| TABLE 6–4 | Examples of Cell Receptors for Human Viruses | |
|---|---|---|
| VIRUS | RECEPTOR | CELLULAR FUNCTION |
| Adenoviruses | Integrins | Cell surface receptors that interact with extracellular matrix |
| Arenaviruses | α -dystroglycan | Dystrophin-associated glycoproteins, transmembrane linkage |
| Cytomegalovirus | Heparan sulfate | Glycoprotein |
| Coronaviruses | Aminopeptidase N | Protease |
| Dengue virus | Heparin sulfate | Glycoprotein |
| | Sulfated glycosaminoglycans | Polysaccharides |
| | Lectins | Glycoprotein |
| Epstein-Barr virus | CR2 (CD21) | Complement receptor |
| Filoviruses (Ebola and Marburg) | TIM-1 | T-cell Ig and mucin domain 1 |
| Hantavirus | Integerins | Cell surface proteins that interact with extracellular matrix |
| Hepatitis A virus | $\alpha_2$-Macroglobulin | Plasma protein (inhibitor of coagulation, fibrinolysis) |
| Herpes simplex | Heparan sulfate | Glycoprotein |
| Human herpes 7 | CD4 | Immunoglobulin superfamily |
| HIV | CD4 | Immunoglobulin superfamily |
| | CXCR4 and CCR5 | Chemokine receptors |
| Influenza A | Sialic Acid | Glycoprotein |
| Measles | CD46 | Complement regulation |
| Papillomavirus | α-6 β-4 integrin | Cell surface proteins |
| Parvovirus B19 | Erythrocyte P antigen | Erythroid precursors |
| Poliovirus | PVR | Immunoglobulin superfamily |
| Polyomavirus | Serotonin | G protein superfamily |
| Rabies | Acetylcholine receptor | Signaling |
| Reoviruses | Sialic Acid | Glycoprotein |

Important cell receptors for human viruses. Important ones are highlighted in red box.

## CHIKUNGUNYA FEVER

Chikungunya (a native term for "that which bends up") is an Alphavirus (Togaviruses) transmitted by mosquitoes (*A aegypti* and some other species), particularly in urban areas of Asia, Africa, and most recently in limited areas of Southern Europe and the Caribbean. The virus may be maintained in a sylvatic subhuman primate reservoir. The incubation period is between 2 and 12 (average 3-7) days and a majority of infected people develop some symptoms.

Symptoms

- Symptoms usually begin 3–7 days after being bitten by an infected mosquito.

- Illness is characterized by an abrupt onset of fever, accompanied by excruciating myalgia (muscle pain) and polyarthritis (inflammation of the joints).
- Infected people may experience additional symptoms such as headache, myalgia, arthritis, conjunctivitis, nausea, vomiting, or maculopapular rash. Symptoms usually last 1 week, but the musculoskeletal complaints can sometimes persist for weeks to months. The most common symptoms are fever and joint pain.
- Chikungunya disease does not often result in death, but the symptoms can be severe and disabling.
- Most patients feel better within a week. In some people, the joint pain may persist for months.
- People at risk for more severe disease include newborns infected around the time of birth, older adults (≥65 years), and people with medical conditions such as high blood pressure, diabetes, or heart disease.
- Once a person has been infected, he or she is likely to be protected from future infections.

Diagnosis- by detecting IgM or RNA by RT-PCR.

Treatment

- There is no vaccine to prevent or medicine to treat chikungunya virus.
- Treat the symptoms:
    - Get plenty of rest.
    - Drink fluids to prevent dehydration.
    - Take medicine such as acetaminophen (Tylenol®) or paracetamol to reduce fever and pain.
    - Do not take aspirin and other non-steroidal anti-inflammatory drugs (NSAIDS until dengue can be ruled out to reduce the risk of bleeding).

# DENGUE VIRUS

Dengue viruses are spread to people through the bite of an infected *Aedes* species (*Ae. aegypti* or *Ae. albopictus*) mosquito. Dengue fever also known as breakbone fever, is a mosquito-borne infection caused by a flavivirus. Dengue is common in more than 100 countries around the world. These viral agents are widespread throughout the world, particularly Africa, the Americas, the Eastern Mediterranean, South Asia, South-east Asia and the Western Pacific, the Middle East, Africa, the Far East, and the Caribbean Islands.

