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DENGUE INFECTION

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ABSTRACT

Dengue is widespread in tropical regions, with local variations in transmission strongly influenced by factors such as rainfall, temperature, urbanization, and the distribution of the primary mosquito vector, *Aedes aegypti*. Endemic transmission of the virus is currently reported in the Eastern Mediterranean, Americas, Southeast Asia, Western Pacific, and Africa. Sporadic local outbreaks have also occurred in Europe and the United States due to the introduction of the virus into areas with the presence of *Aedes aegypti* and *Aedes albopictus*, a secondary vector. While the global burden of dengue remains unclear, its epidemiological trends are concerning for both public health and the global economy. Dengue has been identified as a growing threat, driven by increasing urbanization, water scarcity, and potentially environmental changes. The World Health (WHO) suggests that dengue control is technically achievable with coordinated international support for national programs. This primer offers an overview of dengue, covering its epidemiology, control strategies, disease mechanisms, diagnosis, treatment, and key research priorities.

I. INTRODUCTION

Dengue is one of the world's most significant neglected tropical diseases, with its incidence increasing over 30-fold in recent decades. This rise parallels the geographic spread of *Aedes* mosquitoes and dengue viruses (DENVs). Currently, dengue transmission occurs in regions such as the Eastern Mediterranean, Americas, Southeast Asia, Western Pacific, and Africa, with new cases emerging in non-endemic areas of the United States and Europe. Dengue epidemics place a substantial burden on health services, families, and the economies of affected nations.

The term "dengue viruses" refers to four closely related, genetically and antigenically distinct viruses, known as serotypes 1–4, each of which is further categorized into genotypes. Infection with any of the four serotypes can result in various clinical outcomes, with the timing or sequence of infections playing a key role in determining disease severity and progression. Dengue is classified clinically as either dengue with or without warning signs, or severe dengue, a system introduced by the WHO in 2009 to improve clinical management. Warning signs are used to identify patients at risk of more severe disease, who may require supportive therapy. Dengue illness is also divided into three phases: the acute (febrile) phase, the critical (plasma leakage) phase, and the convalescent (reabsorption) phase. This classification replaced the 1997 WHO system, which focused on two key pathological features of the disease: plasma leakage and abnormal haemostasis. Under the previous system, patients were classified as having either dengue fever, the most common manifestation of DENV infection, or dengue haemorrhagic fever and dengue shock syndrome (DHF/DSS), which involve plasma leakage, coagulopathy, and sometimes bleeding that can lead to circulatory shock and organ failure.

This Primer focuses on the epidemiology, diagnosis, clinical management, pathogenic mechanisms, and control of dengue, and discusses research priorities in the field.

II. EPIDEMIOLOGY

Dengue viruses (DENVs) are maintained in an endemic-epidemic cycle involving humans and mosquitoes, particularly in densely populated tropical urban areas. These viruses are fully adapted to humans, and the primary vector, *Aedes aegypti*, has long since evolved from sylvatic cycles involving non-human primates and canopy-dwelling *Aedes* mosquitoes in the rainforests of Asia and Africa. While these sylvatic cycles still exist, their relevance to public health remains uncertain. *Aedes aegypti* was introduced to the Americas during the 1600s through the slave trade and later spread globally with the expansion of the shipping industry. This mosquito species thrives in close association with humans, feeding on them, resting in their homes, and laying eggs in artificial water containers. While the average lifespan of a female mosquito is about one week, some can live for up to two weeks or more.

