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Effectiveness of Tetravalent Dengue Vaccines (Qdenga and Dengvaxia) Against All Dengue Virus Serotypes

Karina Putri Aulia [1] and Lynda Rossyanti [2,*]

[1] *Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia.*
[2] *Department of Parasitology, Faculty of Medicine Universitas Airlangga, Surabaya, Indonesia.*

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Abstract

Background: Dengue virus (DENV), which can manifest as dengue fever, this fever has become a global health threat, with about 3 billion people, nearly 50% of the population, living in 100 different countries, most of which are tropical and subtropical regions, where this disease is prevalent. The increasing number of DENV infections has driven research into vaccination as a strategy to reduce cases. Currently, two licensed vaccines are available are TAK-003 and CYD-TDV, both of which are tetravalent vaccines designed to become protector against all four dengue serotypes. This study aims to evaluate the effectiveness of these vaccines against each serotype.

Methods: An online engine search was completed in PubMed and Google Scholar, that match the theme of study.

Result: Both vaccines are effective at preventing DENV infection, but they differ in efficacy. TAK-003 is more effective against DENV-2, while CYD-TDV shows better effectiveness against DENV-3 and DENV-4.

Conclusions: In summary, both vaccines demonstrate considerable potential in reducing the incidence of dengue fever. However, their efficacy varies according to the serotype, emphasizing the necessity for a strategic deployment of vaccinations tailored to the predominant serotype distribution in endemic regions to enhance control over the virus

Keywords: DENV; Vaccine Dengue; TAK-003; CYD–TDV

1. Introduction

Dengue virus is a member of the Flavivirus genus and transmitted to humans by the Aedes mosquito vector. This virus has positive-sense single-stranded RNA can cause dengue fever in infected individuals [1]. This virus has three structural proteins and seven non-structural (NS) proteins, restricted into four serotypes (DENV-1, DENV-2, DENV-3, DENV-4). While these serotypes share some of genetic similarity, they exhibit variations in their surface protein characteristics, which serve as receptors that will be identifies by the immune system, particularly antibodies.

Clinical manifestations that show individuals infected with dengue virus infection range from mild severe symptoms, which can lead to life-threatening and may result a shock condition [2]. The varied and complex clinical manifestations in individuals infected with the dengue virus underscore the necessity of vaccination as an essential strategy for reducing or preventing infection. At present, two licensed tetravalent vaccines, Qdenga and Dengvaxia, have been developed using live attenuated pathogens [3].

* Corresponding author: Lynda Rossyanti

Research on these vaccines has been extensively conducted. However, studies specifically evaluating their effectiveness against each serotype are still limited. Therefore, this study aims to assess whether the tetravalent dengue vaccine exhibits strong efficacy against each serotype, considering the genetic differences between the serotypes, in order to determine if the vaccine can elicit a robust immune response to combat symptoms of DENV..

2. Review Content

2.1. Dengue Virus

2.1.1. Definition

The pathogenic Dengue Virus (DENV), a member of the Flavivirus family, can cause dengue fever. This positive-sense single-stranded RNA virus has remarkable environmental adaptability and spreads swiftly in a variety of locations [1]. In female Aedes mosquitoes, the virus multiplies in their salivary glands and is injected into people by the insect. There is no direct human-to-human transmission; instead, it only happens through mosquitoes [4]. Although the four serotypes of the virus are genetically identical, they differ in their antigenic properties, especially in the receptors that the immune system recognizes [2].

2.1.2. Epidemiology

Approximately 3 billion people, or over 50% of the world's population, are afflicted by the dengue virus (DENV), which may cause dengue fever, in more than 100 nations. The disease is most common in tropical and subtropical climates [4]. Annually, dengue leads to approximately 400 million cases and 22,000 fatalities. The persistent outbreak is projected to affect around 5 million people across 80 countries in 2023, with Brazil, Peru, and Bolivia being the countries with the highest case contributions [1].

The widespread occurrence of dengue cases is largely driven by accelerated urbanization, increased human mobility, insufficient mosquito control efforts, and the effects of globalization, which collectively facilitate the spread of DENV infections [5].

2.1.3. Etiology

DENV, which belongs to the Flaviviridae family and has four different serotypes, is the primary cause of dengue fever. When one serotype is infected, antibodies unique to that serotype are produced; these antibodies do not offer cross-protection against other serotypes [6].

Three structural proteins and seven non-structural proteins make up the structure of the virus. Conformational alterations in the M and E proteins, which are impacted by environmental pH levels, govern the virus's capacity to infect a person [7].

