Review Article

iMedPub Journals
www.imedpub.com

Journal of Biomedical Sciences
ISSN 2254-609X

2021
Vol.10 No.S5:003

Impact of Dengue and Vaccines in India: Review

Rya Naik* **and Akash Shetty**

Department of Pharmacy, University of Bharti Vidyapeeth, Maharashtra, Mumbai, India

***Corresponding author:** Naik R, Department of Pharmacy, University of Bharti Vidyapeeth, Maharashtra, Mumbai, India, Tel: + 9082079473; E-mail: arianaik16@gmail.com

Received date: October 18, 2021; **Accepted date:** November 01, 2021**; Published date:** November 08, 2021

Citation: Naik R, Shetty A (2021) Impact of Dengue and Vaccines in India: Review. IPJBS Vol.10 No.S5:003.

Abstract

Objective, The objective of this study was to evaluate the dengue burden in India and to present a review of the vaccine, DENGVAXIA®.

Overview, Dengue fever is a mosquito-borne viral infection that has spread quickly through all regions in recent years. Female mosquitoes, primarily Aedes aegypti and, to a lesser degree, Aedes albopictus, transmit the dengue virus. Dengue fever affects nearly 2.5 billion people worldwide, with an estimated 100 million new cases per year. Dengue fever claimed the lives of 245 people in India in 2016, with 1,29,166 cases recorded. There were 132 dengue deaths and 1,36,422 cases recorded from January to November of 2019.Sanofi's Dengvaxia® was approved by the Food and Drug Administration (FDA) in 2015. Following this, long-term follow-up of participants in the Sanofi phase III efficacy trial revealed significant safety issues. In this article, we aim to provide information about the dengue virus's prevalence in India, as well as a review of Dengvaxia® also describing it results and safety along with other vaccines and its approval in the listed country. Dengvaxia® is indicated for the prevention of dengue fever caused by serotypes 1-4 of the dengue viruses. Dengvaxia® is approved for use in people aged 9-16 who have had a previous dengue infection that has been confirmed in a laboratory and who lives in an endemic area.

Keywords: Pathogen; Vaccine; Global warming; Dendritic cells

Introduction

The dengue virus, which belongs to the Flavivirus genus in the Flaviviridae family, is an arthropod-borne virus with four distinct serotypes (DEN-1, DEN-2, DEN-3, and DEN-4) [1-5]. Dengue Viruses (DENVs) are a new kind of pathogen. Virus transmission from human to human began around three centuries ago with the bite of the mosquito Aedes aegypti [2]. Dengue fever is a major global public health threat in tropical and subtropical countries, according to the World Health Organization (WHO). Dengue fever has risen by 30 times in the world between 1960 and 2010, owing to population growth, global warming, unplanned urbanization, ineffective mosquito control, frequent air travel, and a lack of health-care facilities. Dengue endemic areas have a population of 2.5 billion people, with approximately 400 million infections per year and a death rate of 5-20 percent in some areas. [Number six] Dengue fever is a disease that affects over 100 countries worldwide, including Europe and the United States (USA) [2,3,5].

The first case of dengue fever was reported in Madras in 1780, and the first virologically proven DF outbreak in India occurred in Calcutta and the Eastern Coast of India in 1963-1964. In India, a large number of doctors have treated and reported dengue disease over the last 50 years, but scientific studies addressing various dengue disease issues have only been conducted at a few centres [2].

Literature Review

Burden of disease in India

With a sharp rise in the size of the human population at risk, the accumulated burden of dengue diseases has reached an alarming proportion in recent times. Dengue fever causes a slew of pathophysiological, economic, and environmental issues [6]. The very first medical dengue-like disease outbreak was reported in Chennai in 1780, and the first confirmed dengue fever epidemic occurred in Calcutta and the Eastern Coast of India in 1963-1964 [3,2]. In 2010, the incidence rate was less than 1/100000 population, but it has gradually increased over time and has been consistently high in coastal districts [7,8]. The southern regions had the highest seroprevalence (76.9%), preceded by the western (62.3%) and northern (60.3%) regions. The seropositivity was also higher in urban (70.9%) rather than the rural (42.3%) areas, supporting the inference that rapid urbanization tends to be one of the key causes of the rise in dengue cases [9].

