ABSTRACT: Dengue fever and dengue haemorrhagic fever are important arboviral diseases. Dengue virus belongs to family Flaviviridae, has four serotypes that spread by the bite of infected Aedes mosquitoes. Dengue epidemics can have a significant economic and health toll. Worldwide, an estimated 3.6 billion people are at risk of infection with about 50 - 100 million new cases each year. Illness produced by any of the four dengue virus serotypes varies from mild asymptomatic illness to severe fatal dengue haemorrhagic fever/dengue shock syndrome (DHF/DSS). During the early febrile stage clinicians cannot predict which patients will progress to severe disease. Atypical manifestations were reported are associated with high risk of mortality. The existing WHO dengue classification scheme and case definitions have some drawbacks. A global strategy to reduce the disease burden using integrated vector management in conjunction with early and accurate diagnosis has been advocated. Antiviral drugs and vaccines that are currently under development could also make an important contribution to dengue control in the future.

KEYWORDS: Aedes mosquitoes - dengue - DF/DHF- pathogenesis- cytotoxic factor- atypical manifestation- serology- prevention- vector control.

INTRODUCTION: Dengue is the most common arthropod-borne acute viral infection of humans with potential fatal complications like dengue hemorrhagic fever and dengue shock syndrome. The word “dengue” is derived from the Swahili phrase Ka-dingapepo, meaning “cramp-like seizure”. Benjamin Rush coined the term “break bone fever” because of the symptoms of myalgia and arthralgia. Worldwide, an estimated 3.6 billion people are at risk of, Dengue virus (DENV) infection are living in more than 125 countries, approximately 975 million of whom live in urban areas in tropical and sub-tropical countries in Southeast Asia, the Pacific and the Americas. It is estimated that more than 50 million infections occur each year, including 500,000 hospitalizations for dengue hemorrhagic fever, mainly among children, with the case fatality rate exceeding 5% in some areas.

The first major epidemic of the DHF occurred in 1953-1954 in Philippines followed by a quick global spread of epidemics of dengue fever/DHF. The first major wide spread epidemics of DHF/DSS occurred in India in 1996 involving areas around Delhi & Lucknow which then it spread to all over the country mostly affecting the children. Recently it is becoming more of an adult disease. The annual average number of dengue fever/dengue haemorrhagic fever (DF/DHF) cases reported to the World Health Organization (WHO) has increased dramatically in recent years. For the period 2000–2004, the annual average was 925,896 cases, almost double the figure of 479,848 cases that was reported for the period 1990–1999. The burden of dengue is approximately 1,300 disability-adjusted life years (DALYs) per million population, which is similar
to the disease burden of other childhood and tropical diseases, including tuberculosis, in these regions and all four dengue virus serotypes (DENV-1–4) are now circulating in Asia, Africa and the Americas. \[8\] In hyperendemic Asian countries, where there is concurrent transmission of several serotypes, primary dengue virus infections are seen in young children whereas symptomatic dengue generally occurs during secondary dengue virus infections in school-age children or young adults. Dengue-associated deaths are usually linked to DHF/ DSS. \[9\]

This Review will provide an update on our understanding of the pathogenesis & atypical manifestations, of this successful pathogen, difficulties of diagnosis and vaccine development.

