Dengue Vaccine

- Clinical Policy Bulletins
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Number: 1010

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Policy

Scope of Policy

This Clinical Policy Bulletin addresses dengue vaccine.

1. **Medical Necessity**

   Aetna considers dengue tetravalent vaccine, Dengvaxia, medically necessary for the prevention of dengue disease caused by dengue virus serotypes 1, 2, 3 and 4 in individuals 9 through 16 years of age with laboratory-confirmed previous dengue infection and living in endemic areas.

   Aetna considers dengue tetravalent vaccine, Dengvaxia, not medically necessary for use in individuals not previously infected by any dengue virus serotype or for whom this information is unknown. Those not previously infected are at increased risk for severe dengue disease when vaccinated and subsequently infected with dengue virus. Previous dengue infection can be assessed through a medical record of a previous laboratory-confirmed dengue infection or through serological testing prior to vaccination.

2. **Experimental, Investigational, or Unproven**

   Aetna considers dengue tetravalent vaccine, Dengvaxia, experimental, investigational, or unproven for individuals living in dengue non-endemic areas who travel to dengue endemic areas because the safety and effectiveness for this indication has not been established.

3. **Related Policies**

   1. CPB 0650 - Polymerase Chain Reaction Testing: Selected Indications

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CPT Codes / HCPCS Codes / ICD-10 Codes

CPT codes covered if selection criteria are met:

Code	Code Description
90584	Dengue vaccine, quadrivalent, live, 2 dose schedule, for subcutaneous use
90587	Dengue vaccine, quadrivalent, live, 3 dose schedule, for subcutaneous use

Other CPT codes related to the CPB:

90460	Immunization administration through 18 years of age via any route of administration, with counseling by physician or other qualified health care professional; first vaccine/toxoid component
+90461	each additional vaccine/toxoid component

Code	Code Description
90471	Immunization administration (includes percutaneous, intradermal, subcutaneous, or intramuscular injections); one vaccine (single or combination vaccine/toxoid)
+90472	each additional vaccine (single or combination vaccine/toxoid) (list separately in addition to code for primary procedure)

Other HCPCS codes related to the CPB:

G0310	Immunization counseling by a physician or other qualified health care professional when the vaccine(s) is not administered on the same date of service, 5 to 15 mins time (this code is used for Medicaid billing purposes)
G0311	Immunization counseling by a physician or other qualified health care professional when the vaccine(s) is not administered on the same date of service, 16-30 mins time (this code is used for Medicaid billing purposes)
G0312	Immunization counseling by a physician or other qualified health care professional when the vaccine(s) is not administered on the same date of service for ages under 21, 5 to 15 mins time (this code is used for Medicaid billing purposes)
G0313	Immunization counseling by a physician or other qualified health care professional when the vaccine(s) is not administered on the same date of service for ages under 21, 16-30 mins time (this code is used for Medicaid billing purposes)

ICD-10 codes covered if selection criteria are met:

Z86.19	Personal history of other infectious and parasitic diseases [previous dengue disease]
A90	Dengue fever
A91	Dengue hemorrhagic fever

Background

Dengue is a mosquito-borne flavivirus disease that has spread to several tropical and subtropical areas. The disease is caused by four closely related viruses, the dengue virus serotypes 1 through 4. Dengue is endemic in the U.S. territories of American Samoa, Guam, Puerto Rico and the U.S. Virgin Islands.

The first dengue vaccine, Dengvaxia (CYD-TDV) by Sanofi Pasteur, was first registered in Mexico in December, 2015. CYD-TDV is a live recombinant tetravalent dengue vaccine that has been evaluated as a 3-dose series on a 0/6/12 month schedule in Phase III clinical studies. It has been registered for use in individuals 9-45 years of age living in endemic areas (WHO, 2018) and 9-60 years of age for those living in high dengue endemic areas (Scott, 2016). Approximately five additional dengue vaccine candidates are in clinical development, with two candidates (developed by Butantan and Takeda) that are currently in Phase III trials (WHO, 2018). Butantan's trial is being carried out in multiple sites in Brazil, whereas Takeda's trial is being conducted worldwide; however, does not include the United States (Clinicaltrial.gov, NCT02406729 and NCT02747927). WHO recommends that countries should consider introduction of the dengue vaccine CYD-TDV only in geographic settings (national or subnational) where epidemiological data indicate a high burden of disease. Although dengue rarely occurs in the continental United States, it is endemic in Puerto Rico and in many popular tourist destinations in Latin America, Southeast Asia and the Pacific islands (CDC, 2018).

