Dengue: A Growing Problem With New Interventions

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abstract

Dengue is the disease caused by 1 of 4 distinct, but closely related dengue viruses (DENV-1–4) that are transmitted by *Aedes* spp. mosquito vectors. It is the most common arboviral disease worldwide, with the greatest burden in tropical and sub-tropical regions. In the absence of effective prevention and control measures, dengue is projected to increase in both disease burden and geographic range. Given its increasing importance as an etiology of fever in the returning traveler or the possibility of local transmission in regions in the United States with competent vectors, as well as the risk for large outbreaks in endemic US territories and associated states, clinicians should understand its clinical presentation and be familiar with appropriate testing, triage, and management of patients with dengue. Control and prevention efforts reached a milestone in June 2021 when the Advisory Committee on Immunization Practices (ACIP) recommended Dengvaxia for routine use in children aged 9 to 16 years living in endemic areas with laboratory confirmation of previous dengue virus infection. Dengvaxia is the first vaccine against dengue to be recommended for use in the United States and one of the first to require laboratory testing of potential recipients to be eligible for vaccination. In this review, we outline dengue pathogenesis, epidemiology, and key clinical features for front-line clinicians evaluating patients presenting with dengue. We also provide a summary of Dengvaxia efficacy, safety, and considerations for use as well as an overview of other potential new tools to control and prevent the growing threat of dengue .

Dengue is the disease caused by 4 closely related but distinct viruses, dengue virus 1–4 (DENV-1–4), referred to as virus types or serotypes. DENVs are most commonly transmitted by the bite of an infected female *Aedes* spp. mosquito. It is the most common arboviral disease globally, with an estimated 390 million dengue virus infections and 96 million symptomatic cases annually.[1] Global incidence has almost doubled in the last 3 decades and is expected to continue growing in Asia, sub-Saharan Africa, and Latin America. About half of the global population now lives in areas that are suitable for dengue transmission (Fig 1).[2,3] Historically, the highest burden of dengue has been in children, adolescents, and young adults.[4] In 2019, countries across the Americas reported more than 3 million dengue cases, the highest number ever recorded,[5] with a greater proportion of severe dengue cases and increased mortality in the pediatric population of children aged 5 to 9 years.[6] Dengue is increasingly common as an etiology of fever in international travelers[7] and has been reported as the leading febrile disease etiology for travelers from some endemic regions during epidemic years.[8] In addition to circulation of all four

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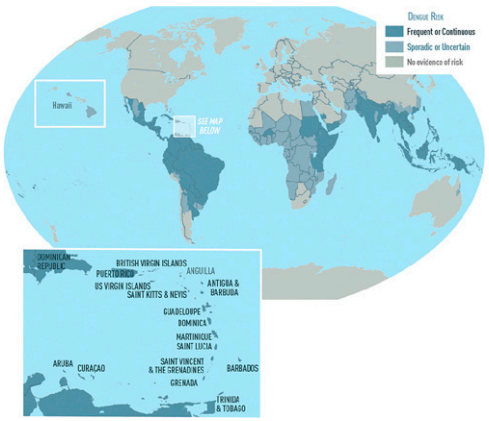

FIGURE 1

Map showing the risk of dengue by country as of 2020. "Frequent or Continuous" risk indicates that there are either frequent outbreaks or ongoing transmission. "Sporadic or Uncertain" indicates that risk is either variable and unpredictable or that data from that country are not available. For updated information, visit https://www.cdc.gov/dengue/areaswithrisk/around-the-world.html.

DENVs worldwide, surveillance of returning travelers with dengue has demonstrated high genetic diversity among circulating DENV genotypes within serotypes, with potential implications for immune or vaccine escape.[9,10]

A GROWING PROBLEM IN THE UNITED STATES

Increasing numbers of dengue cases in the United States are a growing concern. In parts of the United States and freely associated states with endemic dengue transmission, including American Samoa, Puerto Rico, US Virgin Islands, Federated States of Micronesia, Republic of Marshall Islands, and the Republic of Palau, dengue outbreaks can be explosive, overwhelming the health care system capacity. In Puerto Rico, the largest US territory where dengue is endemic, the highest incidence of dengue cases and hospitalizations from 2010 to 2020 occurred among children aged 10 to 19 years.[11] For the same period, confirmed dengue cases ranged from a minimum of 3 cases in 2018 to a maximum of 10 911 cases in 2010,[11] although suspected case counts during outbreak years were considerably higher.[12]

Although local dengue transmission does not occur frequently in most states, increasing numbers of US travelers[13] with dengue have been reported in recent years, with a record 1475 cases in 2019, more than 50% higher than the previous peak in 2016 (Fig 2).[14] Viremia among travel-associated dengue cases can also result in focal outbreaks in nonendemic areas, with competent mosquito vectors for dengue present in approximately half of all US counties.[15] Local dengue cases have been reported in multiple states in recent years, including 70 cases in Florida in 2020,[14] 200 cases in Hawaii in 2015,[14] and 53 cases in Texas in 2013.[16]

ENVIRONMENTAL FACTORS CONTRIBUTING TO DENGUE AS A PUBLIC HEALTH THREAT

In dengue-endemic areas, environmental factors such as standing water where mosquitoes lay eggs, poor housing quality, lack of air conditioning, and climatic factors (ie, temperature, precipitation, and humidity) increase the abundance, distribution, and risk of exposure to *Aedes aegypti*, the main vector responsible for dengue transmission, or other *Aedes* spp. mosquitoes that can also transmit dengue.[2,17–21] Climate change is predicted to further increase the population at risk for dengue primarily through increased transmission in currently endemic areas and secondarily through expansion of the geographic range of *Aedes* spp. mosquitoes (Fig 3).[2,22] Urbanization, increasing population density, human migration, and

