Chapter 9
Dengue

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Dengue Infection

Etiology

Dengue, or dengue fever, is a mosquito-borne infection endemic to tropical and subtropical areas of the world caused by dengue virus. Dengue viruses are enveloped, single-stranded RNA members of the family *Flaviviridae*, genus *Flavivirus*. Four serologically and genetically distinct serotypes, 1, 2, 3, and 4 exist. Natural disease is believed to confer life-long immunity to the infecting serotype but only partial and temporary protection against the other 3 serotypes. Following the bite of an infected mosquito, the disease has an incubation period of 4–7 days, occasionally longer.

Epidemiology: Global Burden of Disease

Dengue is the most common and most rapidly spreading arbovirus infection in the world, presenting major public health challenges in tropical and subtropical regions. Seasonal outbreaks are affected by rainfall, temperature, relative humidity, and urbanization. Specific regions can be hyperendemic for any or all four dengue serotypes. Worldwide, cases of dengue are underreported because most infections are asymptomatic or mild, and therefore easily managed without seeking medical care. Globally, of the estimated 300–500 million people infected with dengue each year, approximately 100 million develop symptomatic disease, 0.5 million develop severe

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illness requiring hospitalization, and 20,000 die. Prior to 1970, only 9 nations worldwide reported widespread dengue epidemics. Now, just 50 years later, dengue has become endemic to more than 100 countries in tropical and subtropical regions of Asia, Africa, Central and South America, the Caribbean, and island nations of the Western Pacific. The 30 countries that reported the greatest numbers of dengue cases to the WHO between 2006 and 2015 are shown in Fig. 9.1**.** Infection is likely to be just as widespread, or even more so, throughout parts of Africa despite the overall lower numbers that are reported. Dengue has also spread to areas along the Gulf Coast of the USA, and to the most northern coastal areas of Australia.

More than three million people were infected with dengue during the 2019 epidemic in the region of the Americas. Of those infected, nearly 1% developed severe disease and 1,538 died. At least 34 countries were affected. In early 2020, ongoing higher-than-usual number of dengue cases led the US Centers for Disease Control and Prevention (CDC) to issue a level 1 travel alert for the nations of Belize, Brazil, Colombia, Costa Rica, Dominican Republic, El Salvador, Guadeloupe, Guatemala, Honduras, Mexico, Nicaragua, Peru, and Saint Martin. During this same period, increased dengue activity across areas of Asia and the Western Pacific disproportionately affected the countries of Bangladesh, Sri Lanka, Nepal, Pakistan, the Philippines, Singapore, Micronesia, French Polynesia, the Marshall Islands, and Palau. Problematic areas of Africa included the countries of Benin, Ivory Coast, Réunion, and Tanzania.

Epidemiology: Burden of Disease in the USA

In 2010, with the recognition that the epidemiology was changing quickly, the CDC added dengue to the list of nationally notifiable diseases. Infection had already been endemic in Puerto Rico for at least 50 years where 60% and 80% of the island's

Fig. 9.1 Shown is a world map indicating the 30 countries that reported the highest numbers of dengue cases to the World Health Organization between 2006 and 2015. (Source of data used to generate figure: https://www.who.int/activities/improving-data-for-dengue)

population are infected by at least one serotype before age 20 or 30 years, respectively. Similarly, dengue is endemic in the US Virgin Islands and sporadically endemic in American Samoa, Northern Marianas, and Guam.

Prior to World War II (prestatehood), dengue was also endemic to Hawaii where autochthonous transmission was once very common. Since World War II, only three outbreaks of dengue have been described. The most recent Hawaiian cluster, reported in 2015, involved 107 cases, 15 hospitalizations, and no deaths. Similarly, dengue was once endemic to the region of the Gulf Coast. Outbreaks in Texas, for example, were a regular occurrence until mosquito prevention campaigns, started in the 1940s, effectively eliminated disease transmission in the region. As reports of disease waned, mosquito prevention campaigns slowed, until eventually being discontinued altogether. As a result, mosquito populations resurged, resulting in dengue outbreaks in 1980, 1999, and 2005. More recently, in 2013, a cluster of 53 cases in Texas followed a much larger outbreak of more than 5,500 cases in the neighboring Mexican state of Tamaulipas. The states of Texas and Tamaulipas share a 200-mile-long border extending along the Rio Grande from Brownsville to Loredo, Texas. Sporadic cases, and occasional small outbreaks, are also described from the state of Florida. Despite the potential for autochthonous transmission of dengue in the USA, most cases reported outside of Puerto Rico and other island territories are related to leisure travel to endemic areas including the islands of the Caribbean (Fig. 9.2). In addition to the 1,183 travel-associated infections reported in 2019, 20 locally transmitted cases of dengue were reported from 3 US states and the District of Columbia (DC): 1 each from North Carolina and DC, 2 from Texas, and 16 from Florida.