In 2019, the U.S. Food and Drug Administration (FDA) approved dengue tetravalent vaccine, Dengvaxia (Sanofi Pasteur Inc.), for the prevention of dengue disease caused by dengue virus serotypes 1, 2, 3 and 4 in individuals 9 through 16 years of age with laboratory-confirmed previous dengue infection and living in endemic areas. "The safety and effectiveness of the vaccine was determined in three randomized, placebo-controlled studies involving approximately 35,000 individuals in dengue-endemic areas, including Puerto Rico, Latin America and the Asia Pacific region. The vaccine was determined to be approximately 76 percent effective in preventing symptomatic, laboratory-confirmed dengue disease in individuals 9 through 16 years of age who previously had laboratory-confirmed dengue disease. Dengvaxia has already been approved in 19 countries and the European Union" (FDA, 2019).

Dengvaxia is a live, attenuated vaccine that is administered as 3 separate subcutaneous injections (0.5 mL each) given 6 months apart (at month 0, 6, and 12). The most commonly reported side effects by those who received Dengvaxia were headache (40%), myalgia (29%), malaise (25%), asthenia (25%), injection site pain (32%) and low-grade fever. The frequency of side effects was similar across Dengvaxia and placebo recipients and tended to decrease after each subsequent dose of the vaccine.

Dengvaxia is not approved for use in individuals not previously infected by any dengue virus serotype or for whom this information is unknown. Those not previously infected are at increased risk for severe dengue disease when vaccinated and

subsequently infected with dengue virus. Previous dengue infection can be assessed through a medical record of a previous laboratory-confirmed dengue infection or through serological testing prior to vaccination. Furthermore, the safety and effectiveness of Dengvaxia have not been established in individuals living in dengue nonendemic areas who travel to dengue endemic areas (Sanofi Pasteur, 2019).

Dengvaxia is contraindicated in immunocompromised individuals.

The Centers for Disease Control and Prevention (CDC) "recommends dengue vaccination for children 9 through 16 years old, but only when they have been previously infected with dengue and living in areas where dengue is common. This previous infection should be confirmed by laboratory testing. This vaccine is different from other vaccines in that it is only recommended for people who have already been infected with dengue virus. Children must also be living in areas where dengue occurs frequently or continuously, which include American Samoa, Puerto Rico, and the U.S. Virgin Islands, and the freely associated states of the Federated States of Micronesia, the Republic of Marshall Islands, and the Republic of Palau"(CDC, 2022b).

Laboratory confirmation of previous dengue virus infection is required and can be obtained by evidence of prior acute dengue virus infection with positive dengue RT-PCR test result, or positive dengue NS1 antigen test result; or positive results on both of the following anti-dengue virus immunoglobulin G (dengue IgG antibody) tests in a two-step testing algorithm: such as EUROIMMUN Anti-Dengue Virus NS1 Type 1-4 ELISA (IgG) and CTK BIOTECH OnSite Dengue IgG Rapid Test. The CDC evaluated these 2 IgG tests, and when used together in a two-test algorithm, met the test performance requirements (sensitivity ≥75% and specificity ≥98%). Only children with positive results on both tests are considered eligible for vaccination with Dengvaxia. A single positive anti-dengue virus immunoglobulin M (dengue IgM) test result is not sufficient proof of dengue virus infection for vaccination with Dengvaxia due to potential cross-reactivity with other circulating flaviviruses (e.g., Zika virus) in dengue-endemic areas (CDC, 2022a).