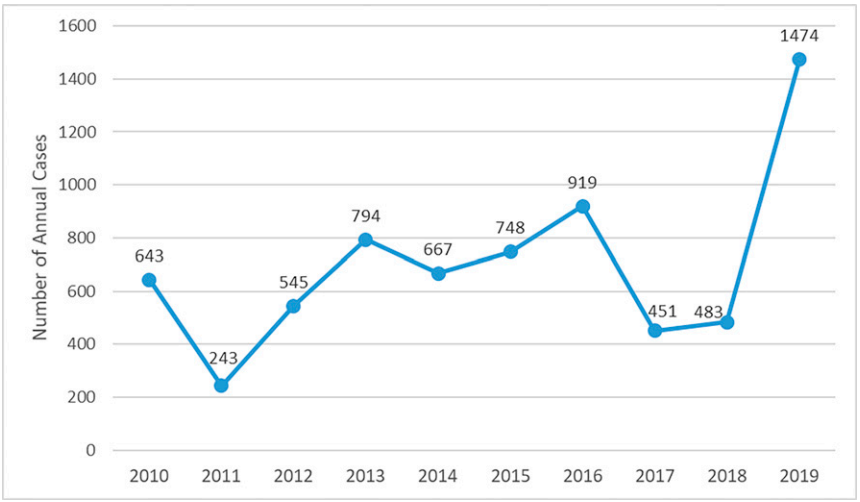

FIGURE 2

Annual number of travel-associated cases of dengue reported into ArboNET, the national arboviral surveillance system managed by the CDC, from all US jurisdictions from 2010 to 2019 ($n = 6967$).

growing social and environmental factors associated with poverty and forced displacement are also expected to drive the increase in dengue incidence and force of infection globally.[21,23–26] Travel is an important driver of dengue expansion by introducing dengue into nonendemic areas with competent vectors[13,23] or by introducing new serotypes into endemic areas naïve to the new serotype, thereby increasing the risk for antibody-dependent enhancement (ADE) and severe disease.[27,28] Combined environmental effects of poverty and the increased scale and rapidity of human movement can also increase the risk for dengue.[24,29] The combined environmental effects of climate change, urbanization, poverty, and human migration together expand the threat of dengue for both individuals and public health systems in the future.

PATHOGENESIS

DENVs belong to the genus *Flavivirus* in the family *Flaviviridae*. Because there are 4 dengue serotypes, individuals living in endemic areas can be infected up to 4 times in their life. Although most dengue virus infections are asymptomatic or only cause mild disease, severe disease can occur and is characterized by plasma leakage, a pathophysiologic process by which the protein rich fluid component of blood leaks into the surrounding tissue, leading to extravascular fluid accumulation resulting in shock, coagulopathy, or end organ impairment.[30,31]

Infection with 1 dengue serotype induces life-long protection against symptomatic infection with that specific serotype (homotypic immunity)[32,33] and induces only short-term cross-reactive protection from disease to the other serotypes (heterotypic immunity) for several months to years.[34,35] Older children and adults experiencing their second dengue infection are at the highest risk for severe disease because of ADE. ADE has also been observed among infants, in that infants born to mothers with previous dengue virus infection had the lowest risk