Forty percent of the world's population, about 3 billion people, live in areas with a risk of dengue. Dengue is often a leading cause of illness in areas with risk. Each year, up to 400 million people get infected with dengue. Approximately 100 million people get sick from infection, and 22,000 die from severe dengue.

In 1943, Ren Kimura and Susumu Hotta first isolated the dengue virus. Dengue virus (Flavivirus) has four related serotypes (DEN 1-4), any of which may exist concurrently in a given endemic area. Dengue infections are caused by four closely related viruses named DEN-1, DEN-2, DEN-3, and DEN-4. These four viruses are called serotypes because each has different interactions with the antibodies in human blood serum. The four dengue viruses are similar — they share approximately 65% of their genomes.

## Dengue Virus Genome and Structure

The dengue virus genome is a single strand of RNA. It is referred to as *positive-sense RNA* because it can be directly translated into proteins. The viral genome encodes ten genes (Figure 2). The genome is translated as a single, long polypeptide and then cut into ten proteins.

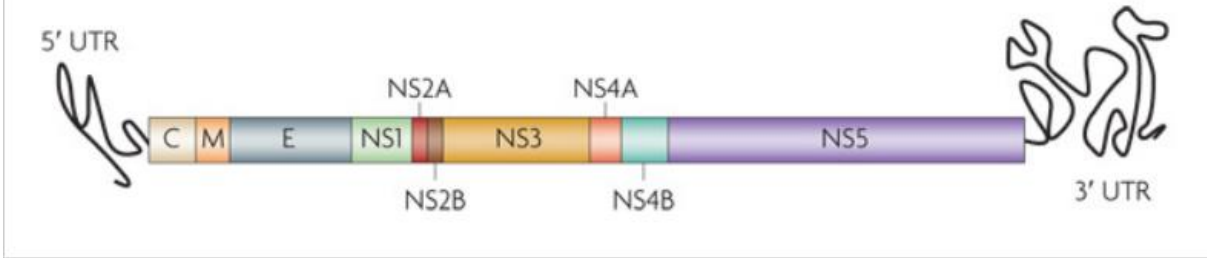
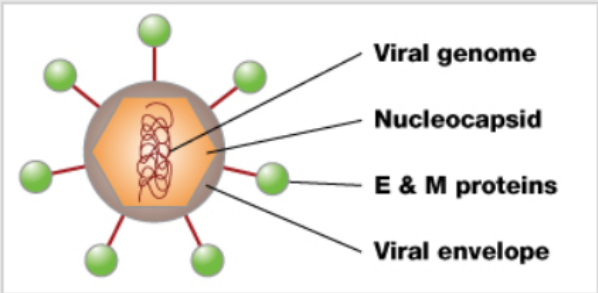



**Figure 2: Dengue virus genome**
The dengue virus genome encodes three structural (capsid [C], membrane [M], and envelope [E]) and seven nonstructural (NS1, NS2A, NS2B, NS3, NS4A, NS4B, and NS5) proteins.

Three are structural proteins: the capsid (C), envelope (E), and membrane (M) proteins. Seven are non-structural proteins: NS1, NS2A, NS2B, NS3, NS4A, NS4B, and NS5. These non-structural proteins play roles in viral replication and assembly.




**Dengue virus structure**
The dengue virus has a roughly spherical shape. Inside the virus is the nucleocapsid, which is made of the viral genome and C proteins. The nucleocapsid is surrounded by a membrane called the viral envelope, a lipid bilayer that is taken from the host. Embedded in the viral envelope are E and M proteins that span through the lipid bilayer. These proteins form a protective outer layer that controls the entry of the virus into human cells.