**Agent: Dengue virus and its serotypes:** Dengue viruses belong to the genus flavivirus within the Flaviviridae family. There are four serotypes of the virus referred to as DENV-1, DENV-2, DENV-3 and DENV-4, all of which entered the urban cycle independently an estimated 500–1,000 years ago. \[10\] The virion is an enveloped spherical particle, 40–50 nm in diameter. The genome is a positive sense, single-stranded RNA that encodes for three structural proteins namely the capsid (C), membrane (M) and envelope (E) glycoproteins- and seven non-structural proteins viz. (NS1, NS2A, NS2B, NS3, NS4A, NS4B and NS5). DV-1 was isolated in 1956 at Vellore. All the Indian DV-1 isolates belong to the American African (AMAF) genotype. \[11\] The American genotype of DV-2 which circulated predominantly in India during the pre-1971 period, was subsequently replaced by the Cosmopolitan genotype. DV-2 strains were isolated in India over a time span of more than 50 years (1956-2011). The re-emergence of an epidemic strain of DV type-3 in Delhi in 2003 and its persistence in subsequent years marked a changing trend in DV circulation in this part of India. \[1,12\] Occasional reports of circulation of DV-4 are also seen, though it is not the predominant type in India. \[13\] The phylogenetic analysis by the Molecular Evolutionary Genetics Analysis programme suggests that the 1996 Delhi isolates of DV-2 which circulated predominantly in India during the pre-1971 period, was subsequently replaced by the Cosmopolitan genotype. DV-2 strains were isolated in India over a time span of more than 50 years (1956-2011). The re-emergence of an epidemic strain of DV type-3 in Delhi in 2003 and its persistence in subsequent years marked a changing trend in DV circulation in this part of India. \[1,12\] Occasional reports of circulation of DV-4 are also seen, though it is not the predominant type in India. \[13\] The phylogenetic analysis by the Molecular Evolutionary Genetics Analysis programme suggests that the 1996 Delhi isolates of DV-2 were genotype IV. The 1967 isolate was similar to a 1957 isolate of DV-2, from India, and was classified as genotype V. This study indicates that earlier DV-2 strains of genotype V have been replaced by genotype IV. \[14\]

**Vector and Transmission Cycle:** The mosquito vectors, principally *Aedes aegypti* prefer to bite humans typically during the day particularly in early morning and in the evening and become infected when they feed on humans during the usual period of five-day viremia. Dengue is transmitted by several species of mosquito within the genus *Aedes*, principally *A. aegypti*. Vector depending on the geographic area, includes *A. aegypti*, *A. albopictus*, *A. polynesiensis* and other members of the *A. scuteris* group. \[15\] Dengue 1 virus became prevalent in Hawaii where it was transmitted by *Aedes salbopictus*. \[16\] The virus passes from the mosquito intestinal tract to the salivary glands, a process which takes approximately 10 days. Subsequent to this extrinsic incubation period, the mosquito bite results in infection. The virus enters the skin along with the mosquito’s saliva, invades the white blood cells and multiplies intracellularly. While being carried throughout the body. The viruses are maintained in an *A. aegypti* - human - *A. aegypti* cycle with periodic epidemics [Figure: 1] Often, multiple virusserotypes co-circulate in the same city (hyperendemicity). \[17\] The geographical areas in which dengue transmission occurs have expanded in recent years. Travellers from endemic areas might serve as vehicles for further
During outbreak in Delhi in 2003-2004 co-circulation of DENV serotypes has also been reported, which may have implications for increased DHF/DSS. Further, replacement of DV-2 and 3 with DV-1 as the predominant serotype in Delhi over a period of three years (2007-2009) has been reported.

Dengue fever causes more illness and death than any other arbovirus disease of humans. The factors responsible for the dramatic resurgence and emergence of epidemic dengue and DHF are not fully understood. Two major factors have been the unprecedented global population growth and the associated unplanned and uncontrolled urbanization, especially in tropical developing countries. Besides, substandard housing, crowding, and deterioration in water, sewer, and waste management systems associated with unplanned urbanization have created ideal conditions for increased transmission of mosquito-borne diseases in tropical areas.

A third major factor has been the lack of effective mosquito control in areas where dengue is endemic and population densities of A. aegypti have increased, especially in urban areas of the tropics. A fourth factor responsible for the global emergence of dengue and DHF is increased air travel, ensuring repeated introductions of new dengue virus strains and serotypes into areas where the mosquito vectors occur and which provides the ideal mechanism for the transport of dengue.

Dengue Pathogenesis: It has been established that complications of dengue such as DHF/DSS are caused by a "Cytokine Tsunami". Despite extensive studies for over four decades, their genesis is still not fully understood. Various cytokines have been implicated in the immunopathogenesis of DF/DHF. The vascular permeability is increased due to combined effect of cytokine tsunami, release of histamine, free radicals, the products of the complement pathway and antibody-dependent enhancement (ADE) etc. Thus the key player appears to be CF/CF2, but the activity is regulated by CF-autoantibodies generated in patients with dengue disease in severe infection, the virus production inside the body is greatly increased, and many more organs such as the liver and the bone marrow can be affected.

