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LIVE ATTENUATED VACCINE FOR DENGUE: QDENGA & DENGVAXIA

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ABSTRACT

Dengue vaccine is a vaccine used to prevent dengue fever in humans. Development of dengue vaccines began in the 1920s but was hindered by the need to create immunity against all four dengue serotypes. As of 2023, there are two commercially available vaccines, sold under the brand names Dengvaxia and Qdenga. Dengvaxia is only recommended in those who have previously had dengue fever or populations in which most people have been previously infected due to a phenomenon known as antibody-dependent enhancement. The value of Dengvaxia is limited by the fact that it may increase the risk of severe dengue in those who have not previously been infected. In 2017, more than 733,000 children and more than 50,000 adult volunteers were vaccinated with Dengvaxia regardless of serostatus, which led to a controversy. Qdenga is designated for people not previously infected. There are other vaccine candidates in development including live attenuated, inactivated, DNA and subunit vaccines.

KEYWORDS: Qdenga, dengvaxia, serostatus, dengue, mosquito, vaccine.

INTRODUCTION

Qdenga (TAK-003) is the primary, globally recognized, live-attenuated vaccine for dengue, approved in countries like the UK, EU, and India for individuals aged 4 to 60+ (depending on the region) to protect against all four serotypes, typically given in two doses three months apart. Dengvaxia (CYD-TDV) is an older vaccine restricted to those with prior dengue infection.[1-2]

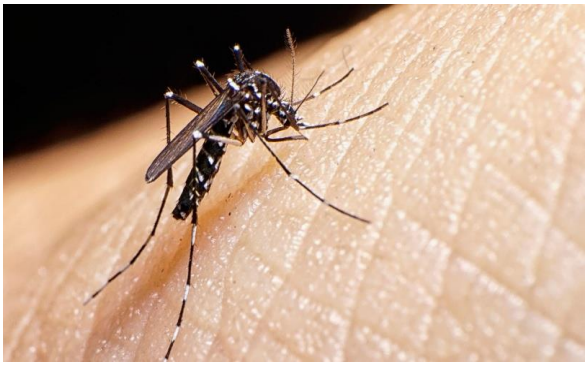

Figure 1: Qdenga & Dengvaxia and Takeda Industry.

Key Dengue Vaccine Information

Approved Vaccine (Qdenga): Takeda's Qdenga (TAK-003) is a tetravalent vaccine protecting against all four dengue strains, utilizing a weakened Dengue-2 strain as its backbone.

Target Population: It is approved for children and adults, usually starting from age 4, and is recommended in high-transmission areas.[3]

Dose Schedule: Administered as a 2-dose series, with 3 months between injections.

Previous Infection: Unlike Dengvaxia, Qdenga generally does not require a prior infection test, making it more flexible, though regional guidelines vary.

Efficacy & Safety: It is effective in reducing hospitalization and severe dengue. Side effects are minor, such as pain at the injection site, headache, and fatigue.

Other Candidate: TV003/TV005 is in clinical trials, showing promise as a potential alternative.

Vaccine Options and Differences

Qdenga (TAK-003): Suitable for both individuals with and without prior dengue infection, making it highly useful for widespread vaccination campaigns.[4]

Dengvaxia (CYD-TDV): Approved only for people with a confirmed past dengue infection, as studies showed it could increase the risk of severe dengue in those who had never had the disease.

Always consult a healthcare provider for the most current, region-specific recommendations regarding dengue vaccination.

Qdenga (TAK-003) is a live-attenuated tetravalent vaccine containing weakened versions of all four dengue virus serotypes (1, 2, 3, and 4). It is produced in Vero cells via recombinant DNA technology, using a dengue 2 backbone to express surface proteins from the other types. It also contains stabilizing ingredients and buffers.[5]

Active Ingredients

Live attenuated dengue virus serotype 1 ($\geq 3.3 \log_{10}$PFU/Dose)
Live attenuated dengue virus serotype 2 ($\geq 2.7 \log_{10}$PFU/Dose)
Live attenuated dengue virus serotype 3 ($\geq 4.0 \log_{10}$PFU/Dose)
Live attenuated dengue virus serotype 4 ($\geq 4.5 \log_{10}$PFU/Dose)

Excipients (Other Ingredients)

Stabilizers: Trehalose dihydrate, Poloxamer 407, and Human serum albumin

Buffer/Salts: Potassium dihydrogen phosphate, Disodium hydrogen phosphate, Potassium chloride, and Sodium chloride

Solvent: Water for injections

Note: Qdenga is considered essentially sodium-free and potassium-free (< 1 mmol per 0.5 mL dose).