## Dengue Virus Replication and Infectious Cycle

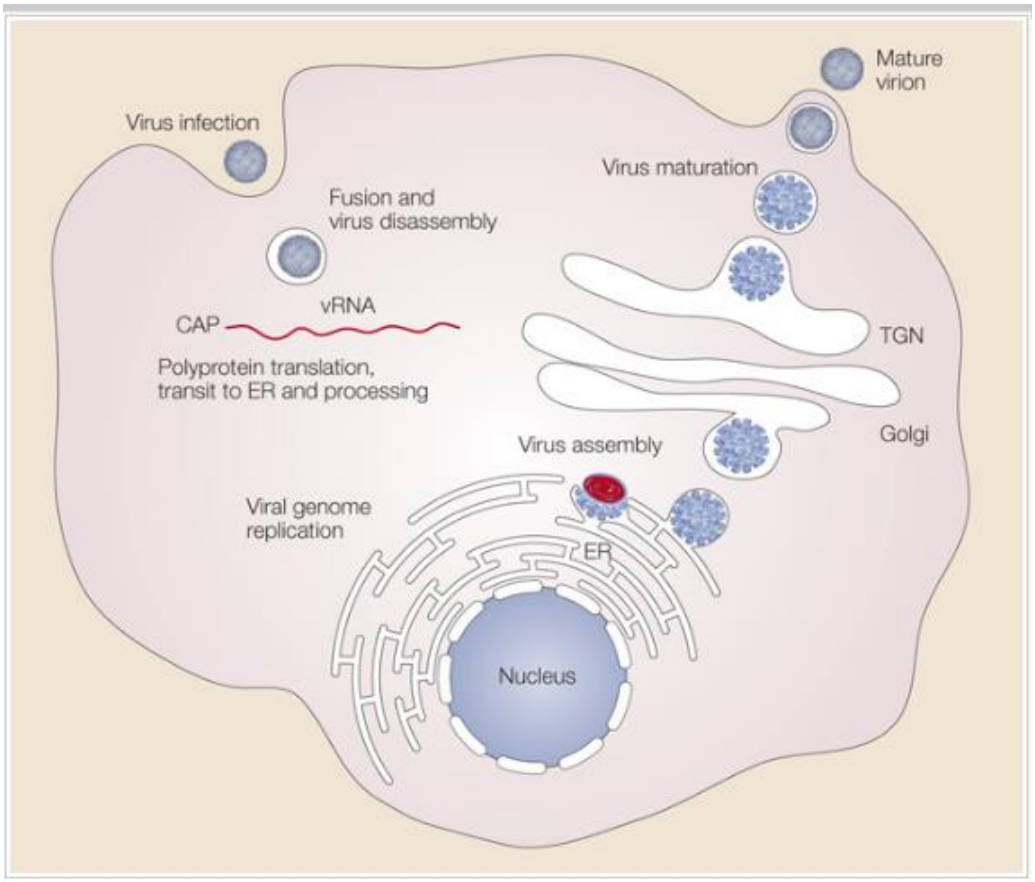



**Figure 4: Dengue virus replication**
The dengue virus attaches to the surface of a host cell and enters the cell by a process called endocytosis. Once deep inside the cell, the virus fuses with the endosomal membrane and is released into the cytoplasm. The virus particle comes apart, releasing the viral genome. The viral RNA (vRNA) is translated into a single polypeptide that is cut into ten proteins, and the viral genome is replicated. Virus assembly occurs on the surface of the endoplasmic reticulum (ER) when the structural proteins and newly synthesized RNA bud out from the ER. The immature viral particles are transported through the trans-Golgi network (TGN), where they mature and convert to their infectious form. The mature viruses are then released from the cell and can go on to infect other cells.

The mosquito vector (*A aegypti*) is the same as the domestic vector of yellow fever. The known transmission cycle is human–mosquito–human, although a sylvatic cycle involving monkeys may also exist. The incubation period is 4 to 7 days. The symptoms last for 3 to 10 days.

The characteristic clinical illness usually results in high fever, an erythematous rash, and severe pain in the back, head, eyes (behind eyes), muscles, bone and joints. There is also sometimes mild bleeding manifestation such as nose or gum bleed, or bruising. Especially in the Far East (Philippines, Thailand, and India), dengue has periodically assumed a severe form characterized by shock, pleural effusion, severe abdominal pain and vomiting, and hemorrhage often followed by death. Severity of the dengue disease is seen more in children.

