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OVERVIEW

Challenges and solutions in the development of vaccines against emerging and neglected infectious diseases

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ABSTRACT

Emerging and emergent infectious diseases (EIDs) represent a significant and growing cause of morbidity and mortality with increased potential for pandemics due to globalization and international trade. Challenges remain to the approach toward vaccine development for EIDs. This Special Feature explores areas related to vaccine development and testing, including unique challenges posed in the developing world. Vaccines against multiple pathogens spanning a number of viral families are explored with respect to past activities through to future commercialization. Cost drivers balanced against clinical need are discussed and unique challenges posed by rare diseases are considered.

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Introduction

Emerging and emergent infectious diseases represent a significant and growing cause of morbidity and mortality. Historically, the global burden of disease has been disproportionately borne by economically disadvantaged countries in Africa, South America and Asia. Parasitic diseases such as malaria, hookworm, and schistosomiasis and bacterial illnesses including *Mycobacterium tuberculosis* and *Chlamydia trachomatis* affect a large fraction of the world's population and have dominated as disease concerns. Over the past 25 years, there has been increasing appreciation of newly emergent and re-emergent infectious viral diseases, as well as pathogens such as Zika virus (ZIKV) causing previously unrecognized complications.[1] Globalization, international travel, and intercontinental commerce have all increased the potential for microbial spread, resulting in global epidemics beyond their respective regions of origin caused by highly fatal infectious agents including severe acute respiratory syndrome (SARS) coronavirus, Middle East respiratory syndrome coronavirus (MERS-CoV), and Ebola virus (EBOV).

In this Special Feature of Human Vaccines and Immunotherapy, the framework and challenges to prevent both old and newly recognized infectious diseases are explored. A detailed assessment of the biology and prevention of a number of pathogens provides conceptual approaches to pathogens spanning the gamut from less well-known viruses and relatively rare viruses with significant morbidity to World Health Organization (WHO) targeted infectious diseases. Given the wide array of viral vaccines that have been developed successfully, the responses to the many recent emerging infectious diseases have sparked considerable interest in molecular-based vaccine platforms based on recombinant proteins and nucleic acid or viral-vector expressed antigens.[1,2] Practical considerations regarding clinical trial conduct, clinical trial design, and cost of development all temper the path to regulatory approval and commercialization.

Since emerging diseases affect mostly underdeveloped countries, the development and manufacturing programs of vaccines for emerging diseases are generally much more challenging from a financial and business perspective than those for available vaccines of diseases in developed countries. Most of the emerging-disease vaccines lack an available commercial market and thus can be sold only at very low prices or are provided for free using financing from donor non-governmental organizations (NGOs) – as a result, attracting full investment from a commercial company may not be guaranteed. On the other hand, the ability to charge a price sustainable in developed countries as well as a clearly identifiable commercial market enables a clear business plan with return on investment that attracts commercial companies to bring developed-market vaccines to market rapidly and efficiently through well-established product development plans. This means that the development plans for emerging-disease vaccines need to be designed and implemented in different and sometimes novel ways.

Framework considerations for vaccine development

Three principal factors drive the development of vaccines and therapies for emerging infectious diseases: need, availability and cost. Need, either globally or locally, can be enumerated with regard to the number of individuals affected versus the impact of the disease, either acute or chronic. Availability depends on suitable arrangements for commercial manufacturing at a sufficient scale that enables sufficient and affordable supply that enable the manufacturer to cover costs and make a suitable return on investment. Cost of development and the return on investment necessarily drives the question

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of whether activities are more likely to be pursued by industry or subsumed within the global public health structure. A previous analysis by Gouglas et al. estimated the costs (not including the expense for a manufacturing facility) to bring a single vaccine candidate through Phase 2a development as US$31–68 million without regard to failure, with a cumulative expense of US $319–469 million to successfully develop a vaccine through to the end of Phase 2a when one includes candidates that fail to meet expectations either preclinically or during clinical evaluation.[3]

Despite clear unmet need, economic considerations are central to vaccine development for essentially all emerging and neglected infectious diseases. It is with such challenges in mind that the paper by Bottazzi and Hotez[4] discusses a developmental framework for neglected diseases utilizing as examples the programs for hookworm and schistosomiasis. Building on the funding pathways established through existing organizations such as Coalition of Epidemic Preparedness and Innovation (CEPI), the Bill & Melinda Gates Foundation (BMGF), and the Wellcome Trust, they highlight the significant economic cost to develop prophylactic vaccines against neglected tropical diseases. The authors highlight the need for significant investment and the reliance on partnerships involving the abovementioned and other donor groups that are active in global public health.

