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Review Article

TAK-300/DENVax -The Most Necessary Vaccine of the Future - A Review

*Aditya Rai[1], Ashwin Rai A[2] and Prasad DN[3]**

[1]*Sri Lakshmi Narayana Institute of Medical Sciences, India*

[2]*Department of Neurosurgery, Jawaharlal Institute of Postgraduate Medical Education and Research, India*

[3]*Department of Pharmacology, Shivalik College of Pharmacy, India*

Abstract

Dengue is a mosquito-borne viral disease spread by female mosquitoes, primarily of the *Aedes aegypti* species. Dengue fever is caused by a virus from the Flaviviridae family. There are four serotypes of the virus which cause dengue fever DENV-1, DENV-2, DENV-3 and DENV-4. It's expected that after you've recovered from an infection, you'll be immune to that serotype for the rest of your life. After recovery, however, cross-immunity to the other serotypes is partial and short lived. Following infections with other serotypes, the risk of developing severe dengue increases. Within a territory, these serotypes can coexist, and many countries are hyper-endemic for all four serotypes. Dengue has a serious impact on human health as well as global and national economics.

Keywords: Dengue fever; TAK-300; DENVax; CYD-TDV; Mosquito-borne viral disease; WHO

Introduction

The majorities of people infected with the dengue virus are asymptomatic (80%) or have mild symptoms like a fever [1-4]. Others suffer more serious illnesses (5%), and a small percentage of them are life-threatening [2,4]. The incubation period can be anywhere from 3 and 14 days, but it is most commonly 4 to 7 days [5].

Infections are divided into 3 stages: febrile, critical, and recovery. The febrile phase includes high fever (40°C/104°F) in a saddle-back pattern and is accompanied by symptoms like severe headache, retro-orbital pain, muscle and joint pains, nausea, vomiting, swollen glands, rash [3].

Critical phase is when the patient can develop severe dengue which is a potentially fatal complication due to plasma leaking, fluid accumulation, respiratory distress, severe bleeding, or organ impairment [3]. There is no specific treatment for Dengue and it has to be managed with Intravenous Hydration, NSAIDs, Platelet and Packed cell transfusions. Prevention measures include protection against the mosquitoes by habitat elimination, insecticide or biological control measures [5].

Vaccination of Dengue is available in a number of countries and is recommended to specific individuals [6], however integration of the vaccine in immunization schedules varies vastly depending on local priorities, pre-vaccination screening and cost [3,7].

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***Corresponding author:** Prasad DN, Department of Pharmacology, Shivalik College of Pharmacy, India, E-mail: debu663@rediffmail.com

Epidemiology

Dengue fever is present in over 120 countries [3]. Dengue rates increased 30 times between 1960 and 2010. A combination of urbanisation, population expansion, greater international travel, and global warming is thought to be responsible for this increase [2]. The equator is the centre of the geographical distribution. Seventy percent of the 2.5 billion people who live in locations where it is common are from the WHO Southeast Asia and Western Pacific Regions. Dengue fever is one of seventeen neglected tropical diseases identified by the World Health Organization [8].

The 3.83 (3.45-4.09) billion people (approximately 53 percent of the global population) live in dengue-infested areas, the vast majority of whom reside in Asia, Africa, and the Americas [9]. By 2050, much of the south-eastern United States is expected to be suitable, and dengue fever is expected to spread to higher altitudes in central Mexico, northern Argentina, along with inland Australia. By 2050, many of the most populous cities in eastern China and Japan are also projected to be suitable [9]. By this metric most of the world population is at risk of Dengue fever in the future including areas that have previously had little to no previous history with the disease in the population (Figure 1).

Dengvaxia

Sanofi Pasteur manufactures Dengvaxia (CYD-TDV). It's a recombinant DNA-derived live attenuated tetravalent chimeric vaccine [10]. Although CYD-TDV is partially successful in avoiding infection, it may increase the risk of severe disease in persons who have never had illness and subsequently become infected [11]. This was seen in the 2017 and 2018 Philippine dengue vaccine controversy, when over 800,000 schoolchildren were vaccinated regardless of serostatus [12].