Pathophysiology of dengue

Experimental challenge studies in humans have yielded valuable information on dengue virus infection, detailed data on virus distribution *in vivo* is only available from a small number of patients with more severe disease or unusual manifestations [7]. Dengue Viruses (DENV) cell and cell tropism may have a significant role in the decision of Dengue Viruses (DENV) infections. Our knowledge of the significance of Dengue Viruses (DENV) virulence is hindered by the lack of an adequate animal disease model. The immune system, the liver, and the Endothelial Cell (EC) linings of the blood vessels all appear to

play a part in the aetiologia of DHF/DSS, according to in vitro data and post-mortem investigations [7].

Dengue Viruses (DENV) transmission to humans is carried out by two arthropod vectors from the Aedes genus, Aedes aegypti and Aedes albopictus. Because the hematophagous female requires a blood meal for oviposition, Aedes mosquitoes usually breed near humans. The virus spreads to other organs/tissues *via* the circulatory system, including the tracheal system, fat body, salivary glands, nervous system, esophagus, hemocyte's, compound eye ommatidia, and Malpighian tubules. This period of replication, which is to reach the salivary glands, is known as the intrinsic incubation period, and it lasts about five to seven days [10-12].

Severe dengue is distinguished by endothelial dysfunction, which results in vascular leakage. The critical phase is when a vascular leak becomes clinically evident 3-6 days after the onset of illness. This critical phase occurs after peak viraemia and lasts for 24-48 hours, with rapid and complete reversal, indicating that it is likely to occur as a result of inflammation [8,10,13-14]. Dengue Viruses (DENV) could indeed infect cutaneous Langerhans Dendritic Cells (DCs) at the site of mosquito inoculation. Two important events occur as a result of the infection of these cells. First, their activation and migration through the lymphatic system transports Dengue Viruses (DENV) to sites of active viral replication (secondary lymphoid tissue), and second, in the recruitment of immune competent cells via cytokine and chemokine expression [11,12].Platelets have also been shown to significantly contribute to endothelial dysfunction by inducing monocytes to create inflammatory cytokines and producing interleukin through activation of the NLRP3 inflammasome [7]. Rhesus monkeys develop viremia in a pattern similar to humans, but they do not develop clinical disease.

Prevention

The best way to avoid mosquito bites and prevent dengue fever is to eliminate stagnant water that serves as mosquito breeding sites at home, schools, workplaces etc., and their surroundings [15]. The bite of an infected Aedes species (Aedes aegypti and Aedes albopictus) mosquito is the primary mode of transmission for all four dengue viruses. Chikungunya and Zika viruses are also spread by these mosquitos [16].

Few environmental management and modification to prevent mosquitoes from accessing egg-laying habitats and prevention from our side such as-

Prevent mosquito bites- Dengue virus is found in an infected person's blood during the first week of infection. The mosquito becomes infected if it bites an infected person. Through bites, the infected mosquito can spread the virus to other people [16].

Use insect repellent-using an insect repellent could prevent the biting of an infected dengue mosquito [15].

Wear long sleeved shirts and pants [15].

Using mosquito nets [15].

Removing artificial man-made habitats and properly disposing of solid waste [13].

Weekly covering, emptying, and washing of domestic water storage containers putting insecticides in outdoor water storage containers that are appropriate [13].

Window screens, insecticide-treated materials, coils, and vaporizers are examples of personal household protection [13].

One of the emergency vector-control measures is to apply insecticides as space spraying during outbreaks [13].

Management of dengue

Dengue can be treated by drinking plenty of fluids. Reduction of high fever, use paracetamol only. Oral feeding should be encouraged by a soft diet, and an Oral Rehydration Solution (ORS). If there is no vomiting and moderate/severe dehydration, avoid IV fluid [17]. Patients with thrombocytopenia, reduced appetite, or poor clinical conditions should be admitted. Infants, obese patients, patients with prolonged shock bleeding, encephalopathy, underlying conditions, and pregnancy are all high-risk patients should also be admitted [18].

Antibiotics are used locally to remove bowel flora. If systemic antibiotics are given, this is not required. Vitamin K1 IV administration: 3 mg for children under the age of one year, 5 mg for children aged five years, and 10 mg for children aged ten years and adults [18].

Drugs that inhibit downstream immunological mediator pathways, such as Platelet Activating Factor (PAF), may be useful in the treatment of severe disease [10].

Vaccine

Due to the significant rise of dengue in India and globally a safe and effective vaccine is needed to prevent the disease. There is no specific antiviral medication, and treatment relies only on vector prevention. Numerous efforts to build an integrated immunization have indeed been conducted during the past three decades [19].

Sanofi Pasteur's Dengvaxia® is the only authorized dengue vaccine, and it has been approved by regulatory bodies in the European Union (EU) and the United States (US).

