

ORIGINAL ARTICLE

REVIEW ARTICLE: DEVELOPEMENT AND USING DENGUE VACCINE FOR DENGUE INFECTION VIRUS

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ABSTRACT

Tropical and subtropical countries are regions with high incidence of dengue infection. Dengue virus infection is estimated to cause 300 million new infections in one year and approximately 1 million severe cases with $2 \pm 5\%$ deaths. The case of dengue in Indonesia has continued to increase since 1968 until 1980 where all provinces in Indonesia have been affected by the dengue virus. Dengue virus is a virus carried by the *Aedes aegypti* mosquito in its salivary gland. The virus which is a family group of Flaviviruses has four homologous serotypes, namely DENV-1, DENV-2, DENV-3, and DENV-4, which can cause dengue infection in individuals. Currently there is a shift in the target population from children to adults. This is a problem that needs to be resolved by the government and the community itself. Solution to overcome this, the government needs early prevention efforts to reduce the severity of dengue infection by developing and researching dengue vaccines. Currently a vaccine has been found that can be used as prophylaxis for dengue virus, namely Dengvaxia. This vaccine has been recommended by the World Health Organization (WHO) as prophylaxis for dengue infection, but Dengvaxia is only used in areas that are very endemic to dengue fever. The Indonesian Food and Drug Supervisory Agency (BPOM RI) has also approved the use of Dengvaxia as an indication of prevention of dengue infection since August 31, 2016. This vaccine has been approved globally only given to individuals aged between 9-16 years.

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INTRODUCTION

Dengue fever is a disease caused by the bite of the *Aedes aegypti* mosquito carrying dengue virus (DENV) in its salivary gland. Dengue is found in tropical and subtropical regions throughout the world.⁽¹⁾ Estimates that arise due to infection from the dengue virus are obtained around 300 million new infections per year and approximately 1 million cases of serious illness with a death of $2 + 5\%$. The DENV virus presents a new challenge for controlling the main mosquito vectors, but it is also known that there is no effective antiviral to treat DENV infection.⁽²⁾ At

present, an efficient prophylactic strategy for dengue infection is needed by reviewing the epidemiological trends of dengue virus, biology, and clinical diseases, which in the next stage are expected to help to make efficient vaccine strategies.⁽³⁾

DENGUE DISEASE

Epidemiology of dengue

From 1968 to 2009, the World Health Organization (WHO) has noted that Indonesia is the country with the highest DHF cases in Southeast Asia. Before the DHF case (Dengue Hemorrhagic Fever) then spread widely in the

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territory of Indonesia, this disease first appeared in 1968 in the city of Surabaya, with a total case of 58 people infected and 24 other people dying. Although it was first discovered in 1968, confirmation of a new virological dengue was obtained in 1972. In 1980, all provinces in Indonesia were affected by dengue and the cases continued to increase every year.⁽⁴⁾

Replication of dengue virus

There are four different types of antigen serotypes which are divided homologically by 60-80%: DENV-1, DENV-2, DENV-3, and DENV-4. DENV is a virus particle that is about 50 nm in size which is enveloped by a lipid membrane. RNA which contains about 11,000 long nucleotide frames encodes a large polyprotein and at the post translational stage is divided into 3 structural proteins such as capsid (C), membrane precursor (prM), and envelope (E), and seven non-structural proteins such as NS1, NS2a, NS2b, NS3, NS4a, NS4b, and NS5. The surface of the virion composed of glycoprotein E is used as the main target of DENV to neutralize antibodies. The ectodomain of E consists of a centrally located I (EDI) domain, containing loop fusion II (EDII), and domain III which carries almost all antibody-specific epitope antibodies.⁽³⁾