TAK-300

TAK-003, also known as DENVax, is a recombinant chimeric vaccine incorporating DENV1, DENV3, and DENV4 components on a dengue virus type 2 (DENV2) backbone that was created at

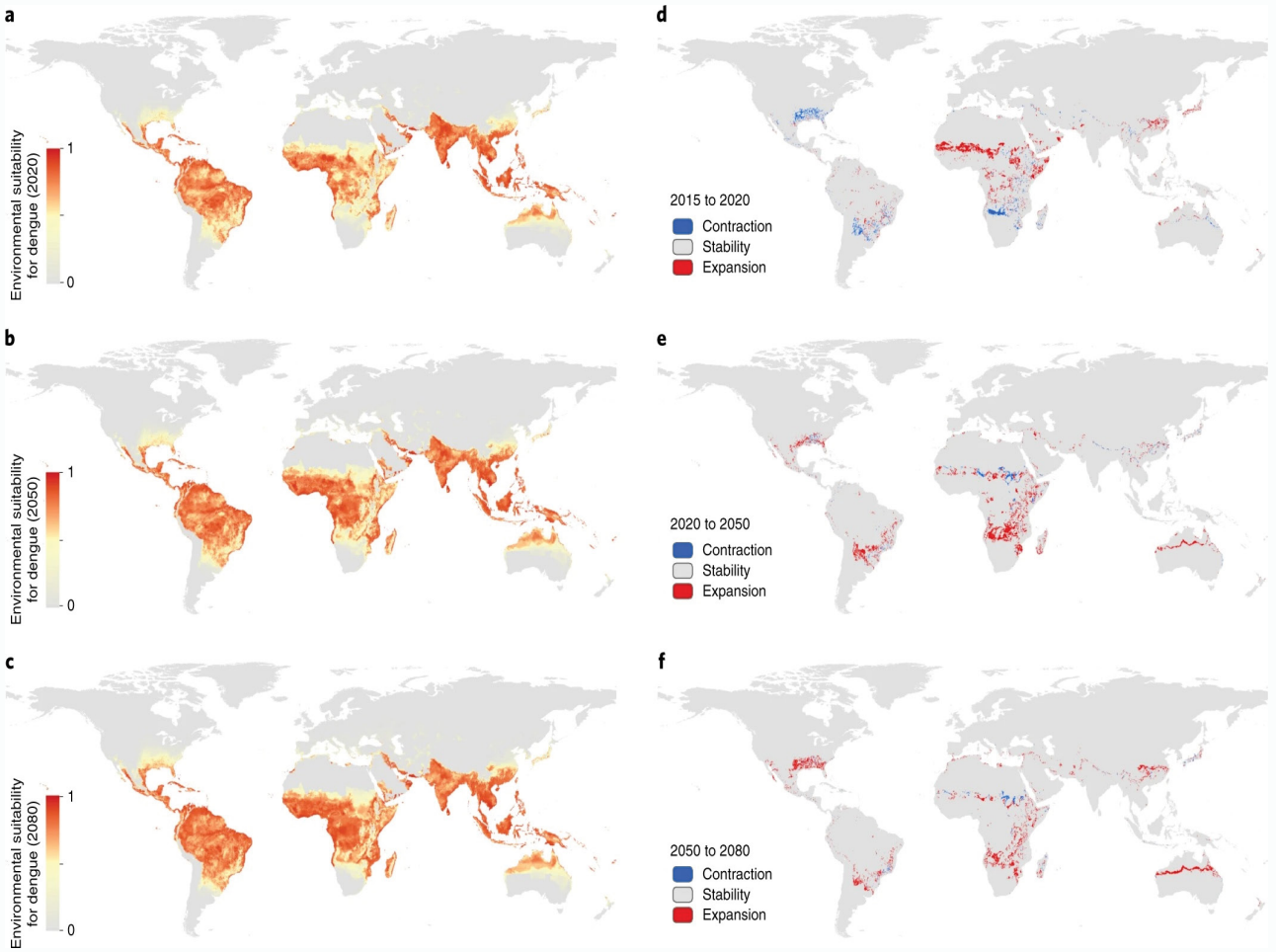

Figure 1: Data projections for 2020 (a), 2050 (b), and 2080(c) are shown. (d–f), Changes in at-risk locations (based on a suitability threshold of 0.467) [9].