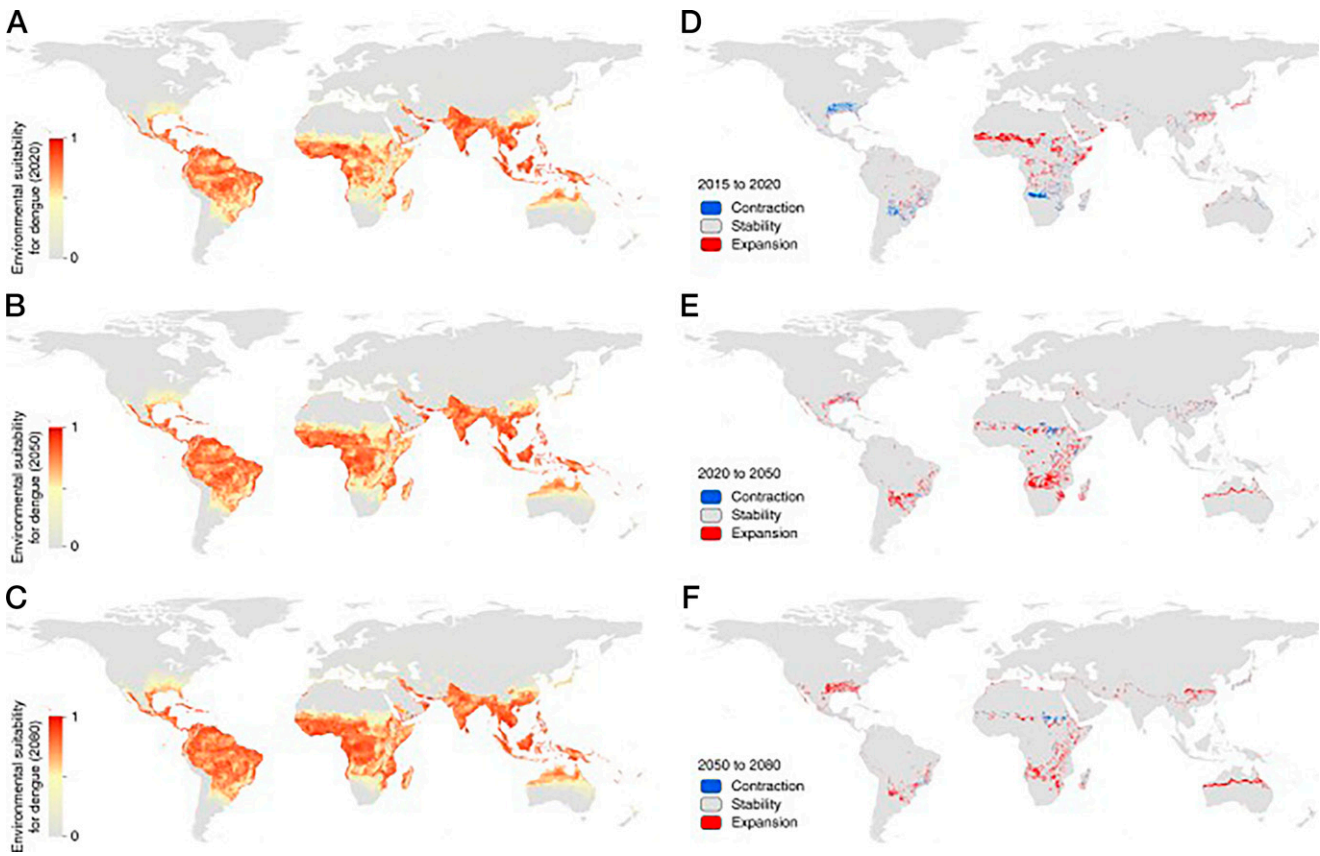

FIGURE 3

A-C, Projections of average trends in environmental suitability for dengue transmission from 2015 to 2020, 2020 to 2050, and 2050 to 2080. D–F, Areas with expansion or contraction of the Aedes vector range over the same time periods. (Reprinted with permission from Messina JP, Brady OJ, Golding N, Kraemer MUG, Wint GRW, Ray SE, et al. The current and future global distribution and population at risk of dengue. Nature Microbiology. 2019;4(9):1510.)

for dengue shortly after birth and a period of higher risk for severe disease approximately 4 to 12 months after birth, followed by a decrease in risk for severe disease from approximately 12 months after birth.[36] The initial period of lowest risk was correlated with high levels of passively acquired maternal dengue antibodies immediately after birth, and the period of enhanced risk with a decline in these antibodies to subneutralizing levels. After further degradation of these maternal antibodies, there was neither protection from dengue afforded by high levels of antibodies postnatally nor enhanced risk of dengue and severe disease from the intermediate levels of antibodies.[37] Later work showed that lower heterotypic antibody titers are ineffective at neutralizing the virions but still bind them, facilitating binding to Fcγ receptors on circulating monocyte cells, and result in higher viremia than in primary infections (Fig 4).[38] The feared sequela of plasma leakage is believed to be mediated by high levels of DENV nonstructural protein 1 (NS1), a key protein for viral replication and pathogenesis,[39,40] that damages endothelial glycocalyces and disrupts endothelial cell junctions.[41,42] Cell-mediated immunity through dengue-specific CD8 T cells is thought to protect against ADE and severe disease.[43,44]

Although ADE occurs in infants due to the interaction between maternal antibodies and primary infection, it is also explanatory for severe disease in older children and adults where the heterotypic antibodies produced after a primary dengue infection will wane over time to subneutralizing levels, resulting in the highest risk for severe disease with secondary infection. Following secondary infection, potent cross-neutralizing/multitypic antibodies are induced that then protect against severe disease in tertiary and quaternary infections.[45,46] Although the risk of severe dengue is highest with secondary infection, it can also occur in primary, tertiary, and quaternary infections, and possibly following Zika virus infection.[47,48] Identifying cases of severe dengue and understanding the pathogenesis of disease severity is an active area of research with important implications for future vaccines and interventions.[49]

CLINICAL CONSIDERATIONS

Presentation and Evaluation

DENV infections have a wide range of presentations from asymptomatic infection (approximately 75% of all infections[50]) to mild to moderate febrile illness to severe disease with associated coagulopathy, shock, or end organ impairment (Table 1).[30,31] Symptomatic infections most commonly present with fever accompanied by nonspecific symptoms such as nausea, vomiting, rash, myalgias, arthralgias, retroorbital pain, headache and/or leukopenia.[51] Severe disease develops in as many as 5% of all patients with dengue, although certain populations such as infants aged ≤1 year, pregnant individuals, and adults aged ≥65 years, or individuals with specific underlying conditions such as diabetes, class III obesity, hypertension, asthma, coagulopathy, gastritis or peptic ulcer disease, hemolytic disease, chronic liver disease, anticoagulant therapy, or kidney disease, are at increased risk of severe disease.[52,53] In all patients with dengue, warning signs are specific clinical findings that can predict progression to severe disease and are used by the World Health

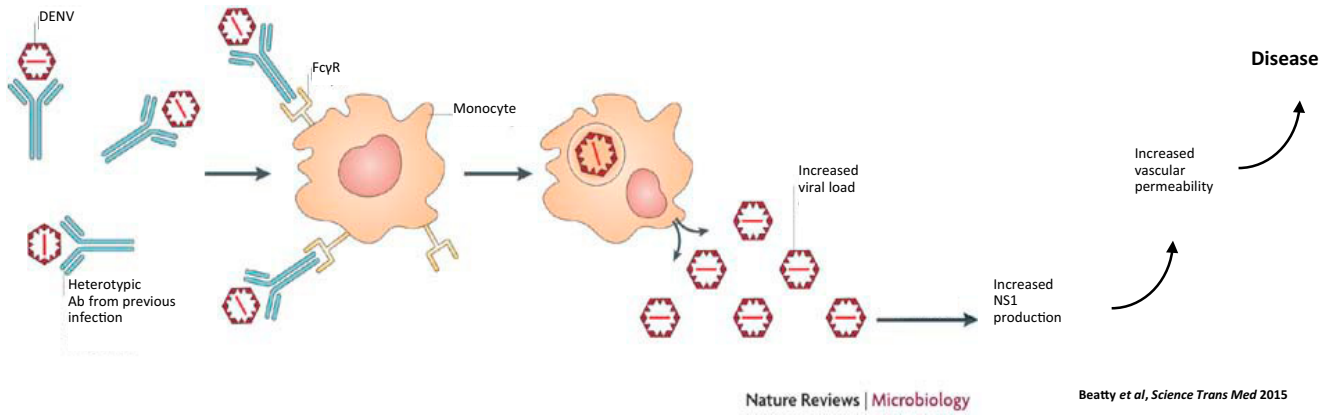

FIGURE 4
The proposed mechanism of antibody-dependent enhancement with heterotypic antibodies binding to the dengue viruses and entering monocytes through Fcγ receptors. Viral replication occurs in the infected monocyte and releases high levels of virus and dengue virus NS1 protein, which, in turn, lead to increased vascular permeability contributing to severe disease. (Reprinted with permission from Whitehead SS, Blaney JE, Durbin AP, Murphy BR. Prospects for a dengue virus vaccine. Nature Reviews Microbiology. 2007;5(7):524.)