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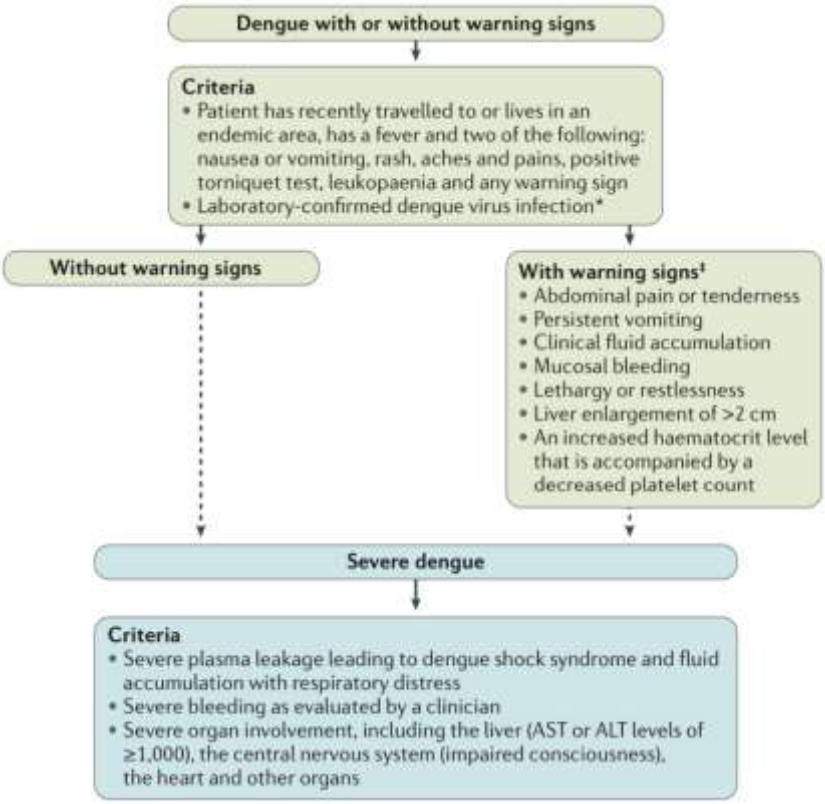
III. MECHANISM

Dengue viruses (DENVs) are part of the *Flavivirus* genus within the *Flaviviridae* family. The four serotypes of DENV are spherical, enveloped viral particles with a diameter of around 500 Å. Each serotype's genome consists of approximately 11 kb of positive-sense, single-stranded RNA, encoding ten proteins. Three of these are structural proteins: the membrane (M) protein, envelope (E) protein, and capsid (C) protein. The remaining proteins are non-structural (NS), including NS1, NS2A, NS2B, NS3, NS4A, NS4B, and NS5.

Structure and Function of the E and M Proteins

The process of delivering the DENV genome into the host cell cytoplasm is complex and involves several steps. Initially, the viral membrane fuses with the host plasma membrane, followed by endocytosis of the virus into an endosome. A pH-dependent fusion then occurs between the viral and endosomal membranes. Inside the virus particle, the RNA is complexed with capsid proteins and is enclosed by a lipid bilayer membrane.



IV. STRUCTURE AND FUNCTION OF NS PROTIEN

The non-structural (NS) proteins play crucial roles in viral replication and packaging, processes closely linked to the host's endoplasmic reticulum (ER) and secretory pathways. *NS1* is a 46 kDa glycoprotein that exists in three forms: an ER-resident form, a membrane-anchored form, and a secreted form. Initially synthesized as a soluble monomer, *NS1* associates with the membrane after dimerization within the ER lumen. Recent structural studies of *NS1* have revealed hydrophobic domains in the dimer that likely facilitate this membrane association.

Intracellular *NS1* is involved in early stages of viral RNA replication and is found in virus-induced vesicular compartments that contain viral replication complexes. *NS1* is also transported to the cell surface, where it either stays associated with the cell membrane or is secreted as a soluble, lipid-associated hexer (*sNS1*). *sNS1* can be detected in the blood of infected individuals as early as the first day of symptoms, with levels ranging from ng/mL to mg/mL during the acute phase of infection. The concentration of *sNS1* correlates with peak viral load and disease severity, particularly in secondary DENV infections.

Several studies suggest that *sNS1* plays a key role in dengue pathogenesis. For example, highly purified recombinant *NS1* (rNS1), free from bacterial endotoxin activity, directly activates mouse macrophages and

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human peripheral blood mononuclear cells via Toll-like receptor 4 (TLR4). This activation triggers the release of pro-inflammatory cytokines and chemokines. Additionally, in both in vitro and in vivo models of vascular leakage, exposure to *NS1* disrupts endothelial cell monolayer integrity, contributing to the pathophysiology of the disease.