Mahidol University in Bangkok and is presently financed by Inviragen (DENVax) and Takeda (TAK-003) [13,14].

It is currently in Phase III of Clinical trials which have been ongoing since September 2016. Part 1 of the Phase III trials had the following Efficacy and Safety findings.

Efficacy

In the per-protocol population, the vaccine effectiveness against virologically confirmed dengue caused by any serotype was 80.2 percent with a 95% Confidence Interval (CI), 73.3 to 85.3; P<0.001; 61 cases of virologically confirmed dengue in the vaccine group and 149 cases in the placebo group (Table 1) [11].

The vaccine had 97.7% efficacy against DENV-2, 73.7 percent efficacy against DENV-1, and 62.6 percent efficacy against DENV-3, according to exploratory analysis of the secondary efficacy end points. However, efficacy against DENV-4 was inconclusive (63.2 percent; 95 percent CI, 64.6 to 91.8). In general, efficacy was similar across age groups (72.8 percent to 83.3 percent) [11].

Safety

In both the vaccine and placebo groups, the percentage of patients who experienced significant adverse events was identical (3.1 percent and 3.8 percent, respectively). During the experiment, there were four deaths in the vaccine group and one death in the placebo group, all of which were ruled unconnected to the trial (Table 2). Asphyxia, cerebrovascular arteriovenous malformation, malignant ependymoma, gunshot wound, and aseptic meningitis were the causes of these deaths [11].

Discussion

Dengue is a viral neglected tropical disease. Dengue fever is expected to affect 2.25 (1.27-2.80) billion more individuals in 2080 than in 2015, raising the overall number of people at risk to approximately 6.1 (4.7-6.9) billion, or 60 percent of the worlds populations [9].

Dengue transmission is greatly influenced by global warming. When the average temperature was less than 27.27°C, between 27.27°C and 30.17°C, and greater than 30.17°C, the predicted value of the dengue vector index increased by 0.29, 0.63, and 1.49 units, respectively, as the temperature increased by 1°C. Extreme weather and climatic events, including extreme temperature events, are projected to become more common and severe in the future, leading to increased transmission of vector-borne diseases like Dengue fever [15].

In the future, it is likely that increased temperatures, overpopulation and dense urbanization of the tropical and subtropical areas may cause large scale epidemics of Dengue. Mortality of any

Table 1: Vaccine Efficacy against Any Dengue Virus Serotype.

End Point and Population	Incidence				Vaccine Efficacy (95% CI)
	Vaccine Group		Placebo Group		
	no./total no.(%)*	Cases/100 person-yr	no./total no.(%)*	Cases/100 person-yr	%
Primary end point: virologically confirmed dengue from 30 days after second dose to end of part 1 of trial					
All participants in per- protocol population†	61/12,700 (0.5)	0.5	149/6316 (2.4)	2.6	80.2 (73.3 to 85.3)
Virologically confirmed dengue from first dose to end of part 1 of trial					
All participants in safety population‡	78/13,380 (0.6)	0.5	199/6687 (3.0)	2.5	80.9 (75.2 to 85.3)
Cases contributing to primary end point (per-protocol population)					
Virologically confirmed dengue					
Baseline serostatus§					
Seropositive	41/9165 (0.4)	0.5	110/4587 (2.4)	2.7	82.2 (74.5 to 87.6)
Seronegative	20/3531 (0.6)	0.6	39/1726 (2.3)	2.5	74.9 (5 7.0 to 85.4)
Dengue virus serotype					
DENV-1	16/12,700 (0.1)	0.1	30/63 16 (0.5)	0.5	73.7 (51.7to 85.7)
DENV-2	3/12,700 (<0.1)	<0.1	64/6316 (1.0)	1.1	97.7 (92.7to 99.3)
DENV-3	39/12,700 (0.3)	0.3	51/6316 (0.8)	0.9	62.6 (43.3 to 75.4)
DENV-4	3/12,700 (<0.1)	<0.1	4/63 16 (0. 1)	<0.1	63.2 (-64.6 to 91.8)
Age group					
4-5 Yr	I3/1619 (0.8)	0.9	23/801 (2.9)	3.2	72.8 (46.2 to 86.2)
6-11 Yr	34/7009 (0.5)	0.5	85/3491 (2.4)	2.7	80.7 (71.3 to 87.0)
12-16 Yr	T4/4072 (0.3)	0.4	41/2024 (2.0)	2.2	83.3 (69.3 to 90.9)
Region					
Asia-Pacific region	54/5894 (0.9)	1	127 /2942 (4.3)	4.9	79.5 (71.8 to 85.1)
Latin America	7/6806 (0.I)	0.1	22/ 3374 (0.7)	0.7	84.3 (63. 1 to 93.3)
Virologically confirmed dengue leading to hospitalization					
Baseline serostatus§					
Seropositive	4/9165(<0.1)	<0.1	35/45 **Table 2:** Safety Analysis (Safety	0.8	94.4 (84.3 to 98.0)
Seronegative	1/3531 (<0.1)	<0.1	18/1726 (IO)	1.2	97.2 (79. T to 99.6)
Dengue hemorrhagic fevers¶					
All participants	1/12,700 (<0.1)	<0.1	4/63 I6 (0.1)	<0. l	87.3 (-13.5 to 98.6)
Severe virologically confirmed dengue‖					
All participants	1/12,700 (<0.1)	<0.1	1/63 16 (<0.1)	<0.1	50.8 (-686.9 to 96.9)