When genomic RNA is released into the cytoplasm and after the fusion of viral membranes with endosomal membranes, the translation of viral RNA then begins to approach the endoplasmic reticulum (RE). After the virus replication complex occurs, the translation is stopped, and viral RNA synthesis occurs. During the replication process of DENV, the viral genome will be degraded by the enzyme exonuclease (XRN1) to produce small species of subgenomic flavivirus RNA (sfRNAs) that are in accordance with the majority of the non-transplanted genomic region (NTR) at the end of 3 genomic RNA. The accumulation of sfRNAs results in viral replication, but also changes the activity of the host cell antiviral to be resistant to viral replication. The synthesis of artificial RNA molecules contributes to the massive production of viral proteins. The RE surface is the assembly location of the virus that has not yet matured, the

virus is carried through the Golgi complex and then the PRM is processed into M until it undergoes maturation and is ready to be released into extracellular.⁽³⁾

Symptomatic features of dengue disease

There are three phases that occur in dengue conditions, namely the febrile phase, critical phase, and recovery phase.

1. Febrile phase: dehydration, high fever which causes disorders of the nervous system, and causes seizures in children.
2. Critical phase: shock from plasma leakage, severe haemorrhage, impairment organs.
3. Recovery phase: hypervolemia, acute pulmonary edema.⁽¹⁾

HUMAN SUSCEPTIBILITY TO DENGUE VIRUS INFECTION

Currently DHF cases are still considered trivial, so it is very easy for every individual who lives in an endemic area to be infected with dengue. Based on this information, then WHO recommends using Dengvaxia Vaccine as a preventive measure. The nature of the pathogen DENV has been widely reported as infection because DENV-2 is the biggest cause of severe dengue compared to other serotypes. Clinically the majority of people infected with dengue are asymptomatic. According to Ten Bosch et., Al., The fastest spread of DENV occurs in endemic areas where most are caused by an increase in transmission of disease by vectors.⁽³⁾

MECHANISM OF DENGUE VACCINE

The general mechanism of action of the dengue vaccine is to stimulate antibody activation to be able to fight the four dengue virus serotypes measured through PRNT50. After vaccination, titre is seen to be higher in seropositive compared to seronegative. Furthermore, T cells will be stimulated by the presence of foreign structures of antigens from the dengue virus and against non-structural antigens from the YF vaccine virus.⁽⁵⁾

DENGUE VACCINE DEVELOPEMENT

At present, it is known that there are vaccines that have passed the clinical phase test and are registered as vaccines for the dengue virus. This vaccine has been registered in several countries in the world, namely the CYD-TDV vaccine or Dengvaxia vaccine which is produced by a pharmaceutical company in France owned by Sanofi Pasteur. Several other candidates besides the Dengvaxia vaccine are also starting to be developed, but are still in the phase III clinical trial phase. The development of vaccines is inseparable from the supervision and protection of the World Health Organization (WHO) regarding the quality, safety and effectiveness of the dengue vaccine. The CYD-TDV vaccine represented by CYD14 and CYD 15 has been evaluated by phase III clinical trials using the Randomized Controlled Trials (RCT) method in several countries in the world. The CYD14 vaccine was evaluated for 10,275 participants aged 2-14 years in 5 countries in Asia in the first vaccination, namely Indonesia, the Philippines, Malaysia, Vietnam and Thailand. Whereas for CYD15 vaccine, 20,869 participants were aged 9-16 years in the first vaccination in Latin America, namely Brazil, Colombia, Honduras, Mexico, and Puerto Rico. In this evaluation, RCT patients were randomized to compare vaccines with placebo (0.9% solution of sodium chloride) with a ratio of 2: 1. This study was carried out for 13 months which was calculated from the last dose of vaccination to see the primary efficacy endpoint and included surveillance data at the Hospital as an additional data security for a period of 4 years.⁽⁵⁾

The Efficacy of Vaccine CYD14 and CYD15

Dengue viruses has been tested and assessed based on surveillance data (25 months after being registered). This effectiveness test is carried out on CYD14 and CYD15 vaccines. Assessments carried out on a per protocol basis were based on serotypes, namely 56.5% (95% CI 43.8% -66.4%) in CYD14 and 60.8% (95% CI 52.0% -68.0%) in CYD15 (from one month post dose 3 for 12 months). Furthermore, vaccine effectiveness in fighting dengue virus was shown starting from the lowest

based on serotypes, ie 1 (50.2%, 95% CI 35.6% - 61.5%), 2 (39.6%, 95% CI 18.7 % -55.2%), 3 (74.9%, 95% CI 65.1% -82.0%) and 4 (76.6%, 95% CI 65.0% -84.4%).⁽⁵⁾