IMMUNE STATUS

Infection with any DENV serotype provides long-term immunity to the specific serotype that caused the infection (homotypic immunity), along with a brief period of immunity to other serotypes (heterotypic immunity). In individuals who are immune to only one serotype (monotypic immunity), only a small fraction of circulating antibodies are capable of neutralizing the homologous DENV. These polyclonal antibodies target several epitopes, some of which are located at the hinge region between domains I and II of the E protein on the surface of the intact virion.

Shortly after the first DENV infection, antibodies may neutralize heterotypic DENVs in vitro. However, over the following months, the antibodies become increasingly specific to the serotype causing the current infection. These in vitro changes in neutralizing antibody specificity correlate with in vivo observations. In monotypic-immune individuals, there is an initial short period of cross-protection (approximately two months) against infection with heterotypic DENVs, as well as a longer period (about two years) of protection against severe disease from such infections. Recently, a class of broadly cross-neutralizing antibodies has been identified and characterized. It remains unclear whether these antibodies are selectively produced during second heterotypic DENV infections and contribute to broad protection across all DENV serotypes. Neutralizing antibodies are thought to persist for a lifetime and are believed to provide long-lasting protection against reinfection with the homologous DENV serotype.

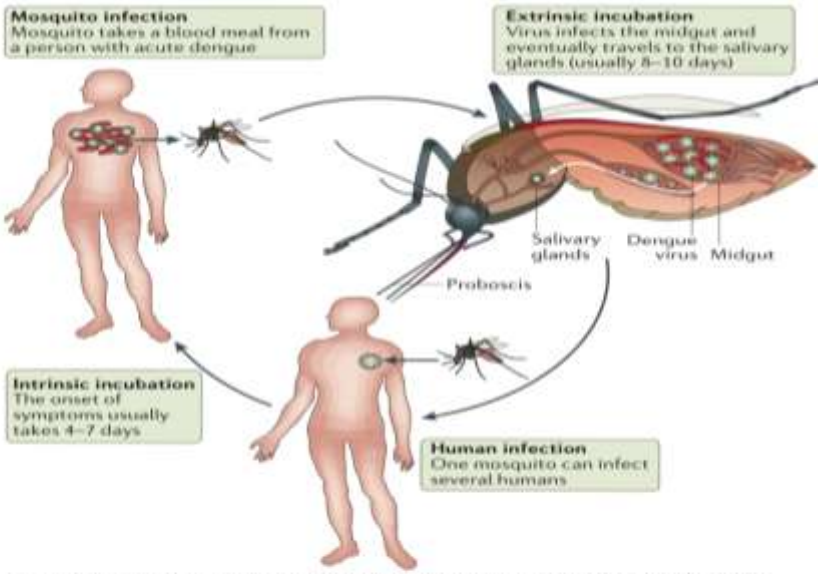

Figure 2 | **The urban dengue virus cycle in humans and mosquitoes.** An Aedes aegypti mosquito can become infected by feeding on a person in the viraemic phase of infection. During the extrinsic phase of the cycle, dengue viruses first infect mosquito midgut cells and other tissues before disseminating to the salivary glands. An infected mosquito can then transmit the dengue virus to several humans as it feeds or attempts to feed. Once infected, it takes an average of 4–7 days for the onset of symptoms and for a person to become capable of transmitting dengue virus to a new mosquito. Both symptomatic and asymptomatic individuals can transmit dengue virus to mosquitoes.

VIRAL STEROTYPES

Although all four DENV serotypes are transmitted by *Aedes* mosquitoes and, in theory, cause similar clinical manifestations with comparable patterns of systemic spread, there are some biological differences between them. Specific associations between certain serotypes or genotypes and factors such as disease severity, epidemic potential, and transmission efficiency have been observed. However, these associations may be influenced by factors beyond the intrinsic properties of the virus, including host immunity, the ability of the

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mosquito vector to become infected and transmit the virus to humans, and environmental conditions that may drive the displacement of one genotype by another—factors that are not yet fully understood.

The idea that certain DENV strains may have higher "virulence" and epidemic potential than others was proposed in the 1970s. The polyprotein of DENV shows a 30% divergence across the four serotypes, and within each serotype, multiple genotypes exhibit distinct geographical distributions. Some data suggest that genetic variations in DENV could directly influence transmission efficiency in mosquitoes or disease outcomes in humans. For example, studies have shown that DENV2 strains of Asian origin replicate at higher levels in human dendritic cells, infect *Ae. aegypti* mosquitoes more effectively, and are transmitted more efficiently than American DENV2 strains. Additionally, certain strains of DENV3 replicate more rapidly in mosquitoes than other DENV3 strains, which may enable them to displace established DENV3 strains.