Dengvaxia®

Dengvaxia® (CYD-TDV) developed by Sanofi Pasteur is the only dengue vaccine to be approved.Dengvaxia® is a live virus tetravalent vaccine made up of chimaeras composed of structural Pre-membrane (prM) and Envelope (E) DNA from the four Dengue Viruses (DENV) types mixed with non - structural genes from the chimera yellow fever dengue-CYD immunization strain [17].

Preclinical trials and *in vivo* studies- Monkey sera collected two weeks after Dengvaxia® injection in cynomolgus macaques neutralized a broad variety of Dengue Viruses (DENV) representing all kinds and genotypes, indicating that the vaccine has the potential to protect against a broader range of

circulating strains in vitro [20]. In a monkey model, interferences between the four serotypes of ChimeriVax Dengue vaccines (CYDs) when they were present in equal amounts inside a tetravalent formulation were examined, Yellow Death (YD) was given to cynomolgus macaques Subcutaneously (SC), showing tetravalent neutralize antibody seroconversion. Although most of the National Health Protection (NHPs) had inappropriate immune antibody response following challenge, likely reflecting moderate infection, 22 of 24 monkeys were protected from Dengue Viruses (DENV) viremia when challenged with Subcutaneously (SC) Dengue Viruses (DENV) 6 months later. Twenty-two out of 24 monkeys were protected, as evidenced by the absence of viremia after the test hence showing 92% efficacy. Over all it was found that Dengue Viruses (DENV) 2 chimaera dose modifications led to a better response against Dengue Viruses (DENV) 1, 2, and 3 viruses, but a slightly stronger reaction against chimeric Dengue Viruses (DENV) 4 virus. The above suggests that more dose-adjustment should be investigated in primates in order to find the best one for humans [21].

Phase 1-In the United States, a phase 1 trial was conducted with a monovalent DENV-2 formulation (CYD01). 52 Subsequent phase 1 trials (CYD02, CYD04, CYD05, CYD06) assessed the safety of a tetravalent Dengvaxia® in adults from non-endemic cities in America (CYD02, CYD04), and also adults and children from non-endemic (CYD06) and endemic (CYD05) areas in Mexico and the Philippines, respectively. Prior to vaccination, the studies were performed in non-endemic areas to collect data from people who were seronegative to flaviviruses, especially dengue fever. These phase 1 study, as well as three phase 2 studies (CYD10, CYD11, and CYD12), provided information on the protection and immune responses elicited by various vaccine formulations and immunization schedules. The result showed that these studies backed up the final vaccine formulation and schedule: 5 log10 CCID50 of each live, attenuated Dengue Viruses (DENV) type 1,2,3,4, given as three injections six months apart. The vaccine was safe, well-tolerated, and immunogenic [17].

Phase 2- Dengvaxia® was also tested in endemic and non-endemic countries in Asia such as India, Philippines, Singapore, Vietnam also Latin America (Brazil, Colombia, Honduras, Mexico, Peru), Australia, and the United States (CYD13, CYD22, CYD24, CYD28, CYD30), raising concerns about dosage, schedule, priming by other flaviviruses or flavivirus vaccines, and the protection of co-administration of administration of other vaccine [22]. In India, CYD47 was used to evaluate Dengvaxia® protection and immunogenicity in Indian populations. A Phase 2 research (CYD08) evaluating Dengvaxia® in combination with the Measles Mumps and Rubella (MMR) vaccine in toddlers under the age of two was also performed. In a phase 2 adult study in the United States, an indication for travelers/non-endemic populations was investigated (on a shorter schedule) (CYD51 and CYD56). A booster dose (5 years after dose three of the primary series) is being tested in two phase 2 trials in CYD63 and CYD64, using subsets of people who took part in CYD28 and CYD13, respectively. In addition, in the Philippines and Colombia, a study was started to evaluate alternative vaccine schedules and booster doses in people aged 9 to 50. (CYD65) [17].

Phase 3- The phase 3 efficacy and trials were taken place in dengue-endemic areas in five Asian countries, accounting for more than 70% of the worldwide dengue burden. The study included 10-275 healthy children aged 2 to 14 years old who were randomly assigned to receive three injections of the CYD-TDV vaccine (6851) or a placebo (3424) at 0, 6, and 12 months, and were then monitored for up to two years [17].

