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Current status, challenges and perspectives in the development of vaccines against yellow fever, dengue, Zika and chikungunya viruses

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ABSTRACT

Emerging and re-emerging viral infections transmitted by insect vectors (arthopode-borne viruses, arbovirus) are a serious threat to global public health. Among them, yellow fever (YFV), dengue (DENV), chikungunya (CHIKV) and Zika (ZIKV) viruses are particularly important in tropical and subtropical regions. Although vector control is one of the most used prophylactic measures against arboviruses, it often faces obstacles, such as vector diversity, uncontrolled urbanization and increasing resistance to insecticides. In this context, vaccines may be the best control strategy for arboviral diseases. Here, we provide a general overview about licensed vaccines and the most advanced vaccine candidates against YFV, DENV, CHIKV and ZIKV. In particular, we highlight vaccine difficulties, the current status of the most advanced strategies and discuss how the molecular characteristics of each virus can influence the choice of the different vaccine formulations.

1. Introduction

Currently, more than 500 arboviruses (arthropod-borne viruses) have been identified, out of which nearly 150 are associated with human infection (Lanciotti, 2016). The majority of these arboviruses belongs to the following viral families: *Peribunyaviridae* (*Oropouche orthobunyavirus*), *Nairoviridae* (genus *Nairovirus*), *Phenuiviridae* (*SFTS phlebovirus*), *Flaviviridae* [*yellow fever* (YFV), *dengue* (DENV), *Zika* (ZIKV), *Japanese encephalitis* (JEV), *West Nile* (WNV) and *Tick-borne encephalitis* (TBEV) viruses] and *Togaviridae* [*chikungunya* (CHIKV) and *Venezuelan equine encephalitis* (VEEV) viruses] (Blitvich, 2016; ICTV, 2016).

Recently, outbreaks of YFV, DENV, CHIKV and ZIKV have been reported mostly in tropical and subtropical regions of the planet: DENV (2017) in Côte d'Ivoire (DENV-1, -2 and -3) and Sri Lanka (DENV-2) (WHO, 2017a); CHIKV (2017) in France (WHO, 2017b); YFV (2017) in Brazil and Suriname (WHO, 2017c); and ZIKV (2017) in India (WHO, 2017d). Among them, ZIKV has emerged recently as one of the most important arboviruses for public health. This is particularly due to the increase in the number of ZIKV outbreaks, occurrence of congenital ZIKV infection syndrome (ZVCS) and the increasing list of species of culicidae in which the virus has been isolated (e.g., *Mansonia uniformis*, *Culex perfuscus* and *Anopheles coustani*) or that have demonstrated vector competence (*Aedes hensilli*, *Ae. vexans* and *C. quinquefasciatus*) (Benelli and Romano, 2017).

The (re-) emergence and persistence of these arboviruses in the human population depend on multiple events, such as the globalization (Imperato, 2016), presence of vectors in the new environments favorable for their proliferation (Liang et al., 2015), absence of specific antiviral therapies and limitations in the availability of vaccines (CDC, 2017; Parashar and Cherian, 2014; Dawes et al., 2016), and the viral adaptation to the urban settings (Blitvich, 2016).

The viral control strategies should use adequate vector control programs in combination with vaccination, performing an integrated vector management (IVM) (Benelli and Beier, 2017; Benelli and Mehlhorn, 2016; Ishikawa et al., 2014; Zara et al., 2016). Vector control policies aimed at decreasing viral transmission, however often face obstacles, for example, chemical insecticides resistance (WHO, 2016), uncontrolled urbanization (Liang et al., 2015) and ethical limitations concerning the use of transgenic vectors (Resnik, 2014). On the other hand, some control measures, such as the use of plant-borne metabolites with mosquitocidal activity against *Aedes*, *Ochlerotatus*, *Anopheles* and *Culex*, and the symbiont-based mosquito control can be a powerful tool to combat mosquito vectors (Benelli and Mehlhorn, 2016).