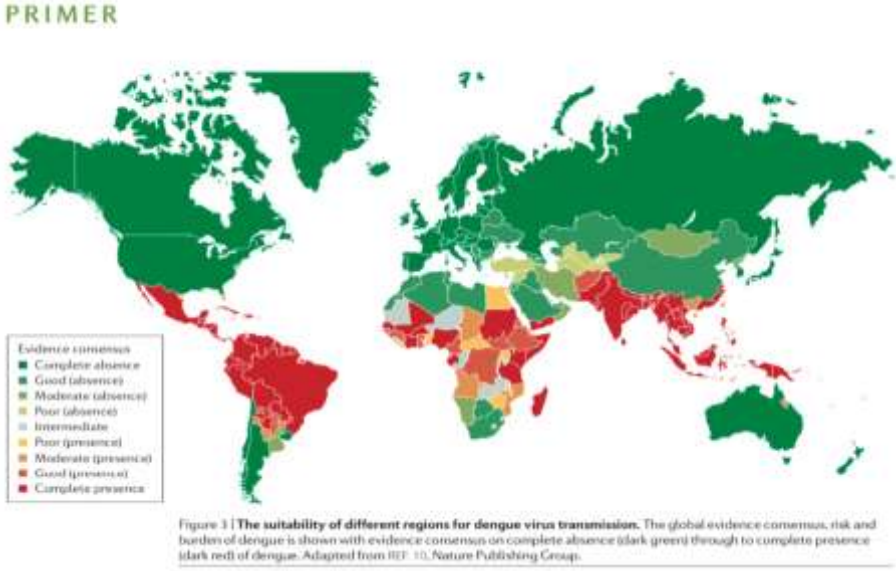

Figure 1 | **The suitability of different regions for dengue virus transmission.** The global evidence consensus, risk and burden of dengue is shown with evidence consensus on complete absence (dark green) through to complete presence (dark red) of dengue. Adapted from REF. 10, Nature Publishing Group.

PATIENT AGE AND SEX

Age influences the expression of dengue disease in complex ways. Disease severity following a first DENV infection is closely tied to age. In young, susceptible children, the first DENV infection is typically mild or asymptomatic, while adults with a first infection usually develop dengue fever. More severe outcomes are often seen in older adults or those with chronic conditions like diabetes, chronic obstructive pulmonary disease, or cardiovascular disease. Bleeding events are common in both the elderly and individuals with comorbidities. For example, adult women may experience menorrhagia during primary DENV infections, and individuals with peptic ulcer disease may have gastrointestinal bleeding.

The risk of progressing to dengue hemorrhagic fever (DHF) or dengue shock syndrome (DSS) in individuals with prior exposure (sensitized individuals) decreases with age. In a population exposed to the same rates of secondary DENV2 infection, DHF rates were more than five times higher in children than in adults. This is likely due to differences in host susceptibility to vascular permeability during secondary infections, with children being more prone to capillary fragility than adults. The greater density and surface area of microvessels in growing children may contribute to this higher microvascular permeability. Additionally, the outcome of secondary DENV infections is influenced by sex, with girls over 4 years old having higher rates of DSS than boys of any age.

Mature dengue virus particles attach to host cells through the binding of the envelope (E) protein to unknown receptors. Viral entry occurs via receptor-mediated endocytosis. Once inside the host cell, a pH-dependent rearrangement of the E protein enables the fusion of the viral and endosomal membranes, releasing the nucleocapsid. The nucleocapsid disassembles to release the capped viral genomic RNA, which is then translated into a single long polyprotein. This polyprotein is cleaved by the viral proteases NS2B or NS3, and host proteases, into individual proteins. The resulting non-structural (NS) proteins are directed to replication sites on vesicles derived from the endoplasmic reticulum (ER) to initiate transcription.