The rapid spread of dengue worldwide, fueled by the proliferation of its mosquito vector, has been linked to population growth and higher population densities, human migration from rural to urban settings, absence of readily available clean water, inadequately funded or organized public mosquito control programs, global travel, and climate change that favors mosquito survival, leading to longer transmission seasons and further geographical spread. Together, these and other factors have been associated with a 15-fold increase in reported dengue cases since 2000. Epidemiologic modeling estimates that between 3.5 and 4 billion people worldwide are currently at risk for dengue infection. Prediction models show that during the next 30 years, dengue is likely to expand further into the southeastern United States, along coastal regions of China, Japan, Turkey, and Spain, and into northern Argentina, southern Africa, and inland Australia.

Transmission

Dengue is transmitted primarily by the bite of infected female *Aedes aegypti* mosquitoes. *Ae. aegypti* mosquitoes are daytime biters and are also recognized as the primary vector for the transmission of Zika, yellow fever, and chikungunya viruses. The less efficient vector of transmission, *Ae. albopictus*, has a geographic spread across 32 US states due to its tolerance of colder conditions.

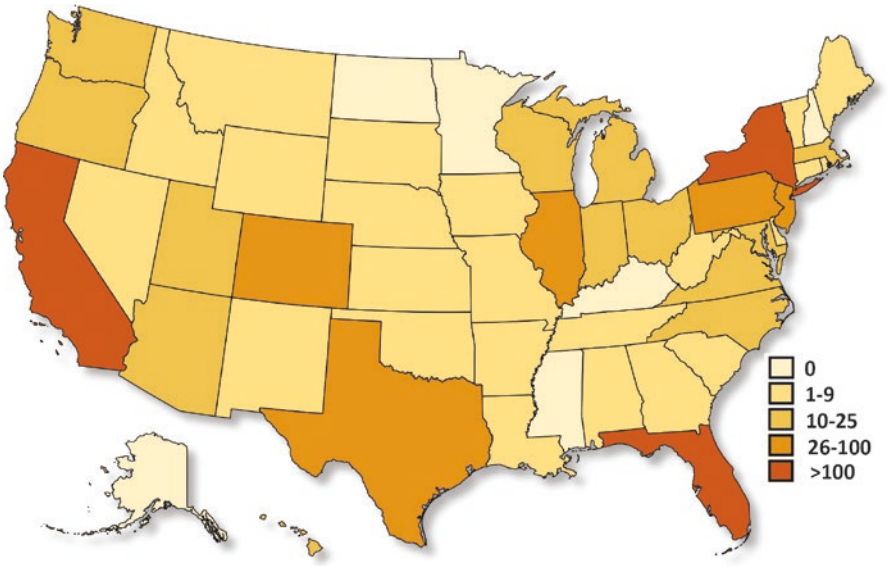

Fig. 9.2 Shown is a state by state distribution map of travel-associated dengue cases reported to the US Centers for Disease Control in 2019. (Source of data used to generate figure: Centers for Disease Control and Prevention, https://www.cdc.gov/dengue/statistics-maps/2019.html. This material is available on the agency website at no charge: Reference to specific commercial products, manufacturers, companies, or trademarks does not constitute its endorsement or recommendation by the US Government, Department of Health and Human Services, or Centers for Disease Control and Prevention)

The transmission cycle of infection begins when a female *Ae. aegypti* mosquito takes a blood meal from a dengue-infected individual. Virus, present in the blood meal, replicates in the mosquito midgut and then disseminates to the mosquito's salivary glands. During her next blood meal, virus from the mosquito's salivary glands infects the new human host. After the bite of the infected mosquito, virus replicates in local dendritic cells and tissue macrophages. Infected cells migrate to the lymphatics and the bloodstream, resulting in the dissemination of the infection to multiple target tissues and organs.

