Progress and Development of Three Types of Live Attenuated Vaccines for Dengue Fever

Yujing Chen [1, *, †], Audrey Huang [2, †], Yuepeng Sui [3, †], Xuanyi Tong [4, †], Fanghai Yu [5, †]

[1] Shanghai University of Medicine&Health Sciences

[2] Tianjin Teda Maple Leaf International School

[3] Guangzhou Medical University

[4] Nanjing Jinling High School International Department

[5] Windermere Preparatory School

* Corresponding Author Email: chenyujing@stu.sumhs.edu.cn

† These authors contributed equally.

Abstract. Dengue fever is a disease spread by mosquitoes infected with the dengue virus (DENV) that bite people. It is produced by any of the four serotypes of DENV. Dengue fever has become one of the most widespread mosquito-borne infectious diseases in the world. According to the World Health Organization (WHO) dengue fever is a serious global public health concern. To suppress the spread of dengue fever and reduce the social, medical, and economic burden brought by dengue fever, vaccination is an effective measure to prevent the disease. Research teams around the world have worked on the development of a dengue vaccine for many years. At present, three live attenuated vaccines have made great progress and entered the final stage of clinical trials. In order to enable dengue vaccine researchers to grasp the latest research status and promote faster development of the dengue vaccine, this paper provided a comprehensive overview of the research progress of three different live attenuated vaccines: CYD-TDV, TAK-003, and TV003/005.

Keywords: Dengue fever, live attenuated vaccines.

1. Introduction

Dengue fever is an acute systemic infectious disease in humans caused by the bite of mosquitoes that carry DENV, whose main vectors are Aedes aegypti and Aedes albopictus [1, 2]. The non-mosquito-borne transmission routes of dengue fever include mother-to-child transmission, sexual contact, organ transplantation transmission, and blood transfusion transmission [3].

In the last 30 years, public health has been affected by uncontrolled global population expansion, disorderly urbanization, failure of mosquito control methods, increased international travel, and deteriorating infrastructures [2], worldwide epidemic regions of dengue fever are expanding and the number of hospitalizations and deaths caused by DENV infection is increasing [4]. According to one experiment, over 390 million individuals will be infected with dengue fever each year, with 96 million showing overt clinical symptoms, with the most dangerous places being Africa, America, Southeast Asia, and the Western Pacific [5]. Over the past 20 years, the cases of dengue fever reported to WHO have astonishing increased more than 10 times [6]. Nowadays, WHO has recognized dengue fever as a major public health problem [7].

The severity of the symptom of dengue fever varies from person to person and most patients have no symptoms or mild symptoms [6]. However, if patients were not treated in due course, they would suffer a series of complications such as dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS), which means the patients have got severe dengue fever and organ damage leading to death [5].

Currently, there is no effective therapeutic measure or specific medicine aiming at dengue fever and the patients could only have symptomatic treatments [8]. In addition, the effects of controlling mosquito-borne transmission of DENV are not good and the technologies of that are immature [9].

Therefore, the most cost-efficient and successful way to reduce dengue disease is to develop and use safe vaccinations. To let researchers timely understand the newest progress of researches on DENV vaccines and to promote the development of vaccines, this article was aimed to summarize three types of preventive live attenuated vaccines, including CYD-TDV, TV003/005, and TAK-003, which are developed a bit faster at present.

2. Three types of Vaccines for Dengue Fever

DENV has 4 serotypes (DENV1-4) [10]. When a person is infected with one of these 4 viruses and eventually recovers, his body will produce homologous antibodies (IgG), which give the body lifelong immunity to this serotype virus and certain resistance to other serotypes cross-protection [11]. However, if the body is infected with another serotype of the virus months or years later, antibody-dependent enhancement (ADE) occurs, which can lead to more severe clinical symptoms in patients and significantly increase the risk of severe dengue [12].

Because of ADE, the antigen specificity of different serotypes of DENV is large, and cross-immunity may occur. Researchers need to do what they can to address the challenge of quadrivalent vaccines, considering both immune response and safety concerns. Three live attenuated vaccines are currently in clinical trials. The following is a detailed description of the three live attenuated vaccines.