*Percentages were calculated on the basis of the number of participants who underwent evaluation for virologically confirmed dengue.

†In the per-protocol population, 12,700 of 12,704 participants in the vaccine group and 63 16 of 6317 in the placebo group were included in the evaluation of the primary end point. The per-protocol population was determined after exclusion of participants in a blinded manner be- fore database lock in accordance with prespecified criteria. For analyses involving the per-protocol population, data from participants who discontinued were censored at the day of discontinuation.

‡One participant had two instances of virologically confirmed dengue during part I; only the first case was included in the efficacy calculation. For the analysis involving the safer population, data from participants who discontinued but agreed to continue surveillance to detect febrile illness for safety monitoring were not censored at the time of discontinuation. All cases of virologically confirmed dengue that were reported until either the last contact or the end of part T (whichever came first) were included in the safety population analysis of part 1.

§Participants were considered seronegative if they were seronegative for all dengue virus serotypes at baseline. Participants were considered to be seropositive at baseline if they had a reciprocal neutralizing antibody titer of TO or higher to at least one dengue virus serotype.

¶Category includes cases of virologically confirmed dengue that met World Health Organization 1997 criteria for dengue hemorrhagic fever.

||Neither of the two cases of severe virologically confirmed dengue was classified as dengue hemorrhagic fever.

Table 2: Safety Analysis (Safety Population).

Adverse Event	Vaccine Group (N =13,380)	Placebo Group (N =6687)
Serious adverse event-no. (%)	409 (3.1)	255 (3.8)
Serious adverse event not related to vaccine or placebo - no. (%)†	408 (3.0)	251 (3.8)
Serious adverse event related to vaccine or placebo - no. (%)†	1 (<0.1)	4 (0.1)
Serious adverse event leading to withdrawal of vaccine or placebo or to trial discontinuation -	18 (0.1)	8 (0.1)
Death - no. (%)	4 (<0.1)	1 (<0.1)
Death related to vaccine or placebo-no. (%)	0	0
Adverse events in the safety subpopulation - no./total no. (%)		
Unsolicited adverse event within 4 wk after either dose	487/2663 (18.3)	249/1329 (18.7)
Unsolicited adverse event related to vaccine or placebo within 4 wk after either dose†	23/2663 (0.9)	18/1329 (1.4)
Solicited systemic adverse event within 2 wk after either dose‡	1107/2635 (42.0)	501/1317 (38.0)
Solicited system ic adverse event related to vaccine or placebo within 2 wk after either dose†‡	821/2635 (31.2)	371/1317 (28.2)
Solicited local reaction within 1 wk after either dose‡§	967/2633 (36.7)	338/1317 (25.7)

*Data are numbers and percentages of participants with at least one adverse event after any injection (vaccine or placebo); the denominators for the calculation of percentages were the numbers of participants who underwent evaluation in the analysis set.

†The determination of whether an adverse event was related to vaccine or placebo was made by the investigator.