In contrast, viral diseases such as those caused Kyasanur Forest disease virus (KFDV)[5] and the Severe Fever and Thrombocytopenia Fever virus (SFTSV),[6] discussed in this Special Feature, have been geographically restricted to a single country or have low incidence, making the economics and logistics of vaccine development more challenging or virtually undoable in certain cases. Corollary considerations are outbreaks such as EBOV, ZIKV, and MERS-CoV, which all sustained significant decreases in disease incidence at the time that vaccines were being developed and deployed.[7] Maslow et al. discuss the additional challenges posed for clinical trial design and conduct for infectious diseases such as SFTSV having very low incidence, which may require sample sizes greater than the entire population being studied for a classical placebo-controlled efficacy trial.[6] Such a situation requires innovative approaches to clinical development.

Critical to the conduct of vaccine trials are the laboratories that process samples and conduct the immunologic and diagnostic assays. Roberts discusses the challenges facing immunology laboratories involved in the conduct of clinical trials for emerging infectious diseases (EID).[8] In this monograph, the tenets previously introduced for ZIKV[9] are further explored for a generic EID. There is the need for standardized reference reagents, control samples, and diagnostic assays – that for EIDs might not exist at the time that clinical trials commence.[9] A corollary question, which is taken for granted for an established vaccine, is how to compare results across disparate vaccine platforms at a time that assays have not yet been standardized.

Racine and Kobinger discuss a much more basic problem encountered with clinical trials for EIDs – that laboratory facilities for sample collection, initial processing, shipment, and analysis are located in major academic centers, typically in major cities, but are often non-existent in remote underdeveloped regions where disease outbreaks are occurring.[10] The authors provide a novel solution: the use of mobile laboratories Key challenges and solutions are discussed in the context of field laboratories that were deployed successfully during the West African Ebola virus epidemic. In addition to basic logistical questions, the authors discuss the need to confront adverse social and safety environments and the difficulties in handling specimens for a level 4 pathogen.

Fathi et al. present a detailed review of the VSV-vectored vaccine platform as applied to the panel of WHO target agents.[11] The authors focus on the rVSV-EBOV vaccine that was a critical component in the response to the West African Ebola virus epidemic and is now being deployed in the Democratic Republic of the Congo (DRC), as a paradigm for novel vaccine approaches that allow for a rapid response against new pathogens. Of interest, Ma et al.[12] show that rVSV pseudovirions can be also used to assess and titer neutralizing antibodies generated against any vaccine. Importantly, pseudovirions, considered as biosafety level 2 pathogens and thus relatively easy to use and handle, can provide early immunologic readouts while avoiding both the logistical and safety concerns of Level 3 or 4 infectious agents. A further interesting use of such technology is that fluorescent-tagged pseudovirions may allow for *in vivo, in situ* assessment of vaccine effectiveness in animal models, which may be pivotal for development of vaccines for which the prelicensure demonstration of clinical efficacy is not feasible technically or financially.[12]

The remaining articles address a number of viral diseases that present both specific and generalizable lessons in vaccine and therapeutics development.

Flaviviruses

The flaviviruses are a diverse group that includes both the more-well-known dengue virus (DENV), Yellow fever virus (YFV), West Nile virus (WNV), tick-borne encephalitis virus (TBEV), and ZIKV, as well as other less-well-known viruses such as Powassan virus (POWV) and KFDV. While most of these viruses are mosquito-borne, POWV and KFDV utilize tick vectors for spread. Approved vaccines include those for YFV, TBEV, DENV, and KFDV. The 17D YFV live attenuated virus (LAV) vaccine, the KFDV inactivated whole virus vaccine, and the TBEV protein-based vaccine have been in use for decades globally, in India, and in Europe, respectively, whereas the CYD-TDV vaccine for DENV, a chimeric LAV, was recently approved.