TABLE 1 Classification of Dengue Severity and Case Management[51,134,135]

Dengue without Warning Signs	Dengue with Warning Signs	Severe Dengue
Any patient who has traveled to or lives in a dengue-endemic area and presents with fever (typically 2–7 d in duration) and at least 1 of the following:	Any patient who meets the criteria for dengue without warning signs and, typically around the time of defervescence, has at least 1 of the following:	Any patient meeting the criteria for dengue with or without warning signs and has at least 1 of the following:
• Nausea	• Severe abdominal pain or tenderness	• Severe plasma leakage leading to shock or extravascular fluid accumulation with respiratory distress.
• Vomiting	• Persistent vomiting	• Severe bleeding from the gastrointestinal tract or vagina requiring medical intervention such as intravenous fluid resuscitation or blood transfusion.
• Rash	• Clinical extravascular fluid accumulation	• Severe organ impairment such as elevated transaminases ≥1000 IU/L, impaired consciousness, or heart impairment.
• Aches and pains (headache, eye pain, muscle ache or join pain)	• Postural hypotension	
• Positive tourniquet test	• Any mucosal bleeding	
• Leukopenia	• Lethargy/restlessness	
	• Liver enlargement	
	• Progressive increase in hematocrit (ie, hemoconcentration) with concurrent rapid decrease in platelet count	
Case Management		
Outpatient management	Hospital or observation admission	ICU admission

Organization (WHO) to help clinicians in triage and management decisions. Dengue warning signs include abdominal pain or tenderness, persistent vomiting, clinical fluid accumulation, mucosal bleeding, lethargy or restlessness, liver enlargement of >2 cm, and increasing hematocrit concurrent with rapid decrease in platelet count (Table 1).[52]

Although warning signs are useful for evaluating patients with a high suspicion of dengue (for example, during an outbreak), they are not intended to differentiate dengue from other infectious and noninfectious diseases such as influenza, coronavirus disease 2019, malaria, Zika, measles, leptospirosis, rickettsial disease, typhoid, Kawasaki, or idiopathic thrombocytopenic purpura. Because prompt recognition and early treatment of dengue can greatly reduce morbidity and mortality,[54,55] clinicians practicing in the United States and other nonendemic areas should keep dengue in the differential diagnosis for febrile illness in travelers and in areas with competent mosquito vectors.

Diagnostic Testing for Symptomatic DENV Infection

For symptomatic dengue patients, nucleic acid amplification tests (NAATs) on serum, plasma, or whole blood detect DENV RNA during the first 7 days of illness with high sensitivity and specificity.[56,57] Likewise, NS1 antigen can also be detected within the first 7 days and provides confirmatory evidence of DENV infection.[58] For patients with a negative NAAT or patients presenting more than 7 days after symptom onset, a positive anti-DENV immunoblobulin M (IgM) can suggest recent infection, although with less certainty than NAAT or NS1 testing, owing to cross-reactivity with other flaviviruses. Notably, Zika virus is a flavivirus that has been transmitted in most countries where DENV transmission is present.[59] In patients from areas with ongoing transmission of another flavivirus (eg, Zika virus) and whose only evidence of dengue is a positive anti-DENV IgM test, plaque reduction neutralization tests (PRNT) quantifying virus-specific neutralizing antibody titers can distinguish DENV from other flaviviruses, in some but not all cases. PRNTs, however, are rarely available in clinical laboratories and typically do not provide results within a timeframe that is meaningful for clinicians managing acute disease. PRNT's may be valuable in circumstances where confirming the diagnosis may have important clinical implications, such as distinguishing dengue from a Zika virus infection in a pregnant individual, or epidemiologic implications for a region, such as distinguishing yellow fever from dengue.[60,61]

The US Food and Drug Administration (FDA) has approved a NAAT for use on serum and whole blood, an NS1 antigen enzyme-linked immunosorbent assay test in serum, and an IgM enzyme-linked immunosorbent assay in

serum.[56,59,62–64] Other non–FDA-approved tests for DENV infection are used in clinical practice and are commercially available at accredited laboratories.

Treatment

Although several medications have been explored as potential therapeutics for dengue, none have demonstrated a reduction in viremia, clinical manifestations, or complications.[30,65] As such, dengue treatment focuses on supportive care. Clinicians should evaluate all patients at presentation and in follow-up for warning signs or other signs and symptoms of severe dengue (Table 1). Most patients without warning signs may be treated as outpatients, whereas patients at high risk of progression to severe disease based on age or underlying conditions, patients with warning signs, or patients with challenging social circumstances should be evaluated for observation or inpatient management.[66]

For outpatients, fever can be controlled with acetaminophen and physical cooling measures; because of the risk of bleeding and thrombocytopenia, aspirin and nonsteroidal anti-inflammatory drugs are not recommended. Early, abundant oral hydration has been associated with lower hospitalization rates in children with dengue and is a key component of outpatient dengue care.[67–69]

Early recognition of warning signs or severe dengue is essential for the prompt initiation of systematic intravenous fluid management to restore intravascular volume and avoid related complications and disease progression.[30,70] Large-volume resuscitation with isotonic solutions is recommended for patients in shock.[54,71–73] Fluid management in dengue requires continuous clinical and laboratory monitoring and rate adjustments to maintain adequate volume but also to prevent fluid overload. Mortality for untreated severe dengue can be 13% or higher[74,75] but can be reduced to <1% with early diagnosis and appropriate management.[55] Detailed information on systematic fluid management is provided in the current WHO, Pan American Health Organization, and Centers for Disease Control and Prevention (CDC) guidelines.[72,73,76]

Corticosteroids,[77] immunoglobulins,[78] and prophylactic platelet transfusions[79,80] have not demonstrated benefits in patients with dengue and are not recommended.