Agent–Host Interaction: In the skin, dengue viruses infect immature dendritic cells which mature and migrate to local or regional lymph nodes where they present viral antigens to T cells, initiating the cellular and humoral immune responses. There is also evidence of abundant replication of DENVs in liver parenchymal cells and in macrophages in lymph nodes, liver and spleen, as well as in peripheral blood monocytes. The increased number of infected cells present targets for CD4+ and CD8+ T cells, resulting in large quantities of interleukin (IL)-10, IL-2, interferon (IFN)-γ and TNF that might contribute to endothelial damage and altered haemostasis. Virions released from infected cells might also directly damage endothelial cells. The uptake of the non-structural protein NS1 by hepatocytes might promote viral infection of the liver. During DHF, the complement cascade is also activated and the levels of the complement activation products C3a and C5a correlate with the severity of illness. Soluble and membrane-associated NS1 have been demonstrated to activate human complement. The levels of the terminal SC5b–9 complement complex and plasma NS1 correlated with disease severity, suggesting links between the viruses, complement activation and the development of
Alternative hypotheses of dengue pathogenesis include the suggestions that secondary T-cell responses are blunted because stimulation of T-cell memory results in the production of heterotypic CD4+ and CD8+ cells that have a diminished capacity to kill but nonetheless release inflammatory cytokines that contribute to disease severity[28] and the suggestion that cross-reactivity between NS1 and human platelets and endothelial cells raises antibodies that damage these cells.[29]

Cytotoxic factor (CF), a unique cytokine, is produced by CD4+ T cells in DV infected man and producing immunosuppression to heterologous antigens Most of the patients with dengue virus infection have CF in their sera, with peak amounts in the most severe cases of DHF.[30] The mechanism of cerebral oedema was studied in mouse model. A breakdown of the blood-brain barrier occurs in mice inoculated intracerebrally or intraperitoneally with DV 2 resulting in leakage of CSF into the brain tissue. Similar breakdown of the blood-brain barrier also occurred in mice inoculated intravenously with CF and CF2. Thus CF/CF2-mediated breakdown of the blood-brain barrier leads to cerebral oedema during DV infection. One of the cardinal features of severe dengue is capillary leakage resulting into accumulation of fluids in various body cavities. It was observed that CF or CF2 in mice results in increased capillary permeability. CF purified from the pooled sera of the DHF patients on intravenous inoculation into mice increased capillary permeability and damaged the blood-brain barrier.[31] DV-2 inhibits induces apoptotic cell death in a subpopulation of early megakaryocytic progenitors which may contribute to thrombocytopenia in dengue disease. It was shown that DV-2 may directly interact with platelets and thus may be responsible for thrombocytopenia.[32]

Important biological properties of dengue viruses are that the induction of neutralizing antibodies and the protective immune response, are associated with the E glycoprotein. The acquired immune response to dengue infection consists of the production of antibodies that are primarily directed against the virus envelope proteins. The response varies depending on whether it is a primary or secondary infection.[33] Antibody dependent enhancement (ADE) occurs when mononuclear phagocytes are infected through their Fc receptors by immune complexes that form between DENVs and non-neutralizing antibodies. These non-neutralizing antibodies result from previous heterotypic dengue infections.[34]

DENVs produce several syndromes that are conditioned by age and immunological status. During initial dengue infections, most children experience subclinical infection or mild undifferentiated febrile syndromes. Infection provides life-long immunity against the infecting viralsero type, but not against the other serotypes. During secondary dengue infections the pathophysiology of the disease changes dramatically, particularly sequential infections in which infection with DENV-1 is followed by infection with DENV-2 or DENV-3, or infection with DENV-3 is followed by infection with DENV-2.[35] Host factors that increase the risk of severe dengue disease include female sex, several human leukocyte antigen (HLA) class I alleles, a promoter variant of the DC-SIGN receptor gene, a single-nucleotide polymorphism in the tumor necrosis factor (TNF) gene and AB blood group. Dengue infections can be life-threatening when they occur in individuals with asthma, diabetes and other chronic diseases. Secondary dengue infections in adults can produce the classical DSS or severe disease complicated by
haemorrhages. Tertiary dengue infections can cause severe disease, but only rarely. Severe
disease is more common in babies and young children.\[36\]