Foucambert et al (2022) noted that dengue is a vector-borne disease caused by the dengue virus (DENV) and is a major health concern worldwide, especially in regions of endemic disease. Dengue usually presents as a self-limited febrile illness. In some cases, more severe forms with hemorrhage and shock can occur, and children are especially prone to develop it. These forms can be lethal without appropriate management, and no anti-viral treatment exists today. In the absence of a curative treatment for dengue, its clinical prevention remains essential. One vaccine, the chimeric yellow fever dengue-tetravalent dengue vaccine (CYD-TDV), has been approved for use in some populations, and several others are currently in development, including Takeda's tetra-valent dengue vaccine candidate (TAK-003). In a systematic review, these investigators examined the available evidence to evaluate the effectiveness of the dengue vaccines in preventing severe dengue in children. This review focused on the vaccines CYD-TDV and TAK-003. This systematic review was carried out according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. PubMed, PubMed Central (PMC), Medical Literature Analysis and Retrieval System Online (Medline), Cochrane Library, and Google Scholar were the databases used to find the relevant data. The studies were selected using specific inclusion and exclusion criteria, and quality appraisal was realized with standardized quality assessment tools. The authors concluded that this study showed that the dengue vaccines CYD-TDV and TAK-003 confer protection against severe dengue in children. Some distinctions exist depending on the vaccine type, the age, and the dengue sero-status of patients. While demonstrating encouraging results, this review also emphasized the need for more in-depth studies regarding the safety and effectiveness of dengue vaccines.

The authors stated that children (age of 0 to 18 years) were the population of interest in this study. These investigators aimed to study children because they are at particular risk of developing severe diseases; thus, they did not analyze adult subjects. However, adults are also affected by dengue and its severe forms, and the need for a review of vaccine effectiveness in populations above 18 years of age is still relevant. These researchers chose only to include studies in English and excluded articles written in other languages. Where dengue is endemic, many regions are non-English speaking, and studies written by physicians from these areas not published in English could have been useful to investigators.

Note, these tests are not yet cleared by the U.S. FDA. To perform pre-vaccination screening with EUROIMMUN Anti-Dengue Virus NS1 Type 1-4 ELISA (IgG) and the CTK BIOTECH OnSite Dengue IgG Rapid Test, laboratories must validate and implement these tests in accordance with federal and local regulations (CDC, 2022a).

According to the CDC, the Dengvaxia vaccine will be available starting in 2022.

Bengolea et al (2024) stated that in Argentina, the dengue virus has experienced an increase in recent years. In a systematic review, these investigators examined the safety and effectiveness of the TAK-003 tetravalent dengue vaccine in this context. They carried out a systematic review of randomized controlled trials (RCTs) comparing the safety and effectiveness of the vaccine with placebo in the general population. The search was performed in Epistemonikos, and 2 researchers independently examined the studies. Risk of bias was examined using the Cochrane Rob 2 tool. A meta-analysis of the results was conducted, and the certainty of evidence was assessed using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach. The authors concluded, with high certainty of evidence, that the tetravalent dengue vaccine reduced severe infections (risk ratio [RR] 0.17, 95 % confidence interval [CI]: 0.12 to 0.24) and infections by the dengue virus (RR 0.40, 95 % CI: 0.36 to 0.45) in a population 17 years or less of age. The vaccine may not increase the risk of serious adverse events (AEs), although it is important to note the low certainty of evidence (RR 1.04, 95 % CI: 0.69 to 1.55). These investigators stated that the use of the tetravalent dengue vaccine lowered the risk of severe and non-severe dengue infections

in this population; however, there is low certainty of evidence regarding the vaccine's safety. The decision to vaccinate should consider the magnitude of benefits relative to the risk of infection.

Medina et al (2024) noted that the Advisory Committee on Immunization Practices (ACIP) has set forth recommendations that dengue pre-vaccination screening tests must exhibit at least 98 % specificity and 75 % sensitivity. These investigators examined the performance of various commercial tests against these benchmarks using well-characterized specimens from Puerto Rico. The findings from this trial were especially relevant given FDA approval and ACIP recommendation of Sanofi Pasteur's Dengvaxia vaccine, highlighting the need for accurate pre-vaccination screening tools.

References

The above policy is based on the following references:

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Policy History

- Last Review 12/20/2024

  Effective: 11/11/2022

  Next Review: 10/09/2025

- Review History
- Definitions

Additional Information

- Clinical Policy Bulletin Notes