Editorial

Dengue Vaccine: Past, Present and Future

BACKGROUND

Dengue infection, one of the most devastating mosquito-borne viral diseases in human, is now a significant problem in many countries like Bangladesh. It is estimated that some 500 000 people with dengue require hospitalization due to warning signs or severe dengue,[1] and causes about 20 000 deaths every year.[2] Considering fatal and non-fatal outcomes together, dengue was responsible for 114 million disability-adjusted life-years (DALYs).[2]

The causative dengue viruses are members of the genus Flavivirus, within the family Flaviviridae. There are four closely related serotypes, the dengue viruses (DENV) 1-4 and at least four genotypes within each serotype. Flaviviruses are lipid-enveloped, positive-strand RNA viruses, that encodes three structural proteins, namely capsid protein (C), precursor membrane/membrane protein (PrM/M) and envelope protein (E). Besides structural proteins, there are seven nonstructural proteins (NS) which are associated with viral replication and disease pathogenesis. The disease, caused by the four-dengue virus serotypes, ranges from asymptomatic infection to undifferentiated fever, dengue fever (DF), and severe dengue hemorrhagic fever (DHF). The primary vector, the urban-adapted Aedes aegypti, has become widely distributed across tropical and subtropical latitudes.

The 4 dengue serotypes are serologically and genetically distinct,[3] although they share several structural antigens. Following an infection with one DENV serotype, the antibodies induced are typespecific and also cross-reactive with other DENV serotypes. After human inoculation via the bite of an infected female mosquito, the virus replicates in local dendritic cells. Subsequent entry into macrophages and activation of lymphocytes is followed by entry into the bloodstream. Dengue viruses primarily infect cells of the myeloid lineage, including macrophages, monocytes, and dendritic cells. Haematogenous spread is the likely mechanism for infection of peripheral organs.

Prevention depends primarily on control of the mosquito vector which has achieved only limited success in reducing transmission of dengue. The primary vector, the urban-adapted Aedes aegypti, has become widely distributed across tropical and subtropical latitudes. It has spread globally with the advent of increased travel and trade in the past 50 years.

CURRENT DEVELOPMENT OF DENGUE VACCINES

The first dengue vaccines were evaluated in 1929.[4] Development of safe and effective dengue vaccines faces many challenges. Infection by one of the four dengue virus serotypes has been shown to confer lasting protection against homotypic reinfection, but only transient protection against a secondary heterotypic infection. Moreover, secondary heterotypic infection is associated with an increased risk of severe disease. Due to these dengue-specific complexities, vaccine development focuses on the generation of a tetravalent vaccine aimed at providing long-term protection against all virus serotypes. Despite those challenges, vaccine development has made remarkable progress in recent years, and the current dengue vaccine pipeline is advanced, diverse, and overall promising. At present, several dengue vaccines have been tested in human clinical trial, and a single candidate is now in phase III clinical trials. Different approaches in dengue vaccine development are discussed herein.

Live attenuated virus vaccine: The first major effort at live attenuated dengue vaccine development began at the University of Hawaii using the traditional method of serial passage of virus in a nonhuman host and then transferred to Mahidol University in Bangkok, Thailand for further passage and development of candidate vaccines and testing.[5,6] The candidate vaccine was used for phase I and II clinical trials in Thai adults and children. Not all of the volunteers seroconverted to all four dengue serotypes and some showed unacceptable reactogenicity, consequently further clinical testing was stopped.[7,8] Although the

development of this candidate vaccine was not successful, the initiative was responsible for the subsequent progress that has been made in developing a live attenuated tetravalent dengue vaccine.[9]

Chimeric virus vaccine: The US Centers for Disease Control and Prevention (CDC) developed a tetravalent chimeric dengue vaccine by inserting DENV-1, -3 and -4 prM and E genes into cDNA derived from the successfully attenuated DEN-2 component of the Mahidol University-Sanofi Pasteur live attenuated dengue virus vaccine (DEN-2, 16681 PDK-53). Dengue-dengue chimeras tetravalent vaccine candidate was then formulated and licensed to Inviragen, Inc. and Takeda respectively and has undergone clinical testing [10-13]