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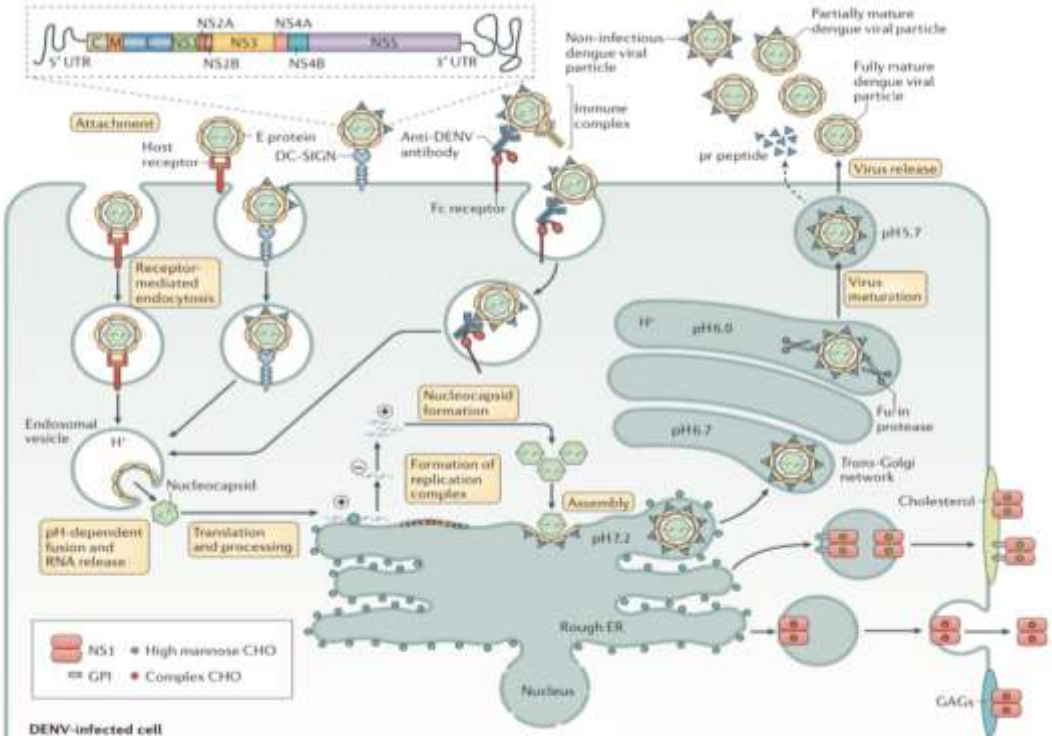
NS1 is initially expressed in the ER, where it is modified by the addition of high-mannose carbohydrate (CHO) groups, facilitating its association with the membrane. Some NS1 proteins acquire glycosyl-phosphatidylinositol (GPI) anchors. Both membrane-bound and GPI-anchored NS1 are trafficked to the cell surface via an unknown pathway, where they interact with lipids like cholesterol. A portion of the cell surface-associated NS1 may be secreted NS1 that binds directly to cell surface glycosaminoglycans (GAGs). Additionally, some NS1 is secreted from the host cell.

Meanwhile, the precursor membrane (prM) protein and E protein are embedded in the ER membrane and encapsulate the newly formed nucleocapsid. This immature particle buds into the ER lumen. It is then transported via the secretory pathway, where the low pH of the trans-Golgi network induces substantial rearrangement of the prM and E proteins. This rearrangement allows for cleavage of prM by the furin protease, converting it into the mature M protein. The mature virion is then released from the host cell, along with the cleaved pr peptide. Some viral particles are released with prM still intact, rendering them unable to infect new host cells. Positive-sense and negative-sense RNA are indicated by + and - signs, respectively. Key components include the capsid (C), dendritic cell-specific ICAM3-grabbing non-integrin (DC-SIGN), and untranslated regions (UTRs). Adapted from REF. 302, *Nature*.



LIVE ATTENUATED VACCINE

Live attenuated vaccines offer several advantages, such as inducing an immune response that closely resembles that of a natural infection, stimulating strong B cell and T cell responses, and providing long-lasting immune memory. These vaccines can be produced at relatively low cost and may be effective after just one dose. Early efforts to develop a dengue vaccine focused on attenuating wild-type DENV strains by passing them through various primary cells or cell lines, such as primary dog kidney (PDK) cells and African green monkey kidney (GMK) cells. This in vitro passaging reduces the virus's virulence in humans and was explored in two main research series.