Clinical Presentation

The illness is very mild or completely asymptomatic in 75% of those infected. The remaining 25% of cases can be divided into two general categories: dengue fever and severe dengue.

Dengue fever is a mild-to-moderate disease that presents as an acute influenza-like illness. Symptoms usually last no more than 2–7 days. The nonspecific, and often vague symptom, complex overlaps those of many other viral illnesses. Most cases of

dengue are self-limiting and resolve without sequelae. The World Health Organization defines dengue as an illness associated with the abrupt onset of high fever and 2 or more of the following additional clinical findings: severe headache, retro-orbital pain, generalized myalgia, arthralgia and bone pain, abdominal pain, nausea, vomiting, anorexia, altered taste sensation, adenopathy, or a generalized maculopapular rash.

Severe dengue, a condition previously referred to as dengue hemorrhagic fever, is a dengue illness with a critical phase that develops between 3 and 7 days after symptom onset. Severe dengue develops in approximately 5% of symptomatic individuals. This risk is increased during an individual's second heterotypic dengue infection when the 2 bouts of illness are separated by more than 18 months. Severe dengue can develop in anyone, but approximately 95% of severe cases are associated with the second dengue infection. Severe infection can be explained, at least in part, by the phenomenon referred to as antibody-dependent enhancement (ADE) of disease. Pre-existing antibodies that were formed in response to the first dengue infection that cross-react with the second dengue virus bind to it, thereby facilitating its entry into dendritic cells, and macrophages via the antibody's Fc receptor. This early virus-host interaction allows the newly infecting virus to evade the host responses that normally limit infection. The resulting higher viral burden and imbalanced immune response trigger capillary endothelial pathology that leads to vascular leakage and bleeding. In regions hyperendemic for dengue, ADE is seen primarily in children less than 15 years of age. Across low endemic regions, ADE is more commonly seen in adults. Pregnancy is another well-recognized risk factor for the development of severe dengue, especially during the third trimester.

Severe dengue is a medical emergency. Signs for the development of this complication are usually first noticed at the time of defervescence, then last for 24–48 hours. Warnings signs for severe dengue include intractable abdominal pain, persistent vomiting, fluid accumulation, tachypnea, bleeding of the gums or nose, hematemesis, hematochezia, fatigue, restlessness, irritability, and the development of hepatomegaly.

Patients with marked vascular permeability develop severe disease within hours with rapid development of pleural effusions, ascites, hypoproteinemia, and hemoconcentration. Bleeding from the mucous membranes and gastrointestinal tract may be severe and difficult to control. Hypovolemic, hemorrhagic shock leads to severe organ impairment, coma, and death. If proper, aggressive supportive care can be maintained for 48–72 hours, the vascular leakage will resolve. This subgroup of patients generally recovers completely, although adults may have prolonged weakness and myalgias that last for several months.

Management

There is no specific treatment or cure for dengue infection. Infected individuals should pay close attention to maintaining hydration. Headache, bone pain, and fever should be managed with acetaminophen, not aspirin or other nonsteroidal

anti-inflammatory medications such as ibuprofen. Early detection of severe dengue by recognizing the early warning signs is the key to improving survival rates. Hospitalization with maintenance of proper fluid volume reduces fatality from 20% to less than 1%.

Prevention

Mosquito control and bite prevention is a key component to dengue prevention programs. Environmental controls known to reduce or eliminate mosquito breeding include managing or removing sources of free-standing water, the proper disposal of solid waste, weekly emptying and cleaning of domestic water storage vessels, and application of insecticide to outside water storage containers. Environmental measures that reduce the risk for mosquito bites include the use of window screens, insect repellants, and insecticide-treated materials. Clothing that minimizes skin exposure should be worn when possible. Community engagement and education on the importance and logistics of mosquito control can be highly effective.