Key Facts

Mechanism: It works by inducing an immune response against all four serotypes of the dengue virus.

Administration: It is given as a 0.5 mL dose, typically in a two-dose schedule 3 months apart.

Target: Approved for the prevention of dengue disease in individuals 4 years of age and older.

Trehalose is a natural, stable disaccharide formed by two glucose units, functioning as a stabilizer, humectant, and sweetener in foods, cosmetics, and pharmaceuticals. It preserves freshness, protects cells during freezing, and has a mild, sweet taste. Found in fungi, plants, and insects, it is widely used in processed foods to retain moisture and texture.[6]

Key Properties and Uses of Trehalose

Composition: A non-reducing sugar ($C_{12}H_{22}O_{11}$) consisting of two glucose units linked by a 1–1 alpha bond.

Food Industry: Used in bakery goods, beverages, and

frozen foods as a stabilizer, texturizer, and to prevent oxidation, thus extending shelf life.

Stability: Highly resistant to acid hydrolysis and heat, allowing it to maintain integrity in varied conditions.

Sweetness: Approximately 45-50% as sweet as sucrose, providing a lower-intensity sweetness.

Biological Function: Acts as a protective agent against environmental stressors (dehydration, freezing) in many organisms.

Safety: Recognized as safe (GRAS) and used in consumer products.

Natural Sources and Production
Trehalose is found in small quantities in mushrooms, honey, yeast, and various plants. It is commonly used as a food additive.[7]

Other Applications: Beyond food, it is used in the pharmaceutical industry to stabilize antibody drugs and in cosmetic formulations.

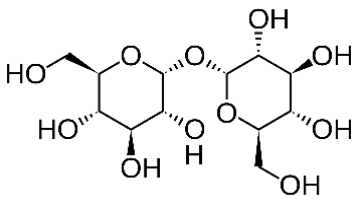

Figure 2: Trehalose.

Trehalose [α-D-Glucopyranosyl α-D-glucopyranoside], CAS: 99-20-7 (anhydrous), 6138-23-4 (dihydrate)] is a sugar derived from two molecules of glucose. Trehalose is a disaccharide formed by a 1,1-glycosidic bond between two α-glucose units. It is found in nature as a disaccharide and also as a monomer in some polymers. Two other stereoisomers exist: α,β-trehalose, also called neotrehalose, and β,β-trehalose, also called isotrehalose. Neither of these alternate isomers has been isolated from living organisms, but isotrehalose has been found in starch hydroisolates. Some bacteria, fungi, plants and invertebrate animals synthesize trehalose as a source of energy, and to survive freezing and lack of water.[8]

Poloxamer 407 (also known as Pluronic® F127) is a non-ionic surfactant and copolymer used widely as a thickening agent, emulsifier, and solubilizer in cosmetics and pharmaceuticals. Its key feature is thermoreversible gelation, forming gels at body temperature, making it ideal for drug delivery (oral, topical, ophthalmic). While generally safe, potential concerns include high-dose toxicity, such as hyperlipidemia and potential renal effects.

Common Uses
Pharmaceuticals: Used as a gelling agent in liquid-to-gel formulations, mucoadhesive drug delivery, and solubilizing poorly water-soluble drugs.[9]

Cosmetics & Personal Care: Found in skin care, hair care, and mouthwashes as a surfactant to cleanse, emulsify, and help dissolve ingredients.

Contact Lens Solutions: Used as a cleaning agent.

Key Properties
Thermoreversible Gelation: Poloxamer 407 forms a gel at body temperature, which is highly valuable for sustained-release drug delivery systems.

Structure: It is a triblock copolymer consisting of a central hydrophobic block of polypropylene glycol flanked by two hydrophilic blocks of polyethylene glycol.

Solubility: Highly soluble in water.

Melting Point: While it doesn't have a sharp melting point in the traditional sense, it forms gels generally at concentrations above 18% w/w in aqueous systems.

Safety Profile and Potential Side Effects
Toxicity Concerns: High doses have been linked to significantly increased plasma lipid levels (hyperlipidemia) in animal studies.[10]

Renal Toxicity: Potential renal toxicity has been reported, sometimes limiting its use in specific injectable formulations.