2.1.4. Structure

DENV belongs to the Flaviviridae family and the Flavivirus genus. It is a positive-sense single-stranded RNA virus. The dengue virion, which has a spherical form and a diameter of around 50 nm, is composed of envelope (E) and precursor-membrane (prM) or membrane (M) protein.. The capsid protein (C) envelops the viral DNA underneath the lipid bilayer. The virus also contains seven non-structural proteins (NS), with structural proteins facilitating virion formation and non-structural proteins playing a role in replication and immune system interference [8].

2.1.5. Pathogenesis

The virus attaches itself to the target cell surface to start the DENV life cycle, facilitated by interactions between the viral surface proteins and cell membrane receptors. This receptor recognition is mediated by the E protein, enabling viral entry through endocytosis. Alternatively, the virus may enter the host cell via direct fusion. Once inside via endocytosis, the virus is contained within an endosome with an acidic environment. The E protein in the endosome dissociates into homodimers, preparing the virus to exit the endosomal membrane. Following fusion, the viral RNA genome is released into the host cell cytoplasm, where it initiates replication and transcription processes [8]

2.1.6. Patofisiology

DENV infection can result in shock or death and can induce a wide variety of symptoms, from moderate to severe. The initial dengue infection, sometimes referred to as the main infection, usually manifests as dengue fever and is either asymptomatic or has moderate clinical symptoms [7].

DENV is not transmitted directly from person to person. Instead, the virus is spread by Aedes mosquitoes, with blood transfusions from an infected individual to a healthy one also being a potential transmission route. During primary infection, the individual generates antibodies specific to the infecting dengue serotype. These antibodies may cross-react with other serotypes, though not fully. If the antibody levels are inadequate to neutralize the virus, they may exacerbate infection by aiding viral entry into host cells. Secondary infection with a different serotype can enhance this process through Antibody-Dependent Enhancement (ADE), leading to an increase in cross-reactive antibodies. This mechanism facilitates viral entry into cells. Once inside, immune cells aggregate and form larger clusters, which contributes to capillary leakage. Furthermore, DENV can infect and activate platelets, making them more prone to phagocytosis and resulting in thrombocytopenia [9].

2.1.7. DENV Strain

DENV is classified into four viral strains based on its serotypes, with more than 30% amino acid sequence differences between them. These strains consist of DENV-1, DENV-2, DENV-3, and DENV-4, each with varying abilities to interact with antibodies in the human body. A meta-analysis has demonstrated that DENV-2 and DENV-4, particularly from Southeast Asia (SEA), are associated with dengue shock syndrome, while DENV-3 and DENV-4 have a higher association with Dengue Hemorrhagic Fever (DHF) [3, 10].

The incidence of symptomatic disease varies across different serotypes. A cohort study revealed that DENV-3 is the most pathogenic, with 24% of infections exhibiting symptoms. DENV-1 and DENV-2 have similar pathogenicity, with estimated symptomatic probabilities of 10% and 13%, respectively. DENV-4, on the other hand, is the least pathogenic, with only approximately 2% of cases presenting clinical symptoms [11].

2.2. Dengue Vaccine

2.2.1. Overview

Dengue virus transmission by mosquitoes has resulted in millions of infections globally, contributing to a rise in symptomatic cases annually, which poses a major public health challenge. Traditional dengue control strategies have primarily concentrated on mosquito control, but these approaches remain complex, expensive, and less effective in light of the growing case numbers. Consequently, a dengue vaccine is necessary to prevent the increasing incidence of the disease. The development of such a vaccine is particularly difficult due to the complexity of the virus, with each serotype presenting distinct challenges [12]. The worldwide dengue burden might be significantly reduced with the development of a safe and effective dengue vaccine. Dengvaxia (CYD-TDV), a live attenuated chimeric yellow fever/dengue vaccine created by Sanofi Pasteur, is the first licensed dengue vaccine after years of development. It has been approved in nations including Thailand, Mexico, Brazil, El Salvador, and Costa Rica. Additionally, TAK-003 (Qdenga), a licensed live attenuated vaccine created by Takeda, is also accessible for usage [13, 14].

2.2.2. Vaccine TAK-003

Takeda created TAK-003, sometimes known as Qdenga, using the DENV-2 backbone. The vaccination is intended to stimulate the body's humoral immune system. However, pregnant and nursing women, as well as those with weakened immune systems, should not use it [15]. The vaccine is developed to target all four dengue serotypes, utilizing a weakened DENV-2 (TDV-2) backbone derived from the DENV-2 Primary Dog Kidney-53 virus, isolated in Thailand. To produce the tetravalent vaccine, viral components from the other three serotypes are incorporated by substituting specific regions (E and PrM) with those from DENV-2, thus offering protection against all four serotypes of dengue [16]. The DENV-2 backbone in this vaccine induces the production of antibodies not only targeting the virus itself but also against non-structural protein 1 (NS1). This response plays a key role in the development of protective immunity, thereby improving the body's defense mechanisms against subsequent infections [17].