Global concerns regarding flavivirus-related illness have increased significantly given that DENV, YFV, and ZIKV have spread globally. While the neurologic propensity of TBEV, WNV, and KFDV have been well documented, the neurologic complications of ZIKV were only recently appreciated coincident with the outbreaks in the South Pacific islands and the Americas.

DENV vaccine development has been a significant focus for decades given the widespread occurrence of disease, complicated by the need to address all four DENV serotypes with their varying epidemiology and immunology. While DENV infection is relatively asymptomatic in many infected subjects,

a small fraction of those infected develop dengue hemorrhagic fever (DHF), a highly morbid and potentially fatal complication that more commonly affects young children. Two articles in this Special Feature provide further insights into the approved CYD-TDV live attenuated DENV vaccine.

Thomas and Yoon provide a comprehensive review of the CYD-TDV vaccine (Dengvaxia®) and the landscape for other dengue vaccines in development.[13] The authors discuss the construction of each vaccine and the difficulties in defining immunologic correlates of protection. Administration of CYD-TDV across 26 clinical trials was without observations of immediate significant safety concerns. They note that studies have suggested how a longer delay (≥4 months) between the first two doses may improve immunogenicity. Among those with pre-existing immunity to DENV, vaccination is protective against future infection. However and unexpectedly, sero-naïve individuals, especially children younger than 5 years of age, showed an increased incidence of DHF, especially following serotype 2 DENV infection. The authors address the controversy around the correlation of these clinical results with the in vitro observation of antibody-dependent enhancement (ADE) of infection and discuss the lessons learned from this vaccine.

The paper by Tran et al. in this special feature presents detailed serologic data from two Phase 2, randomized, observer-blind studies of the CYD-TDV vaccine conducted between 2009 and 2014 in Singapore and Vietnam.[14] Seroconversion directly correlated with baseline serostatus: greater for Vietnamese subjects (20–40% seropositive at baseline) than Singaporean subjects (≤5% seropositive at baseline). While ~72–95% of seropositive subjects achieved vaccine titers of ≥10 in the first year post-vaccination, only ~25% of sero-naïve persons achieved titers ≥10 against serotype 1 and ~50% against serotypes 2 and 3. While titers were generally maintained in sero-positive individuals, antibody levels waned by two years post-vaccination to only ~10% against serotype 1 and 30% against serotype 2 among those DENV-naïve at baseline. Importantly, immune responses were independent of the age of the participants. This highlights a significant challenge in defining the optimal vaccination regimen.

Clear interpretation of the results of the varied vaccine studies is therefore difficult. For example, a four-year follow-up of the CYD-TDV Phase 3 studies showed that children younger than 6 years of age had an increased risk of incident infections in two of the three reported studies.[15] Study CYD14 showed a relative risk (RR, 95% confidence interval (CI)) of 7.45 (1.15–313.80) for age group of 2–5 years, while the year-3 RR in study CYD 57 of 2.44 (0.27–115.54) dropped to a year-4 RR of 0.81.[15] However, a post-hoc analysis by Sridhar of the CYD14 and CYD15 studies showed that baseline serostatus, rather than the age of the enrolled children, may be the more important predictor of later hospitalizations for DENV infection.[16] This re-analysis showed that vaccinated DENV seronegative children aged 2–8 years had an almost 5-fold greater relative incidence of serotype 2 infections relative to non-vaccinated control subjects, with smaller increased rates for serotype 3 (2.1-fold greater for vaccinees) and serotype 3 (1.5-fold increase).[16] However, these data are complicated by the serotype 1 vaccine component being the least immunogenic and fastest to wane, whereas serotype 2 DENV caused the greatest pathology, suggesting that the magnitude of responses alone cannot predict future complications. Thus, as counseled by Thomas and Yoon,[13] care should be taken with the assumptions and characterization of the results of vaccine studies.