**Clinical Presentation:** Dengue virus infection causes a spectrum of illnesses ranging from an
asymptomatic infection (80%), or a flu-like mild uncomplicated fever, to classic dengue fever
(DF) or DF with haemorrhagic manifestations (DHF). After an incubation period of 3 to 14 days
(average 7 days), is the early febrile stage (the symptoms of which include fever, malaise,
headache, body pains and rash. During this, clinicians cannot predict which patients will progress
to severe disease. Later symptoms such as bleeding, thrombocytopenia of <100,000 platelets
mm\(^3\), ascites, pleural effusion, hematocrit >20% and clinical warning signs, such as severe and
continuous abdominal pain, persistent vomiting and a sudden reduction in temperature (from
fever to subnormal temperature) associated with profuse perspiration, and sometimes fainting,
can be indicative of plasma leaking and the imminence of shock.\[37\] Serotype cross-reactive
antibodies synthesized from primary infection with particular serotype are not highly specific for
the another dengue serotypes involved in subsequent infections; so they bind to the virions but
do not neutralize them. However, when no neutralizing antibodies are present i.e. infection due
to another serotype of dengue virus, the second infection is under the influence of enhancing
antibodies and the resulting infection and disease are sever. Other complications, such as
massive hemorrhage, disseminated intravascular coagulation, multiple organ failure, and
respiratory failure due to non-cardiogenic pulmonary oedema.\[37,38\]

Recent publications have suggested that the WHO syndromic case definition of DHF/DSS
should be evaluated for clinical utility.\[38\] The classical clinical presentation of dengue virus
infection has been observed in the country, however, several atypical clinical presentations have
also been reported. Hepatic involvement as acute liver failure, hepatic encephalopathy,
hepatomegaly and jaundice;\[39\] Acute renal dysfunction, acute kidney injury, acute myositis, pure
motor quadriplegia;\[40\] neurological manifestations as encephalopathy, acute motor weakness,
seizures, neuritis, paralysis acute viral myositis and acute encephalitis;\[41\] cardiac involvement as
acute reversible cardiac insult, sinoatrial block and atrioventricular dissociation;\[42\] and
haemophagocytic syndrome were reported and the risk of death in such cases is high.\[43\]

**WHO Classification Scheme and its Limitations:** The WHO 2009 classification divides
dengue fever into two groups: uncomplicated and severe;\[44\] stil, the 1997 WHO classification is
being widely used\[45\] Several investigators have reported difficulties in using the system, and
some have had to create new categories or new case definitions to represent the observed
patterns of disease more accurately.\[46\] Each country has developed its own clinical training
programme largely based on the WHO guidelines, but no standard training materials or methods
exist.

The WHO scheme classifies symptomatic dengue virus infections into three categories;
undifferentiated fever, dengue fever, and DHF [Figure: 2]. A case must meet all four of the
following criteria to be defined as DHF: fever or history of fever lasting 2–7 days; ahaemorrhagic
tendency shown by a positive tourniquet test or spontaneous bleeding (petechiae or epistaxis);
thrombocytopenia (<100,000 platelets mm\(^3\)); and evidence of plasma leakage shown either by
hemo concentration (an increase in hematocrit 20% above average for age, sex and population), with substantial changes in serial measurements of packed-cell volume, or by the development of ascites or pleural effusions, or both.[45] DHF is further classified into four severity grades according to the presence or absence of spontaneous bleeding and the severity of plasma leakage. The term dengue shock syndrome (DSS) refers to DHF grades III and IV, in which shock is present as well as all four DHF defining criteria. Moderate shock, identified by narrowing of the pulse pressure or hypotension for age, is present in grade III DHF, whereas profound shock with no detectable pulse or blood pressure is present in grade IV DHF [Table:1].[47] Several study reports shows that some cases did not meet all four WHO criteria for DHF. Study in Vietnam[48] 18% cases and in Nicaragua[49] 77% cases with shock and laboratory confirmed dengue did not fulfill the WHO criteria for DHF. Several groups have also investigated the usefulness of the tourniquet test- said to be a measure of capillary fragility and thrombocytopenia. The findings show that the test differentiates poorly between dengue fever and DHF and it is uncomfortable for the patient, many choose not to use it, yet the test remains an integral part of the existing scheme.[50]

Frequently, assessment and classification are not possible in first-level referral centers, mainly because basic measurements such as packed-cell volume and platelet counts cannot be done. Moreover, the DHF/DSS classification excludes severe dengue disease associated with “unusual manifestations”.[47]

