


Challenges for The Development of Dengue and Zika Virus Vaccines



Abel Gutiérrez Ortega and Darwin Elizondo Quiroga*

Unidad de Biotecnología Médica y Farmacéutica, CIATEJ

Received:  August 21, 2018; **Published:**  August 28, 2018

***Corresponding author:** Darwin Elizondo Quiroga, Unidad de Biotecnología Médica y Farmacéutica, Centro de Investigación y Asistencia en Tecnología y Diseño del Estado de Jalisco, Normalistas 800, Colinas de la Normal, Guadalajara, Jalisco, 44270, México

Opinion

Dengue (DENV) and Zika virus (ZIKV) are very close relatives belonging to the Flavivirus family and thus share many structural and antigenic features, as well as their infectious cycle. Both viruses are transmitted to humans through mosquito bites mainly from *Aedes* genus (*Ae. aegypti* and *Ae. albopictus*) [1], which have been expanded their habitats to an extent that half the World's population is now at risk of DENV/ZIKV infection. The most severe consequences of having either virus would be dengue shock syndrome which normally leads to death [2], or in the case of ZIKV, microcephaly in newborns from infected mothers and Gillian-Barré syndrome [3-4]. For DENV, it has been well documented that a second infection with a different serotype, increases the chance of having the most severe dengue form, through a mechanism called antibody-dependent enhancement (ADE) [5], a phenomenon which has not been related in ZIKV infection in patients previously exposed to DENV or other Flaviviruses [6]. The fatal consequences, along with the lack of an effective treatment, have pushed forward a great effort from several research groups to develop vaccines against DENV, and it seems that some key learnings from DENV have accelerated the development for ZIKV vaccines.

DENV Vaccine Candidates

A vaccine candidate comprising a mixture of four populations of chimeric viruses, each for a different DENV serotype (tetravalent), having the non-structural proteins from yellow fever virus and structural proteins from DENV, reached phase III clinical trial; unfortunately, the trial results were not as expected, since protection against DENV-2 was not good enough and most important, children that had not been infected with DENV before vaccination, were more susceptible to develop severe dengue symptoms in a subsequent DENV infection [7-8]. Another vaccine candidate, which is also a tetravalent formulation, containing DENV pre-membrane (pre-M) and envelope (E) proteins in a DENV-2 backbone, has been recently evaluated in a phase II clinical trial, resulting in sustained serotype-specific antibody titers (at least, for 18 months) and a low incidence of DENV infections in vaccinated

2-17 years-old individuals. Nonetheless, a follow-up of vaccinated individuals is critical in order to assess long-term safety and efficacy of this vaccine [9].

ZIKV Vaccine Candidates

The fact that there is only one ZIKV serotype, opposite to the DENV experience, makes the development of a safe and effective vaccine an apparently easy task, at least in theory, because, so far, there would not be a concern about ADE and the concomitant increase in the susceptibility of vaccinated individuals to ZIKV infection. At present, some of the most promising ZIKV vaccine candidates are in phase I clinical trials and are based mainly on DNA or inactivated viruses. For example, a DNA vaccine containing consensus sequences from ZIKV preM and E proteins, elicited good neutralization titers in more than half of immunized subjects [10]. Regarding inactivated virus vaccines, a formalin-inactivated, alum-adjugated isolate from Puerto Rico, induced neutralization titers in more than 90 percent of the immunized individuals [11]. At this point, the results from these vaccine candidates are promising, but they are merely suggesting that protection could be achieved.

Further Approaches

Given the sequence similarities in these close related viruses, some other approaches arise. For instance, parting from the well-known cross-neutralization in this family that led researchers to cluster Flaviviruses in serocomplexes [12], a new research group has hypothesized that developing a vaccine directed to the fusion loop of flaviviruses (a highly conserved region among several flaviviruses) could induce protection not only against the four DENV serotypes and ZIKV simultaneously, but all the viruses included in this super serogroup [13]

Concluding Remarks

It appears that effective and safe vaccines against DENV and ZIKV, will be available for massive immunization programs shortly. Nevertheless, serostatus assessment before immunization based on

accurate diagnostics, as well as long-term surveillance of antibody titers, will play a pivotal role in the success of the vaccination programs and it is likely that, based on these parameters, the boost regime will have to be adjusted in order to achieve a better protection against these viruses. The use of affordable and accurate diagnostic tools that can be performed on-site for measuring antibody titers, will contribute to the success of these programs. Finally, monitoring the possible appearance of new virus mutated strains by means of whole genome sequencing, will also be necessary in preparedness for a possible re-emergence or side effects arising from ADE phenomenon for the vaccinated population.

