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Review Article
Advances in Designing and Developing Vaccines Against Zika Virus

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Abstract

The recent outbreaks of Zika virus (ZIKV) infections has changed the ZIKV status from a very mild self-limiting febrile virus to a highly pathogenic virus causing visual impairment, autoimmune response against myelin layer and microcephaly in affected fetus. The serious social impact on society has drawn the attention of the researchers globally. The search for an effective vaccine against ZIKV is on the way. Several researches as well as commercial organizations are indulged in developing vaccine for prophylactic and treatment purposes. In the present review, various vaccine strategies have been described including inactivated, attenuated, DNA, subunit, recombinant viral vectored and nucleic acid based vaccines. The vaccines developed should be clinically tested in animal models, which are susceptible for ZIKV infection like Stat2$^{-/-}$ mice, A129 (IFNAR$^{-/-}$) Mice, Swiss Jim Lambert (SJL) mice or Rhesus macaques. Efficacy of each vaccination strategy is required to be meticulously evaluated. The use of vaccinomics could also help to discover appropriate vaccine candidate to induce the effective immune response. DNA and subunit vaccines may not be that much beneficial in endemic areas due to poor immunogenic potential; however, by adjuvanting or using specific devise to deliver DNA vaccine construct, efficacy may be improved. Investigations exploring the cross reaction between the already existing immunity and immunity against newly developed vaccines would be of interest and useful for researchers. Further, researches should target whether vaccines and/or antibodies against ZIKV can induce Antibody Dependent Enhancement (ADE) resulting in subsequent enhancement of flavivirus infection. There are utmost requirements of sufficient resources in terms of infrastructure, funding, manpower, along with producing effective and safe ZIKV vaccine in commercial basis.

Key words: Zika virus, zika fever, vaccines

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INTRODUCTION

At present one of the most significant emerging viruses in the world is Zika virus (ZIKV). In recent years, it has caused outbreaks as well as epidemics; has been found in association with severe clinical outcomes along with birth defects. But till date as far as the pathogenicity of the virus and the consequences of the infection are concerned little is known. This has lead to development of control strategies too including vaccine production[1-3].

The outbreaks of ZIKV infections have drawn the attention of the researchers throughout the globe. The internet and other media channels have acted as pioneers for rapid and wild spread of the informations. The public health impact the disease imposed strongly the need of rapid as well as specific diagnostic tests and at the same time the requirement to develop vaccines and that too commercially[4-6].

Several approaches have been considered in recent past to develop vaccines against four flaviviruses. These are, live attenuated 17D strain based vaccine for yellow fever virus; inactivated as well as live attenuated 14-14-2 strain based vaccine for Japanese encephalitis virus; an inactivated vaccine for tick borne encephalitis virus; and a chimeric vaccine for dengue virus. The adoption of the same approaches can lead to developing Zika virus (ZIKV) vaccine development. Identification of functionally conserved epitopes, between ZIKV and other flaviviruses may help in rationally design a vaccine effective against broad range of flaviviruses. Moreover, subunit vaccines that represent ZIKV proteins; DNA vaccines that express proteins of the virus along with other vectors (viral) that express antigens of the virus can be explored. Side by side there is also requirement of assessing the role of passive immunisation pre- and post-exposure to ZIKV. Modified Vaccinia Ankara (MVA) virus, Virus-like particle (VLP), subunit vaccine, synthetic DNA vaccine encoding for pre-membrane and envelope proteins; self-inactivating and non-integrating lentivirus vectors which are capable of replication in dividing and quiescent cells; nanoparticle based vaccine; inactivated virus vaccine; measles vaccine as vaccine backbone, are the few modalities upon which several workers are working to develop effective ZIKV vaccine. Apart from efficacy, the vaccine must be safer to be used in pregnant women. The simultaneous exploration of the complementary approaches for development of advanced vaccine for ZIKV is the need of the hour[7-10].