In addition to seeing the effectiveness test, it is also necessary to find out the results of testing the effectiveness of dengue vaccines in several countries. The results of the effectiveness tests from several countries are quite varied. The effectiveness of the dengue vaccine in Mexico ranges from 31.3% (95% CI 1.3% -51.9%) and by 79.0% (95% CI 5.3% -91.5%) in Malaysia.⁽⁵⁾

This vaccination is carried out at the age of 9 years and above. Because at the age of <9 years and 2-5 years the child's immunity is still low. When exposed to this vaccine, the vaccine can act as a natural infection. The duration of protection from vaccines to strengthen the body's immunity against dengue virus is ranging from 5-6 years after administration of vaccination.⁽⁵⁾

Current status of Dengvaxia vaccine developement

The developmental status of the Dengvaxia vaccine test is interesting to continue to follow. While undergoing the 3rd phase clinical trial, Sanofi Pasteur stated that he did not collect blood samples used to determine the serostatus (had had previous dengue infection or not) before the vaccination process was carried out. Collection of blood data for all participants was only carried out at the 13th month (1 month after the 3rd vaccine dose was given). The assay method is used to recognize antibodies with a non-structural code of dengue protein (NS1) where the patient's status can still be known even though he has received previous vaccinations. This is because the NS1 protein code for Dengvaxia is a protein code from the Yellow Fever vaccine.⁽⁶⁾

Dengue vaccine Dengvaxia

Dengvaxia vaccines are known to be widely accepted and can induce balanced immunity to all four serotypes. Based on this, the tetravalent CYD-TDV dengue vaccine is known to be produced using a live attenuated flavivirus-17D vaccine and a yellow fever virus (YF-17D) strain as its

backbone. The CYD-TDV contained four YM-17D chimeric viruses which gave rise to prM and E proteins from each of the 4 dengue serotypes. The dengvaxia vaccine was developed by OraVax for 10 years through preclinical testing to clinical trials, but this development did not continue until Acambis Inc. come to continue. The same thing happened, the development did not go as expected, until in 2005 Sanofi Pasteur bought the company. Furthermore, Sanofi Pasteur carried out a massive development and research on dengue vaccines which eventually could be patented under the trade name Dengvaxia.⁽⁷⁾

In 2015, several countries such as Brazil, EL Salvador, Mexico, and the Philippines, Dengvaxia vaccine was received and had security data. Indonesia through the RI POM agency issued a marketing permit on August 31, 2016 with indications as preventive for dengue cases caused by dengue serotypes 1,2,3 and 4 and given to individuals aged between 9-16 years, and with individual conditions they live in endemic areas.⁽⁸⁾

The CYD-TDV vaccine is available in the form of a single dose vial injection or multi dose (5 dose) vial. This vaccine product is stored in frozen form which can then be reconstituted if it is to be used. In the use for single dose purposes, it can be reconstituted with 0.4% NaCl solution, whereas for multi dose purposes it can be reconstituted with 0.9% NaCl. Then after the preparation has been reconstituted, then 0.5 mL of the dose can be taken and given by injecting via the subcutaneous route (SC). While for the remaining solution can be put into the syringe for single dose administration or stored in a vial for multi dose administration. It is important to know that the CYD-TDV vaccine does not contain adjuvants or preservative ingredients and has a shelf-life of 36 months when stored at a temperature of 2 oC - 8 oC. This causes when the vaccine has been reconstituted with a compatible solvent, when the vaccine has not been used it must be stored at a temperature between 2 oC - 8 oC and protected from sunlight or UV light. The WHO policy is related to multi-dose after reconstitution and there is a dose left in the vial, so the leftover part should be discarded within 6 hours

of reconstitution or at the end of the vaccination session, depending on which one is first.⁽⁵⁾

