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Barriers to Effective Dengue Vaccination, Cross Reactions and Immune Responses: A Review

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Abstract

One of the most prevalent diseases spread by the mosquitoes in the world is the dengue fever which is a major health issue to the people of the tropical and subtropical regions. They have approximated that 390 million people annually are infected by dengue virus (DENV) of which approximately 96 million get into clinical conditions. Besides, health impacts, dengue has a high cost, and this is in the economic sphere. In contemporary times, there exist no specific antiviral drugs and the only approved vaccine given is protection to seropositive (had been exposed to dengue before) and not seronegative (dengue naive) patients. This review explores the key immune responses and their interaction with DENV and the current innovations in the production of vaccines. The mechanisms through which the vaccines may work are also addressed e.g. preexisting immunity, and the long-term barriers to an effective vaccine: antigenic diversity of four DENV serotypes, antibody-dependent enhancement (ADE) and cross- reactivity to related flaviviruses. Finally, we mention the therapeutic potential of targeting T follicular helper (Tfh) cells as critical controllers of the production of high-affinity antibodies as a means of improving vaccine response irrespective of whether the individual had been previously exposed to dengue.

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Keywords: Dengue virus (DENV), antibody-dependent enhancement (ADE), vaccine development problems, T follicular helper cells (Tfh), cross-reactivity, vaccine precision.

Introduction

Dengue is a major global epidemic in the tropical and subtropical regions that impacts the estimated 390 million cases per year of which 96 million become clinical disease. As of 2019, there were over 3 million confirmed cases across the globe with the Americas (especially Brazil) having most cases but Brazilian cases (1.5 million) surged by more than 10-fold in 2018. Also, significant surges in such countries as Bangladesh, Malaysia, Maldives, the Philippines, Cambodia (56,000 cases), Vietnam (370,702), Thailand (136,000), and Indonesia (110,000) were also observed in the region of Southeast Asia. Those outbreaks spread to the Indian Ocean (e.g., Mayotte: 904 cases in 2020), to the Pacific Islands (e.g., French Polynesia: 3,496 in 2019), and also to Australia (1,038 in 2019), and even beyond as Table 1 indicates.

Not only does Dengue have an enormous financial effect on the population but also a tremendous health cost that is approximated at $5.71 billion/year in 2016 which is an enormous growth over 1.51 billion/year in 2013 and is projected to rise even higher. This brings out the hopeless attempts of vaccines, which are motivated by international health bodies.

Dengue Virus Virology

As a flavivirus, Dengue virus (DENV) is an arthropod-hosted virus that is transmitted to human beings by bites of the Aedes aegypti mosquito or Aedes albopictus but not humans. Its first targets are dendritic cells (DCs) and macrophages and the virus takes advantage of its lymphotropic capability to infect skin-draining lymph nodes (dLNs) and migrating monocytes to establish viremia and systemic dissemination.

DENV virions in their mature form contain three structural proteins- capsid (C), envelope (E), and membrane (M) and seven non-structural proteins (NS1, NS2A, NS2B, NS3, NS4A, NS4B, NS5) which are critical in viral replication, immunogenicity, virion assembly, and genome replication. The antigens have four serotypes (DENV1-4), which are antigenically diverse though the difference in the genome is about 65 percent, posing considerable problems in vaccine design.

Cellular Entry and Replication: DENV enters host cells (using clathrin-mediated endocytosis) by binding DC-SIGN (CD209) and ICAM-3 C-type lectin receptors on monocytes, DCs and macrophages in early infection. The secondary infections utilize the non-neutralizing antibodies that already exists and use its help to go through the uptake of Fcg receptor. E protein change of conformation occurs when low PH induces this endocytosis with a release of genomic RNA in the cytoplasm.

Subsequently the virion Maturation Translated structural/non-structural proteins are nucleocapsidally discharged into the endoplasmic reticulum (ER) that comprises lipid envelope prM and E proteins to create spiky immature virions. They are then carried to Golgi body where furin cleaves prM into full-sized M protein and a released peptide and produce smooth infectious virions which they exocytose out of the cell. The differences between serotypes and maturation processes make universal vaccine strategies very complex.

Cross Reactivity with the other Flaviviruses

The likeness in the structure between the dengue virus (DENV) and the other members of the Flaviviridae that include; Zika virus (ZIKV), yellow fever virus (YFV), Japanese encephalitis virus (JEV) and West Nile virus (WNV) are some of the setbacks that have been experienced in the development of a good dengue vaccine. The envelope (E) protein which is primary neutralisation target in antibodies is highly conserved in flaviviruses with three different domains known as EDI, EDII and EDIII. DENV E protein is over 50 per cent homologous to ZIKV and this has led to cross-reactivity of antibodies.

This cross-reactivity depicts two responses, which are the protection or enhancement of disease in the recurrent infestations in line with specificity and extent of antibody. The second cause that contributed to the issues was that the 2016 outbreaks of the ZIKV in the nations included in the DENV-infected areas in north Brazil and Mexico were likely to alter the severity of the disease in case of the interference of immunity. Even though the humoral responses are the most responsible in pathogenesis of the antibody-dependent enhancement (ADE), cellular immunity plays a role in the pathogenesis.