**Laboratory Diagnosis of Dengue Infection:** Laboratory confirmation of dengue infection is crucial as the broad spectrum of clinical presentations, ranging from mild febrile illness to several severe syndromes, can make accurate diagnosis difficult. Among the methods available the diagnosis of dengue fever may be confirmed by microbiological laboratory testing. This can be done by virus isolation in cell cultures, nucleic acid detection by PCR, viral antigen detection (such as for NS1) or specific antibodies (serology)[Table:2].[51]

*a. Virus isolation:* Among the methods available for dengue diagnosis, virus isolation provides the most specific test result. However, facilities that can support viral culture are not always available. Serum is often used for virus isolation but plasma, leukocytes, whole blood and tissues obtained at autopsy can also be used. The *Aedes albopictus* mosquito C6/36 cell line is the method of choice for DENV isolation, although other mosquito (such as *Aedes pseudoscutellaris* AP 61) and mammalian (including Vero cells, LLC-MK2 cells and BHK21 cells) cell lines can also be used 70,71 viral identification is performed using dengue-specific monoclonal antibodies in Immunofluorescence and PCR assays.[52]

*b. Serological testing:* Serological assays are most commonly used for diagnosis of dengue infection as they are relatively inexpensive and easy to perform compared with culture or nucleic acid-based methods.

Seroconversion of IgM or IgG antibodies is the standard for serologically confirming a dengue infection. The presence of IgM or high levels of IgG in acute serum collected from a suspected dengue case suggests a probable dengue infection. A primary infection is characterized by a slow and low-titre antibody response. Immunoglobulin (IgM) antibodies are the first isotype to appear, by day 3–5 of illness in 50% of hospitalized patients and by day 6–10 of illness in 93–
99% of cases. The IgM levels peak ~2 weeks after the onset of fever and then generally decline to undetectable levels over the next 2–3 months [53][Figure:3]. When a dengue infection occurs in individuals who have experienced a previous dengue infection, a secondary immune response occurs, which generates high levels of IgG through the stimulation of memory B cells from the previous infection as well as an IgM response to the current infection. The kinetics of the IgM response are more variable; as IgM levels are significantly lower in secondary dengue infections, false-negative test results for dengue-specific IgM have been reported during secondary infections.[54] Because high levels of IgG compete with IgM for antigen binding, an IgM capture assay can be used.

**MAC-ELISA:** The Armed Forces Research Institute of Medical Sciences (AFRIMS) developed an IgM antibody-capture enzyme-linked immunosorbent assay (MAC-ELISA). Compared to the Haemagglutination inhibition assay as the gold standard, MAC-ELISA shows a sensitivity and specificity of 90% and 98%, respectively, in samples collected after 5 days of fever. In addition to serum, dengue-specific IgM can be detected in whole blood on filter paper (sensitivity 98.1% and specificity 98.5%). Presence of IgM indicate recent or acute infection.[55] False-positive results due to dengue-specific IgG and cross reactivity with other flaviviruses is a limitation of the MAC-ELISA.[56]

**IgG ELISA:** An ELISA for dengue-specific IgG detection can be used to confirm a dengue infection in paired sera. It is also widely used to classify primary or subsequent infections. In general, an IgG ELISA lacks specificity within the flavivirus sero complex groups, however it has been demonstrated that the IgG response to the prM membrane glycoprotein is specific to individual flaviviruses as no cross reactivity was observed.[53,57]

**IgM: IgG ratio:** IgM capture and IgG capture ELISAs are the most common assays for this purpose. According to this method, a dengue infection is defined as a primary infection if the IgM: IgG OD ratio is greater than 1.2 (Using patient sera at 1:100 dilution) or 1.4 (using patient sera at 1:20 dilution), or as a secondary infection if the ratio is less than 1.2 or 1.4.[58] Clinical laboratory findings associated with dengue fever include a neutropenia followed by a lymphocytosis, often marked by atypical lymphocytes. Liver enzyme levels in the serum maybe elevated; the elevation is usually mild, but in some patients, alanine aminotransferase and aspartate aminotransferase levels reach 500 to 1,000 U/liter. In one epidemic of DEN-4, 54% of confirmed patients with data reported on liver enzymes had elevated levels. As hepatic involvement is a prominent feature of dengue hemorrhagic fever (DHF), estimation of aminotransferase can be used as a surrogate marker for it in children.[59]