Dengue vaccine candidate TDV

TDV vaccine (Takeda's Dengue Vaccine Tetravalen) is a vaccine made as a candidate for another vaccine for dengue virus. This vaccine is made from the original DENV-2-PDK-53 vaccine that has been attenuated by the addition of mutations in NS3. TDV vaccine has been reported as a candidate for a safe and tolerable vaccine based on phase 1 and 2 clinical trials. There are three chimeric viruses, namely TDV-1, TDV-3, and TDV-4 which aim to replace PRM and E genes from DENV-1, DENV-3, or DENV-4 to TDV-2. At present, TDV vaccines are still in phase 3 clinical trial stages which are expected to be completed by the end of 2021.⁽³⁾

Dengue vaccine candidate LAV Delta 30

This type of vaccine has been developed by the National Institute of Health (NIH) which has specific characteristics with the elimination of 30 contiguous nucleotides (Δ 30) and subsequently inserted into domain II from the tip of 3' NTR RNA genomic. Removal (Δ 30) aims to weaken viruses DEN-1, -3, and -4. Furthermore, Butantan Institute licensed the Delta 30 LAV vaccine and changed its name to TV003. Phase 1 and 2 clinical trial results showed good safety and immunogenicity results with seroconversion rates starting at 50% (DENV-2) to 100% (DENV-1, -3, and -4) after single dose administration. However, the presence of viruses in the blood is still detected in vaccinated individuals using TV003. Similar to the TDV vaccine, this vaccine is also still in the phase 3 clinical trial phase which is expected to be completed by 2022.⁽³⁾

Dengue vaccine involving DNA technology

The more sophisticated technology in this modern era, becomes an opportunity to design and develop new dengue vaccines as a preventive measure against dengue virus. This vaccine is still under development and pre-clinical testing and is still awaiting its safety data and effectiveness. Vaccine involving DNA technology has

recombinant subunits that require heterologous expression systems such as vectors, plasmid DNA, virus-like particles that only express PRM and protein E, or only reveal ED III from all four serotypes.⁽³⁾

AGE OF GIVING DENGUE VACCINE

Based on research data, currently dengue vaccines can be given starting at the age of 9 years or older in several countries in the world. A dengue vaccine (CYD-TDV) has a high effectiveness on all serotypes of dengue when given before exposure and its effectiveness increases with age. Based on seropositive values in children, overall vaccine effectiveness increased with age, ie 35.9% (95% CI: -7.6, 69.3) for children aged ≤5 years, 65.6% (95% CI: 40.3, 84.2) for ages 6-8 years, 73.4% (95% CI: 62.6, 82.1) for ages 9-11 years, and 80.6% (95% CI: 72.9, 87.3) for ages 12 years or older.⁽⁹⁾

Table 1. Estimated Levels of Effectiveness of Vaccines (EV%) Through Basic Immunity Status and Age Group CYD14 dan CYD15.

Age Group	Baseline Immunity Status			
	Seropositive		Seronegative	
	Est.	95% CI	Est.	95% CI
≤ 5	35.9	(-7.6, 69.3)	29.2	(-13.5, 63.7)
6 ≤ . ≤ 8	65.6	(40.3, 84.2)	38.9	(-6.3, 74.7)
9 ≤ . ≤ 11	73.4	(62.6, 82.1)	34.6	(3.6, 59.4)
≥ 12	80.6	(72.9, 87.3)	23.6	(-15.3, 54.3)

According to the World Health Organization (WHO), CYD-TDV is a viral vaccine that is prophylactic. The dengue vaccine is given by injection of 0.5 mL 3 times with a range of administration for 6 months from each vaccination time. Early indications (licenses) for administering this vaccine are efforts to prevent dengue illness by dengue virus serotypes 1,2,3 and 4 in individuals aged 9-45 years or 9-60 years who live in endemic areas. Meanwhile, for 9-year-olds, safety data is needed and for children aged 2-5 years the security data is still in phase III clinical trial stage.⁽⁵⁾