Dengue Vaccine

The commercially available dengue vaccine is a replication-competent, tetravalent product known as CYD-TDV. Its name is based on the unique manner in which the vaccine is formulated. The first three letters, CYD, are used to denote that the vaccine is a *C*himeric derivative of the live, attenuated *Y*ellow fever vaccine strain 17*D*. Yellow fever and dengue are both flaviviruses. Basic similarities in their genomes allowed for genetic manipulation of the live attenuated yellow fever virus whereby coding sequences for surface proteins could be removed and replaced with the homologous sequences from each of the four dengue virus serotypes. The second three letters in the vaccine name, TDV, reflect the change by denoting *T*etravalent *D*engue *V*accine. The chimeric viruses included in the CYD-TDV vaccine are, therefore, capable of inducing the production of antibodies directed against the surface proteins of all 4 dengue serotypes. When administered to dengue-naïve individuals, CYD-TDV partially mimics primary dengue infection, thereby increasing the risk for severe dengue during their first natural dengue infection. This risk is similar to that observed epidemiologically among individuals who develop a second dengue infection. CYD-TDV is, therefore, only recommended for individuals who have already had their first natural infection with dengue. The vaccine is given as three injections over a year. It was first licensed in 2015 for use in Mexico. In its 2018 position paper, the World Health Organization recommended that the vaccine be administered to individuals between the ages of 9 and 45 years who live in endemic regions with a high burden of disease, defined as seroprevalence of greater than 70% in the target age group. Vaccine is not recommended in endemic regions

where seroprevalence is below 50% in the target age group. Vaccine should only be administered to individuals with documentation of at least one previous dengue infection or a positive serologic test result at the time of vaccination. The CYD-TDV dengue vaccine was approved by the US FDA on May 1, 2019, and added to the World Health Organization's list of prequalified vaccines on March 25, 2020.

Type of Vaccines Available in USA

In the USA, the CYD-TDV dengue vaccine is marketed by Sanofi Pasteur under the trade name Dengvaxia. The vaccine is approved for use in children between the ages of 9 and 16 years who live in dengue endemic regions and who have laboratory-confirmed evidence of previous infection with at least one dengue serotype. The vaccine is a live attenuated, recombinant tetravalent (representing four serotypes) product comprised of a yellow fever virus 17D strain backbone. It is considered a genetically modified organism (GMO).

Each dose of the vaccine contains between 4.5 and 6.0 log10 median cell culture infectious doses of each of the four chimeric yellow fever-dengue virus serotypes. The three-dose vaccine series is administered as 0.5 mL injections at 6-month intervals (at month 0, 6 and 12). Each dose is provided by the manufacturer in two vials: one containing the lyophilized vaccine immunogens and the other containing the 0.4% sodium chloride diluent for reconstitution. Prior to use, vaccine should be stored under refrigeration between 2 °C and 8 °C protected from light. Vaccine should never be frozen.

To prepare a dose for injection, the caps from both vials are removed. The top stoppers are cleaned with alcohol before withdrawing 0.6 mL from the diluent vial and transferring it to the vial containing the lyophilized vaccine. The vaccine is suspended using a gentle swirling movement. The reconstituted product is clear and colorless. Trace amounts of white to translucent proteinaceous particles are acceptable, cloudy solutions should be discarded. Once the fluid appears homogeneous, 0.5 mL is drawn into a syringe. Vaccine should be administered immediately after reconstitution; however, refrigeration at 2 °C to 8 °C for 30 minutes is acceptable if necessary. Vaccine not administered within 30 minutes of reconstitution should be discarded.

Immunizing Antigen

Researchers developed the CYD-TDV dengue vaccine using recombinant DNA technology. They began with the live attenuated virus used to manufacture yellow fever 17D204 vaccine. The sequences of DNA encoding the yellow fever vaccine virus premembrane (prM) and envelope (E) proteins were removed, then replaced with the homologous coding sequences from dengue virus serotypes 1, 2, 3, and 4, resulting in

the formation of four new chimeric viruses. Each chimeric virus has the same yellow fever vaccine virus "backbone" with one of the four dengue virus serotype-specific prM and E gene sequences. Each of the four chimeric viruses is grown separately in Vero cell cultures under serum-free conditions, then harvested, and purified by membrane chromatography and ultrafiltration. A proprietary stabilizer solution is added, producing four monovalent drug substances. The four monovalent substances are combined, sterilized by filtration, filled into vials, and freeze-dried.

Additives and Excipients

The final vaccine product contains 2 mg sodium chloride, 0.56 mg essential amino acids 0.2 mg nonessential amino acids, 18.75 mg sucrose, 9.38 mg D-sorbitol, 0.18 mg, and 0.63 mg urea per 0.5 mL dose. No adjuvant or preservatives are added.