Advances in designing and developing Zika vaccines: The search for an effective vaccine against ZIKV is on. The National Institute of Allergy and Infectious Diseases is working on ZIKV vaccine. Unlike dengue virus (DENV), where heterologous infection increases the risk of the severe disease condition, in ZIKV the primary infection was found protective against heterologous challenge through robusting T cell, NK cell, B cell and neutralizing antibodies[11,12]. However, still information lacks on the time point of appearance of protective immunity or how long it will endure. The N-linked glycosylation is known to play an important role in the infectivity and assembly of viruses; for example, the completely attenuated neuro-invasiveness was achieved by deglycosylation of both E and NS1 proteins of WNV, while same strain could be used to get protective immunity[13]. The continuous passage in mice brain or cell culture may lead to loss of glycosylation site and preservation of glycosylation site is essential for retaining efficient replication of ZIKV in primates. This may be a major concern for efficient vaccine design, therefore strains of ZIKV having non-glycosylated proteins, with reduced neural virulence, might be of greater importance for vaccination purpose. As there is lesser variation among ZIKV strains, it is quite possible that an effective vaccine can be developed for all the circulating strains of ZIKVs[14,15]. Using Indian-origin rhesus macaques as an animal model for Asian-lineage ZIKV infection, it was demonstrated that the immune response elicited against the infecting strain could protect animals from re-infection with the homologous strain[16,17].

Interestingly, when experimental macaques were exposed to African prototype MR766 lineage of ZIKV, the animals were protected against re-infection with Asian ZIKV strain implicated in the recent outbreaks in Yap, French Polynesia and the Americas. This signifies that vaccine may be developed with a broader immunity. The difference in amino acid sequence or structural heterogeneity had the least impact on antibody pool present in ZIKV immune sera from mice as there exists only one ZIKV serotype and immunization with single lineage could elicit immunity against all lineages[18,19]. At present three different ZIKV lineages viz. Asian, East African (MR766 prototype cluster) and West African (Nigerian cluster) are circulating globally[20-22]. All the three ZIKV lineages possess highly-conserved region in their E glycoprotein with similar interacting profiles and immunological properties.

Several vaccine strategies are being employed in direction of constructing a vaccine against ZIKV. Some of the examples are listed below.

Inactivated ZIKV vaccine: Inactivated flaviviral vaccines are available for JEV, TBEV8 and Kyasanur Forest disease. It required multiple shots of immunization and high viral protein content is require to elicit sufficiently protective antibody titre. The development of an inactivated ZIKV vaccine with the

African strain MR 766 has been reported. in AG 129 mice lacking type I and II interferons 100% efficacy is noticed with double doses of the vaccine by challenging with MR 766 (homotypic) and FSS 13025 ZIKV (heterotypic) strains[23,24]. The licensed JEV vaccine requires approximately ~6 µg purified, inactivated JEV proteins and TBEV8 requires 3 µg inactivated TBEV proteins mainly adjuvanted with aluminum salts. This vaccination is sufficient to provoke immunity; lasting for 3-5 years[25]. Other potentiating adjuvants with purified and inactivated ZIKV proteins might be helpful in achieving protective immunity.

Live attenuated flavivirus vaccines: Live attenuated vaccines (LAV) provide protective immunity by eliciting both the humoral as well as cellular immunity. Though, these vaccines are protective but there is always a risk of reversion to the virulence. The principle for the development of vaccine against West Nile fever has been employed for ZIKV vaccine development too; and by that way a live attenuated vaccine has been developed. Licensed chimeric recombinant LAVs, based on YF 17D vaccine virus backbone have been developed for JEV and DENV, while replacing YF 17D prM/E genes with those of JEV and DENV, respectively[26-28]. A similar strategy may be employed for ZIKV vaccine development too.

Modified mRNA based vaccines: Lipid nanoparticle-encapsulated nucleoside modified mRNA (mRNA-LNP), encoding prM and E glycoproteins of a ZIKV from 2013 outbreak, was able to elicit a protective immune response in mice against ZIKV challenge[29]. The mRNA vaccines have been developed protecting rodents against ZIKV infection. Also, in non-human primates, mRNA-LNP elicited a durable immune response against ZIKV and thus appears to be a putative vaccine candidate in the near future[29,30].