Traditional Prevention Measures

Prevention of dengue involves protection against mosquito bites. Travelers to and residents of endemic areas can prevent mosquito bites by using US Environmental Protection Agency–approved insect repellents (https://www.epa.gov/insect-repellents) and wearing clothing that covers arms and legs. The use of screened windows and doors, air conditioning, and bed nets has been associated with protection from dengue infections.[24,81–87] Sites where mosquitoes lay eggs should be eliminated by emptying and scrubbing, covering, or eliminating standing water receptacles around the house. Mosquito bite prevention measures are important for all persons at risk for dengue, including vaccinated children.

Novel Vector Control Efforts

Traditional vector control interventions can be time consuming and inefficient.[88] Furthermore, chemical control is limited by widespread insecticide resistance in endemic areas.[89] In response to these challenges, novel vector control methods have been developed including several strategies employing genetically modified mosquito technology and 2 strategies using *Wolbachia pipientis*, an intracellular bacterium found in about 60% of all insects but not commonly found in wild *Aedes* mosquitos.[90–92]

The first strategy utilizing *Wolbachia* is *Wolbachia*-mediated suppression, in which a reduction in wild populations of *Aedes* mosquitoes is achieved by continuously releasing infected males into the environment.[93] When the infected males mate with wild females, the resultant eggs are inviable, leading to a decline in wild mosquito populations.[94] Some reports have documented reduction of the wild populations that can transmit dengue by more than 80%.[95,96]

The second strategy is the *Wolbachia* replacement method, where both *Wolbachia*-infected male and female mosquitoes are released. Because *Wolbachia* is transmitted maternally, the mosquitoes that hatch from the eggs of infected females will be infected with *Wolbachia* from birth.[97,98] *Wolbachia* infection in female mosquitoes taking a bloodmeal reduces transmission of arboviruses, including dengue, chikungunya, and Zika. This method has demonstrated significant reductions of nearly 80% for the outcomes of dengue infection and related hospitalizations in areas where it has been implemented[99] and is currently being deployed in several countries.

Extensive studies have found no evidence of *Wolbachia* in the plants, soil, or other insects in contact with the *Wolbachia*-infected mosquitoes or any evidence of *Wolbachia* transmission to humans from the bites of infected mosquitoes, indicating that safety risks from *Wolbachia*-based interventions for humans and the environment are low.[100]

Current Dengue Vaccines

ACIP made the first recommendation of a dengue vaccine (Dengvaxia) for use in the United States on June 24, 2021, marking an historic moment for dengue control following decades of global efforts to develop a safe and effective vaccine. Two other vaccines, TAK-003 developed by Takeda and TV003 developed by the National Institutes of Health, are in late-stage trials with efficacy results published or expected in 2022.

Principles of Live-Attenuated Dengue Vaccines

All 3 are live vaccines and contain 4 different attenuated vaccine viruses (tetravalent) targeting each of the dengue virus serotypes (Fig 5) with the goal of achieving balanced protective immunity against all 4 serotypes, in both those who are DENV naïve and those who have been previously infected with DENV. Vaccine virus replication (infectivity) of each vaccine serotype after immunization will lead to antigenic stimulation, which then results in homotypic immunity. Infectivity by vaccine virus serotype differed among the 3 vaccines (Table 2).

These differences in vaccine serotype specific infectivity mirrored the induction of neutralizing homotypic antibody titers. Dengvaxia induced approximately 70% homotypic antibody for DENV-4 but <50% for DENV-1, DENV-2, and DENV-3.[101] Antibodies induced by TAK-003 were 83% homotypic for DENV-2 and 5%, 12%, and 27% homotypic for DENV-1, DENV-3, and DENV-4, respectively.[102] TV003 induced a balanced homotypic antibody response to DENV-1 (62%), DENV-2 (76%), DENV-3 (86%), and DENV-4 (100%).[103] Although homotypic antibody titers are associated with serotype specific vaccine efficacy, immune correlates that reliably predict vaccine efficacy have not yet been identified and remain an area of active research.[46]

DENGVAXIA

History of Dengvaxia

Dengvaxia uses a 3-dose schedule with each dose given 6 months apart (at months 0, 6, and 12). It was developed by Washington and St Louis Universities and Acambis and licensed to Sanofi Pasteur in the 2000s, entered phase 3 trials in the 2010s, and was first recommended by WHO in 2016 for persons aged 9 years and older living in highly endemic areas. Long-term follow-up data (over 5 years) from the phase 3 trials and further analyses of the efficacy results[104–107] demonstrated that children with evidence of previous DENV infection were protected from virologically confirmed dengue illness, including severe dengue if they were vaccinated with Dengvaxia. However, risk of hospitalization for dengue and severe dengue was increased among children without previous dengue infection who were vaccinated with Dengvaxia and had a subsequent dengue infection in the years after vaccination. In children without a previous dengue infection, the vaccine acts as a silent primary dengue infection resulting in a "secondary-like" infection upon their first infection with wild-type DENV and an increased risk of severe disease due to ADE (Fig 6).[108,109] After these findings, WHO revised their recommendations for the vaccine to only be given to children with laboratory-confirmed evidence of a past infection. Following WHO's recommendation, the FDA licensed Dengvaxia in 2019, and in 2021, ACIP recommended routine use of Dengvaxia for children aged 9–16 years with laboratory confirmation of previous DENV infection and living in areas where dengue is endemic. Dengvaxia is the first dengue vaccine recommended for use in the United States.