The strategy of controlling other arthropod-borne diseases, such as malaria, interestingly also ranges from vector control actions to mass

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Table 1
General aspects of licensed vaccines and most advanced vaccine candidates against yellow fever, dengue, chikungunya and Zika viruses.

Virus Family	Main difficulty	Vaccines						
		Licensed			Under development			
		Identification/seed	Manufacter[1]	Strategy	Identification/seed	Manufacter	Current status	Strategy
Yellow fever Flaviviridae	–	YFV-17DD	Bio-Manguinhos (Fiocruz)	Attenuation by passage in animal, tissue and cell culture	XRX-001	Xcellerex[2]	Phase I (Completed)	YFV-17D inactivated
		YFV-17D-204	Sanofi Pasteur Pasteur Institute Chiron/Novartis	Attenuation by passage in animal, tissue and cell culture	–	–	–	–
		YFV-17D-213	Federal State Unitary Enterprise of Chumakov Institute	Attenuation by passage in animal, tissue and cell culture				
Dengue Flaviviridae	Multiple serotypes	CYD-TVD	Sanofi Pasteur	Live attenuated chimeric	TV003	NIH/NIAID/Butantan Institute	Phase III (In progress)[3]	Live attenuated chimeric
					TDV	Inviragen/Takeda	Phase III (In progress)[4]	Live attenuated chimeric
Chikungunya Togaviridae	High virulence	–	–	–	TSI-GSD-218	USAMRIID/Salk Institute for Biological Studies	Phase II (Completed)	Attenuation by passages in cell culture
					VRC−CHKVLP059-00-VP	NIAID	Phase II (In progress)[5]	VLP
Zika Flaviviridae	GBS[10] Neurotropism ZVCS[11]	–	–	–	GLS–5700	Inovio	Phase I (In progress)[6]	DNA
					VRC 5288 (ZKADNA085-00-VP)	NIAID	Phase I (In progress)[7]	DNA
					VRC 5283 (VRC-ZKADNA090-00-VP)	NIAID	Phase I[8]/II[9] (In progress)	DNA

[1] Word Health Organization prequalified vaccine (Monath, 2005; Barret et al., 2017).
[2] Originally developed by Xcellerex. GE Healthcare acquired the intellectual property for the investigational product through its acquisition of Xcellerex in 2012. In 2016, PnuVax acquire GE's intellectual property. See at http://www.biopharminternational.com/ge-healthcare-sells-rights-inactivated-yellow-fever-vaccine-pnuvax.
[3] Completed in December 2022 (NCT02406729).
[4] Completed in December 2021 (NCT02747927).
[5] Completed in December 2017 (NCT02562482).
[6] In healthy adults: completed in December 2017 (NCT02809443)/in Dengue virus seropositive adults: completed in June 2018 (NCT02887482).
[7] Completed in December 2018 (NCT02840487).
[8] Completed in December de 2018 (NC T02996461).
[9] Completed in January 2020 (NCT03110770).
[10] Guillain-Barré Syndrome.
[11] Zika Virus Congenital Syndrome.

immunization. Although is not a viral agent, relevant progress has been made in the field of malaria vaccine. For instance, the RTS,S/AS01, the falciparum vaccine in the most advanced development, although conferring an immunity that rapidly declined in children, it has been recommended to control malaria in low-endemicity areas (Benelli and Beier, 2017; Gosling and von Seidlein, 2016).

Considering the factors outlined above, here we review the major aspects concerning the vaccinology of the contemporary arboviruses YFV, DENV, ZIKV and CHIKV. We have highlighted both difficulties and perspectives of vaccines for each target, the current status of development of more advanced vaccines and discuss how an understanding of the characteristics and molecular differences of these viruses could result in adequate choice for vaccine strategies (Table 1).