Care must also be taken when one tries to extrapolate from immunologic observations to define correlates of protection. Neutralizing antibodies, typically performed by assessing the ability of dilute immune serum to block infection of Vero cells, has been cited as a standard measure of protection. However, the results of post-hoc passive transfer experiments reported as part of the GLS-5700 ZIKV DNA vaccine study raise important questions.[17] In this study, administration of immune serum from vaccinated subjects protected 92% of immunosuppressed IFNAR mice against lethal ZIKV challenge infection independent of the presence (or absence) of neutralizing antibodies as defined by Vero cell assay, whereas neutralization was 95% against infection of U87MG neuroblastoma cells, paralleling the *in vivo* infection studies.[17]

Galula et al.[18] further discusses the dengue vaccine landscape and the effect of maturation of envelope dimers that coat and protect the virion. The authors note that antibodies against E dimer epitopes present on fully formed virions are highly neutralizing at picomolar concentrations, whereas antibodies against the fusion loop (FL) region of domain II of the envelope that is exposed prior to full maturation are highly immunogenic but poorly protective, especially for serotype 2. They note that genetic modifications to the envelope coding sequence may improve serotype 2-specific immune responses.

Vaccine development for two other flaviviruses is presented in this Special Feature. Rahaiah reviews KFDV epidemiology, infection, and considerations for vaccine development.[5] KFDV is a hemorrhagic fever virus spread primarily via nymph forms of the *H. spinigera* tick, with a mortality rate in humans ranging of 3–10%. Since the initial reports in the 1950s, KFDV has spread north and south along the western coast of India from Karnataka state. A formalin-inactivated, whole-virus cell-culture-derived vaccine has been used since the 1990s requires frequent booster injections following a two-dose primary series. This complicated vaccination schedule limits vaccine uptake such that only one-third of subjects received the priming series and first booster.[19] Moreover, vaccine efficacy for fully vaccinated individuals was only 62% compared to 95% as originally published, with a notable occurrence of vaccine failure in the year following immunization.[19] Thus, Rajaiah argues for a more effective vaccine and, because KFDV is epizootic with a reservoir in multiple primate species, suggests that a one-health approach targeting both humans and primates may be more desirable.

Ulbert reviewed the current status and challenges in the development of vaccines against WNV.[20] Of the many WNV vaccines with experimental data, six have been tested in clinical trials with one advancing to Phase 2. Ulbert discusses in detail the question of whether ADE of infection could be induced by subsequent heterologous flavivirus infection following WNV vaccination. While not definitive to answer the question of WNV vaccination as a primary vaccine, the multiple studies related to cross-immunologic effects between DENV and ZIKV are instructive. A few preclinical studies

found that sub-neutralizing concentrations of antibodies against DENV can potentiate ZIKV infection in tissue culture[21,22] and initial reports out of Brazil suggested that DENV-specific antibodies may enhance ZIKV infection.[23] However, others have found that DENV-specific $CD8^+$ T cells are protective against ZIKV infection in pregnant immunosuppressed IFNAR mice[24,25] and a comprehensive study in non-human primates showed that primary infection with either DENV or ZIKV did not potentiate later heterologous infection with the other virus.[26] Importantly, a large case-control study from Brazil found no increased risk for severe ZIKV infection relative to DENV serostatus.[27]

Bunyaviruses

Approaches to vaccine development for two bunyaviruses, Rift Valley fever virus (RVFV) and SFTSV, are included in this Special Feature. RVF is a hemorrhagic illness endemic in Sub-Saharan Africa with a mortality rate of ~10–20%. Ma et al. present data on the development and effectiveness of a DNA vaccine directed against the RVFV glycoproteins.[12] Guinea pigs immunized five times with 200 μg vaccine followed by electroporation developed high titers of glycoprotein-specific antibodies. Mice immunized five times with 50 μg of vaccine were protected against infection with a vesicular stomatitis virus (VSV) pseudovirus expressing the RVFV glycoproteins. Actual RFV infection studies were not reported.

SFTSV causes a hemorrhagic febrile illness with mortality rate of 10–30%. Cases are restricted to the East Asian countries of China, Japan, and South Korea, although a recent case was reported in Vietnam. As reviewed by Maslow et al.,[6] although disease incidence has increased since discovery a decade ago, SFTSV remains relatively rare. This very low incidence precludes standard approaches to demonstrate vaccine efficacy since a placebo-controlled study would require a sample size exceeding the population being studied. The authors provide an alternative evaluative framework that combines animal rule approval (demonstration of efficacy in two animal infection models) with post-licensure public health follow-up through use of a registry that follows cumulative disease incidence among the general population relative to vaccine recipients.