Doctor Ari Prayitno, Sp.A (K) said that dengue vaccine can be started at any time since children aged 9-16 years. In addition, he also explained that vaccination after infection with dengue is still recommended. This is because,

when a person (child) is infected with dengue it is usually only infected by one type of serotype from DENV and rarely is it directly infected by 4 serotypes at once. This then raises the perception that by giving vaccinations containing 4 serotypes at once, the child's immunity will be formed to be immune to other serotypes that have not infected the child. In addition, giving vaccines to individuals who have had previous dengue infection can be beneficial to prevent the risk of more severe or severe dengue infection (dengue shock by secondary infection from other serotypes).⁽¹⁰⁾

The data that is owned by the NRAs is in harmony with what was conveyed by doctor Ari Prayitno, Sp.A (K). Although there is no correlation that can be used as a link during age grouping in the effectiveness test, a phase 2 clinical trial shows that seropositive baseline is associated with increased age and stability of titres after vaccination. The results of this effectiveness are shown between the ages of 9-16 years and this condition is predicted to be similar to the adult population in endemic areas.⁽⁵⁾

USE AND SECURITY OF DENGUE VACCINE

Research on vaccination, especially dengue vaccines, is very important for an endemic country. It is known that 4 dengue virus serotypes (DEN-1, DEN-2, DEN-3, DEN-4) revolve globally and the most reported annually is in endemic countries. WHO states that dengue vaccine can only be used in areas that are very endemic to dengue fever. In addition, to obtain the best population level strategy, WHO recommends looking at seroprevalence as a basis for consideration of the efficacy and safety level of protection in seropositive individuals. These considerations are based on the SAGE (Strategic Advisory Group of Experts). Seroprevalence is a level of seropositivity to a particular pathogen in a population. Mathematically, the calculation to determine the optimal seroprevalence is obtained in the age group targeted for vaccination which is around 70% or more, if it is in the range of 50% - 70% it is still acceptable but with lower effectiveness. This is

different from seroprevalence below 50%, WHO does not provide recommendations for vaccination. Because in addition to its low effectiveness, it can also cause a potential long-term risk for the occurrence of severe dengue fever in seronegative individuals.⁽⁵⁾

The safety of the dengue vaccine needs to be considered during the use process. This is related to adverse reactions that can occur in the CYD TDV vaccine. For example, the reaction of the adverse effects of this vaccine is local and systemic. Systemic reactions occurred at 66.5% in CYD-TDV recipients and 59% in placebo recipients. In general, systemic reactions that occur are like headache (> 50%), malaise (> 40%), and myalgia (> 40%). Whereas symptoms of fever occur at 5% in the age group 18 - 60 years and 16% in the age group 9-17 years. Local reactions occurred at 49.6% in the group receiving CYD-TDV and by 38.5% in the group receiving placebo. In general, local reactions that occur are pain of 45.2% felt by the age group 18-60 years and 49.2% in the age group 9-17 years. In general, the outcome of serious adverse reactions to date still has no relevant data found.⁽⁵⁾

The provision of the Dengvaxia vaccine as a preventive measure against dengue virus has attracted the attention of the Indonesian Food and Drug Administration to evaluate the safety of this vaccine. The results of re-evaluation of the Indonesian Food and Drug Administration on the Dengvaxia vaccine are divided into two parts, namely individuals who have never had dengue virus infection (seronegative) will be at high risk of experiencing severe dengue and at risk of being hospitalized higher than seronegative individuals only given a placebo. In addition, it is also known that the administration of Dengvaxia vaccine in children aged > 9 years with seronegative has lower efficacy compared to individuals who have had dengue infection (seropositive). Reaffirmed by the Indonesian Food and Drug Administration, the efficacy of the Dengvaxia vaccine is better when given to seropositive individuals ranging in age from 9-16 years.⁽⁸⁾