Efficacy clinical endpoints were not assessed in four phase 3 clinical trials (CYD17,CYD29, CYD32, and CYD33). CYD17 compared lots of consistency in dengue-naive adults up to 60 years old in Australia, and provided evidence to support phase 2 to phase 3 bridging, which was needed due to new manufacturing processes [23]. Dengvaxia® was tested in a phase 3 study in Malaysian children (2-11 years old) to determine its protection and immunogenicity (CYD32). Dengvaxia® co-administration with Yellow fever vaccine in infants and toddlers less than 2 years of age (CYD29), while DTacP-IPV (diphtheria and tetanus toxoids and acellular pertussis adsorbed and inactivated poliovirus vaccine) as a booster administered with the second injection of Dengvaxia® was studied in Mexico (CYD33). In Malaysia (CYD67) and Mexico (CYD14), three co-administration trials with the human papillomavirus (HPV) vaccine were completed in individuals aged 9-13 years [9,17].

The third study (Philippines) looked at the effects of giving a tetanus, diphtheria, and pertussis vaccine to people aged 9-60. (CYD66) [24].

Dengvaxia® efficacy and safety

Dengvaxia® was developed using decades of lessons learned from the development of live virus dengue vaccine candidates, preclinical and early clinical evidence showing a promising safety and immunogenicity profile, and recommendations from organizations such as the World Health Organization. The prevention of viremia or RNAemia in NHPs challenged with wild-type viruses was thought to be a good predictor of human clinical benefit. Anti-DENV neutralizing antibodies were also expected to emerge as a correlate or surrogate of defense, bolstering the case for a neutralizing antibody response to protect against dengue [23]. One theory for the safety problems with Dengvaxia® in seronegative recipients is that vaccination mimics a primary infection, increasing the recipient's risk of clinically noticeable and/or serious disease when he or she encounters a subsequent sequential infection, which in this case will be the recipient's first natural infection [11].

The failure of Dengvaxia® to reach the primary efficacy end-point in CYD23 was unexpected. Vaccine recipients will receive long-lasting Dengue Viruses (DENV-4) homotypic protection but only a brief duration of cross-protective immunity against other serotypes in this case. This may explain why the efficacy signal was reasonably positive in study years 0-2 of the efficacy trials, but there was no safety signal. First dengue infections seldom cause serious dengue in unvaccinated people, but second dengue infections with a different serotype are linked to a higher risk of severe dengue [24].

Dengvaxia's® administration to individuals who have never been infected with dengue virus is associated with an increased

risk of severe dengue disease if the vaccinated individual becomes infected with any dengue virus serotype. As a result, healthcare providers must screen people for prior dengue infection to prevent vaccinating people who have never been infected with the virus [25].

Discussion

Overview of the vaccine

More than 28 days following the third injection, the researchers reported 250 dengue cases, with 117 in the vaccine group and 133 in the placebo group, indicating a 56.5 percent overall preventive effect. After three doses, the vaccine showed 88.5 percent efficacy against severe sickness (dengue hemorrhagic fever), which causes almost half a million people (mainly children) to be hospitalized each year, and 67 percent against dengue-associated hospitalization. The researchers discovered that the vaccine provided just 35% protection against DENV 2, but over 75% protection against Dengue Viruses (DENV) 3 and 4, and 50% protection against DENV 1 suggesting that the vaccine had ppor protection against Dengue Viruses (DENV) 2. In general, the vaccination was well tolerated. There were 647 significant adverse events reported in total, including 402 (62%) in the vaccine group and 245 (38%) in the placebo group [26-29].

Dengvaxia® by Sanofi in 2017 finally announced that the vaccine's labelling would be changed to restrict its use to individuals who have previously been affected with the infectious disease [30]. The vaccine's utility is limited by the fact that it could influence the incidence of severe dengue in people who have never been infected [31,32]. This was primarily noticed in the Philippines in the years 2017-2018 which led to political conflicts and huge controversies [33,34]. inflammation of organs and Internal bleeding in the heart, lungs, and brain caused the deaths, which are symptoms of hemorrhagic dengue which were found in children who died after taking the Dengvaxia® vaccine [35].

In India the vaccine approval is ought to happen since Sanofi's Dengvaxia® in the year 2016 approached Indian medical authorities to Fast Track the vaccine and to waive off phase three trials, but the Indian ministry of health and family welfare rejected the proposal saying that "the evidence was not sufficient to waive conducting a clinical trial in India. "The company then asked the authorities to reconsider the proposal, and few institutes in India suggested rolling out the vaccine under strict conditions. The launch of the Sanofi dengue vaccine Dengvaxia® in India is being done cautiously. "It might be safe to wait for a little more data to get generated and to see its uptake and experience in other countries before we proceed in India" says one of the lead Indian scientists [36].