Other viral illnesses

Hand-foot-and-mouth disease (HFMD) is a well-recognized febrile illness of young children presenting with a painful vesicular eruption involving the palms, soles, and oropharynx. HFMD can be caused by multiple viruses within the enterovirus genus. The most common viruses causing HFMD are Coxsackie A16 (CA16) followed by Enterovirus serotype 71 (EV71). While infection with CA16 is typically self-limited, infection with EV71 has been associated with more severe complications such as encephalitis. Many studies into prophylaxis and therapeutic approaches against EV71 have been published, including treatment with monoclonal antibodies. Du et al. provide data on a monoclonal antibody to CA16[28] that was able to fully protect BALB/c mice against lethal infection at doses of ≥0.1 μg/g when given 1 day post-infection, with treatment of 10 μg/g protective even when given up to 4 days post-exposure.

Similar to ZIKV and DENV, Chikungunya virus (CHKV) infection has gained increasing notoriety over the past decades with its spread into the Western hemisphere from tropical Asia and Sub-Saharan Africa. CHKV causes a symptom complex consisting of fever, neuralgia, rash, with an associated severe joint and bone pain. Although typically self-limited, post-infectious arthralgia can persist for months such that infection can be debilitating in some. Sandoval reviews the history of the development of vaccines against CHKV that spans a period of >50 years.[29] An early LAV vaccine candidate elicited potential safety concerns due to the development of arthralgias in vaccinees, whereas numerous subsequent vaccine candidates have been successfully tested without safety concerns. Of the numerous vaccines in clinical trials, a measles-vectored vaccine and recombinant virus-like protein (VLP) have progressed to Phase 3.

The filoviruses including Ebola (EBOV) and Marburg were recognized in 1976 as causing a highly fatal hemorrhagic disease. Work on EBOV vaccines was ongoing for over a decade prior to the 2014 outbreak in West Africa; however, few candidates had been tested in humans. During the 2014 outbreak, vaccine development accelerated with the rVSV-EBOV vaccine developed by Merck advancing the furthest and is being used to stop the outbreak in the DRC. A second vaccine that involves a prime-boost strategy using Ad26 and MVA-vectored components developed by Janssen Pharmaceuticals is being deployed in the ongoing DRC epidemic. Suschak and Schmaljohn review the history, efficacy, and status of vaccines against the filoviruses,[30] including work to combat Ebola has sparked development across many platforms.

Conclusion

This Special Feature details many thematic issues concerning vaccine development for emerging infectious diseases. The lessons from each individual pathogen inform other emerging-disease vaccine programs. The keys to continued development, especially for rare or uncommon infections and those diseases centered in resource-limited countries, are access to i. sufficient and continued funding streams from NGOs and governments, ii. development and manufacturing expertise of commercial companies, iii. regulatory pathways that allow approval, and iv. post-approval follow-up to measure vaccine effectiveness.

Abbreviations

ADE	antibody-dependent enhancement
CEPI	Coalition of Epidemic Preparedness and Innovation
CoV	Coronavirus
DENV	dengue virus
DHF	dengue hemorrhagic fever
DRC	Democratic Republic of Congo
EBOV	Ebola virus
HFMD	hand foot and mouth disease
KFDV	Kyasanur Forest disease virus
LAV	Live attenuated virus
MERS	Middle East respiratory syndrome (coronavirus)
NGO	non-governmental organization
POWV	Powassan virus
SARS	severe acute respiratory syndrome (coronavirus)
SFTSV	severe fever and thrombocytopenia syndrome virus

TBEV	tick borne encephalitis virus
US	United States
WNV	West Nile virus
WHO	World Health Organization
YFV	yellow fever virus
ZIKV	Zika virus