**Antigen Detection:** PCR and viral antigen detection are more accurate in the first seven days of illness. Dengue antigens can be detected in tissues such as liver, spleen and lymph nodes as well as tissues from fatal cases using an enzyme and a colorimetric substrate with antibodies that target dengue-specific antigens. NS1 is a glycoprotein produced by all flaviviruses and is essential for viral replication and viability. Because this protein is secreted into the bloodstream,
many tests have been developed to diagnose DENV infections using NS1 as an antigen-capture ELISA. Detection of NS1 during the febrile phase of a primary infection may be greater than 90% however is only 60–80% in subsequent infections. NS1 antigen along with viremia presents in blood and may detect from first day of illness. NS1 antigen detection kits are now commercially available.[60] [Figure: 3]

c. **Genome Detection:** Many nucleic acid amplification tests (NAATs) have been developed for the diagnosis of dengue infection. However, none has been commercialized to date and quality assurance materials are not widely available to ensure the quality of the results.

**Reverse Transcriptase PCR (RT-PC):** Many dengue RT-PCR assays have been described in the past 10 years. The most commonly used NAATs are based on a single RT-PCR assay[95, 96, anested RT-PCR assay[96 or a one-step multiplex RT-PCR assay. The sensitivity of RT-PCR assays in comparison to virus isolation in mosquito cell culture varies between 25% and 79%.[61]

**Real-time RT-PCR:** The real-time RT-PCR assay is a one-step assay that allows virus titre to be quantified in approximately 1.5 hours. Many real-time RT-PCR assays have been developed that are either 'singleplex', detecting one single serotype per reaction, or 'multiplex', identifying all four serotypes from a single sample.[62]

**Treatment of Dengue:** There are no specific antiviral drugs for dengue. The management of uncomplicated dengue cases is only supportive, including plenty of oral fluids during the febrile period and paracetamol (acetaminophen). When dengue shock becomes prolonged or recurrent, intravenous fluids should be given carefully according to age and dosage to prevent fluid overload as this can result in pulmonary oedema. A rapid response to platelet and fresh frozen plasma (FFP) transfusion is reported in a study. Early resuscitation can prevent other complications, such as massive hemorrhage, disseminated intravascular coagulation, multiple organ failure, and respiratory failure due to non-cardiogenic pulmonary oedema.[53,63]

**Prophylaxis of Dengue:** A global strategy for dengue prevention and control was implemented more than 10 years ago [Table: 3].[61] The 2002 World Health Assembly Resolution urged greater commitment among Member States and WHO to implement this strategy. Of particular significance in the 2005 revision of the International Health Regulations which includes mention of DF (and yellow fever) as an example of a health ‘event that may constitute a public health emergency of international concern’ and which, under such circumstances, should be notified to WHO.[64,65] In recent years several new, improved or validated tools and strategies for dengue control and prevention have been developed and are available to public health practitioners and clinicians.

**Vector Control:** To reduce or prevent dengue virus transmission there is currently no alternative to vector control. The primary method of controlling *A. aegypti* is by eliminating its habitats.
Containers used for water storage, such as 55-gallon drums, cement cisterns, and even septic tanks, are important in producing large numbers of adult mosquitoes in close proximity to human dwellings. Due to its diurnal behaviour and close association with humans, the principal vector *A. aegypti* requires the use of a combination of vector-control methods, notably environmental management methods and chemical control methods based on the application of larvicides and adulticide space sprays. Environmental management is generally considered to be an essential component of dengue prevention and control. Source reduction, ‘cleanup’ campaigns, regular container emptying and cleaning installation of water supply systems, solid waste management and urban planning all fall under the rubric of environmental management. Biological control agents, including larvivorous fish and copepods, have had a demonstrable role in controlling *A. aegypti*. Most efforts in vector control are centred at the household and community levels, but with few exceptions, the achievements to date have been largely unspectacular.

