Editorial

Dengue Virus Infection

Dengue, an illness caused by dengue virus (an arbovirus), is one of the neglected tropical diseases.[1] The infection is endemic in more than 100 countries. Of the estimated 390 million dengue viral infections that occur worldwide annually,[2] around 1% require hospital admission.[3] Since the isolation of the dengue virus in India in 1945, an upsurge has been reported in the number of cases,[2] with 99 913 cases during 2015.[4] Although the mortality rate of dengue is low (0.3%–0.4%),[1] large financial resources required for its control[5] pose a huge challenge in developing countries such as India.

The dengue virus has four serotypes (DENV 1–4) and a fifth one has been reported recently.[6] The most common vectors for this virus are female *Aedes aegypti* (*A. aegypti*) mosquitoes; other mosquito species that are known to transmit this virus include *Aedes albopictus, Aedes polynesiensis,* and *Aedes niveus.* Outbreaks of dengue are seasonal as the climate influences the survival of this vector.[7] Transmission of dengue is facilitated by the increase in urbanization, air travel, global trade, and use of materials that support collection of water, e.g. non-biodegradable plastic products, paper cups, coconut shells, air coolers, flower pots and discarded tyres. Water collected in any receptacle makes for breeding of mosquitoes.[3]

Illness caused by dengue virus infection ranges from the asymptomatic non-specific viral variety to the life-threatening dengue haemorrhagic fever (DHF) and dengue shock syndrome (DSS). The typical dengue illness has three phases.[3] The incubation period is followed by a febrile phase with high-grade fever accompanied by facial flushing, myalgia, arthralgia and retro-orbital pain. The 'critical phase' may have complications such as plasma leakage, shock and end-organ dysfunction. The 'recovery phase' is characterized by the resolution of symptoms and return of extravasated fluid into the intravascular compartment. Circulatory fluid overload and pulmonary oedema can occur during this period, especially in patients with comorbid conditions and due to overzealous administration of intravenous fluids.[8] 'Expanded dengue syndrome' in some people may unusually manifest with severe involvement of organs, such as the heart, liver, kidneys and brain.[1]

Persons previously infected with one serotype of dengue virus, when infected with a different serotype, are at an increased risk of severe illness.[9] This could be due to the production of heterotypic antibodies that provide immunity against a particular serotype, but not against the other serotypes. The phenomenon is known as antibody-dependent enhancement (ADE), by which antibodies bind to but fail to neutralize the heterotypic virus particles, leading to their opsonization by the host cells, resulting in an augmented inflammatory response, a cytokine storm and marked capillary leakage.[9] The presence of cross-reactive antibodies against vascular endothelium and platelets also appears to contribute to the pathogenesis of severe disease.[1] These mechanisms ultimately lead to vasculopathy and coagulopathy, which cause haemorrhage, shock and organ dysfunction.

Tests for diagnosing dengue virus infection detect the NS1 antigen using enzyme immunoassays (ELISAs). These tests are useful within 5 days of the onset of symptoms. Thereafter, the diagnosis is based on the detection of specific IgM antibodies using MAC-ELISA. The commercially-available rapid diagnostic tests (RDTs) detect both antigens and antibodies, and have a high rate of false-positivity for other febrile illnesses, which frequently leads to diagnostic confusion. However, the use of RDTs for antibodies during the initial 5 days of illness may lead to a high rate of missed diagnosis.[1]

The severity of clinical illness is classified for triage, hospital admission and management. The WHO system classifies the disease severity into grades A, B and C.[3] Health authorities

in India classify these patients into mild, moderate and severe categories.[1] No antiviral agent has proven efficacy against the dengue virus. Therefore, management involves careful administration of fluids based on clinical features, and supportive management for organ failure. Prophylactic platelet transfusion has no role in dengue infection; such transfusions should be considered only for patients with moderately severe mucocutaneous or internal bleeding (irrespective of platelet count) and for those with platelet count <10 000/cmm.

During the 2015 upsurge of dengue in Delhi, DEN-2 was the dominant serotype, with DEN-4 being responsible for some cases. A few patients had bleeding manifestations despite the platelet count being in excess of 100 000/cmm. Atypical clinical presentations with encephalitis, retroperitoneal haematomas, acute liver failure and myocarditis were also reported in hospitalized patients.[10] Some of these manifestations could have been due to the coexistence of other acute febrile illnesses such as leptospirosis, acute viral hepatitis A and E, enteric fever, malaria and scrub typhus. However, a majority of patients had uncomplicated disease. Deaths were reported only among patients who presented late.

This upsurge was related to untimely heavy rainfall that created conditions favourable for breeding of the *Aedes aegypti* mosquitoes.[11] A high optimum ambient temperature during this period hastened their life cycle, and the resulting small-sized mosquitoes bit human hosts more frequently, and spread the infection widely.[12]

Since reporting and surveillance for the disease are inadequate, the incidence of dengue reported from India may be an underestimate. The situation is compounded by a 'dengue panic syndrome'—i.e. of chasing the platelet count resulting in unnecessary and repeated platelet transfusions in persons with platelet count >50 000/cmm and no bleeding manifestations.[13] The healthcare system becomes prone to denying scarce blood products to patients with DHF/DSS who need and deserve these.[13] Thus, there is an urgent need to train doctors to use intravenous fluid therapy and platelet transfusion, only when indicated.

Control of dengue virus infection is a challenge as there is neither a drug to mitigate the consequences of infection nor one to break the transmission of the disease. Therefore, vector control strategies should have intersectoral coordination by integrating mosquito control with community involvement. It is possible to interrupt virus transmission through residual indoor sprays, effective elimination of potential mosquito breeding sites before the onset of the rainy season, and the use of medicated mosquito nets.[8] Some future vector-control methods could be the release of genetically-modified male mosquitoes, use of larvivorous fishes such as *Gambusia* in the ponds, embryonic introduction of obligate intracellular bacterium (*wolbachia*) resulting in *A. aegypti* that are partially resistant to dengue virus.[14]

The approval of CYD-TDV, a tetravalent, live-attenuated, chimeric dengue vaccine in a yellow fever 17D backbone, for individuals 9–45 years of age in Mexico in December 2015 may be a paradigm shift. In April 2016, WHO recommended this vaccine, albeit only in areas (national or subnational) with high disease endemicity.[15] However, some concerns remain. First, in clinical studies of this vaccine, there was an increased risk of hospitalization among vaccinated children below 9 years of age.[16] Second, the overall efficacy of the vaccine was only 67%–80%, and was low (35%–50%) for DEN-2 serotype; this may be important for India since the 2015 Delhi upsurge was caused by this serotype. Third, the efficacy of the vaccine was lower in recipients with seronegative status, i.e. those who had no previous exposure to the dengue virus, at enrolment than in those with seropositive status.[17] Finally, the duration of protection and need for boosters is yet unclear. Also, the novel fifth serotype, DEN-5, is not included in this vaccine. This additional risk could undo the control of disease caused by the four known serotypes using the tetravalent vaccine.[6]

At the global level, WHO has set a target of reducing mortality due to dengue by 50% and its morbidity by 25% by the year 2020.[8] The Ministry of Health and Family Welfare, Government of India will observe 16 May as National Dengue Day (NDD), to increase public awareness about the prevention and control of dengue. However, a massive campaign is required to educate the public about preventing mosquito breeding, as also about methods for personal protection against mosquito bites. The newly developed tetravalent dengue vaccine should be used only after countrywide surveys of seroprevalence identify the most appropriate age range for vaccination.

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