References

- Funk S, Kucharski AJ, Camacho A, Eggo RM, Yakob L, et al. (2016) Comparative analysis of dengue and Zika outbreaks reveals differences by setting and virus. *PLoS neglected tropical diseases* 10(12): e0005173.
- (2018) Dengue Virus Net. *Dengue Haemorrhagic Fever*.
- Fauci AS, Morens DM (2016) Zika virus in the Americas—yet another arbovirus threat. *New England journal of medicine* 374(7): 601-604.
- Rozé B, Najioullah F, Fergé JL, Dorléans F, Apetse K, et al. (2017) Guillain-Barré Syndrome Associated with Zika Virus Infection in Martinique in 2016: A Prospective Study. *Clinical Infectious Diseases* 65(9): 1462-1468.
- Katzelnick LC, Gresh L, Halloran ME, Mercado JC, Kuan G, et al. (2017) Antibody-dependent enhancement of severe dengue disease in humans. *Science* 358(6365): 929-932.
- Terzian ACB, Schanoski AS, Mota MTDO, da Silva RA, Estofolete CF, et al. (2017) Viral load and cytokine response profile does not support antibody-dependent enhancement in dengue-primed Zika virus-infected patients. *Clinical Infectious Diseases* 65(8): 1260-1265.
- Sridhar S, Luedtke A, Langevin E, Zhu M, Bonaparte M, et al. (2018) Effect of Dengue Serostatus on Dengue Vaccine Safety and Efficacy. *New England Journal of Medicine* 379: 327-340.
- Hadinegoro SR, Arredondo-García JL, Capeding MR, Deseda C, Chotpitayasunondh T, et al. (2015) Efficacy and long-term safety of a dengue vaccine in regions of endemic disease. *New England Journal of Medicine* 373(13): 1195-1206.
- Sáez-Llorens X, Tricou V, Yu D, Rivera L, Jimeno J, et al. (2018) Immunogenicity and safety of one versus two doses of tetravalent dengue vaccine in healthy children aged 2-17 years in Asia and Latin America: 18-month interim data from a phase 2, randomized, placebo-controlled study. *The Lancet Infectious Diseases* 18(2): 162-170.
- Tebas P, Roberts CC, Muthumani K, Reuschel EL, Kudchodkar SB, et al. (2017) Safety and immunogenicity of an anti-Zika virus DNA vaccine—preliminary report. *New England Journal of Medicine*.
- Modjarrad K, Lin L, George SL, Stephenson KE, Eckels KH, et al. (2018) Preliminary aggregate safety and immunogenicity results from three trials of a purified inactivated Zika virus vaccine candidate: phase 1, randomised, double-blind, placebo-controlled clinical trials. *The Lancet* 391(10120): 563-571.
- Calisher CH, Karabatsos N, Dalrymple JM, Shope RE, Porterfield JS, et al. (1989) Antigenic relationships between flaviviruses as determined by cross-neutralization tests with polyclonal antisera. *Journal of General Virology* 70(1): 37-43.
- Barba-Spaeth G, Dejnirattisai W, Rouvinski A, Vaney MC, Medits I, et al. (2016) Structural basis of potent Zika-dengue virus antibody cross-neutralization. *Nature* 536(7614): 48-53.

ISSN: 2574-1241

DOI: [10.26717/BJSTR.2018.08.001653](https://doi.org/10.26717/BJSTR.2018.08.001653)

Darwin Elizondo Quiroga. *Biomed J Sci & Tech Res*



This work is licensed under Creative Commons Attribution 4.0 License

Submission Link: <https://biomedres.us/submit-manuscript.php>



Assets of Publishing with us

- Global archiving of articles
- Immediate, unrestricted online access
- Rigorous Peer Review Process
- Authors Retain Copyrights
- Unique DOI for all articles

<https://biomedres.us/>