Vaccine Recommendations

US Pediatric Immunizations

The vaccine is approved for use in children 9–16 years old living in US regions with endemic disease including American Samoa, Guam, Puerto Rico, and the US Virgin Islands, who have laboratory-confirmed evidence of prior infection with at least one dengue serotype. Formal ACIP recommendations are pending discussion at an upcoming meeting.

Contraindications to the CYD-TDV Dengue Vaccine

The contraindications to receiving the CYD-TDV dengue vaccine include a history of a severe allergic reaction to a previous vaccine dose or to any vaccine component and the presence of a known immunodeficiency or treatment with immunosuppressive medications.

Warnings and Precautions for Vaccine Use

The CYD-TDV dengue vaccine is not approved for use in dengue seronegative or unknown serostatus individuals, because it may place those individuals at increased risk for the development of severe disease from natural dengue infection. This caveat is complicated by the lack of FDA-approved serologic tests to determine

dengue serostatus. Available non-FDA-cleared tests may produce false-positive results from cross-reacting antibody to other flaviviruses. Vaccine may not protect all vaccinees. It is important to maintain personal protective measures against mosquito bites when visiting or living in a dengue endemic region.

Data are not available on the safety and efficacy of the vaccine when administered concomitantly with other recommended adolescent vaccines. Safety has not been established for use during pregnancy. Inadvertent administration during pregnancy should be reported to the pregnancy registry maintained by the manufacturer at 1-800-822-2463.

Side Effects and Adverse Events

Common Side Effects

Adverse events reported from the administration of a three dose series to 2000 clinical trial subjects, aged 9–16 years from Latin America over a 12-month period, included pain (23–32%), erythema (2–4%), and/or swelling (2–4%) at the injection site. Systemic reactions included headache (30–40%), myalgias (20–29%), malaise (19–25%), asthenia (16–25%), and fever (6–7%). Over the course of nine clinical trials performed in children aged 9–16 years, serious adverse events were reported in 0.6% of vaccine recipients and 0.8% of placebo recipients. None of the serious adverse events were considered to be related to the CYD-TDV dengue vaccine.

Estimated Effectiveness or Efficacy from Clinical Vaccine Trials

Two phase III vaccine trials in Latin America showed similar efficacies of 81% and 77% against symptomatic, virologically confirmed dengue caused by any serotype, among subjects who were seropositive for dengue at baseline. Estimated vaccine efficacy derived from post licensure experience outside of the USA, prior to US licensure, showed 76% efficacy against confirmed symptomatic dengue in baseline seropositive recipients at 2-year follow-up, but only 39% efficacy against confirmed symptomatic dengue in baseline seronegative recipients. Seronegative recipients also showed an increased risk of hospitalization for severe dengue 18 months after vaccination. Follow-up 5-years later in areas with 70% or higher seroprevalence showed one excess case of severe dengue in seronegative vaccine recipients for every four cases of severe dengue that were prevented in the seropositive vaccine recipients. These data led to the US labeling indication for the CYD-TDV dengue vaccine to be used only in children 9–16 years of age who are confirmed to be dengue seropositive prior to vaccination.

In September 2018, 51 childhood deaths were reported during a large-scale vaccination campaign in the Philippines that involved 830,000 children. During review,

it was determined that 15 deaths were caused by dengue infection. The WHO reviewed the deaths, but was unable to make a causality determination. Unfortunately, despite the vaccine's potential to reduce dengue morbidity in this hyperendemic region of the world, vaccine confidence was eroded, ultimately leading to the revocation of its license in the Philippines.

Conclusion

Dengue is the most common and most rapidly spreading arbovirus infection in the world. The global burden of disease is associated with substantial morbidity and mortality, especially among children. Severe dengue can develop in anyone, but approximately 95% of severe cases are associated with the second dengue infection, largely explained by the enhancement of disease in presence of pre-existing antibody. Vector control efforts, and protection from mosquito bites, help to prevent the spread of dengue and related arbovirus infections. The tetravalent, chimeric dengue vaccine, CYD-TDV, has been shown to be safe and modestly effective at preventing disease when administered to children who have already been infected by natural dengue virus. In the absence of previous dengue exposure, however, the CYD-TDV vaccine partially mimics primary infection and increases the risk of severe dengue during subsequent infection.

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