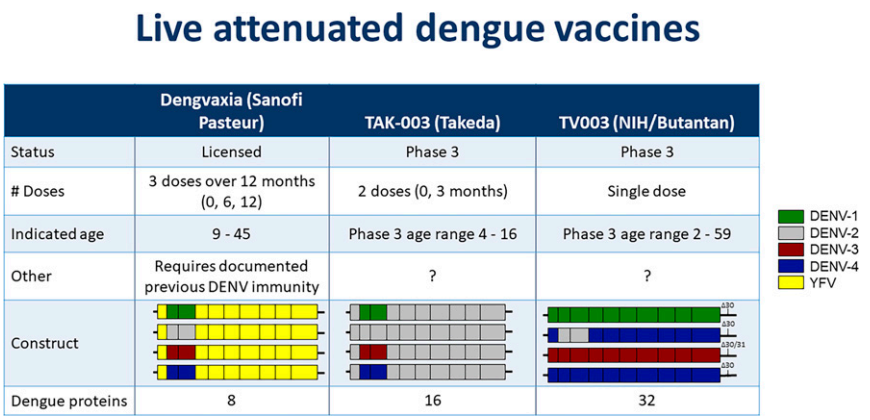

FIGURE 5

Key features of the 3 live attenuated dengue vaccines. Each DENV serotype is represented by a color (DENV-1 = green, DENV-2 = gray, DENV-3 = crimson, and DENV-4 = blue). Dengvaxia is comprised of 4 chimeric viruses in which the prM and E of each DENV serotype replaces those of yellow fever 17D (yellow).[132] TAK-003 is comprised of 1 full-length DENV-2 and 3 chimeric viruses (prM and E of DENV-1, DENV-3, and DENV-4 on a DENV-2 background).[133] TV003 is comprised of 3 full-length DENV and 1 chimeric virus.[123] The total number of dengue proteins in each vaccine is also shown.

Safety and Efficacy

For children aged 9 to 16 years with evidence of previous dengue infection, Dengvaxia has an efficacy of about 80% against the outcomes of symptomatic virologically confirmed dengue (VCD) followed over 25 months as well as

TABLE 2 Percentage of Vaccine Recipients with Detectable Vaccine Virus Serotype by RT-PCR after a Single Dose of the Indicated Vaccine in Persons without Previous Dengue Virus Infections

	DENV-1	DENV-2	DENV-3	DENV-4
Dengvaxia (n = 95)[136]	7.4	0	12.6	44.2
TAK-003 (n = 74)[137]	0	68.9	0	0
TV003 (n = 36)[138]	63.9	69.4	52.8	52.8

Data are presented as percentage.

hospitalization for dengue and severe dengue as defined by criteria set by the trial's independent data monitoring committee and followed over 60 months (Table 3).[105,106] The efficacy by serotype mirrored its induction of a homotypic immune response[101] with highest protection against DENV-4 (89%), followed by DENV-3 (80%), and lowest against DENV-1 (67%) and DENV-2 (67%) (Table 3).[106] Protection against mortality could not be reported because there were no dengue-related deaths in the phase 3 trials.

The most frequently reported side effects (regardless of the dengue serostatus before vaccination) were headache (40%), injection site pain (32%), malaise (25%), asthenia (25%), and myalgia (29%) (n = 1333).[108] Serious adverse events (ie, life-threatening events, hospitalization, disability or permanent damage, and death) within 28 days were rare in both vaccinated participants (0.6%) and control participants (0.8%) and were not significantly different. At 6 months, fewer severe adverse events were reported in the vaccine (2.8%) than in the control arm (3.2%).[108]

Children who were seronegative for dengue at the time of vaccination had increased risk of severe illness on subsequent dengue infections. Risk of dengue-related hospitalization was approximately 1.5 times higher, and risk of severe dengue was approximately 2.5 times higher among seronegative children aged 9 to 16 years who were vaccinated than control participants over a 5-year period.[106]

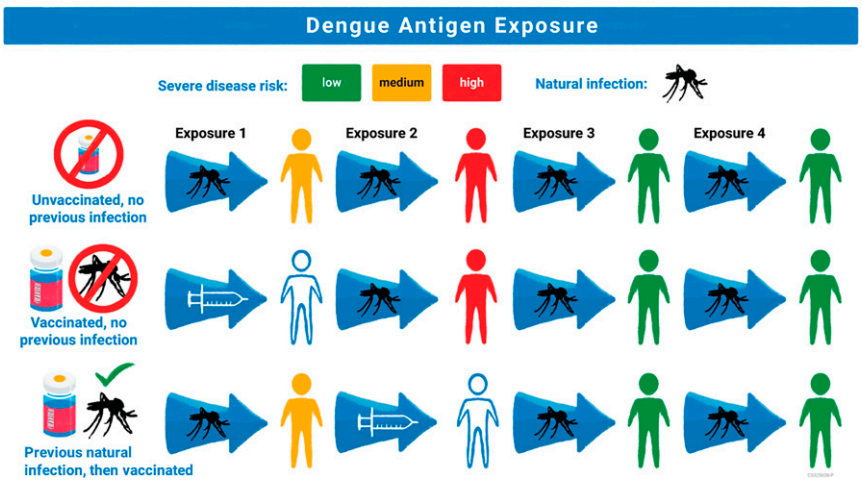

FIGURE 6
Proposed mechanism of Dengvaxia efficacy based on prior dengue antigen exposure. Risk of severe disease is represented by color (low = green, medium = yellow, and high = red). Exposure to dengue antigens is represented by mosquito figure for wild-type exposure and by a syringe for Dengvaxia exposure. The first row shows an unvaccinated individual exposed to 4 different dengue serotypes in their life with highest risk for severe disease with second infection and low risk of severe disease in the third and fourth infection. The second row shows an individual without previous dengue exposure who receives Dengvaxia, which acts as a silent primary infection, and then has higher risk for severe disease upon their first exposure to wildtype dengue, the equivalent of the second exposure to dengue antigen. The third row shows an individual with previous wild-type infection who receives Dengvaxia which acts as a silent second dengue exposure with lower risk for severe disease in subsequent exposures to wild-type dengue.