TAK-003

The TAK-003® (TDV) developed by Takeda Pharmaceutical Company Limited (TSE: 4502/NYSE: TAK) studies aim is to determine the effectiveness, protection, and immunogenicity of two doses of TAK-003® in both dengue-infected and naive people.TAK-003®, Takeda's tetravalent dengue vaccine candidate, is based on a live-attenuated dengue serotype 2 virus, which serves as the genetic "backbone" for all four vaccine viruses [20].

Phase 1-The trial began in September of 2016.After the second dose; Part 1 had a 12-month follow-up to determine the primary endpoint (22).

Phase 2-In patients with rare leukemia, including higher-risk myelodysplastic syndromes, the study compared pevonedistat plus azacitidine to azacitidine alone (HR-MDS). These findings indicate that the combination of pevonedistat and azacitidine is a highly successful, promising therapeutic solution in the HR-MDS subgroup, with benefits.Pevonedistat-2001 (NCT02610777) is a multi-center, national, randomized, regulated, open-label, Phase 2 clinical trial comparing the safety and efficacy of pevonedistat in combination with azacitidine versus single-agent azacitidine in patients with higher-risk MDS or CMML, or low-blast AML, who are inappropriate for bone marrow transplant and have not undergone prior therapies. A total of 120 people from all over the world were enrolled in the study. OS is the trial's main endpoint [20,21].

Phase 3-The research is divided into five sections. Part 1 and the primary endpoint analysis assessed Vaccine Efficacy (VE) and safety up to 15 months after the initial dose (12 months after the second dose). Part 2 lasted an additional six months to complete the assessment of the secondary endpoints of Vaccine Efficacy (VE) by serotype, baseline serostatus, and disease severity, including VE against bedridden dengue. Part 3 involves monitoring participants for another two and a half to three years to assess VE and long-term protection. Part 4 will assess safety 13 months after booster vaccination, and Part 5 will assess long-term safety one year after Part 4 is completed [20].The trial is taking place in dengue-endemic areas of Latin America, including Brazil, Colombia, Panama, the Dominican Republic, and Nicaragua, as well as Asia, including the Philippines, Thailand, and Sri Lanka. Takeda has enrolled over 20,000 healthy children and adolescents aged four to sixteen living in dengue-endemic areas in the phase 3 TIDES trial, which is double-blind, randomized, and placebo-controlled. The TIDES trial is still ongoing, according to the company, and further data, as well as results from other phase 3 trials, are expected by the end of the year (19).

Results showed that in 4-16 year olds in dengue-endemic countries, Takeda's tetravalent dengue vaccine (TAK-003®) showed benefit in reducing dengue regardless of baseline serostatus up to 2 years after completion of vaccination, with some decline in efficacy during the second year of trials [22,23].

TDENV PIV

Tetravalent purified inactivated dengue vaccine developed by the GlaxoSmithKline/Walter Reed Army Institute of Research has undergone its Interventional Clinical Trial phase and its phase 1-phase 2

In rhesus macaques, the immunogenicity and protective efficacy of a candidate Tetravalent Dengue Virus Purified Inactivated Vaccine (TDENV PIV®) formulated with alum or an

Adjuvant System (AS01, AS03 tested at three dose levels, or AS04) were assessed in a 0-1month vaccination schedule [37].

The immunogenicity of two vaccine doses of different TDENV PIV® formulations in rhesus macaques was assessed using vaccine-induced NAb responses against all four Dengue Viruses (DENV) serotypes in two trials. Both monkeys in both experiments tolerated the two vaccine doses with no signs of systemic or local injection-site reactivity [38].

First study:-The first research looked at formulations with 0.5 or 0.125 g of antigen per serotype adjuvanted with alum or an Adjuvant System (AS01E, AS03A, or AS04D), as well as formulations with 2.0 g of antigen per serotype adjuvanted with alum or an Adjuvant System (AS01E, AS03A, or AS04D) [39].