2. Yellow fever virus

The prototype vaccine YFV-17D was developed by an empirical attenuation of the African YFV Asibi strain isolated by passage in rhesus monkeys (Stokes et al., 1928). The Asibi strain was adapted to grow in mouse embryonic tissue, followed by culture in normal and denervated embryonic chicken tissues until a reduction in the viral neurotropism (Lloyd and Ricci, 1936; Theiler and Smith, 1937a). It has been suggested that the reduction in neuro- and viscera- tropism is due to the substitution of 32 amino acids and six nucleotides in the 3′ untranslated region (UTR) of the viral RNA (Hahn et al., 1987). This allowed the use of this strain in the first YFV vaccine (Theiler and Smith, 1937b).

Currently, there are six YFV vaccines based on YFV-17DD, YFV-17D-204 and YFV-17D-213 substrains that have been licensed by WHO: a) YFV-17DD (passage 286, Bio-Manguinhos/Fiocruz); b) YFV-17D-213 (passage 239, Federal State Unitary Enterprise of Chumakov Institute, Russia); c) YFV-17D-204 strain: YF-VAX (passage 237, Sanofi Pasteur, US), Stamaril (passage 235, Sanofi Pasteur, France), Amaril Stabilisé (passage 235, Institute Pasteur, Senegal) and ARILVAX (passage 235, Chiron/Novartis, UK) (Barrett, 2017; Galler et al., 1997; Monath, 2005).

Although YFV has three lineages (Eastern/Central Africa, West and South Africa) (Li and Yang, 2017) only one serotype has been described. This fact, together with the low mutation rate of YFV, is the main reason making the YFV vaccine one of the less laborious among those against arboviruses. Analysis of two howler-monkey YFV sequences during a recent outbreak in Brazil showed that in both cases the viruses had eight unique amino acid changes, which could influence their capacity to infect both vertebrate and invertebrate hosts (Bonaldo et al., 2017). In spite of the occurrence of some genetic and phenotypic changes, the YFV-17DD vaccine is currently used without reports of a decreased vaccine efficacy.

Although its efficacy has been demonstrated, few cases of neurological and viscerotropic diseases associated with administration of YFV attenuated vaccines have been reported. Consequently, YFV vaccines are not indicated to pregnant women, children under six years old, individuals with sensitivity to egg or chicken proteins and immunosuppressed individuals (e.g. individuals with thymus disease, with HIV and under immunosuppressive therapies) (Thomas, 2016).

Thus, alternative vaccine strategies based on inactivated virus, vaccinia virus vectors and DNA vaccines have been proposed to avoid the aforementioned adverse reactions and increase its safety (Maciel et al., 2015; Monath et al., 2011; Schäfer et al., 2011). For instance, an inactivated YFV-17D vaccine (XRX-001) protected mice, hamsters and monkeys against YFV and induced neutralizing antibodies in 100% of the subjects that received 4.8 μg of antigen in a phase I clinical trial (NCT00995865) (Monath et al., 2011). One DNA vaccine containing the complete envelope protein fused to the lysosomal-associated membrane protein signal 1 also conferred 100% protection against YFV in challenged mice (Maciel et al., 2015).

In two additional strategies, the YFV prM/E genes was inserted into the non-replicating modified Ankara or into the D4R-defective vaccinia virus, resulting in the MVA-YF and dVV-YF, respectively. These candidates led to a full protection against lethal challenge and a 100% survival rate after intracerebral administration of 1×10^7 $TCID_{50}$ to mice (Schäfer et al., 2011). Currently, MVA-BN-YFV is a vaccine candidate based on a version of attenuated MVA produced by the Danish company Bavarian Nordic in collaboration with The National Institute of Allergy and Infectious Diseases (NIAID) and is undergoing phase I trial (NCT02743455).

3. Dengue virus

Multiple DENV serotypes have been described, making the development of a vaccine more challenging and practically dependent on reverse genetic systems, as observed in the most advanced vaccines CYD-TVD (licensed) (Halstead, 2016), TV003 (Kirkpatrick et al., 2016) and TDV (Takeda, 2016). Notwithstanding the different vaccine strategies used, all of them must induce long-term protection for homotypic and heterotypic serotypes infection in order to hopefully minimize the chance of antibody-dependent enhancement (ADE) and increase vaccine safety. To complicate things further, prior exposure to ZIKV has shown to increase DENV-2 infections in rhesus macaques (George et al., 2017) and this brings implications regarding the safety of DENV vaccines, mainly in regions of co-circulation of these arboviruses.