2.1. CYD-TDV (Dengvaxia)

CYD-TDV, chimeric yellow fever virus-DENV tetravalent dengue vaccine, is a live-attenuated vaccine also named Dengvaxia. It was invented by Sanofi Pasteur and became the first dengue vaccine to obtain formal licensure and authorization in 2015 [13]. Nevertheless, Dengvaxia can be used only for individuals who have previous dengue infections confirmed by the laboratory. In 2019, U.S. FDA also approved Dengvaxia to be used for children from the age of 9 to 16 living in areas where the DENV is common and who have previous dengue infection. To be fully vaccinated, a person needs to receive 3 doses of Dengvaxia each every six months apart [14].

The main mechanism of the invention of CYD-TDV depends on the yellow fever vaccine strain and the use of recombinant DNA technology. Shown in Figure 1, the premembrane (prM) and envelope genes commonly found within the 17D strain of yellow fever polypeptide backbone are replaced by genes of one of the four wild-types DENV serotypes including Thailand PUO-359/TVP-1140 (serotype 1), Thailand PUO-218 (serotype 2), Thailand PaH881/88 (serotype 3), and Indonesia 1228 (TVP-980) (serotype 4) [15]. After DNA transcription and RNA transfection, four individual chimeric DENV will be produced. The four live-attenuated viruses will be combined into a single vaccine, which is the CYD-TDV vaccine [16]. When the vaccine enters the body, it will trigger the creation of neutralizing antibody titers against each 4 viral strain components in the vaccine.

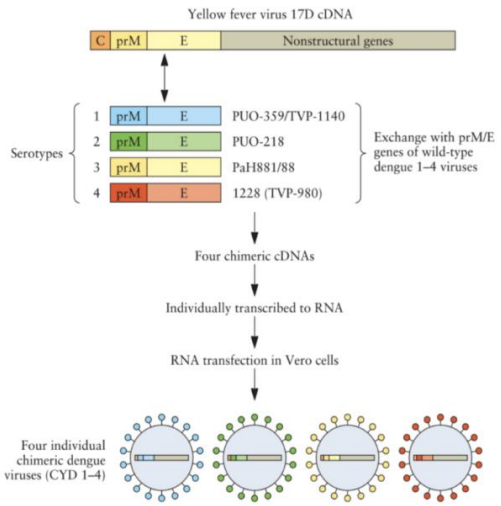

Figure 1. Detailed steps of the construction of the CYD-TDV vaccine [16]

The overall strength of the CDV-TDV vaccine is that it is the first and the only licensed vaccine against dengue fever. Moreover, according to the clinical trials data, this vaccine effectively protects children against dengue fever for at least 6 years and reduces the chance of hospitalization and severe dengue to 20% [17].

Phase III data of a vaccine is important as the efficacy and safety of the vaccine are investigated in a large sampling size. Two studies collecting Phase III studies of CYD-TDV provided valuable insights. CYD14 is the phase III trial conducted in five countries in the Asia-Pacific region in 2011 with a sampling size of 10275 children aged 2-14 years [18]. CYD15 is another trial conducted in five countries in Latin America between 2011 to 2012 with a sample of 20869 children aged 9-16. Participants were assigned randomly to receive the vaccine or placebo [19]. The data is collected and compared in the following Table 1.

Table 1. Main findings of the Phase III clinical studies with CYD-TDV [18]

	CYD14 (11 sites in Asia trial; n=10,275		CYD15 (22 sites in Latin America; n=20,869)			
	2-9 years old		9-14 years old		9-16 years old	
Virologically-confirmed dengue	196/3,532 (5.5%)	173/1,768 (9.8%)	90/3,316 (2.7%)	136/1656 (8.2%)	277/13,914 (2.0%)	385/6,940 (5.5%)
Overall vaccine efficacy	44.6%		67.8%		64.7%	
DENV1	46.6%		65.7%		54.8%	
DENV2	33.6%		36.8%		50.2%	
DENV3	62.1%		69.5%		74.2%	
DENV4	51.7%		87.9%		80.9%	
Seropositive	70.1%		79.2%		83.7%	
Seronegative	14.4%		61.6%		43.2%	
Dengue hemorrhagic fever (DHF)	6/3,532 (0.17%)	9/1,768 (0.5%)	2/3,316 (0.06%)	11/1,656 (0.66%)	1/13,914 (0.007%)	11/6,940 (0.16%)
	66.7%		90.9%		95.5%	

As seen in the data, the overall efficacy of the vaccine was 67.8% for children aged 9-14 in the Asia trial and 64.7% for children aged 9-16 in the Latin America trial. However, when breaking it down into efficacy for each serotype, we see a relatively low efficacy for dengue serotype 2 and high efficacy for dengue serotype 4. More significantly, without prior dengue infection (seronegative at baseline), the efficacy of CYD-TDV decreases dramatically.