The treatment is supportive and there is no vaccine available for protection. Avoiding mosquito bites is the best preventive measure. Protection after recovery is serotype specific. People who recover from infection of a serotype are protected for life against the same serotype. There is some cross-reactive immunity to other serotypes, which is only temporary and partial. More importantly, subsequent infections with other serotypes increase the risk of developing severe dengue disease, most likely by antibody-dependent enhancement (enhancing antibodies) that do not neutralize the virus rather enhance viral entry into the host cells.

Clinical Findings

Clinical disease begins 4–7 days (range, 3–14 days) after an infective mosquito bite. The onset of fever may be sudden or there may be prodromal symptoms of malaise, chills, and headache. Pains soon develop, especially in the back, joints, muscles, and eyeballs. Fever lasts from 2 to 7 days, corresponding to peak viral load.

The temperature may subside on about the third day and rise again about 5–8 days after onset (“saddleback” form). Myalgia and deep bone pain (breakbone fever) are characteristic. A rash may appear on the third or fourth day and last for 1–5 days. Lymph nodes are frequently enlarged. Classic dengue fever is a self-limited disease. Convalescence may take weeks, although complications and death are rare. Especially in young children, dengue may be a mild febrile illness lasting a short time. A severe syndrome—dengue hemorrhagic fever or dengue shock syndrome—may occur in individuals (usually children) with passively acquired (as maternal antibody) or preexisting nonneutralizing heterologous dengue antibody caused by a previous infection with a different serotype of virus. Although initial symptoms simulate normal dengue, the patient’s condition worsens.

The key pathological feature of dengue hemorrhagic fever is increased vascular permeability with plasma leakage into the interstitial spaces associated with increased levels of vasoactive cytokines. This can lead to life-threatening shock in some patients.

Monocytes are the major target cell in the blood for dengue virus infection. Circumstantial evidence suggests that secondary infection with dengue type 2 after a type 1 infection is a particular risk factor for severe disease. The pathogenesis of the severe syndrome involves preexisting dengue antibody. It is postulated that virus–antibody complexes are formed within a few days of the second dengue infection and that the nonneutralizing enhancing antibodies promote infection of higher numbers of mononuclear cells followed by the release of cytokines, vasoactive mediators, and procoagulants, leading to the disseminated intravascular coagulation seen in the hemorrhagic fever syndrome. Crossreactive cellular immune responses to dengue virus may also be involved.

Laboratory Diagnosis

- Reverse transcriptase PCR (RT-PCR)-based methods are available for rapid identification and serotyping of dengue virus in acute-phase serum, roughly during the period of fever.
- The current favored approach is inoculation of a mosquito cell line with patient serum coupled with nucleic acid assays to identify a recovered virus.
- A variety of methods are available; the most commonly used methods are envelope/membrane viral protein-specific capture IgM or IgG ELISA and the HI test. IgM antibodies develop within a few days of illness. Neutralizing and hemagglutinationinhibiting antibodies appear within a week after the onset of dengue fever.

Immunity

Four serotypes of the virus exist that can be distinguished by molecular-based assays and by neutralization tests. Infection confers lifelong protection against that serotype, but cross protection between serotypes is of short duration. Reinfection with a virus of a different serotype after the primary attack is more apt to result in severe disease (dengue hemorrhagic fever). The changing disease patterns are probably related to rapid urban population growth, overcrowding, and lax mosquito control efforts.

Treatment and Control

There is no antiviral drug therapy. Dengue hemorrhagic fever can be treated by fluid replacement therapy. There is no vaccine, but candidate vaccines are under development. Vaccine development is difficult because a vaccine must provide protection against all four serotypes of virus. Therapeutic antibodies able to neutralize multiple genotypes of dengue are also under development. Control depends on antimosquito measures, including elimination of breeding places and the use of insecticides. Screened windows and doors can reduce exposure to the vectors.

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