The CYD-TVD (ChimeriVax-Dengue/Dengvaxia®) tetravalent vaccine was the first DENV vaccine licensed (2015) and is currently is approved in 19 countries (WHO, 2017e). CYD-TVD consists in a mix of chimeric attenuated viruses produced by replacement of prM/E YFD-17D proteins with wild-type (wt) prM/E from DENV PUO-359/TVP-1140 (DENV-1), PUO-218 (DENV-2), PaH881/88 (DENV-3) and 1228 (TVP-980) (DENV-4) (Guirakhoo et al., 2001).

During the phase IIb trial, a high vaccine efficacy was shown against DENV-3 (81.9%) and DENV-4 (90%), a moderate efficacy against DENV-1 (61.2%) and an absence of statistically significant efficacy against DENV-2 (59%). Concerning DENV-2, it is possible that the low vaccine efficacy was due to antigenic mismatch between the CYD-TVD wtDENV-2 and the DENV-2 circulating in Thailand (2009–2010) or between the CYD-TVD wtDENV-2 and the viruses responsible for the infection in the cohort (Sabchareon et al., 2012). This antigenic disparity between viruses of the same serotype suggests the importance to develop a DENV vaccine with a broad-spectrum of action ("universal DENV vaccine") or a "regionalized vaccine", adapting the vaccine composition to the currently circulating DENV strains in a determined area.

In Indonesia, Malaysia, Philippines, Thailand and Vietnam, the phase III trials have shown similar results when compared with phase IIb trials in Thailand. The observed prevention of infection was > 75% for DENV-3 and DENV-4, 50% for DENV-1 and non-statistically significant protection for DENV-2 (Capeding et al., 2014). Interestingly, the results were similar in Latin America: vaccine showed a high efficacy for DENV-3 and DENV-4 (74% and 77.7%), a moderate efficacy for DENV-1 (50.3%) and a low efficacy for DENV-2 (42.3%) (Villar et al., 2015). In addition, a recent study reported that DENV-2 infections lead to a higher proportion of severe disease than DENV-1 and DENV-4 (Vicente et al., 2016). Thus, these findings about a diminished protection by CYD-TVD against DENV-2 raise important questions about the future of this vaccine.

Fulfilling the safety and non-ADE prerequisites, individuals vaccinated in Asian and Latin American countries did not show adverse reactions compared with the placebo group. However, unexplained higher incidence of hospitalization caused by DENV among children younger than nine years old three years after phase II and III have been reported (Hadinegoro et al., 2015).

Another approach combines two attenuation strategies: nucleotide deletion within the 3′UTR (Δ30 and Δ30/31) of DENV (followed or not of additional attenuation by passages in SCID-HuH-7, mice and in rhesus macaques) and prM/E chimerization between viruses from

different serotypes, resulting in eight monovalent vaccine prototypes. Of all these, it was possible to select six prototypes that were used in five different tetravalent (TV) admixtures (TV001-TV005) for vaccine efficacy evaluation in humans (Durbin et al., 2011).

Among them, TV003 (composition DEN1Δ30, rDEN2/4Δ30, rDEN3Δ30/31 and rDEN4Δ30) is in the most advanced developmental status, phase III trial. The phase I report indicated 100% protection when challenged with rDEN2Δ30 and 100% seroconversion for DENV-2, -3, -4 and 91.7% for DENV-1 (Kirkpatrick et al., 2016).