DNA vaccine: Recently, immunization with plasmid DNA, encoding the pre-membrane (prM) and Envelope (E) protein has been found successful in protecting mice from a lethal challenge with ZIKV[31,32]. The protective immunity mounted in ZIKV-challenged mice was due to the induction of E protein specific antibodies. While, in rhesus macaques model, partial success has been obtained using inactivated ZIKV and DNA vaccine. The experimental successes provide hope to prevent ZIKV infection in humans as well[33]. Several pharmaceutical firms have already claimed the success of developing ZIKV vaccine. A DNA vaccine, GLS5700, has entered phase I trial; which is delivered subcutaneously[19]. Two other recent DNA vaccines developed, viz. VRC5283 and VRC5288, targeting prM and E proteins have been found protective in studies among monkeys against ZIKV challenge[34]. DNA and subunit vaccines may not be that much beneficial in endemic areas due to poor immunogenic potential, even if they induce strong immune responses in naïve flavivirus infected populations. Investigations exploring the cross-reaction between the already existing immunity and immunity against newly developed vaccines would be of interest and useful for researchers involved in studies related to Zika virus[35,36].

Virus-vectored vaccines: Virus-vectored (adenovirus serotype 5-vectored vaccine- Ad5.ZIKV-Efl) vaccine has also been developed and is under clinical trials[37,38]. There are ongoing researches to develop genetically engineered vaccine[39-41]. Prototype subunit and adenoviral based vaccine (that encodes the envelope gene of ZIKV) has also been developed[38]. In an interesting study, recombinant Vesicular Stomatitis Virus (rVSV) expressing ZIKV envelop protein (ZENV) (full length) has been constructed and in murine models such rVSV-Zikv construct has shown higher immunogenicity[42]. Adenoviral-based Zika vaccines comprising envelope gene (E) fused to the T4 fibritin fold on trimerization domain demonstrated 100% protection in C57BL/6 mice[38].

Recombinant subunit vaccines: Robust immunity to specific antigenic epitopes. Cryoelectron microscopy revealed similar overall structure of ZIKV virions with that of DENV[43]. Recombinant envelope gene (E) of ZIKV fused to the T4 fibritin foldon trimerization domain (Efl), delivered through carboxymethyl cellulose microneedle array (MNA) were partially protected the mice pups against lethal viral challenge[38].

Computer aided vaccine designing: Since there is no approved vaccine for preventing ZIKV infections, the use of vaccinomics could help to discover appropriate vaccine candidate to induce the effective immune response[44]. Computer aided vaccine designing has also been recently attempted by targeting the E, NS3 and NS5 proteins of ZIKV that can pave the path towards development of synthetic peptide vaccine[45]. The antigens having similar ISM value (a virtual spectroscopy technique to determine protein-protein interactions frequency), are immunologically cross reactive. Similar frequency component (0.295) is present in hemagglutinin subunit 1 (HA1) of pdmH1N1 influenza virus and ZIKV E protein, indicating that antibodies elicited against the H1 protein of pdmH1N1 influenza virus can neutralize ZIKV and might affect virus entry in the cell. Thus, it has also been

proposed that seasonal influenza vaccine with a pdmH1N1 component can be employed to check the ZIKV spread till the development of any specific vaccine against this virus[46,47]. This shift in the field of vaccine development from classical methods, where vaccine production was based on isolation and inactivation of an infectious agent, has grown to include individual host genetic differences in mind while designing vaccine candidate[48].

Further, a thorough understanding of the host immune system might help in designing highly effective vaccines. All this is possible using the reverse immunology, system biology, immune profiling, advanced bioinformatics, mathematical and computational modeling[49,50]. Immunoinformatics can help to predict both linear and conformational B-cell epitopes and the Cytotoxic T-Lymphocyte (CTL) epitopes. Further, immunogenic CTL epitopes can be analyzed for their MHC antigen presentation and their stability by molecular dynamics study. In a study of Mirza *et al.*[45], around 15 conformational CTL epitopes were used to dock with three MHC I proteins and conditions were simulated for their interactions. These results might present preliminary set of the peptide for use in generation of the future peptide based vaccine. Certain peptides such as QTLTPVGRL (MHC class I) and IRCIGVSNRDFV (MHC class II) have been elucidated to be highly conserved antigenic T cell epitopes of ZIKV[51].