Second Study:-In a second sample, we looked at NAb responses elicited by TDENV PIV® formulations with 0.5 g per serotype adjuvanted with alum, AS01E, or one of three dose levels of AS03 (AS03A, AS03B or AS03C; in decreasing order). The AS03A category had the highest GMTs, which was similar to the first study's findings. Indeed, GMTs against Dengue Viruses (DENV-2) for this group were significantly higher (at least threefold) on days 56 and 112 than for the groups obtaining alum (P 0.014), AS03C (P 0.021), or AS01E (P 0.010), and GMTs against Dengue Viruses (DENV-3) for the AS03A group were significantly higher (at least threefold) on day 56. Furthermore, vaccine-induced NAb responses against DENV-1 were significantly (roughly threefold) higher in the AS03A group than in the AS03C group across time points (P = 0.034), implying a dose response for AS03.However, no major differences in Dengue Viruses (DENV-4) specific responses were found between any of the three AS03 groups, or between these groups and the alum and AS01E groups [37].

The National Institute of Allergy and Infectious Diseases' Live Attenuated Tetravalent Vaccination (LATV) is now being tested in a number of clinical trials. The vaccination consists of four recombinant live attenuated Dengue Viruses (DENV) components with molecularly defined attenuating mutations [39]. After two immunizations, there was no difference between the AS04D and alum classes, so additional testing of AS04 (which includes alum and MPL) was not warranted, and alum was maintained as the benchmark adjuvant in the subsequent analysis. With the 0.5 g per serotype antigen dose, there was an overall trend for higher NAb responses (supported by important and non-significant results). These findings sponsored further preclinical testing of formulations containing the 0.5 g per serotype antigen dose in combination with alum, AS01, or AS03 [37-39].

V180-001

V180-001 developed by the Merck & Co's adjuvanted is a, tetravalent subunit vaccine which contains truncated forms of envelope proteins (DEN-80E) derived from dengue virus strains of all four serotypes (DEN-1 strain 258848, DEN-2 strain PR159 S1, DEN-3 strain CH53489, and DEN-4 strain H241).The DEN-80E subunits are formulated with either ISCOMATRIX (saponin, cholesterol, and phospholipid adjuvant; CSL) or AL hydrogel, and are expressed from plasmids in the Drosophila S2 cell expression system (aluminium hydroxide gel adjuvant; Brenntag Nordic) [36].This vaccine helps in prevention of the dengue fever.

A variety of clinical trials are now underway for the Live Attenuated Tetravalent Vaccine (LATV) produced by the National Institute of Allergy and Infectious Diseases. Four recombinant live attenuated Dengue Viruses (DENV) components with molecularly specified attenuating mutations make up the vaccination [24].

A qualified Focus Reduction Neutralization Test with a 50% neutralization cut-off was used to assess immunogenicity Focus Reduction Neutralization Test (FRNT50). The immunogenicity of all six V180 formulations with ISCOMATRIXTM adjuvant was high, while the immunogenicity of the one aluminium adjuvanted and two unadjuvanted formulations was low. At 6 months and 1 year after PD3, geometric mean antibody titers typically decreased. All nine V180 formulations were well tolerated in general. Adverse events were more common in ISCOMATRIXTM adjuvant formulations than in aluminum-adjuvanted or unadjuvanted formulations [26].

TV-003/005

TV-003/005 developed by the National Institute of Allergy and Infectious Diseases is a tetravalent admixture of monovalent vaccines produced by the National Institute of Allergy and Infectious Diseases (NIAID) and tested separately for protection and immunogenicity. In the United States, Thailand, Bangladesh, India, and Brazil, the vaccine passed Phase I and Phase II trials. In the United States, the National Institutes of Health (NIH) has conducted Phase I and Phase II studies with over 1000 participants. It has also successfully completed Human challenge studies as well as National Health Protection (NHP) model studies [27].

Phase III studies are being carried out in Brazil by Instituto Butantan in-collaboration with National Health Protection (NIH) Panacea biotec.The National Institutes of Health has licensed their technology to Panacea Biotec, Instituto Butantan, Merck, and Medigen for further development and commercial scale manufacturing [28].

The results showed that the vaccine was well tolerated, and there was no fever. The only side effect that was even more common in TV003 recipients than in placebo controls was a moderate, asymptomatic rash, which occurred in 79.2% of vaccinees. The rash consisted of a few maculopapular lesions on the proximal upper parts of the body and chest wall. It was totally unknown to the subjects [25,40-48].

Conclusion

In conclusion, though Dengue does not have a cure and can be managed with supportive treatment, it is definitely a preventable disease. Dengvaxia® vaccine is effective in patients who have been exposed to virus earlier. Study results are awaited to prove the safety and effectiveness of newer vaccines.