The TDV vaccine (DENVax), similarly to the TVs vaccines mentioned above, is a combination of chimeric and attenuated viruses (Osorio et al., 2011). A DENV-2 strain isolated from a patient in Thailand was attenuated after 53 passages in primary dog kidney cells, resulting in the PDK-53 strain. The main mutations responsible for this attenuation were placed in the 5′UTR and in the non-structural proteins NS-1 and NS-3 (Butrapet et al., 2000; Osorio et al., 2011). For TDV vaccine, a DENV-2 PDK-53-V variant infectious clone was used to immunize against this serotype. Similarly to CYD-TVD, the recombinant DENV-2 PDK-53-V variant was modified by replacement of their prM/E proteins with those from wtDENV-1 16007, wtDENV-3 16562 and wtDENV-4 1036 (Osorio et al., 2011). The Phase II trial showed a seropositivity > 95% for DENV-1, -2 and -3 and 72.7–100% for DENV-4 (Sirivichayakul et al., 2016). The TDV is presently undergoing phase III trial (NCT02747927).

Despite different strategies, all DENV vaccines reviewed above are based on completely attenuated viruses or on prM/E proteins as target molecules. The prM/E proteins are highly immunogenic and the presence of conserved regions within their sequences might entail cross-reaction between antibodies against viruses with distinct serotypes. This could lead to ADE and disease complications (Chotiwan et al., 2014; Smith et al., 2015).

Alternatively, some vaccines based on the soluble extracellular protein NS-1 of DENV have shown promising results, especially against DENV-2 (Costa et al., 2006; Wu et al., 2003). In addition, the soluble NS-1 protein acts as a Pathogen-associated molecular patterns (PAMP) ligand to Toll-like receptor-4 (TLR-4) and triggers an inflammatory response. Since such response contributes to the vascular leak present in dengue patients (Modhiran et al., 2015), the possibility of anti-NS-1 DENV vaccines is strengthened. As a possible disadvantage of NS-1 as a vaccine target, anti-NS1 antibodies could cross-react with host proteins, inhibiting platelet aggregation (Cheng et al., 2009) and leading to endothelial cells apoptosis (Lin et al., 2003).

4. Zika virus

Distinct ZIKV lineages (African and Asian) have been reported, but similarly to YFV and CHIKV (discussed below), only one ZIKV serotype has been described. Consequently, the immunological response against one viral strain may protect against all other ZIKV circulating strains. Multiple sequences alignment of ZIKV envelope glycoprotein E (viral target for neutralizing antibodies) of African and Asian lineages showed a similarity > 95% of amino acid identity. In addition, it has also been shown that antibodies from mice infected with either African or Asian ZIKV are able to neutralize equivalently homologous and heterologous ZIKV (Dowd et al., 2016a).

An important obstacle for the ZIKV vaccine is the ZVCS (Lucey et al., 2017). The requirement that ZIKV vaccines should stimulate enough immunological memory as to prevent fetal infection is perhaps the most important concern about a ZIKV vaccine. This feature does not exist in relation to other arboviruses. Other aspects to be considered for a ZIKV vaccine are the ZIKV neurotropism (Mlakar et al., 2016), especially in the case of an attenuated vaccine, and the role of the immune response to ZIKV in the development of the Guillan-Barré Sydrome (GBS) (Parra et al., 2016).

Regarding a sera-cross-reactivity between ZIKV and DENV, previous studies showing ADE *in vitro* (Dejnirattisai et al., 2016; Stettler et al., 2016) have raised concerns regarding DENV and ZIKV vaccination strategies (Fernandez and Diamond, 2017; Marston et al., 2016; Silva Jr. et al., 2017). However, recent studies performed in rhesus monkey and humans suggest that previous immunization for DENV does not result in a more severe zika disease (Pantoja et al., 2017; Terzian et al., 2017). Another study has also shown that DENV infection does not induce a persistently high level of ZIKV cross-reactive neutralizing antibodies (Collins et al., 2017). Therefore, ADE does not seem to be an issue for ZIKV vaccines concerning previous exposures to DENV.