An illustration describing the progress and advances in developing different types of Zika virus vaccines is presented in Fig. 1. An overview of some potential vaccine candidate's is presented in Table 1.

Advances in developing effective, safer and novel vaccines need to be explored to their full potential for countering Zika fever. These include DNA vaccines, edible vaccines, vector vaccines, protein/peptide vaccines, reverse genetics-based vaccines, Virus Like Particles (VLP), gene-deleted mutant vaccines, immunomics based vaccines and computer-aided vaccine designing[52-54]. Use of immunoadjuvants like Toll Like Receptors (TLR) agonists and other newer adjuvants as well as vaccine delivery systems including nanoparticle-based delivery may be exploited for enhancing vaccination immunity and desired level of protection against ZIKV. The advances in understanding the immunity against ZIKV and identification of various vaccine

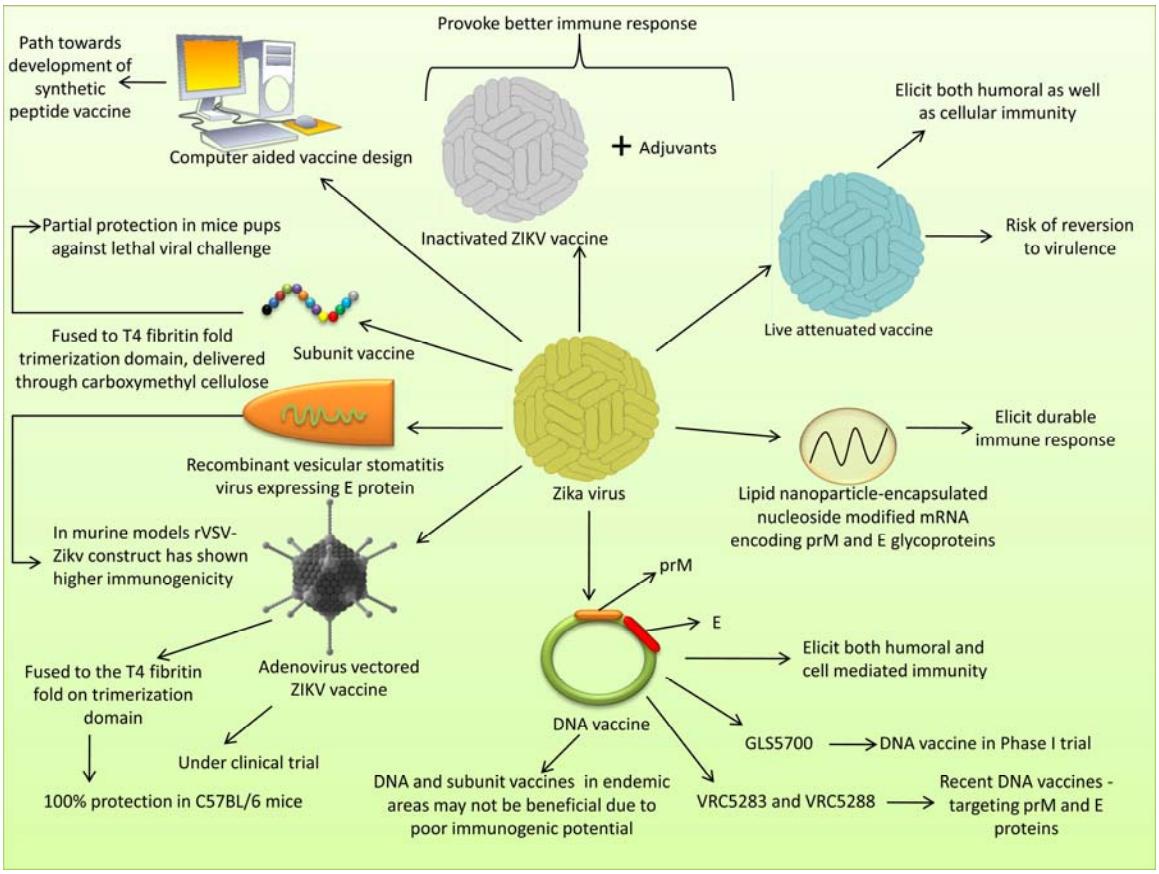

Fig. 1: An overview on the progress and advances in developing different types of zika virus vaccines

Table 1: Different candidate vaccines available or in clinical trial or under development for ZIKV prophylaxis

Candidate name	Therapeutic modality/description	Modus operandi	Advantages	Inventor and collaborator
GEO-ZM05	Modified Vaccinia Virus Ankara (MVA) (replication deficient attenuated pox viral vector) based Virus-like particle (VLP) technology	Pre-membrane and Envelope (prME) viral antigens assemble into VLPs inside the vaccinated (VLPs have been demonstrated inside the cells they formed as well as secreted in extracellular fluid)	Elicit both humoral and cell-mediated immune response and effective in single dose and as prime-boost vaccines	GeoVax Labs, Inc., Centers for Disease Control (CDC), the University of Georgia and Emory University
ZIK-80E	Subunit vaccine technology	Insect cell line produce glycosylated recombinant proteins adjuvanted with Alhydrogel or proprietary adjuvant	Elicit humoral immune response	Hawaii Biotech (Honolulu, Hawaii)
GLS-5700	Synthetic DNA vaccine (GLS-5700) encoding for encoding for pre-membrane and envelope (prME) proteins (1 mg plasmid DNA/dose)	DNA immunotherapy, plasmid DNA vaccine administered with the CELLECTRA®-3P, Inovio's proprietary intradermal DNA delivery device	Protective antibody and therapeutic T cell responses	Inovio Pharmaceuticals and GeneOne Life Science with academic collaborators from the US and Canada