References

1. Maslow JN. Vaccine development for emerging infectious diseases. Vaccine. 2017;35:5437–43. doi:10.1016/j.vaccine.2017.02.015.
2. Graham BS, Mascola JR, Fauci AS. Novel vaccine technologies: essential components of an adequate response to emerging viral diseases. JAMA. 2018;319:1431–32. doi:10.1001/jama.2018.0345.
3. Gouglas D, Thanh LT, Henderson K, Kaloudis A, Danielsen T, Hammersland NC, Robinson JM, Heaton PM, Røttingen J-A. Estimating the cost of vaccine development against epidemic infectious diseases: a cost minimisation study. Lancet Glob Health. 2018;6:e1386–e96. doi:10.1016/S2214-109X(18)30346-2.
4. Bottazzi ME, Hotez PJ. Running the Gauntlet: formidable challenges in advancing neglected tropical diseases vaccines from development through licensure, and a "Call to Action". Hum Vaccin Immunother. 2019;15:2235–2242. doi:10.1080/21645515.2019.1629254.
5. Rajaiah P. Kyasanur forest disease in India: innovative options for intervention. Hum Vaccin Immunother. 2019;15:2243–2248. doi:10.1080/21645515.2019.1602431.
6. Maslow JN, Kwon J, Mikota SK, Spruill S, Cho Y, Jeong M. Severe fever and thrombocytopenia syndrome virus infection: considerations for vaccine evaluation of a rare disease. Hum Vaccin Immunother. 2019;15:2249–2257. doi:10.1080/21645515.2019.1633875. doi: . [Epub ahead of print].
7. Maslow JN. Vaccines for emerging infectious diseases: lessons from MERS coronavirus and Zika virus. Hum Vaccin Immunother. 2017;12:2918–30. doi:10.1080/21645515.2017.1358325.
8. Roberts CC. Emerging infectious disease laboratory and diagnostic preparedness to accelerate vaccine development. Hum Vaccin Immunother. 2019;15:2258–2263. doi:10.1080/21645515.2019.1634992.
9. Roberts CC, Maslow JN. Assay challenges for emerging infectious diseases: the Zika experience. Vaccines. 2018;6(4):E70. doi:10.3390/vaccines6040070.
10. Racine T, Kobinger GP. Challenges and perspectives on the use of mobile laboratories during outbreaks and their use for vaccine evaluation. Hum Vaccin Immunother. 2019;15:2264–2268. doi:10.1080/21645515.2019.1597595.
11. Fathi A, Dahlke C, Addo MM. Recombinant vesicular stomatitis virus vector vaccines for WHO blueprint priority pathogens. Hum Vaccin Immunother. 2019;15:2269–2285. doi:10.1080/21645515.2019.1649532.
12. Ma J, Chen R, Huang W, Nie J, Liu Q, Wang Y, Yang X. In vitro and in vivo efficacy of a Rift Valley fever virus vaccine based on pseudovirus. Hum Vaccin Immunother. 2019;15:2286–2294. doi:10.1080/21645515.2019.1627820.
13. Thomas SJ, Yoon IK. A review of dengvaxia: development to deployment. Hum Vaccin Immunother. 2019;15:2295–2314.
14. Tran NH, Chansinghakul D, Chong CY, Low CY, Shek LP, Luong CQ, Fargo C, Wartel TA, Sun S, Skipetrova A, et al. Long-term immunogenicity and safety of tetravalent dengue vaccine (CYD-TDV) in healthy populations in Singapore and Vietnam: 4-year follow-up of randomized, controlled, phase II trials. Hum Vaccin Immunother. 2019;15:2315–2327. doi:10.1080/21645515.2019.1578595.
15. Hadinegoro SR, Arredondo-García JL, Capeding MR, Deseda C, Chotpitayasunondh T, Dietze R, Muhammad Ismail HIH, Reynales H, Limkittikul K, Rivera-Medina DM, et al. Efficacy and long-term safety of a dengue vaccine in regions of endemic disease. N Engl J Med. 2015;373:1195–206. doi:10.1056/NEJMoa1506223.
16. Sridhar S, Luedtke A, Langevin E, Zhu M, Bonaparte M, Machabert T, Savarino S, Zambrano B, Moureau A, Khromava A, et al. Effect of dengue serostatus on dengue vaccine safety and efficacy. N Engl J Med. 2018;379:327–40. doi:10.1056/NEJMoa1800820.