In the first series, vaccine strains from each DENV serotype, obtained by passaging through PDK or GMK cells, were selected and tested in monovalent, bivalent, trivalent, and tetravalent vaccine trials in Thai adults. Among those receiving the tetravalent vaccine, only one out of ten seroconverted to all four serotypes, and the neutralizing antibody response was primarily directed against DENV3. Subsequent tetravalent formulations showed that the dominant neutralizing antibody response remained focused on DENV3. Building on these findings, the DENV3 vaccine strain was genetically re-derived, cultured in Vero cells, and tested in volunteers.

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SUBUNIT VACCINE

Protein-based vaccines offer several advantages over live attenuated vaccines, including enhanced safety, the potential to induce a balanced immune response against all four DENV serotypes, and the ability to accelerate the immunization schedule. This can help reduce the risk of incomplete immunity and minimize the chances of antibody-dependent enhancement (ADE). However, these vaccines typically require the use of adjuvants and multiple doses to achieve optimal immunogenicity, and they may not be as effective as live attenuated vaccines in inducing long-lasting immunity.

The primary target for subunit vaccine development against dengue has been the E glycoprotein, as it contains most of the neutralizing epitopes on the DENV virion. Recombinant E proteins have been produced using various expression systems, including *Escherichia coli*, baculovirus-infected insect cells, yeast, and mammalian cells. Truncated recombinant E protein subunits (80E) from each serotype have been produced in a *Drosophila melanogaster* Schneider 2 cell expression system and shown to induce neutralizing antibody responses in mice and non-human primates. A Phase I trial of the DENV1-80E vaccine candidate has been completed, and a Phase I trial of a tetravalent formulation started in 2012. The subunit vaccine could play a key role in future dengue control strategies.

INACTIVATED VACCINE

Inactivated vaccines are designed to induce a balanced immune response without the risk of viral interference, where the replication of one virus could hinder the immune response against all four DENV serotypes, as can happen with live attenuated vaccines. Additionally, inactivated vaccines eliminate the risk of viral replication or reversion to a wild-type virus. However, they are generally less effective than live attenuated vaccines in generating long-lasting immunity, requiring multiple doses and the use of adjuvants to achieve optimal immunogenicity in individuals without prior exposure.

A dengue purified formalin-inactivated vaccine (DPIV) is currently under development and has demonstrated immunogenicity in rhesus macaques. A Phase I trial of this vaccine began in 2011, and two Phase I trials of a tetravalent version commenced in 2012—one in a dengue-primed population and another in a non-endemic region. An inactivated vaccine could play an important role in a heterologous prime-boost vaccination strategy.

DNA VACCINE

DNA vaccines stimulate both MHC class I and class II pathways, leading to the activation of CD4+ and CD8+ T cells as well as antibody responses. Because DNA vaccines do not replicate, they are considered safer than live attenuated vaccines and have low reactogenicity. Additional benefits include low production costs, ease of manufacturing, and stability at various temperatures. Most dengue DNA vaccine approaches have focused on inducing immune responses against the prM and E proteins in mice and primates. DNA vaccines targeting the NS1 protein have also been tested in mice, with one DNA vaccine expressing DENV1 prM, E, and NS1 proteins showing better protection than a vaccine without the NS1 protein. Continued development in DNA vaccination may lead to an effective DENV vaccine. Various viral vector platforms, including vaccinia virus, adenovirus, and alphavirus vectors, have been investigated as delivery systems for DENV antigens. These vaccines are primarily aimed at generating and evaluating anti-E protein antibody responses. However, none of these viral vector-based dengue vaccine candidates has yet progressed to Phase I clinical trials.