NI.LV-ZIK	Self-inactivating, non-integrating lentivirus vector infecting both dividing and quiescent cells	PreM/E antigen	Stable expression of protein and humoral and cell-mediated immune response	Institut Pasteur, France
ZIKV EnvD vaccine	Nanoparticle vaccine	Recombinant nanoparticle ZIKV envelope dimmers expressed as Baculovirus-Sf9 insect cell-derived recombinant nanoparticles adjuvanted with Matrix-M™ adjuvant	Elicitation of protective levels of neutralizing antibodies	Novavax, USA
Replikins Zika Vaccine and Bocker	Trivalent ZIKV-DENV-JE Replikins synthetic blocker vaccine	Synthetic peptides	Humoral immunity	Replikins Ltd. And Boston University School of Medicine
--	YF 17D strain of yellow fever virus	PreM/E gene substituted in Live-attenuated vaccine strain attenuated by passaging in embryonated eggs	Humoral and cell mediated immunity	Bio-Manguinhos/Fiocruz, Brazil
Butantan ZIKV	Inactivated virus vaccine	Killed purified whole virion candidate	Humoral immunity	ButantanInstitute (São Paulo, Brazil)
ChAdOx1-Zk	Simian adenoviral vectors	Structural antigens of the Zika virus	Weak antivector immunity and induce robust immune responses Adjuvants not required to stimulate strong immune responses making it superior choice over VLPs Humoral and cytotoxic T cell response	Jenner Institute (Oxford, UK)
Chimerivax-Zika	Backbone of YF 17D strain of yellow fever virus	Non-structural genes	Humoral and cell mediated immunity	Sanofi Pasteur (Lyon, France)
MV-Zika	Measles vaccine as a vaccination vector	Antigens inserted in measles vector- not disclosed	Zika antigens presented directly to potent APCs (macrophages and dendritic cells) triggers powerful, antigen-focused immune response Confer long-term immunity as does the measles vaccine	Themis Bioscience (Austria)
ZIKAVAC	Inactivated vaccine Recombinant vaccine	Inactivated purified virus as priority project Information unavailable	Humoral immune response Cell-mediated response	Bharat Biotech, India
Zika virus purified inactivated vaccine (ZPIV)	-Inactivated Vaccine	-Inactivated purified virus.	Induces neutralizing antibodies against the virus	Walter Reed Army Institute of Research (WRAIR)