Inactivated virus vaccine: Inactivated whole virus vaccines have two advantages since they cannot revert to a more pathogenic phenotype, and they are unlikely to interfere with each other in combination. Moreover, induction of cell-mediated and humoral immune responses have been demonstrated with inactivated flavivirus vaccines.[14]

Subunit vaccines: Recombination subunit approaches offer advantages, including anticipated minimal reactogenicity and freedom from adventitious agents. However, incomplete post-translational processing of proteins can lead to proteins that differ from native proteins and antibody responses.[15] Production in mammalian cells may reduce some of these concerns.[16]

Dengue DNA vaccines: They offer a possible method to raise protective immunity, by passing the problem of interference seen with multivalent live virus vaccines. DNA vaccines are composed of a plasmid or plasmids containing dengue genes. Tetravalent DNA vaccine inoculated in mice and monkeys successfully raised neutralization antibodies. Monkeys resisted challenge with DEN-1 but not DEN-2.[17,18]

A DENV-1 DNA vaccine: It was evaluated in flavivirus-negative volunteers with the three-dose series at day 0, and at 1 and 5 months. None of the volunteers receiving a low dosage and half of those receiving a high dosage developed neutralizing antibodies.[19]

Vectored vaccines: Recombinant poxviruses and adenoviruses expressing foreign proteins have been demonstrated to induce strong humoral and cellular responses in humans against various pathogens. Several live virus vectors such as adenovirus, alphavirus, and vaccinia virus are designed for direct administration to the host and have been engineered to express DENV E protein for further evaluation as dengue vaccine candidates.[12,20]

CONCLUSION

Dengue virus is the causative agent of a wide spectrum of clinical manifestations, ranging from mild acute febrile illness to classical DF and DHF. DHF is caused by the potentially fatal forms of dengue virus infection, which has become an intractable global health problem. Vector control has achieved only limited success in reducing the transmission of dengue and there are currently no licensed antivirals to treat dengue. The most effective way to control dengue diseases in the future will include the use of a safe and effective vaccine. Dengue is a unique and complex disease; developing a dengue vaccine has proven equally complex. Although no licensed dengue vaccine is yet available, several vaccine candidates are under development, including live attenuated virus vaccines, live chimeric virus vaccines, inactivated virus vaccines, and live recombinant, DNA and subunit vaccines. The live chimeric virus vaccine is undergoing a phase III clinical trial. Other vaccine candidates have been evaluated in preclinical animal models or are being prepared for clinical trials.

For the first time in dengue-prone Bangladesh, researchers from International Centre for Diarrhoeal Disease Research, Bangladesh (ICDDR,B) and the Lerner College of Medicine at the University of Vermont in the United States have completed research on an encouraging tetravalent dengue vaccine, i.e., a vaccine that is effective against all four types of dengue virus. The study evaluated the single dose dengue vaccine TV-005 and found it to be safe for use in children, adults and able to induce immunity. The study results were recently published in the Lancet Infectious Diseases journal.[21]

Mugda Med Coll J. 2023; 6(2): 48-50.

Salma Ahmed
Professor & Head
Department of Microbiology
Mugda Medical College, Dhaka-1214
Email: ahmed.salma51@yahoo.com