CAPILLARY LEAKAGE

Capillary leakage typically becomes noticeable towards the end of the febrile phase (days 3–6) and intensifies over the next 24–48 hours. During defervescence, identifying warning signs (see FIG. 1) is crucial for distinguishing patients at risk of severe disease and those requiring hospitalization, as outlined in the 2009 WHO guidelines. Families must also be educated to recognize the warning signs of dengue shock once the fever subsides. Patients should be clinically monitored for markers of severe disease risk when possible. These warning signs act as indicators of impending shock, and once recognized, immediate intervention with intravenous fluid therapy is essential to replace the fluid lost from the circulatory system due to capillary leakage. Crystalloid solutions, such as lactated Ringer's solution or normal saline, are recommended for fluid replacement. Fluid therapy should continue based on the patient's clinical condition and fluid balance. When managed according to WHO guidelines, most patients with dengue will recover.

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However, some patients may show poor clinical progress, with pronounced hypotension, mental confusion, and worsening symptoms. In such cases, intravenous crystalloid therapy should be maintained according to WHO recommendations. If managed appropriately, most patients will recover, but some may require continued fluid therapy, tailored to their clinical situation. For those who do not improve, colloidal solutions (containing human albumin, gelatin, or starch) can be used as alternatives to crystalloids.

IMPAIRED HEMOSTATIS

Hemorrhagic events in dengue are multifactorial. While bleeding can complicate outcomes in patients with dengue shock syndrome (DSS), it does not always correlate with capillary leakage and can occur at any stage of the critical or convalescent phases. Hemorrhage is more common in prolonged shock rather than as a general complication of dengue, such as disseminated intravascular coagulation. Therefore, preventing or quickly managing shock is the most effective way to avoid severe bleeding. Risk factors for major hemorrhage include the duration of shock and low-to-normal hematocrit levels at the onset of shock, while platelet counts do not predict bleeding severity.

A sudden drop in hematocrit and hemoglobin levels, without improvement in the patient's condition, may signal silent hemorrhage. Gastrointestinal bleeding, often presenting as hematemesis (vomiting blood) or melena (black, tarry stools), is the most common manifestation. This is treated with packed red blood cell transfusions. Intracranial or pulmonary bleeding, which carries a poor prognosis and may lead to multi-organ failure, can also occur. Thrombocytopenia is frequently seen during dengue infection, but there is no evidence supporting the use of prophylactic platelet transfusions, which can be costly and sometimes harmful.

V. CONCLUSION

Significant progress has been made over the past decade in vaccine development, antiviral drugs, and vector control efforts. When effectively utilized, these new tools hold the potential to significantly improve disease control. Advances in molecular diagnostics and antigen detection, along with a deeper understanding of pathogenic mechanisms, will facilitate earlier diagnosis and more effective clinical management. Furthermore, enhanced knowledge of virus-vector interactions and DENV transmission dynamics, combined with new vector control tools, will contribute to more efficient prevention and control strategies.

Several vaccine candidates are currently undergoing clinical trials, with live attenuated vaccines being the most successful thus far. The impact of vaccination will depend not only on vaccine efficacy but also on factors such as vaccine coverage, the local epidemiological situation, genetic variations within populations, the immunity status of target populations, and ongoing vector control efforts. Introducing a licensed dengue vaccine into national immunization programs presents a challenge. Countries will need to decide whether to target high-risk groups or the broader population, determine the age groups for vaccination, and identify regions where the vaccine should be introduced. Mathematical models could serve as valuable tools in developing strategies for population-wide dengue control.

As of April 2016, Sanofi Pasteur completed phase III trials and received approval from the WHO's Scientific Advisory Group of Experts on Immunization for its three-dose tetravalent live attenuated CYD vaccine (Dengvaxia), which has been licensed in five countries (Brazil, El Salvador, Mexico, Paraguay, and the Philippines) for individuals aged 9–45 years, 70% of whom should have circulating DENV antibodies.

Despite these advances, dengue remains a research priority. In 2006, the Special Programme for Research and Training in Tropical Diseases and the WHO convened a Dengue Scientific Working Group composed of experts from 20 countries. This group reviewed existing knowledge and established research priorities, which focused on four main areas: reducing dengue-related fatalities and disease severity, improving transmission control through better vector management, advancing primary and secondary prevention strategies, and health policy research to guide public health responses. The goal was to provide policymakers with evidence-based recommendations and foster the development of cost-effective strategies to reverse the growing global burden of dengue. However, due to the complex and evolving nature of dengue epidemiology, progress remains ongoing.

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