candidates gives hope that this viral disease can be eradicated in the near future[37,55,56]. More insights and understanding of ZIKV pathogenesis, molecular and genetic analysis would help in discovering effective vaccine candidates for designing and developing protective and safer vaccines to counter ZIKV.

Factors influencing development of zika virus vaccine: Several factors affect the efficacy and design of a vaccine candidate. ZIKV is a member of flavivirus, which represents some unique phenomenon, greatly affecting the immune response.

Original antigenic sin: Francis Jr.[57] first time described the original antigenic sin during influenza exposure. Subsequent contact with closely related viral variants resulted in activation of better immune response to the first exposed variant. So, every annual encounter with influenza virus leads to reactivation of memory immune response against conserved epitopes results in predominant immune response to the present virus. But, the immune response against these conserved epitopes may not be sufficient and ineffective while neutralizing by non-conserved antigen domains. Dengue virus follows the principle of original antigenic sin[58-60]. Halstead *et al*.[58] reported that patients infected with various dengue virus serotypes showed increased neutralizing antibody titers against first exposed serotype when compared to subsequent exposed serotypes. However, the information regarding the original antigenic sin during Zika virus infection still has not been explored. However, immunization with African prototype protects the animals, when challenged with Asian ZIKV strain depicts the less likelihood of the antigenic sin. The vector that transmits the Zika virus is same for other flaviviruses like dengue, Usutu and yellow fever viruses. The chance of already present antibodies specifically developed against other flaviviruses may prevent the induction of maximum adaptive immune response against Zika virus is hypothetical; this should be explored further, because it might have significant impact in the development of vaccines against Zika virus[59,61,62].

Antibody dependent enhancement: Research on development of vaccine for dengue virus has been going for many years unsuccessfully due to the more complexity of the virus. Dengue virus has four different serotypes and earlier infection due to one serotype results in augmentation of severity and pathogenicity of later infection with different serotype[63]. Antibody Dependent Enhancement (ADE) is the assumed mechanism responsible for improved pathogenicity of this disease[64]. ADE phenomenon occurs when viruses bind to non-neutralizing antibodies and the immune complex is subsequently binds to the Fc-receptor of phagocytic cells. These non-neutralizing antibodies promote the replication of virus, which is highly conducive to dengue virus infection results in enhanced infectivity[65,66].

To overcome such issues, crores of money and tremendous hard work from various researchers resulted in development of effective vaccines to induce optimum immune response against all the serotypes of dengue virus. Currently, various vaccine clinical trials are undergoing to explore the possible interaction between pre-existing antibodies and vaccine mediated immune response[64]. The involvement of ADE in augmenting the infectivity of other flaviviruses needs to be explored completely, due to its multifaceted risk[67]. Currently, Zika virus does not have various serotypes as that of dengue virus. However, Zika virus is closely related to other flaviviruses and cross-reactive antibody may have the risk of aggravating the secondary flavivirus infections through ADE[64]. A recent research has reported that antibodies against dengue virus promoting the Zika virus infection *in vitro*, alarming the involvement of ADE in the pathogenesis of Zika virus[68]. Further, recent researches should target whether vaccines and/or antibodies against Zika virus can induce ADE resulting in subsequent enhancement of flavivirus infection. In addition, investigators should target whether pre-existing antibody against other flaviviruses will cross-react with Zika virus resulting in enhanced infectivity will be of great value. In this context, it must be mentioned that there is also possibility that if there is promotion of ADE of Zika virus caused by antibodies against Dengue virus then antibodies against Zika virus can also augment the Dengue hemorrhagic fever or Dengue shock syndrome. Such possibility must be taken into consideration and requires further testing in animal models (for Zika vaccine) before performing any human trials in areas where there is prevalence of both the viruses[65,67,69]. To conquer ADE, antibodies may be engineered to have such mutations, preventing the binding of immune complex to the Fcγ receptors. One such mutation is LALA mutation, where leucine residue is changed with alanine and resulting antibodies are able to prevent ADE[70].

