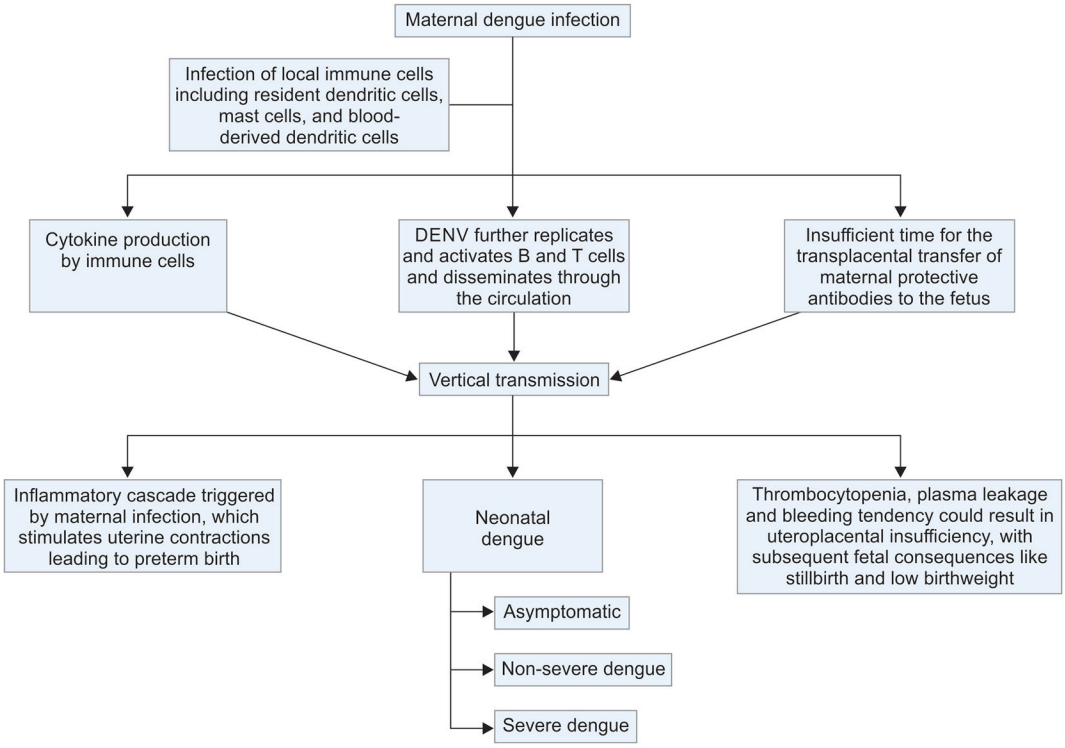

**Figs 6A and B:**
Postnatal MRI on day 8 after birth (A) T1W image; (B) T2W image. Findings show decreased brain parenchymal thickness, especially in the supratentorial lobes with marked simplification of gyral patterns (white arrows), loss of normal fissurization, and operculation. Other findings include ventriculomegaly (blue arrows), cystic changes (red arrows), and altered formation of the cerebral cortex with thinning of the corpus callosum (yellow arrows). Additional features are enlargement of the subarachnoid spaces (green arrows), bilateral open sylvian fissures and cerebellar hypoplasia (purple arrows)



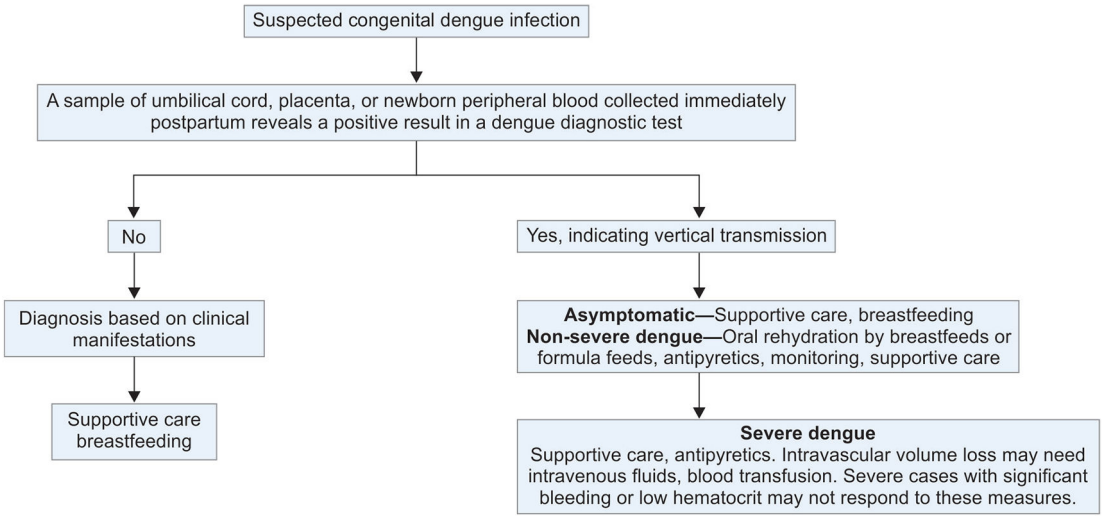

**Figs 7A and B:**
The MRI brain (T2-weighted, two levels) of a 2-year-old child with dengue encephalitis showing periventricular hyperintensities along bilateral lateral ventricles (white arrows). The changes are most prominent along the posterior horns