Cytotoxicity: Aqueous solutions, especially when degraded, may show cytotoxicity to cultured cells.

Safety in Use: Generally considered safe in the low concentrations found in cosmetics.

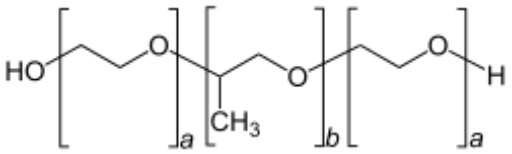

Figure-3: Poloxamer 407.

Handling and Storage: Poloxamer 407 is a white powder. It should be stored at 2-8°C. Preparation often requires a cold process (e.g., dissolving in water at low temperatures) or a hot process (using preheated water at ~70°C).

Poloxamer 407 [IUPAC name: Oxirane, methyl-, polymer with oxirane; CAS: 9003-11-6] is a hydrophilic non-ionic surfactant of the more general class of copolymers known as poloxamers. Poloxamer 407 is a triblock copolymer consisting of a central hydrophobic block of polypropylene glycol flanked by two hydrophilic blocks of polyethylene glycol (PEG). The

approximate lengths of the two PEG blocks is 101 repeat units, while the approximate length of the propylene glycol block is 56 repeat units. This particular compound is also known by the BASF trade name Pluronic F-127 or by the Croda trade name Synperonic PE/F 127. BASF also offers a pharmaceutical grade, under trade name Kolliphor P 407.[11]

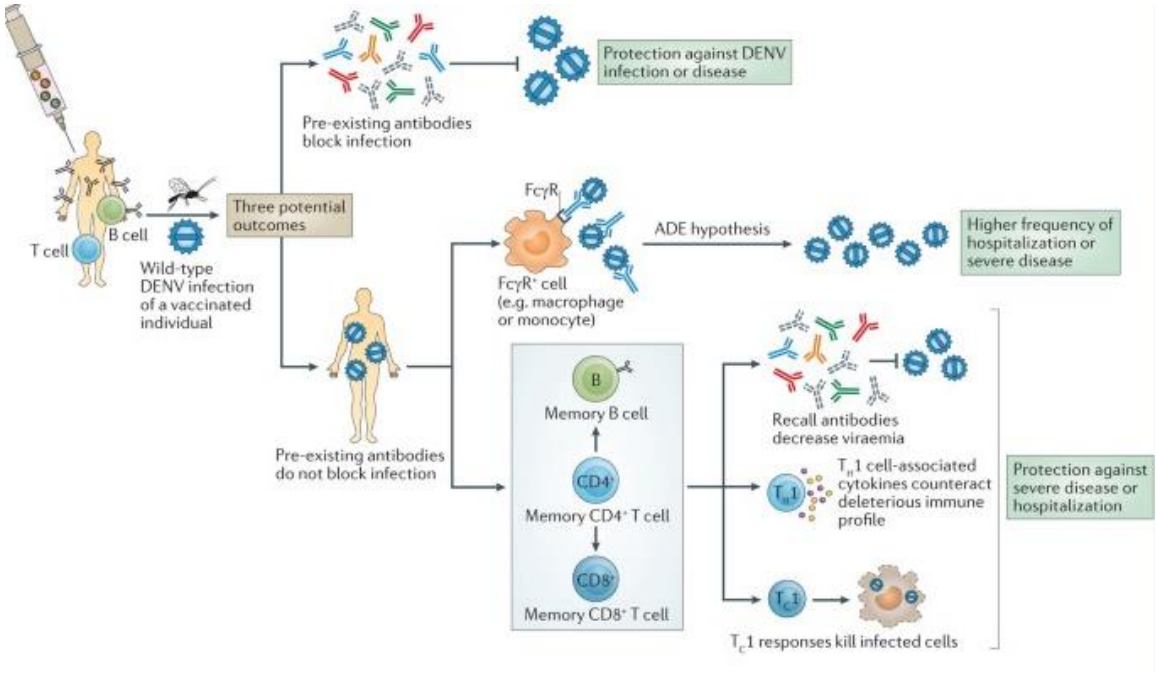

Figure 4: Dengue vaccine mechanism.