REFERENCES

1. World Health Organization (WHO). Dengue and severe dengue. Key Facts. WHO. (March 17, 2023). Retrieved from: https://www.who.int/news-room/fact-sheets/detail/dengue-and-severe-dengue (Accessed May 11, 2023).
2. Stanaway JD, Shepard DS, Undurraga EA, Halasa YA, Coffeng LE, Brady OJ, et al. The global burden of dengue: an analysis from the Global Burden of Disease Study 2013. Lancet Infect Dis. 2016;16(6):712-23.
3. Guzman MG, Harris E. Dengue. Lancet. 2015;385(9966):453-65.
4. Blac G, Caminopetros J. Recherches experimentales sur la dengue. Ann Inst Pasteur Paris. 1930;44:367-436.
5. Bhamarapravati N, Sutee Y. Live attenuated tetravalent dengue vaccine. Vaccine 2000;18(Suppl. 2):44-7.
6. Halstead S, Marchette N. Biologic properties of dengue viruses following serial passage in primary dog kidney cells: studies at the University of Hawaii. Am J Trop Med Hyg. 2003;69:5-11.
7. Sabchareon A, Lang J, Chanthavanich P, Yoksan S, Forrat R, Attanath P, et al. Safety and immunogenicity of a three-dose regimen of two tetravalent live-attenuated dengue vaccines in five- to twelve-year-old Thai children. Pediatr Infect Dis J. 2004;23:99-109.
8. Sanchez V, Gimenez S, Tomlinson B, Chan P, Thomas G, Forrat R, et al. Innate and adaptive cellular immunity in flavivirus-naíve human recipients of a live-attenuated dengue serotype 3 vaccine produced in Vero cells (VDV3). Vaccine. 2006;24:4914-26.
9. World Health Organization (WHO). Dengue Vaccine Development: The Role of the WHO South-East Asia Regional Office. New Delhi: WHO; 2010.
10. Lai C, Zhao B, Hori H, Bray M. Infectious RNA transcribed from stably cloned fulllength cDNA of dengue type 4 virus. Proc Natl Acad Sci USA 1991;88:5139-43.
11. Polo S, Ketner G, Levis R, Falgout B. Infectious RNA transcripts from full-length dengue virus type 2 cDNA clones made in yeast. J Virol. 1997;71: 5366-74.
12. Halstead S, Thomas, S. Dengue Vaccines. In: Plotkin S, Orenstein W, Offit P. eds. Dengue Vaccines. Elsevier: China; 2013. p.1042-51.
13. Huang C, Kinney R, Livengood J, Bolling B, Arguello J, Luy B, et al. Genetic and phenotypic characterization of manufacturing seeds for a tetravalent dengue vaccine (Denvax). PLoS Negl Trop Dis. 2013;7:e2243.
14. Aihara H, Takasaki T, Toyosaki-Maeda T, Suzuki R, Okuno Y, Kurane I. T-cell activation and induction of antibodies and memory T cells by immunization with inactivated Japanese encephalitis vaccine. Viral Immunol. 2000;13:179-86.
15. Smucny J, Kelly E, Macarthy P, King A. Murine immunoglobulin G subclass responses following immunization with live dengue virus or a recombinant dengue envelope protein. Am J Trop Med Hyg. 1995;53:432-7.
16. Konishi E, Fujii A. Dengue type 2 virus subviral extracellular particles produced by a stably transfected mammalian cell line and their evaluation for a subunit vaccine. Vaccine. 2002;20:1058-67.
17. Whalen R. DNA vaccines for emerging infectious diseases: what if? Emerg Infect Dis.1996;2:168-75.
18. Raviprakash K, Apt D, Brinkman A, Skinner C, Yang S, Dawes G, et al. A chimeric tetravalent dengue DNA vaccine elicits neutralizing antibody to all four virus serotypes in rhesus macaques. Virology. 2006;353:166-73.
19. Beckett C, Tjaden J, Burgess T, Danko J, Tamminga C, Simmons M. et al. Evaluation of a prototype dengue-1 DNA vaccine in a phase 1 clinical trial. Vaccine. 2011;29:960-8.
20. Wan SW, Lin CF, Wang S, Chen YH, Yeh TM, Liu HS, Anderson R, Lin YS. Current progress in dengue vaccines. J Biomed Sci. 2013;20(1):37.
21. Walsh MR, Alam MS, Pierce KK, Carmolli M, Alam M, Dickson DM, et al. Safety and durable immunogenicity of the TV005 tetravalent dengue vaccine, across serotypes and age groups, in dengue-endemic Bangladesh: a randomised, controlled trial. Lancet Infect Dis. 2023:S1473-3099(23)00520-0.