The optimum concentrations of already available cross- reactive antibodies can inhibit the development of symptoms due to the entry of viruses but increase the concentrations lead to ADE and neutralization defect. It was already known that Mexican

cohort study that the DENV patient serum contained cross-reactive antibodies against the ZIKV E protein which have the capacity to neutralize or ADE at titer threshold depending on the titer threshold. The duration of prophylaxis of severe disease remains until about 2 years following initial infection and thereafter, prophylaxis begins to rise due to antibodies decadence, and consequent secondary heterologous infection. These neutralizing antibodies are cross reactive and they can be sustained through concomitancy re-exposure.

The adequate vaccination will require long-lasting neutralizing antibodies, which have been produced during germinal center (GC) reaction in secondary lymphoid tissues to produce long-lived plasma cells. One of the targets of pan-serotype dengue vaccine is still Tfh-GC axis.

Current Dengue Vaccines

Problems with Vaccines Development

The dengue vaccine design has a neutralizing effect that makes the vaccine unique as the disease causative organisms have four serotypes (DENV1-4) and tetravalent neutralization of the antibody responses is possible due to the presence of the previous immunity in the vaccine, which requires that the antibody responses are neutralized. These problems have not deterred a number of candidates, which have been subjected to clinical trials.

FDA Registered Vaccine: Dengvaxia (CYD-TDV)

The first FDA approved dengue vaccine is dengue virus vaccine Dengvaxia, an FDA approved vaccine against dengue virus licensed in most countries since 2015 by Sanofi Pasteur. It is a live attenuated, chimeric tetravalent backbone and is a yellow fever 17D backbone that has prM/E protein replaced by all the four serotypes of DENV. It is given in the endemic countries only in seropositive individuals aged between 9-45 years only and in the subcutaneous dose (3 doses and regime). It is highly efficient in respect to serious disease outbreak in already exposed persons but it increases the chances of hospitalization among the non-exposed persons to the dengue virus, which remains a point of concern and causes the development of alternative.

Phase III Candidates

Two versions of phase III tetravalent tetravalent live-attenuated vaccines exist:

TV003/TV005 (NCT01506570): this is a monovalent preparation of 103 PFU in each serotype (104 PFU DENV2 in TV005). TV003 cross serotype is potent and neutral in all the serotypes at the same dose including naive adults to flavivirus.

TAK-003/DENVax (NCT02302066): It is a cross-clominated vaccine Takeda vaccine, which uses prM /E of DENV1, 3 and 4 constructs but utilizes live-attenuated DENV2 PDK-53 as a backbone. It triggers cellular and humoral responses, which are chronic in terms of all the serotypes.

Phases I-III are further separated into other platforms (live-attenuated, inactivated, DNA) to be utilized in order to eradicate the serostatus-dependency restrictions.

Table 1: *Dengue Cases by Region and Country (2019–2020)*

Country/Territory	2019 Cases	2025 Cases (as of June)	Source	Trend Analysis
South Asia				
Pakistan	~24,547	~295 (Sindh, 90% Karachi)	NIH Pakistan, MMI Hospital	Major decline; controlled year (0 deaths)
India	~157,315	Data pending (high burden expected)	NVBDCP India	Persistent high transmission
Indian Ocean				
Reunion	3,048	353	French Regional Health Agency (ARS)	Sharp decline (-88%)
Pacific/Australia				
Australia	1,038	54	Department of Health, Australia	Significant drop (-95%)
Asia				
Cambodia	56,000	330	Ministry of Health	Drastic fall (-99%)
Vietnam	370,702	N/A	Ministry of Health	Data pending
Malaysia	100,803	18,473	Department of Health	Notable decline (-82%)
Philippines	27,245	15,817	N/A	Moderately lower
Thailand	136,000	1,097	WHO	Severe reduction (-99%)
Indonesia	110,000	N/A	WHO	Data pending
Americas				
Central America/Mexico	672,168	30,460	PAHO	Sharp decline (-95%)
Southern Cone/Brazil	2,241,974	273,565	PAHO	Highest volume, -88%

Conclusions

Dengue virus (DENV) poses a major global health challenge, necessitating an optimal vaccine to alleviate its societal burden. The virus's four distinct serotypes complicate vaccine design, requiring simultaneous induction of high-affinity neutralizing antibodies against all serotypes to prevent antibody-dependent enhancement (ADE). The licensed Dengvaxia (CYD-TDV) vaccine by Sanofi Pasteur revealed critical insights: seropositive (previously exposed) individuals achieved protection, while dengue-naïve recipients showed inadequate responses and heightened severe disease risk upon natural exposure. This serostatus disparity warrants investigation at the pre-vaccination microenvironment level. We hypothesize that suboptimal T follicular helper (Tfh) cell activation—specific to each serotype—underlies naïve individuals' poor responses. Strategically incorporating Tfh-potentiating adjuvants, such as adenosine deaminase (ADA), could generate serotype-specific Tfh cells, enabling naïve vaccinees to produce robust, high-affinity neutralizing antibodies comparable to immune counterparts. This approach holds promise for universal dengue vaccine efficacy irrespective of prior exposure.

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