Immune Response Induction: Vaccines prompt B cells to create antibodies that block the virus from entering cells and activate T cells to eliminate infected cells.
Vaccine Viremia (TAK-003): The vaccine can cause temporary, mild viremia (virus in the blood) to prime the immune system, particularly in those not previously exposed to dengue.

Vaccine Types and Technologies
TAK-003 (Qdenga): A live attenuated tetravalent vaccine consisting of DENV1, DENV3, and DENV4 components on a DENV2 backbone.

Dengvaxia (CYD-TDV): A chimeric vaccine using a Yellow Fever Virus 17D backbone.

Inactivated/Subunit/DNA: Other, less common approaches, such as inactivated virus particles or DNA-based, are also being developed, including DENV-like particles (VLP).[12]

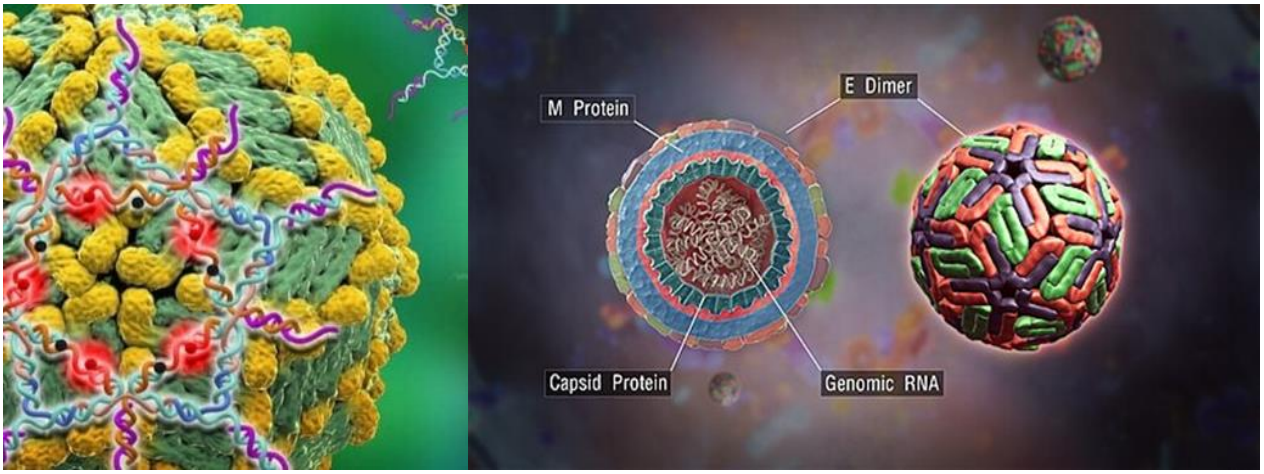

Figure 5: DNA & RNA of virus.

Key Considerations
Antibody-Dependent Enhancement (ADE): A potential risk where non-neutralizing antibodies from vaccination or a previous infection help the virus enter cells during a secondary infection, worsening symptoms.

Serostatus: Efficacy can differ depending on whether the recipient has had a previous infection, with some vaccines requiring prior exposure to avoid increasing severe dengue risk (e.g., Dengvaxia).

Dengue vaccines, specifically Dengvaxia, must be stored in a refrigerator at temperatures between 2^{O}-8^{O}C, protected from light, and never frozen. Lyophilized antigen and diluent require strict refrigeration, and after reconstitution, the vaccine should be used within 30 minutes. Storage and Handling Guidelines (Dengvaxia):

Temperature: Store in a pharmacy-grade refrigerator at 2^{O}-8^{O}C [36^{O}-46F^{O}] protected from light, and never frozen. Lyophilized antigen and diluent require strict refrigeration, and after reconstitution, the vaccine should be used within 30 minutes.[13]

Storage and Handling Guidelines (Dengvaxia)
Temperature: Store in a pharmacy-grade refrigerator at to 2^{O}-8^{O}C [36^{O}-46F^{O}].

Protection: Protect from light at all times.

Freezing: Do not freeze lyophilized antigen or diluent.

Figure 6: Vaccine storage.

Reconstitution: Use the provided saline diluent (0.4% NaCl) for the lyophilized antigen.

After Reconstitution: Administer immediately or store at to 2^{O}-8^{O}C [36^{O}-46F^{O}] and use within 30 minutes. If not used within this time, discard the vaccine.

Handling Errors: If the vaccine is mishandled or left out, contact the manufacturer or local health authority for guidance.