17. Tebas P, Roberts CC, Muthumani K, Reuschel EL, Kudchodkar SB, Zaidi FI, White S, Khan AS, Racine T, Choi H, Boyer J, Park YK, Trottier S, Remigio C, Krieger D, Spruill SE, Bagarazzi M, Kobinger GP, Weiner DB, Maslow JN. Safety and immunogenicity of an anti-Zika virus DNA vaccine – preliminary report. N Engl J Med. 2017 Oct 4. doi:10.1056/NEJMoa1708120. [Epub ahead of print].
18. Galula JU, Salem GM, Chang GJ, Chao DY. Does structurally-mature dengue virion matter in vaccine preparation in post-Dengvaxia era? Hum Vaccin Immunother. 2019;15:2328–2336. doi:10.1080/21645515.2019.1643676.
19. Kasabi GS, Murhekar MV, Sandhya VK, Raghunandan R, Kiran SK, Channabasappa GH, Mehendale SM, Bausch DG. Coverage and effectiveness of Kyasanur forest disease (KFD) vaccine in Karnataka, South India, 2005-10. PLoS Negl Trop Dis. 2013;7(1):e2025. doi:10.1371/journal.pntd.0002025.
20. Ulbert S. West Nile virus vaccines – current situation and future directions. Hum Vaccin Immunother. 2019;15:2337–2342. doi:10.1080/21645515.2019.1621149.
21. Hueston L, Ramirez R, Mahalingam S. Enhancement of Zika infection by dengue virus-specific antibody is associated with low levels of antiviral factors. J Infect Dis. 2017;216:612–14. doi:10.1093/infdis/jix344.
22. Paul LM, Carlin ER, Jenkins MM, Tan AL, Barcellona CM, Nicholson CO, Trautmann L, Michael, S. F, Isern, S. Dengue virus antibodies enhance Zika virus infection. Clin Transl Immunol. 2016;5(12):e117. doi:10.1038/cti.2016.72.
23. Castanha PMS, Nascimento EJM, Braga C, Cordeiro MT, de Carvalho OV, de Mendonça LR, Azevedo EAN, França RFO, Dhalia R, Marques ETA. Enhancement of Zika infection by dengue-specific antibodies does not alter the production of interleukin 6 in FcγRII-expressing K562 cells. J Infect Dis. 2017;216:614–15. doi:10.1093/infdis/jix346.
24. Regla-Nava JA, Elong Ngono A, Viramontes KM, Huynh AT, Wang YT, Nguyen AT, Salgado R, Mamidi A, Kim K, Diamond MS, et al. Cross-reactive Dengue virus-specific CD8+ T cells protect against Zika virus during pregnancy. Nat Commun. 2018;9(1):3042. doi:10.1038/s41467-018-05458-0.
25. Wen J, Elong Ngono A, Regla-Nava JA, Kim K, Gorman MJ, Diamond MS, Shresta S. Dengue virus-reactive CD8+ T cells mediate cross-protection against subsequent Zika virus challenge. Nat Commun. 2017;8(1):1459. doi:10.1038/s41467-017-01669-z.
26. Breitbach ME, Newman CM, Dudley DM, Stewart LM, Aliota MT, Koenig MR, Shepherd PM, Yamamoto K, Crooks CM, Young G, et al. Primary infection with dengue or Zika virus does not affect the severity of heterologous secondary infection in macaques. PLoS Pathog. 2019;15(8):e1007766. doi:10.1371/journal.ppat.1007766.
27. Halai UA, Nielsen-Saines K, Moreira ME, Sequeira PC, Junior P, Zin AA, Cherry J, Gabaglia CR, Gaw SL, Adachi K, et al. Maternal Zika virus disease severity, virus load prior dengue antibodies and their relationship to birth outcomes. Clin Infect Dis. 2017;65:877–83. doi:10.1093/cid/cix472.
28. Du R, Mao Q, Hu Y, Lang S, Sun S, Li K, Gao F, Bian L, Yang C, Cui B, et al. A potential therapeutic neutralization monoclonal antibody specifically against multi-coxsackievirus A16 strains challenge. Hum Vaccin Immunother. 2019;15:2343–2350. doi:10.1080/21645515.2019.1565266.
29. Reyes-Sandoval A. 51 years in of chikungunya clinical vaccine development: a historical perspective. Hum Vaccin Immunother. 2019;15:2351–2358. doi:10.1080/21645515.2019.1574149.
30. Suschak JJ, Schmaljohn CS. Vaccines against Ebola virus and Marburg virus: recent advances and promising candidates. Hum Vaccin Immunother. 2019;15:2359–2377.