Currently, 40–60 institutions around the world are working on almost 20 ZIKV vaccine candidates with different strategies: inactivated viruses, virus-like particles (VLP), recombinant viruses and DNA vaccines (Barrett, 2016; Dawes et al., 2016; Durbin, 2016). Among them, three different DNA vaccines are on clinical trials: one from Inovio (GLS-5700) (Muthumani et al., 2017) and two from the NIAID: VRC-ZKADNA085-00-VP (VRC 5288) and VRC-ZKADNA090-00-VP (VRC 5283) (Dowd et al., 2016b).

Similarly to the most advanced DENV vaccines (Durbin et al., 2011; Guirakhoo et al., 2001; Osorio et al., 2011) and the DNA YFV vaccine under development (Maciel et al., 2015) these ZIKV DNA vaccines targeted prM/E proteins. In summary, the vaccine plasmids express a consensus ZIKV prM/E proteins from several ZIKV isolated in humans between 1952 and 2015 (GLS-5700) (Muthumani et al., 2017), sequences of prM/E H/PF/2013 ZIKV strain (French Polynesian) with the prM signal sequence substituted with the analogous JEV region to improve the protein expression (VRC 5283) (Dowd et al., 2016b) and the VRC 5288 that matches VRC 5283 except for 98 amino acids in the E N-terminal domain, which comprise the stem and transmembrane regions, substituted with the corresponding JEV sequences to increase the secretion of virus-like subviral particles (Dowd et al., 2016b).

Besides differences in prM/E proteins, ZIKV DNA vaccines differ on the phase I vaccine-targeting group. VRC 5288 (NCT02840487) and VRC 5283 (NCT02996461) aim to evaluate the safety and immunogenicity only in health adults, while GLS-5700 targets healthy (NCT02809443) and seropositive DENV adults (NCT02887482). Preliminary results suggest that VRC 5283 induces a stronger immune response than VRC 5288, and it is currently being submitted to a phase II trial (NIH, 2017) (NCT03110770).

The requirement for an induction of maternal immunity protecting also the fetus against ZVCS has been reported in a recent animal study. Two vaccines, one based on a modified mRNA encoding prM/E ZIKV and another based on an attenuated ZIKV strain encoding an unglycosylated NS-1 protein, have shown to protect against placental and fetal damages (Richner et al., 2017).

Thus, considering the current advances in the knowledge of molecular virology field, especially for flavivirus, the number of different effective approaches used on behalf of development of a vaccine against ZIKV in the last year and the lack of evidence of ZIKV multiple serotypes is probable that an effective ZIKV vaccine might be available in the next years.

5. Chikungunya virus

Similarly to the existence of distinct lineages of ZIKV and YFV that does not result in different serotypes, CHIKV presents a single serotype although four lineages have been described to date (West African, East/Central/South African, Asian and Indian Ocean) (Sahadeo et al., 2017). This suggests that vaccination against CHIKV may well provide cross-protection against all CHIKV strains (Smalley et al., 2016).

However, the high virulence of CHIKV (Staples et al., 2009) represents an important obstacle to vaccines development. Consequently, CHIKV vaccine candidates should seek an equilibrium between virulence and immunogenicity so that one of these parameters does not compromise the other and simultaneous protection and safety of vaccinated individuals is ensured. For instance, although live-attenuated vaccines are often highly immunogenic, they are less secure than

inactivated viruses. On the other hand, inactivated vaccines commonly need multiple doses and boosters (Erasmus et al., 2017).

More than 18 CHIKV vaccine candidates, ranging from inactivated and live-attenuated virus to DNA vaccines (Erasmus et al., 2017; Smalley et al., 2016) are presently under study. The most advanced formulations are TSI-GSD-218, completed phase II (Edelman et al., 2000), and the VRCCHKVLP059-00-VP, which is at phase II (NCT02562482).