**Vaccine Development:** Failure of vector control due to several factors, continuing spread and increasing intensity of dengue has renewed interest and investment in dengue vaccine development. Making a safe, effective and affordable tetravalent dengue vaccine a global public health priority. The observation that DHF/DSS is associated with DENV second infection with another serotype poses a special challenge to the development of a dengue vaccine, leading to a requirement that such vaccines should induce a robust immune response against the four serotypes in naive as well as previously immune individuals. The ideal dengue vaccine should be free of reactogenicity, induce life-long protection against infection with any of the four DENV serotypes and be affordable. Significant progress in the development of dengue vaccine candidates has been achieved lately. An Acambis/Sanofi Pasteur yellow fever–dengue chimeric vaccine is in advanced Phase II testing in children in Thailand and others are in Phase 1 or advanced preclinical evaluation. It is expected that a licensed vaccine will be available in less than 10 years.

**Prevention of Dengue in Travelers:** There is no completely effective method of preventing dengue infection in travelers visiting tropical areas. The risk of infection can be significantly decreased, however, by understanding the basic behavior and feeding habits of the mosquito vector and by taking a few simple precautions to decrease exposure to infective mosquito bites. Female *A. aegypti* mosquitoes prefer to feed indoors, with peak biting activity occurring for 2 to 3 hours after daybreak and for 3 to 4 hours before nightfall. Precautions, therefore, include staying in screened or air conditioned rooms, spraying these rooms with aerosol bomb insecticides to kill adult mosquitoes indoors (Especially in bedrooms), using a repellent containing dimethyl-metatoluamide (DEET) on exposed skin, and wearing protective clothing treated with a similar repellent. The risk of exposure maybe lower.

**CONCLUSIONS:** Dengue is now a global threat and in almost every country located in the tropics. Every aspect of dengue viral infection continues to be a challenge; the pathogenesis of severe dengue disease is not known and clinicians cannot predict which patients will progress to severe disease. Cases with atypical manifestations are difficult to define with WHO dengue...
classification scheme and therefore need reassessment. Even though no vaccines or drugs are available and the vector control measures are inadequate, severe disease can be successfully managed by careful monitoring of the warning signs and early initiation of aggressive intravenous rehydration therapy.

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| Grade I   | Fever, Positive tourniquet test, Easy bruising, Tachycardia, normal blood & pulse pressure. |
|-----------|-------------------------------------------------------------------------------------------------|
| Grade II  | Fever, Spontaneous bleeding in form of skin/other bleed Tachycardia, normal blood & pulse pressure. |
| Grade III | Fever, may with cold peripheries, Spontaneous bleeding, Circulatory failure, weak pulse, narrow pulse pressure and hypotension. |
| Grade IV  | Fever, may with cold peripheries, Spontaneous bleeding, Profound shock; undetectable blood pressure or peripheral pulse. |

Table 1: Grading of Dengue Hemorrhagic Fever

**Confirmed Dengue Infection**
1. Antigen detection: NS1
2. IgM capture ELISA
3. IgG ELISA
4. Elevated IgG titre by HAI test
5. Genome detection by NAA tests: PCR
6. Virus isolation

| Primary dengue                              | Secondary dengue                       |
|---------------------------------------------|---------------------------------------|
| 1. Antigen detection: NS1                   | 1. NS1 positive with IgG ELISA positive |
| 2. IgM capture ELISA                        | 2. Both IgM & IgG ELISA positive       |
| 3. Both NS1 & IgM positive                  | 3. IgM:IgG ratio is low                |
| 4. IgM:IgG ratio is high                    |                                       |

Table 2: Laboratory Diagnosis of a Dengue Virus Infection

- Vector control and integrated vector management
- Active disease surveillance.
- Comprehensive health information system, awareness and health education
- Emergency preparedness
- Capacity building and training
- Vector control research

Table 3: The global Strategy for Dengue Prevention and Control
**Figure 1**: Transmission Cycle of Dengue.

![Diagram of Dengue transmission cycle](image)

- **Infected mosquito** (*Aedes aegypti*)
- **Incubation Period**: 3 to 14 days
- **Healthy person**
- **Infected person**

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**Figure 1A**

**Diagram details**:

- **Mosquito**
  - **Bite Acquires Infection**
  - **Extrinsic Incubation Period**
  - **Mosquito Rebite Transmits Infection**
  - **Intrinsic Incubation Period**

- **Viremia**
  - **Days**: 0, 4, 8, 12, 16, 20, 24, 28
  - **Epidemic Cycle**
  - **Illness**

- **Person 1**
- **Person 2**
Figure 2: WHO Classification of Symptomatic Dengue Infection.

Figure 3: Dengue virus, Antigen and Antibody responses used in diagnosis.
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