Reference

1. World Health Organisation (2021) Dengue and severe dengue, accessed on 20 Aug 2021 Dengue and severe dengue (who.int).
2. Swaminathan S, Khanna N (2019) Dengue vaccine development: Global and Indian scenarios. Inter J Infec Dis 84:80-86.
3. Gupta N, Srivastava S, Jain A, Chaturvedi UC (2012) Dengue in India. Indian J Med Res 136:373-390.
4. U S Food and Drug administration (2020) Dengavaxia.
5. Hasan S, Jamdar SF, Alalowi M, Al Ageel Al, Beaiji SM (2016) Dengue virus: A global human threat: Review of literature. J Int Soc Prev Community Dent 6:1-6.
6. Gupta E, Ballani N (2014) Current perspectives on the spread of dengue in India. Infect Drug Resist 7:337-342.
7. Martina BE, Koraka P, Osterhaus AD (2009) Dengue virus pathogenesis: an integrated view. Clin Microbiol Rev 22:564-581.
8. Swain S, Bhatt M, Pati S (2019) Distribution of and associated factors for dengue burden in the state of Odisha, India during (2016-2019). Infect Dis Poverty 8:31-41.
9. The Lancet Global Health (2019) Estimating the Dengue Burden in India, by Annelies Winder Smith and Priscilla, assessed on 13th September 2021.
10. U.S National library of science(2019) Clinical trials. Study of a tertravalent Dengue Vaccine in Healthy children Aged 2 to 11 years in Malaysia, NCT012554422, assessed on 20th September 2021.
11. Malavige GN, Ogg GS (2017) Pathogenesis of vascular leak in dengue virus infection. Immunology 151:261-269.
12. Halstead Scott (2019) Recent advances in understanding dengue. F1000 Faculty Res 8:1-12.
13. McArthur, Monica A, Marcelo B Sztein, Robert Edelman (2014) Dengue vaccines: recent developments, ongoing challenges and current candidates. Expert review of vaccines 12:933-6-953.
14. Centers for Disease Control and Prevention (2020)http://www.cdc.gov/ncezidNational Center for Emerging and Zoonotic Infectious Diseases (NCEZID),http://www.cdc.gov/ncezid/dvbd/index.htmlDivision of Vector-Borne Diseases (DVBD).
15. Reyes-del Valle J, Salas-Benito J, Soto-Acosta R, Rosa Del A (2014)Dengue Virus Cellular Receptors and Tropism. Curr Trop Med Rep 1:36-43.
16. Center for Health Protection (2004) Prevention of dengue fever, assessed on 2nd September 2021.
17. Centers for Disease Control and Prevention,http://www.cdc.gov/ncezidNational Center for Emerging and Zoonotic Infectious Diseases (NCEZID) (2019) Division of Vector-Borne Diseases (DVBD).
18. Thomas, Stephen J, In-Kyu Yoon (2019) A review of Dengvaxia®: development to deployment. Human vaccines & immunotherapeutics 15:2295-2314.
19. Redoni M, Yacoub S, Rivino L, Giacobbe DR, Luzzati R,et al. (2020) Dengue:Status of current and under-development vaccines. Rev Med Virol 30:1-3.
20. Barban V, Munoz-Jordan JL, Santiago GA, Mantel N, Girerd Y, et al. (2012) Broad neutralization of wild-type dengue virus isolates following immunization in monkeys with a tetravalent dengue vaccine based on chimeric yellow fever 17D/dengue viruses. Virology 429:91-98.
21. The Times of India (2016) Why India is struggling to introduce dengue vaccines, by Pallava Bagla, assessed on 15Th September 2021.
22. Diana Leticia CM, Juliana P, Eduardo LM, María RC, Andrés ACB, et al. (2021) Immunogenicity and safety of simplified vaccination schedules for the CYD-TDV dengue vaccine in healthy individuals aged 9–50 years (CYD65): a randomised, controlled, phase 2, non-inferiority study.
23. U S National library of science (2019) Study of a Tetravalent Dengue Vaccine in Healthy Adults in Australia (Clincal trials.gov).
24. Halstead SB (2018) Safety issues from a Phase 3 clinical trial of a live-attenuated chimeric yellow fever tetravalent dengue vaccine. Hum Vaccin Immunother 14:2158-2162.
25. ABS-CBN News (2018) Why are the internal organs of those who died of Dengvaxia swollen?.
26. Robert C, Danielle R (2020) V180 dengue vaccine. PreVacc.
27. Siripen Kalayanarooj (2012) Clinical Manifestations and Management of Dengue/DHF/DSS. Trop Medi Heal Volume 39:83-87.
28. Pharmaceutical Business Review (2019) Takeda's TAK-003 dengue vaccine candidate succeeds in phase 3 efficacy trial. Clini Trail Hum Trail.
29. Takeda (2021)Takeda begins regulatory submission for dengue vaccine candidate in EU and endemic countries.
30. Takeda (2020) Takeda Announces Compelling Data from the Phase 2 Trial of Pevonedistat Plus Azacitidine in Patients with Higher-Risk MDS.
31. Fernandez S, Thomas SJ, De La Barrera, R, Im-Erbsin R, Jarman RG, et al. (2015) An adjuvanted, tetravalent dengue virus purified inactivated vaccine candidate induces long-lasting and protective antibody responses against dengue challenge in rhesus macaques. The American journal of tropical medicine and hygiene 92:698-708.
32. Eduardo López-Medina, Shibadas Biswal, Xavier Saez-Llorens, Charissa Borja-Tabora, Lulu Bravo, et al.(2020) Efficacy of a Dengue Vaccine Candidate (TAK-003) in Healthy Children and Adolescents 2 Years after Vaccination. J Infe Dis.
33. Durbin AP, Pierce KK, Kirkpatrick BD, Grier P, Sabundayo BP, et al. (2020) Immunogenicity and Safety of a Tetravalent Recombinant Subunit Dengue Vaccine in Adults Previously Vaccinated with a Live Attenuated Tetravalent Dengue Vaccine: Results of a Phase-I Randomized Clinical Trial. Ameri J Tropi Medi Hygi 103:855-863.
34. Whitehead SS, Durbin AP, Pierce KK, Elwood D, McElvany BD, et al. (2017) In a randomized trial, the live attenuated tetravalent dengue vaccine TV003 is well-tolerated and highly immunogenic