Prevaccination Laboratory Testing

The requirement for a laboratory test before administration creates a unique challenge for Dengvaxia implementation. In areas with ongoing transmission of flaviviruses other than dengue, qualifying laboratory tests include a positive NAAT or NS1 test performed during an episode of acute dengue or a positive result on prevaccination screening tests for serologic evidence of previous infection that meet specific performance characteristics. In areas without other ongoing flavivirus transmission, a positive dengue IgM assay during an episode of acute dengue is also considered a qualifying laboratory test.[11]

Prevaccination screening is critical because many DENV infections are asymptomatic or do not result in medical visits and testing. Thus, a significant proportion of previously infected individuals who could benefit from the vaccine will not be aware of or have laboratory documentation of their previous dengue infection.[110–113] One of the most challenging aspects in selecting a prevaccination test is defining benchmarks for test performance, as explored by several international working groups.[114,115] To reduce the risk of vaccinating someone without previous DENV infection, test specificity is a priority. Although test specificity and sensitivity are independent of seroprevalence, positive predictive value (PPV) and negative predictive value are

TABLE 3 Dengvaxia Efficacy by Outcome and by Serotype in Persons 9–16 Years Old with Evidence of Previous Dengue Virus Infection

Outcome	VE	95% CI
Virologically confirmed disease (all serotypes)[a,105]	81.9	67.2 to 90.0
By serotype[a,105]		
DENV-1	67.4	45.9 to 80.4
DENV-2	67.3	46.7 to 79.9
DENV-3	80.0	67.3% to 87.7
DENV-4	89.3	79.8% to 94.4
Hospitalization (all serotypes)[b,106]	79	69% to 86
Severe disease (all serotypes)[b,106]	84	63% to 93

Pooled vaccine efficacy data are from CYD14 and CYD15 (clinical trial registration: NCT01373281, NCT01374516). CI, confidence interval; VE, vaccine efficacy. Data are presented as perentages.

[a] Follow-up over 25 mo.

[b] Follow-up over 60 mo.

dependent on seroprevalence and describe the likelihood of a true positive if a patient tests positive or the likelihood of a true negative if a patient tests negative (Table 4). In areas with moderate or low seroprevalence (eg, 30%–50%), high test specificity (>98%) is required to achieve a PPV of 90% and therefore reduce the risk of misclassifying seronegative individuals. In these settings, near-perfect specificity at the expense of sensitivity is preferred to minimize the risk of vaccinating a misclassified negative individual and subsequently increasing their risk of severe dengue. However, high-prevalence areas (eg, >60%) would benefit from a higher test sensitivity and more moderate specificity (eg, 95%), which would increase identification of children who would benefit from the vaccine.[116]

TABLE 4 Test Performance for a Dengue Prevaccination Screening Test in Different Seroprevalence Scenarios[11]

Seroprevalence in the Eligible Population (%)	Test Sensitivity (%)	Test Specificity (%)	PPV (%)	NPV (%)
30	60	95	84	85
30	70	95	86	88
30	75	95	87	90
30	80	95	87	92
30	90	95	89	96
30	60	98	93	85
30	70	98	94	88
30[a]	75	98	94	90
30	80	98	94	92
30	90	98	95	96
50	60	95	92	70
50	70	95	93	76
50	75	95	94	79
50	80	95	94	83
50	90	95	95	90
50	60	98	97	71
50	70	98	97	77
50[a]	75	98	97	80
50	80	98	98	83
50	90	98	98	91
60	60	95	95	61
60	70	95	95	68
60	75	95	95	72
60	80	95	96	76
60	90	95	96	86
60	60	98	98	62
60	70	98	98	69
60[a]	75	98	98	72
60	80	98	98	77
60	90	98	99	87

NPV, negative predictive value; PPV, positive predictive value.

[a] CDC recommends that prevaccination screening tests that determine previous dengue infection have a minimum sensitivity of 75% and a minimum specificity of 98%. The recommendations also specify that the tests should be used in populations where they will achieve a positive predictive value (PPV) of ≥90% and a negative predictive value (NPV) of ≥75%. These rows demonstrate that tests with the same CDC recommended minimum sensitivity and specificity will have different PPV and NPV depending on the seroprevalence of the population in which they are used.

Because dengue seroprevalence at age 9 to 16 years is estimated to be approximately 50% in Puerto Rico[117,118] (where most of the eligible population for Dengvaxia in the United States and its territories and freely associated states reside), the CDC recommends that tests have a minimum sensitivity of 75% and a minimum specificity of 98%. The recommendations also specify that the test performance in the population should achieve a PPV of ≥90% and a negative predictive value of ≥75%.[11] These test characteristics were used to model the risks and benefits of implementing Dengvaxia. Using Puerto Rico's population and an estimated seroprevalence of 50%, the model found that Dengvaxia vaccination would avert approximately 4148 symptomatic disease cases and 2956 hospitalizations over a 10-year period. This implementation would also result in an additional 51 hospitalizations caused by vaccination of people without previous dengue infection who were misclassified by the screening test.[119] The most common cause of hospitalization among vaccinated children will be breakthrough disease because the vaccine is not 100% efficacious.

TAK-003

TAK-003, developed by Takeda, consists of 2 doses given 3 months apart. The clinical trial population was primarily composed of children aged 4 to 16 years. At 18 months after vaccination, vaccine efficacy was found to be 80.2% against VCD, which waned to 62.0% by 3 years after vaccination.[120,121] Efficacy against hospitalization for dengue remained higher, at 83.6% at 3 years after vaccination. Differences in efficacy were observed by history of previous dengue infection, with higher efficacy among persons with previous infection compared with those without previous infection (65.0%–54.3%), and by age, with higher efficacy in older children. In contrast to findings from Dengvaxia at 25 months, children who were seronegative at the time of TAK-003 vaccination did not show an overall increased risk for hospitalization and severe disease compared with the placebo group at 3 years, although efficacy varied by DENV serotype and an age effect could not be ruled out (Table 5).[106,120] Efficacy against both VCD and hospitalization varied by serotype and corresponded to the homotypic antibody titers,[102] with highest efficacy against DENV-2 and lowest against DENV-3 and DENV-4. Among children without previous DENV infection, there was no observed efficacy for VCD against DENV-3 or DENV-4. In the safety analysis, the number of serious adverse events was similar between vaccine (2.9%) and placebo (3.5%) groups.

In March 2021, Takeda submitted TAK-003 to the European Medicines Agency for prevention of dengue from any DENV serotype among people aged 4 to 60 years.[122] The company will also be submitting filings to regulatory agencies in Argentina, Brazil, Colombia, Indonesia, Malaysia, Mexico, Singapore, Sri Lanka, and Thailand during 2021 and has future plans to submit to the FDA.