TSI-GSD-218 is based on an empiric attenuated strain, as well as the licensed YFV vaccines. The CHIKV strain (15561) was isolated from a patient's serum during the 1962 CHIKV outbreak in Thailand. It was passed 18 times in MRC-5 cells, with the criteria to select the vaccine strain (CHIKV 181/clone 25) being: small plaque size, temperature sensitivity, decreased suckling mouse, reduced monkey virulence, induction of neutralizing antibodies and protection against challenge (Levitt et al., 1986). At the end of the phase II trial, 98% of the vaccinated individuals had neutralizing antibodies, 85% remained seroconverted one year after immunization and 8.47% (5/59) showed a temporary arthralgia (Edelman et al., 2000).

A comparison of CHIKV 181/clone 25 and its parental strain AF15561 identified five amino acids differences. Reverse genetic assays suggested that two mutations in the protein E2, T12I and G84R, were responsible for the attenuation observed. In addition, these mutations were found to be naturally reversed (Gorchakov et al., 2012), which may explain the vaccine adverse reactions mentioned above during the phase II trial.

The VLP vaccine (VRC-CHKVLP059-00-VP) was obtained by transfection of a plasmid expressing C and E proteins from the CHIKV 37997 strain. This vaccine stimulated the production of neutralizing antibodies against the protein E from different CHIKV strains and protected monkeys after challenge using a high virus dosage (Akahata et al., 2010). Further tests in humans have also shown the immunogenic efficacy of the vaccine. Moreover, 36% (9/25) and 40% (10/25) of vaccinated individuals showed mild local reactogenicity (pain of tenderness) and mild systemic reactogenicity, respectively. There were no reports of arthralgia after vaccination (Chang et al., 2014). VRC-CHKVLP059-00-VP is presently ongoing phase II trials (NCT02562482).

Recently, a promising vaccine based on a the EILV/CHIKV chimera was reported [74]. This recombinant virus with the backbone of Eilat virus (EILV) and encoding CHIKV structural proteins was observed to induce a robust immunity in nonhuman primates. Since EILV is an insect-specific alphavirus, the chimeric EILV/CHIKV virus is defective for productive replication in vertebrate hosts, thus providing a high degree of safety (Erasmus et al., 2017).

6. Conclusion

Although the emergence and re-emergence of the arboviruses are recognized as multicausal events, vaccination is still one of the most efficient tools for controlling and preventing the infection. The characteristics and molecular peculiarities of each virus must be well understood in order to develop the appropriate vaccine strategy as well as to define better control and prevention policies.

The existence of discordant results regarding the occurrence of ADE between DENV and ZIKV obtained by *in vitro* and *in vivo* experiments should be exhaustively investigated before the introduction of DENV and ZIKV vaccines in areas of co-circulation. If ADE between ZIKV and DENV is confirmed, some ways to overcome it would be, as discussed by Silva Jr. et al. (2017), the identification of DENV- and ZIKV- specific neutralizing epitopes or the simultaneous immunization against these viruses by mean of a DENV-ZIKV universal vaccine or a paired administration of an individual vaccine against DENV and ZIKV.

A safe vaccine against all DENV serotypes is still a challenge. Recently, by reasons still not fully understood, WHO has reported an excess of cases of severe dengue in the vaccinated seronegative population (WHO, 2017e). However, additional DENV vaccines based in DENV chimeric are in phase III trials and are expected to be licensed in the near future. About YFV vaccines, although the available vaccines are effective, other alternatives, such as DNA vaccines, should continue to be developed benefiting the groups that current YFV vaccines have not been recommended.

Efforts have been concentrated in the development of a safe vaccine against CHIKV and ZIKV. CHIKV infections are often marked by considerable morbidity and the vaccines for their prevention, especially those of live-attenuated virus, which may revert to virulence, need to be improved to minimize adverse effects, mainly the arthralgias. Despite the peculiar inconveniences of ZVCS and the risk of GBS, as well as ZIKV-related neurotropism, promising new results are coming out in the field of anti-ZIKV DNA vaccines. Finally, current advancements concerning ZIKV and CHIKV vaccines lead us to believe that both will probably be available soon.

Declarations of interest

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