‡Only participants with available diary card data were included in the evaluation.

§All injection-site (solicited local) reactions were considered to be related to vaccine or placebo.

such epidemics would be vastly higher than past epidemics as the trend of the disease currently dictates.

That is the reason why a highly efficacious and safe dengue vaccine is the most necessary vaccine of the future. Neglected tropical diseases like dengue are rarely a priority in the public and in the governments of emerging economies. Adding to that an unsuccessful attempt to control dengue with Dengvaxia in the past has caused controversy for a number of reasons. Vaccine hesitancy in the Philippines increased significantly as a result [16].

TAK-300/DENVax is a second chance to control and reduce the global burden of Dengue fever worldwide. Some other vaccines are also in development - TDENV PIV (Tetravalent Dengue Virus Purified Inactivated Vaccine) [17], V180 Recombinant Subunit vaccine [18] and Monovalent DNA Plasmid Dengue vaccine to name a few. However, TAK-300 is further along in the developmental process and is currently the only dengue vaccine with a high efficacy and a good safety profile. Therefore it is a vital tool to prepare for and to prevent future dengue epidemics.

References

1. World Health Organization. Dengue and severe dengue. 2022.
2. Whitehorn J, Farrar J. Dengue. Br Med Bull. 2010;95(1):161-73.
3. WHO. Dengue Guidelines for Diagnosis, Treatment, Prevention and Control (PDF). Geneva: World Health Organization. 2009.
4. Reiter P. Yellow fever and dengue: a threat to Europe? Euro Surveill. 2010;15(10):pii=19509.
5. Gubler DJ. "Dengue viruses". In: Mahy BW, Van Regenmortel MH, editors. Desk Encyclopaedia of Human and Medical Virology. Boston: Academic Press. 2010 .p. 372-82.
6. U.S. Food and Drug Administration. "First FDA-approved vaccine for the prevention of dengue disease in endemic regions". FDA. 2019.
7. Dengue vaccines: WHO position paper. Epidemiological record. WER No 36, 2018, 93, 457-76.
8. WHO. Control of Neglected Tropical Diseases. "The 17 neglected tropical diseases". World Health Organization. 22 February 2014.
9. Messina JP, Brady OJ, Golding N, Kraemer M, Wint GR, Ray SE, et al. The current and future global distribution and population at risk of dengue. Nat Microbiol. 2019;4:1508-15.
10. Thisyakorn U, Thisyakorn C. Latest developments and future directions in dengue vaccines. Ther Adv Vaccines. 2014;2(1):3-9.
11. Sridhar S, Luedtke A, Langevin E, Zhu M, Bonaparte M, Machabert T, et al. Effect of dengue serostatus on dengue vaccine safety and efficacy. N Engl J Med. 2018;379(4):327-40.
12. Fatima K, Syed NI. Dengvaxia controversy: impact on vaccine hesitancy. J Glob Health. 2018;8(2):010312.
13. Osorio JE, Huang CY, Kinney RM, Stinchcomb DT. Development of DENVax: a chimeric dengue-2 PDK-53-based tetravalent vaccine for protection against dengue fever. Vaccine. 2011;29(42):7251-60.
14. Schwartz LM, Halloran ME, Durbin AP, Longini IM. The dengue vaccine pipeline: Implications for the future of dengue control. Vaccine. 2015;33(29):3293-8.
15. Tran BL, Tseng WC, Chen CC, Liao SY. Estimating the Threshold Effects of Climate on Dengue: A Case Study of Taiwan. Int J Environ Res Public Health. 2020;17(4):1392.
16. Mendoza RU, Dayrit MM, Alfonso CR, Ong M. Public trust and the COVID-19 vaccination campaign: lessons from the Philippines as it emerges from the Dengvaxia controversy. Int J Health Plann Manage. 2021;36(6):2048-55.
17. McArthur MA, Sztein MB, Edelman R. Dengue vaccines: recent developments, ongoing challenges and current candidates. Expert Rev Vaccines. 2013;12(8):933-53.
18. Manoff SB, George SL, Bett AJ, Yelmene ML, Dhanasekaran G, Eggemeyer L, et al. Preclinical and clinical development of a dengue recombinant subunit vaccine. Vaccine. 2015;33(50):7126-34.