TABLE 5 TAK-003 Efficacy by Serostatus, Outcome, Serotype, and Age Group in Persons Aged 4–16 Years Over 36 Months of Follow-Up[120]

Outcome	VE	95% CI
Vaccinees with evidence of previous dengue virus infection (seropositives)		
Virologically confirmed disease (all serotypes)	65.0	58.9 to 70.1
Virologically confirmed disease by serotype		
DENV-1	56.2	43.7 to 66.0
DENV-2	83.4	76.4 to 88.3
DENV-3	52.3	36.6 to 64.2
DENV-4	60.7	16.0 to 81.6
Hospitalization (all serotypes)	86.0	78.4 to 91.0
Vaccinees with no evidence of previous dengue virus infection (seronegatives)		
Virologically confirmed disease (all serotypes)	54.3	41.9 to 64.1
Virologically confirmed disease by serotype		
DENV-1	43.5	21.5 to 59.3
DENV-2	91.9	83.6 to 96.0
DENV-3	−23.4	−125.3 to 32.4
DENV-4	−105.5	−867.5 to 56.4
Hospitalization (all serotypes)	77.1	58.6 to 87.3
Virologically confirmed disease by age group (all serotypes, serostatus combined)		
4–5 y	42.3	22.5 to 57.0
6–11 y	64.6	57.8 to 70.4
12–16 y	68.9	58.7 to 76.6
Hospitalization by age group (all serotypes, serostatus combined)		
4–5 y	50.6	−13.9 to 78.6
6–11 y	85.7	77.3 to 91.0
12–16 y	89.1	76.6 to 94.9

Vaccine efficacy data are from clinical trial NCT02747927. CI, confidence interval; VE, vaccine efficacy. Data presented as percentage.

TV003

TV003 was developed by the National Institutes of Health and was formulated by selecting serotype-specific components that were determined to provide the most balanced safety and immunogenicity profile based on an evaluation of multiple monovalent and tetravalent candidates.[123,124] Because antibody titers failed to predict the efficacy of Dengvaxia, a human infection model was developed to assess the protective immunity induced by TV003 against DENV-2 challenge. Forty-eight volunteers were enrolled and randomized to receive TV003 (24) or placebo (24). Six months later, volunteers were administered a naturally attenuated DENV-2 challenge virus.[125] The primary efficacy endpoint was protection against detectable viremia after challenge. After challenge, DENV-2 was recovered by culture or reverse transcription-polymerase chain reaction (RT-PCR) from 100% of placebo recipients ($n = 20$) and 0% of TV003 recipient ($n = 21$) ($P < .0001$). Postchallenge, rash was observed in 80% of placebo recipients compared with 0% of TV003 recipients ($P < .0001$).

TV003 has been licensed to several manufacturers globally, including Merck & Co in the United States and the Instituto Butantan in Brazil. Phase 3 trials in Brazil are underway with efficacy and safety results expected in late 2022

(Clinical trial registration: NCT02406729).

CONCLUSION AND FUTURE DIRECTIONS

Dengue is the most common arboviral disease worldwide and is projected to increase in range and global burden of disease. Although advancements in the field have progressed incrementally for decades, the recent approval of Dengvaxia for routine use marks a major step forward for control and prevention efforts in the United States and paves the way for future dengue vaccines.

Dengvaxia has several complexities that necessitate future research, including the possibility of fewer doses in the initial schedule followed by booster doses in later years.[30] Because it is the first vaccine to require laboratory testing before administration, public–private partnerships to develop more specific, sensitive, and accessible tests or testing algorithms will be key to minimize vaccination of persons without previous DENV infection and maximize benefit to those with previous infection. Jurisdictions that wish to use Dengvaxia will need to gather seroprevalence data and ensure that prevaccination screening tests meet the requirements for positive and negative predictive values. Furthermore, behavioral science assessments to elicit community-level perceptions and concerns combined with health systems research on optimal "test-and-vaccinate" strategies will result in dengue vaccination programs that are well accepted, efficient, and tailored to individual communities.

TAK-003 and TV003 are in late-stage trials and could soon be approaching licensure. An indication for use in travelers would offer clinicians in nonendemic areas of the United States a prophylactic therapeutic option for their patients. While awaiting the approval of a vaccine with balanced serotype immunity, a mix-and-match strategy guided by differences in serotype-dominant immune responses in each vaccine (TAK-003 followed by Dengvaxia, for example) could potentially lead to higher levels of protection against dengue, but it has yet to be evaluated for safety and efficacy in clinical trials.[126] For all 3 vaccines, studies evaluating efficacy against emerging DENV serotype variants will be important to assess long-term protection induced by the vaccine strains.[10,127]

Future vaccines against dengue could also benefit from the lessons learned from the COVID-19 pandemic, namely that new vaccine platform technologies plus political will can result in rapid development of safe and effective vaccines and that clear communication with the public is crucial to successful vaccine implementation.[128–130] Dengue vaccines based on an mRNA platform are already under investigation.[131]

Vaccines are a powerful new tool in our arsenal against dengue, but they are only 1 of many interventions, including novel vector control strategies, to control a virus with a complex epidemiology, immunopathogenesis, and clinical picture influenced by climate change, urbanization, poverty, and human migration. Clinicians should remain vigilant in recognizing and diagnosing patients with dengue, because early treatment remains the cornerstone for reducing morbidity and mortality. However, with the recent approval of Dengvaxia, we are 1 step closer on the path to dengue elimination and can expect exciting new developments in dengue interventions in the near future.

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ABBREVIATIONS

ACIP: Advisory Committee on Immunization Practices
ADE: antibody dependent enhancement
CDC: Centers for Disease Control and Prevention
DENV: dengue virus
FDA: Food and Drug Administration
IgM: immunoglobulin M
NAAT: nucleic acid amplification test
NS1: nonstructural protein 1
PPV: positive predictive value
PRNT: plaque reduction neutralization test
VCD: virologically confirmed dengue
WHO: World Health Organization

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