Lessons learned from previous episodes

Guide in a better way: While dealing with a new pathogen, which is little known, it is very difficult to do SWOT analysis for that pathogen. However, in most of the cases cross-reactive antibodies can be advantageous rather than harmful.

Johnson *et al.*[71] reported that individuals vaccinated previously with yellow fever or Japanese encephalitis virus resulted in enhanced antibody levels against these viruses while encountering natural infection with WNV; however earlier immunizations had no protective response on the persons infected with WNV. Izurieta *et al.*[72] reported that pre-existing antibodies against dengue virus, reducing the severity of yellow fever pathogenesis, indicating that cross-reactive immune response resulted in partial protection. Such reports may promote confidence that infection with various flaviviruses may resulted in beneficial of neutral effect rather than detrimental. However, it may not be true in all cases and due care should be taken while handling Zika virus.

CONCLUSION

Even though around eighty years back, the development of flavivirus vaccine begun; however as far as ZIKV is concerned uncertainty prevailed till few years back regarding vaccine development. But as there is urge to intervene in order to blunt the recent ZIKV impact on human health globally so there has been rapid progress in the understanding of biology, pathogenicity as well as immunity to ZIKV infection. Thus, at present we must access technologies for preparing multiple vaccine platforms which can be tested against multiple diseases for safety as well as efficacy. As per the reports available with WHO, 18 different commercial and research organizations are involved in developing the vaccine against ZIKV. Advances in DNA vaccines, edible vaccines, vector vaccines, protein/peptide vaccines, reverse genetics-based vaccines, Virus like Particles (VLP), gene-deleted mutant vaccines, immunomics based vaccines and computer-aided vaccine designing need to be exploited to their full potentials. An efficient vaccine must be able to elicit sufficient protective immune response and free of side effects. While considering ZIKV vaccine ADE, also is an important phenomenon to take under consideration as sub-neutralizing antibodies may enhance ZIKV infectivity. Moreover, the relationship between the pathogenesis of ZIKV and exposure to flaviviruses (pre-existing) can be investigated by clinical studies both prospectively and retrospectively.

Several vaccines developed by commercial and research organizations are under clinical trial and soon it will be available for prophylactic and preventive purposes. There is also need to conduct further investigations in Stat2$^{-/-}$ mice, A129 (IFNAR$^{-/-}$) Mice, Swiss Jim Lambert (SJL) mice or Rhesus macaques, which are all approved animal models for evaluation of preventative candidate vaccine efficacy. All these ultimately will contribute further to the effort of developing ZIKV vaccine. The safe and efficacious ZIKV vaccine development will surely gain momentum if such coordinated efforts are conducted in proper population with appropriate control. Nevertheless, there are utmost requirements of sufficient resources in terms of infrastructure, funding and manpower along with commitment (long-lived) for producing effective and safe ZIKV vaccine in commercial basis. To fulfill such requirements, not only the Government but also private industries and academia must also come forward; which will ultimately help us to control the disease.

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SIGNIFICANCE STATEMENT

- Several upcoming vaccine development strategies which are being explored to curb Zika virus infection, an emerging viral pathogen having high public health concerns, are described in this review compilation. These include inactivated vaccines, live attenuated vaccines, modified mRNA based vaccines, DNA vaccine, virus-vectored vaccines, recombinant subunit vaccines, computer aided vaccine designing and immunoinformatics approaches
- Factors like antigenic sin, antibody dependent enhancement of virus pathogenicity and cross-reactive immune protection which have potential impact on efficacy of vaccine, have been discussed

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