**Flowchart 1:**
Pathogenesis of perinatal dengue infections




**Flowchart 2:**
Pathogenesis of neurological manifestations of DENV infections




**Flowchart 3:**
Management of perinatal dengue infections

**Table 1:**

Major structural components of DENVs

| Structure | Available information |
|---|---|
| Lipid envelope | The nucleocapsid is surrounded by a lipoprotein envelope derived from the nuclear membrane of the infected host cell.[7] |
| Glycoproteins | Projecting from the lipid envelope are viral glycoprotein spikes that bind specific host receptors to facilitate virus entry. DENV binds to cells by the major viral envelope (E) glycoprotein, which is critical for infectivity.[9-11] |
| Receptor binding motifs | Receptor binding motifs are involved in virion attachment to cell surface receptors. DENV infection begins with virus attachment to the target cell by the interaction between viral surface proteins and receptors on the cell surface leading to the internalization of the virus by receptor-mediated endocytosis.[174-176] |
| Envelope protein | The nucleocapsid is surrounded by a trilaminar lipoprotein envelope containing envelope protein or the “E” glycoprotein.[9-11,177] |
| Membrane protein | The virus particles have two surface viral proteins: the E (envelope) glycoprotein, which is the major determining antigen and involved in binding and fusion during viral entry, and the M (membrane) protein, a part of the precursor prM, formed during the maturation of the virus. M acts as a secretory protein analogous to the major envelope protein E.[178] |
| MHC or HLA proteins | Some MHC gene combinations can act synergistically to influence disease expression in previously DENV-exposed individuals.[179] |
| Spike protein | Projecting from the lipid envelope are viral glycoprotein spikes that bind specific host receptors to facilitate virus entry.[178] |
| Surface tubules | Either not expressed or relevance unclear fetal/infantile disease |
| Palisade layer | Either not expressed or relevance unclear fetal/infantile disease |
| Viral tegument | Either not expressed or relevance unclear fetal/infantile disease |
| Lateral bodies | Either not expressed or relevance unclear fetal/infantile disease |
| Capsid | The mature capsid of DENV is a highly basic protein of 12 kDa that forms homodimers in solution and has an affinity for nucleic acids and lipid membranes. It exists as a 100-residue monomer and contains 26 basic amino acids and only 3 acidic residues.[8] |
| Capsomeres | The proteins that compose the structural unit may form three-dimensional structures known as “capsomeres” that are visible in an electron micrograph.[8] |
| Core membrane | Either not expressed or relevance unclear fetal/infantile disease. |
| Protein core | The polyprotein produced by dengue virion is processed into three mature structural proteins (C, prM, and E) and seven nonstructural proteins (NS1, NS2A, NS2B, NS3, NS4A, NS4B, and NS5).[180] |
| Core fibrils | DEN2 virus-infected apoptotic cells also show bundles of intracellular microfibrils which resemble the contractile structures observed in fibroblasts and some glomerular cells. These structures could be related to the apoptotic process, since, filamentous material, clumping of tonofilaments and MyD88 protein.[181] |
| Matrix | Either not expressed or relevance unclear fetal/infantile disease |
| Enzymes | The only known enzymes of DENV are encoded by NS3 and NS5 proteins. The N-terminal domain of NS3 is a protease (with NS2B as a cofactor) and the C-terminal domain is an RNA helicase. NS5 contains a methyltransferase (MTase) at the N terminus and an RNA-dependent RNA polymerase (RdRp) at the C terminus.[148] |
| RNA elements | NS5 polymerase domain helps to synthesize a transient double-stranded replicative RNA intermediate which is composed of viral plus- and minus-strand RNAs. The newly synthesized minus strand serves in turn as a template, allowing the RNA-dependent RNA polymerase to synthesize additional plus-strand genomic RNA.[182-186] |
| Nucleus | Either not expressed or relevance unclear fetal/infantile disease |
| Nucleosome | Either not expressed or relevance unclear fetal/infantile disease |
| DNA | No DNA genome exists |

| Structure | Available information |
|---|---|
| RNA | The dengue virion contains a single-stranded, positive-sense RNA genome of approximately 11 kb which is translated into a large polyprotein during the infectious life cycle.[7,180] |
| Genome-associated polyprotein | RNA genome of dengue virus is translated into a large polyprotein which in turn is processed by cellular and viral proteases into three mature structural proteins (C, prM, and E) and seven nonstructural proteins (NS1, NS2A, NS2B, NS3, NS4A, NS4B, and NS5).[180] |
| DNA polymerase | Either not expressed or relevance unclear fetal/infantile disease |
| RNA polymerase | The C-terminal region of NS5 has five amino acid sequence motifs which form the signature of RNA-dependent RNA polymerases (RdRps). Viral replication begins with the synthesis of minus-strand RNA from the positive-strand RNA genome, which then acts as a template for the formation of plus-strand RNA genomes. Production of new viral particles is catalyzed by the NS5 RNA-dependent RNA polymerase.[182] |
| Reverse transcriptase | Either not expressed or relevance unclear fetal/infantile disease |
| Head | Either not expressed or relevance unclear fetal/infantile disease |
| Base plate | Either not expressed or relevance unclear fetal/infantile disease |
| Integrase | Either not expressed or relevance unclear fetal/infantile disease |
| Tail | Either not expressed or relevance unclear fetal/infantile disease |
| Tail fiber | Either not expressed or relevance unclear fetal/infantile disease |
| Neck | Either not expressed or relevance unclear fetal/infantile disease |