The Indonesian Food and Drug Administration has decided several things after re-

evaluating as above, namely 1) the Dengvaxia vaccine can be used as a preventive measure against the risk of dengue fever occurrence and severity in children aged 9 to 16 years and had previously experienced infection dengue virus (seropositive) and 2) Dengvaxia vaccine is prohibited from using seronegative individuals. Even though there is currently no data on the side effects of the Dengvaxia vaccine, in order to prevent undesirable events, the Indonesian Food and Drug Administration has appealed to all relevant parties including Peer Health Professionals to prioritize patient safety in the administration of vaccines as well as the Indonesian Food and Drug Administration. PT. Aventis Pharma continues to monitor the use of the Dengvaxia vaccine in the territory of Indonesia.⁽⁸⁾

VACCINATION PROGRAMMES

The use of the CYD-TDV vaccine has a significant impact on dengue disease at the age of > 9 years. Based on comparisons of several mathematical models, the vaccination program using the CYD-TDV vaccine is known to reduce symptoms and hospital care due to dengue illness by 10% - 30% over a 30-year period. Based on data for cost effectiveness, One DALY tried to calculate the total cost incurred in dengue cases was 2000 US dollars. Therefore, in overcoming this, efforts are made to prevent dengue or preventive measures and look for alternative vaccines that can be used in at least some endemic countries, as well as cost effectiveness predictions for dengue cases. The results obtained are the total costs incurred for a full vaccination per person is around 15-40 US dollars or when using a societal perspective the total cost incurred for a full vaccination per person is less than 100-150 US dollars. However, this data is only a comparative model and cannot be used as a basis for making decisions based on specific analysis in each country.⁽⁵⁾

HUMAN CONTRAINDICATION TO DENGUE VACCINE

Contraindications to drug use also occur in vaccine administration. According to WHO

(2016), there are several contraindications to the use of dengue vaccine, namely 1) an individual who has a history of allergies to components contained in dengue vaccines or with other vaccines containing the same components as dengue vaccines; 2) individuals with impaired innate immunity or immune deficiencies obtained to mediate immune cells; 3) individuals with symptoms (symptomatic) of HIV infection or asymptomatic HIV infection accompanied by evidence of failure of immune function; 4) pregnant or lactating women; and administration of vaccines should be delayed in patients with moderate to severe febrile conditions or acute disease.⁽⁵⁾

DISCUSSION

The emergence of information about vaccines for dengue virus is now increasingly widespread. According to doctor Hunied Kautsar, the national immunization program for dengue vaccine is still a pro and contra, which is the reason that this vaccine cannot be included in the national immunization program. The unavailability of dengue vaccine in the national immunization program causes the administration to be limited, so clinicians (doctors) need to pay attention to the recommendations that have been submitted by the RI POM and WHO that the Dengvaxia dengue vaccine is only indicated for individuals aged 9 to 16 years with seropositive status and living in the area endemic for dengue.

CONCLUSION

Dengue virus can affect anyone, especially individuals or groups in endemic areas. Every element of society needs to be alert to contracting this virus. Currently several vaccines are being developed as prophylaxis to reduce the severity of dengue virus infection. Until this period, only one vaccine has been allowed to be released by WHO, the Dengvaxia vaccine and has been accepted in several countries in Europe and Asia. Other vaccine candidates are still in the pre-clinical trial phase and phase 3 clinical trial. The use of the Dengvaxia vaccine is still limited by WHO, which

is only at the age of 9-16 years and is in the endemic area of dengue fever. Likewise in Indonesia, the Indonesian Food and Drug Administration also adopted recommendations from the WHO to limit the use of the Dengvaxia vaccine. Based on serovalence, the safety and effectiveness of using Dengvaxia vaccine is better when given to seropositive individuals compared to seronegative individuals or in other words, individuals who have previously had dengue infection are then vaccinated, so the effectiveness and safety are higher compared to individuals who have never experienced infection previous dengue.

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