2.2.3. Vaccine CYD-TDV

This vaccine is based on a live attenuated virus and is based on the yellow fever 17D strain (YF17D). The vaccine is made by substituting the pre-membrane and envelope proteins of YF17D with those from the four DENV serotypes [18]. For those living in endemic areas between the ages of 9 and 45, this vaccination is advised. Phase 3 clinical trials have

demonstrated that age, serological status, and the particular DENV serotypes implicated affect its effectiveness. The three doses in the vaccine regimen are given at intervals of 0, 6, and 12 months [19]. The vaccine is based on the parental strains Thailand PUO-359/TVP-1140 for type 1, Thailand PUO-218 for type 2, Thailand PaH881/88 for type 3, and Indonesia 1228 (TVP980) for type 4. Recombinant DNA technology is utilized to produce each monovalent DENV CYD, with the four DENV chimeric vaccines cultured in Vero cells, which are employed for virus propagation in vaccine production laboratories, and subsequently combined into a single vaccine formulation [20].

2.3. Efficacy of TAK-003

The vaccine's efficacy varies across different studies. In one study involving 20 participants, 14 were vaccinated, and 6 received a placebo. The overall efficacy for seropositive individuals was 76.1%, while for seronegative individuals it was 66.22%. Efficacy also differed across serotypes, with DENV-2 showing the highest efficacy at 95.1%, followed by DENV-1 at 69.8%, DENV-4 at 51%, and the lowest for DENV-3 at 48.9%. A long-term study (4.5 years) conducted with a double-blind methodology showed differences in efficacy between seropositive and seronegative individuals. The efficacy for seropositive individuals was 56.1% for DENV-1, 80.4% for DENV-2, 52.3% for DENV-3, and 70.6% for DENV-4. For seronegative individuals, the efficacy was 45.4% for DENV-1, 80.4% for DENV-2, 52.3% for DENV-3, and 70.6% for DENV-4. Short-term efficacy studies also showed that for seropositive individuals, DENV-1 had an efficacy of 79.8%, DENV-2 100%, and DENV-3 71.3%. For seronegative individuals, DENV-1 showed an efficacy of 67.2%, DENV-2 at 96.5%, and DENV-3 showed inconclusive results. No confirmed dengue cases were reported for DENV-4 in this study. Among the studies conducted, DENV-2 demonstrated the highest vaccine efficacy, likely due to it being the backbone serotype of the TAK-003 vaccine [21, 22]

2.4. Efficacy of CYD-TDV

A study utilizing a Bayesian survival analysis model indicated that the efficacy of the CYD-TDV vaccine is affected by factors such as age, serological status, serotype, and disease severity. In seronegative individuals, DENV-2 exhibited the lowest estimated initial immunity, whereas DENV-3 and DENV-4 showed relatively higher estimates of immunity [23]. The recombinant tetravalent dengue vaccine (CYD-TDV, Dengvaxia) demonstrates an overall pooled efficacy of approximately 60% against virologically confirmed dengue in children aged 2–16 years. However, the efficacy varies significantly by serotype, with around 51% for DENV-1, 34% for DENV-2, 75% for DENV-3, and 77% for DENV-4 [24]. The CYD-TDV vaccine only expresses the PrM and E proteins from the four DENV serotypes; non-structural proteins are not included in the formulation, which explains the variance in effectiveness across these serotypes. Compared to the other serotypes, DENV-2 exhibits lower amounts of PrM and E protein expression, which results in a weaker antibody response. [25].

3. Conclusion

The efficiency and effectiveness of the TAK-003 and CYD-TDV dengue vaccines varies. The adoption of the DENV-2 backbone, which yields the best efficiency for this serotype, is probably the reason TAK-003 exhibits strong efficacy against DENV-2. On the other hand, CYD-TDV has the greatest effectiveness against DENV-3 and DENV-1, while DENV-2 exhibits the lowest effectiveness. This may be explained by the vaccine's incapacity to produce non-structural proteins; instead, it only produces the PrM and E proteins, with DENV-2 exhibiting the lowest levels of these protein expression. Both vaccines have substantial potential in reducing dengue fever incidence; however, their varying efficacy across different serotypes highlights the importance of targeted vaccination strategies based on the prevalent serotypes in specific regions to achieve more effective control of the virus.

Compliance with ethical standards

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Disclosure of conflict of interest

There is no conflict of interest

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