For Qdenga (another dengue vaccine, different from Dengvaxia), similar refrigeration rules apply, but the manufacturer instructions for in-use stability should be strictly followed, as they may differ slightly from Dengvaxia.

Key Considerations: Dengvaxia is generally meant for children and adolescents (ages 9-16) living in endemic areas with laboratory-confirmed previous dengue infection. The vaccine is a live-attenuated vaccine, making proper temperature maintenance critical to preserve potency.[14]

CONCLUSION

TAK-003 (Qdenga) and CYD-TDV (Dengvaxia) are the primary dengue vaccines, with TAK-003 showing 84% efficacy against hospitalization at 4.5 years and WHO recommending it for ages 6–16 in high-burden areas. Dengvaxia is safe for those with prior infection, while Qdenga is approved for ages 4+ without restriction.

Key Vaccine Developments (2025-2026 Reports)
TAK-003 (Qdenga): A live-attenuated tetravalent vaccine.

Efficacy: Shows high protection against hospitalization (84%–90%) and sustained efficacy for up to 7 years.

WHO Recommendation: Recommended for children aged 6–16 years in areas with high dengue burden (seroprevalence >60%).

Dosage: Administered in two doses, with a three-month interval.

Status: Approved for ages 4 and older by EMA and in several endemic countries.

CYD-TDV (Dengvaxia)
Safety: Safe and effective, but only in individuals with prior laboratory-confirmed dengue infection.

Efficacy: 79% to 84% reduction in hospitalization and severe disease.

Risk: Can increase the risk of severe dengue in seronegative individuals (those never infected).

Other Developments: The TV005 vaccine has shown high efficacy and is being studied for its strong response against all four serotypes.

Key Considerations
Safety: The primary challenge has been ensuring safety for seronegative individuals, as seen with Dengvaxia's risks.

Target Population: Current recommendations focus on regions where the disease is endemic to maximize impact, particularly using school-based vaccination strategies.

Limitations: While vaccines provide high protection against severe disease, they do not entirely eliminate transmission.

Dengue vaccines, such as live-attenuated tetravalent vaccines (e.g., Qdenga, Dengvaxia), work by introducing weakened versions of all four dengue serotypes (DENV 1-4) to induce a protective immune response . They stimulate the body to produce antibodies and T-cell responses that neutralize the virus, mimicking natural infection without causing severe disease.

Mechanism of Action: Live Attenuated Tetravalent Vaccine (e.g., TAK-003/Qdenga): Uses a chimeric, weakened DENV-2 backbone to express structural proteins (E and prM) of all four serotypes, inducing broad humoral (antibody) and cellular immunity.

Chimeric Vaccine (e.g., Dengvaxia): Uses a Yellow Fever Vaccine (YFV) backbone to present dengue E proteins, stimulating neutralizing antibodies, primarily suitable for those with prior infection.

Information on the "half-life" of dengue vaccines refers to the duration of protection and the persistence of antibodies rather than a pharmacological half-life. Current data indicates that protection from approved vaccines, particularly Takeda's Qdenga (TAK-003), lasts for at least 4.5 to 7 years, with antibody levels potentially lasting longer.

Key details on dengue vaccine durability
Qdenga (Takeda)
Protection: In a 4.5-year follow-up study, two doses provided 61.2% protection against virologically confirmed dengue (VCD) and 84.1% against hospitalizations.

Antibodies: Antibody levels (geometric mean titers) against all four serotypes were observed to remain high for up to 51 months (4.25 years) following the second dose.

Durability: Protection was demonstrated to persist through seven years.

Dengvaxia (Sanofi Pasteur)
Protection: Immunity induced by this vaccine is reported to last for at least 4 to 6 years.

Target Group: Due to risks of antibody-dependent enhancement (ADE) in seronegative individuals, it is restricted to those with prior dengue infection, as protection wanes after about 30 months in seronegative recipients.

Antibody Kinetics: Studies indicate a pattern of rapid initial decay of antibodies, followed by a slower, long-term decay, with cross-reactive antibodies sometimes decaying within 4 years. .

Vaccine Viraemia: After receiving the Qdenga vaccine, transient, low-level vaccine viraemia (the vaccine virus in the blood) can occur, usually starting in the second week after the first injection and lasting an average of 4 days. This is not the same as the long-term antibody persistence.

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