The most significant limitation of CYD-TDV vaccine is its ADE. Antibodies developed against DENV are highly cross-reactive which means that they can recognize prM of all 4 DENV serotypes. A neutralizing antibody refers to an antibody that is capable of keeping a virus from infecting the cell by neutralizing its effect biologically [21]. The research found out that in the Dengue vaccine, the neutralizing antibodies at suboptimal levels facilitate the binding of non-neutralized DENV to macrophages, which is the site of DENV replication. This means that antibodies developed in the human body for one serotype cannot effectively protect the person against another serotype infection, more significantly, this antibody will help the new serotype virus to quickly replicate and increase the cellular viral load. Besides, the research found that the CYD-TDV vaccine elicited antibodies predominantly specific to DENV-4, which explains why the vaccine efficacy for serotype 4 is relatively higher than others [22].

2.2. TAK-003

Based on Dengvaxia, an "upgraded" version of the vaccine, TAK-003 produced by Tekada, is gradually becoming available. The Takeda Pharmaceutical Company Limited is a Japanese multinational pharmaceutical company with partial US and UK roots. It has announced that the European Medicines Agency (EMA) has accepted the application for its dengue vaccine TaK-003, which is being developed for use in people aged 4-60 years to prevent dengue caused by any dengue

virus serotype. The company intends to file regulatory filings in Argentina, Brazil, Colombia, Indonesia, Malaysia, Mexico, Singapore, Sri Lanka, and Thailand during 2021, also in Asia and Latin America.TAK-003 from Takeda company is an experimental live attenuated tetravalent dengue vaccine "TAK-003 prevents dengue fever caused by any of the four serotypes of the dengue virus that causes dengue fever or Severe Dengue" [23]. TAK-003 targets all four serotypes of dengue fever, indicating its comprehensiveness. It is a live attenuated vaccine based on the denV-2 skeleton and is the most advanced of the dengue vaccine candidates in development.

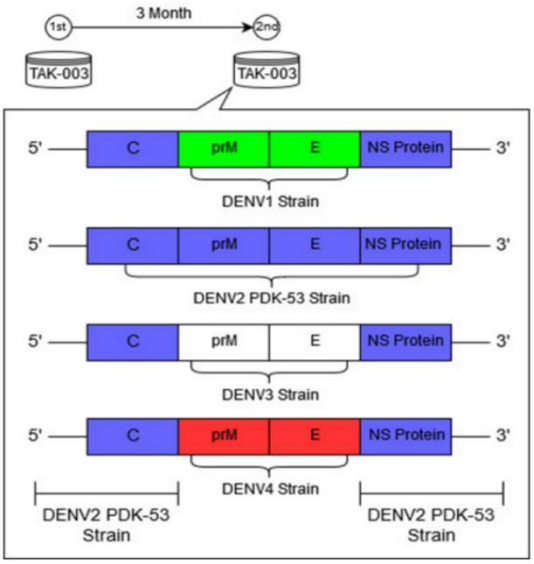

Figure 2. Structure of TAK-003 [25]

The structure of TAK-003 can also show its comprehensiveness against all four serotypes. The immune system of taK-003 receptors is exposed to both structural and non-structural proteins of DENV, as figure 2 shows.TAK-003 is a live tetravalent formulation based on genetically attenuated DENV-2 strain (TDV-2) with three chimeric viruses and a TDV-2 genetic backbone [23]. So all four different kinds of structures have DENV2 PDK-53 strains. To achieve immunity to the four serotypes, prM and E proteins from DENV1, DENV3 and DENV4 have been replaced with the backbone of the DENV2 PDK-53 gene, resulting in strains of vaccine for individual serotypes.

Takeda today announced that The Lancet, a leading international medical journal, published two papers on TaK-003, a dengue vaccine for Takeda, reporting The results of an 18-month analysis of The ongoing pivotal phase III trials of Tetravalent Immunization against Dengue Efficacy Study (TIDES). And final 48-month analysis of Phase II DEN-204 trial. The results were consistent with previously reported safety, immunogenicity, and efficacy data of TAK-003.

In a November 2019 study, Takeda's dengue vaccine candidate demonstrated protection against virologically confirmed dengue. . .in children ages 4 to 16 years [24]. This study, known as Phase 3 TIDES, made a huge contribution to the development and estimation of the efficacy of TAK-003.