in subjects with flavivirus exposure prior to vaccination. PLoS Negl Trop Dis 8:11-15

35. Manoff SB, Sausser M, Falk Russell A, Martin J, Radley D, et al. (2019) Immunogenicity and safety of an investigational tetravalent recombinant subunit vaccine for dengue: results of a Phase I randomized clinical trial in flavivirus-naïve adults. Hum Vaccin Immunother 15:1-10.
36. Robert C, Danielle R (2020) TetraVax-DV-TV003 Dengue Vaccine. Precision Vaccinations.
37. World Health Organization Organisation mondiale de la Santé (2018) Dengue vaccine: WHO position paper September 2018. Weekly Epidemiological Record=Relevé épidémiologique hebdomadaire 93:457-476.
38. Kirkpatrick BD, Whitehead SS, Pierce KK, Tibery CM, Grier PL, et al. (2016) The live attenuated dengue vaccine TV003 elicits complete protection against dengue in a human challenge model. Sci Transl Med 8:330-336.
39. TDENV PIV (2019) Adis Insight.
40. Thomas SJ, Yoon IK (2019) A review of Dengvaxia®: development to deployment. Hum Vaccin Immunother 15:2295-2314.
41. Stephaine S (2017) University of Minnesota Sanofi restricts dengue vaccine but downplays antibody enhancement.
42. World Health Organization = Organisation mondiale de la Santé. (2018). Dengue vaccine: WHO position paper – September. Weekly Epidemiological Record =Relevé épidémiologique hebdomadaire 93: 457-476.
43. Jenella Paris (2019) DOH upholds permanent ban of Dengvaxia.
44. Sofia Tomacruze (2018) Parents stilled scared of govt's free vaccines a years after Dengvaxia scare.
45. US National library of science(2017) Clinical trials.gov, April 12th 2017, TDENV PIV and LAV Dengue Prime-booster Strategy Using AS03B Adjuvant.
46. Fernandez, Stefan Thomas J, Rafael la B, Rawiwan E, Richard T,et al. (2015) An adjuvanted, tetravalent dengue virus purified inactivated vaccine candidate induces long-lasting and protective antibody responses against dengue challenge in rhesus macaques. Ameri j Tropi Medi Hyg 4:698-708.
47. Guirakhoo F, Pugachev K, Zhang Z, Myers G, Levenbook I,et al. (2004) Safety and efficacy of chimeric yellow Fever-dengue virus tetravalent vaccine formulations in nonhuman primates. J Virol 78:4761-4775.
48. Schmidt AC, Lin L, Martinez LJ, Ruck RC, Eckels KH, et al. (2017) Phase 1 Randomized Study of a Tetravalent Dengue Purified Inactivated Vaccine in Healthy Adults in the United States. Am J Trop Med Hyg. 96:1325-1337.