Healthy 4–16-year-olds (n=20,099) were randomized 2:1 to receive TAK-003 or placebo (0, 3 month schedule) [26]. The protocol was composed of the basics serum status examining for all children who participated in the experiment and serotype-specific RT-PCR for all symptomatic dengue fever throughout the trial period. The aim of the study, which is currently being conducted in eight dengue-endemic countries, is to determine whether TAK-003 is effective against symptomatic dengue after three years. Before proceeding, the investigator obtained informed consent from the participants' guardians and the ethics committee approved the study protocol.

After a three-year follow-up of the second dose, the results were gained. Viral infection was analyzed within 30 days after the completion of the two injections, and the overall response rate was shown in the table below. When analyzed together, the overall response rate was 73.3%. Table 2 shows what the response rates of each serostatus were like. Due to the use of the DENV-2 genomic skeleton in all four types of TAK-003 vaccine, the response rate against DENV-2 was much higher

than in the other three types. From figure 3, the record of VCD cases in different countries is showed. Some countries in Southeast Asia or tropical areas, such as Thailand, Sri Lanka and the Philippines, showed a high incidence even after receiving taK-003 vaccine, which may be related to the environmental preference formed by dengue, waiting for further human research.

Table 2. Results of response rates of different serostatus in Tetravalent Immunization against Dengue Efficacy Study

Serostatus	Experimental group	Placebo group	Response rate
DENV-1	38/12700	62/6316	69.8%
DENV-2	8/12700	80/6316	95.1%
DENV-3	63/12700	60/6316	48.9%
DENV-4	5/12700	5/6316	51.0%

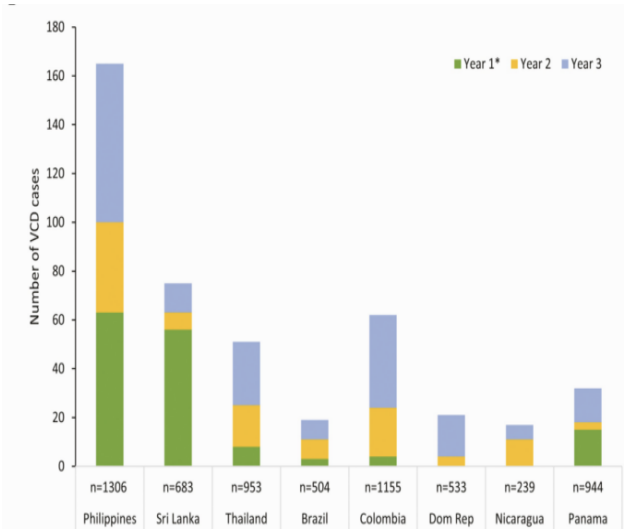

Figure 3. The number of VCD cases in the placebo group in each year of the study after completing vaccination by country (per protocol set data) [26]

TAK-003 is effective against symptomatic dengue for up to 3 years. Efficacy declines over time but remains effective for hospitalized dengue. A booster dose assessment is planned.

Other exploratory analyses showed that TAK-003 reduced dengue-related hospitalizations by 95.4 percent, and the efficacy for the severe disease could not be assessed due to the limited number of cases. TAK-003 showed protection immediately after the first dose of immunization, with 81% vaccine efficacy between the first and second doses.

2.3. TV003/TV005

TV003/TV005 are dengue vaccines produced by the National Institute of Allergy and Infectious Diseases (NIAID) and the Butantan Institute in Brazil. The difference between TV003 and TV005 and other TV serial numbers is the difference in strain modification/dose ratio. TV005 is an upgraded version of TV003. TV005 increases the immune response to DENV-2 by increasing the dose of DENV-2 10-fold. A striking feature of TV005 is the observation that the immunodominance of TV005 following experimental vaccination is very similar to that observed in natural infection. This is because TV005 mainly induces CD4+ T cells to produce coat protein, NS2A, and NS5 proteins, resulting in different immunodominance patterns against NS proteins [27].

In a phase I clinical trial, scientists experimented with a tetravalent mixture of TV003 and TV005, wanting to experimentally try to induce the two vaccines. The results of this trial were that TV003 and a vaccine mixture consisting of rDEN1Δ30, rDEN2/4Δ30, rDEN3Δ30/31 and rDEN4Δ30 appeared to induce the most balanced antibody response across the four DENV serotypes when combined. The researchers tried and induced single doses of TV003 and TV005 over the next 6 months to 1 year of the trial. Using TV003 and TV005, the researchers seroconverted DENV, and

following the single-dose trial, the researchers also performed sterile against a second dose of the immunogen.

In phase II clinical trial, researchers are studying the trial and evaluation of the experimental protocol for TV003's booster. Patients infected and uninfected with DENV in this trial were recruited to participate in this trial. Following injection, the researchers observed no significant adverse differences between DENV-infected and uninfected individuals. However, seroconversion rates were significantly higher in the uninfected compared to those infected with DENV [28]. This could also demonstrate that a single dose of TV003 is sufficient to induce protective immunity against dengue.

In phase III clinical trials, researchers focused on the efficacy and safety of live attenuated, quadrivalent, lyophilised dengue vaccines in vaccines. It is assumed that the vaccine is safe, so that the viral protection against dengue fever is 80% or more [29]. But nowadays it is already still experimental, as all participants will be followed up for 5 years and the results of the trial are not expected to be published until 2024.

Both vaccines showed superiority in phase I clinical trials, and the researchers observed no difference in vaccine adverse event rates between patients who received the two different vaccines, regardless of which mixture was tested. Furthermore, there was no significant difference between TV003 and TV005 in terms of the occurrence of adverse events. TV003 elicited higher DENV-3 viral loads, DENV-2, DENV-3 and DENV-4 antibodies, and a higher frequency of tetravalent responses in subjects previously infected with flavivirus [28]. Using the Dengue Human Challenge Model (DHCM), researchers determined that TV003 provided 100% protection against DENV-2 infection in a randomized, double-blind, placebo-controlled trial [28]. However, the model used in this study cannot be used to assess the efficacy and safety of vaccination in clinical trials. Therefore, more clinical studies as well as long-term observation and follow-up testing are needed to determine the reliability of the vaccine.

The researchers encountered difficulties while studying TV003 and TV005. A disadvantage of TV003 is the difficulty in raising its own mean nAb peak titers. For nearly a year, researchers were unable to significantly increase nAb titers in any serum in TV003 [27]. Although TV005 is an improved version of TV003, it significantly increases seroconversion frequency and overall antibody titers against DENV2. However, by the third month after vaccination, TV005 elicited a fourth-mediated response in more than 90% of the vaccinated population, while TV003 elicited a much lower response rate than TV005.

A common disadvantage of TV003 and TV005 is that people tend to develop rashes after being vaccinated. In both clinical trials, 63% of subjects reported adverse events of vaccine-related mild rash lasting an average of 7.7 days. The main problem that prevented TV003 and TV005 from coming to market is that they both have ADE effects. In experiments, partial protection against DENV protected patients from dengue infection [27]. But as the induced protection of short-term vaccines declined and more vaccines were available to protect recipients, the researchers found that in the event of a breakthrough infection, this condition could make them more susceptible to severe effects from the dengue virus. Researchers must consider whether dengue vaccine recipients have normal serostatus after vaccination and whether serotype-specific protection and maintenance capabilities differ.

3. Conclusion

Under current circumstance, the progress and expectation of the development of vaccines against dengue virus are of great significant. The current research progress of these three live attenuated vaccines is relatively smooth. The first dengue vaccine, CYD-TDY, was approved for use in some countries in 2015 or 2016, and phase III clinical trials have confirmed its safety and efficacy. TAK-003 developed by Tekada and the TV003/TV005 developed by NIAID of the United States are also undergoing clinical phase III trials. The overall effect of the TAK-003 vaccine in phase II clinical trials is good, but the protective effect of DENV-3 and DENV-4 is lower than that of DENV-1 and

DENV-2. TV003/TV005 also showed good immune protection efficacy in single-dose immune experiments. Although effective against all four serotypes, the ADE effect is a common shortcoming of all three vaccines, which makes the vaccine have dual effects in controlling dengue infection. Furthermore, the levels of neutralizing antibody responses differed significantly among the four serotypes. At the same time, some vaccine trials, such as CYD-TDY and TAK-003, have demonstrated protective effects in children, but there is still a lack of more extensive clinical trial data to demonstrate protection rates in all age groups. The development of safer and more balanced dengue vaccines requires further research on dengue epidemiology, immune protection and pathogenic mechanisms, evaluation criteria for protection, animal models and virus interference. It is believed that shortly, a highly effective quadrivalent vaccine against DENV will be developed, which will greatly reduce the morbidity and mortality caused by dengue, and reduce the social, medical and economic burden caused by dengue.

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