



U.S. Government Zika Vaccine Strategy

White Paper

September 7, 2017

U.S. Department of Health and Human Services
Office of the Assistant Secretary for Preparedness and Response



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1.1 Introduction

To address the Zika virus public health threat, the Departments of Health and Human Services and Defense¹ are coordinating efforts to help accelerate the development of Zika virus vaccines. Given the need for a vaccine to prevent disease caused by Zika notably including Congenital Zika Syndrome (CZS),² these departments and their respective agencies (hereafter referred to as U.S. Government or USG) developed this Strategy in support of the following Goal and vaccine development Aims.

Zika virus is a member of the Flaviviridae family, which includes yellow fever, dengue, Japanese encephalitis and West Nile viruses, among others. Approximately 20% of those infected with Zika virus experience symptoms such as rash, conjunctivitis, or fever—the remaining 80% cases are typically asymptomatic. Regardless of the severity of disease, infection of pregnant women can result in transmission of the virus to the fetus and congenital Zika syndrome (CZS), which includes microcephaly and other neurological disorders in infants. Zika virus infection of adults can rarely cause brain or spinal cord inflammation and is associated with Guillain-Barré syndrome, a form of paralysis. Since 2015, 84 countries and territories have reported evidence of mosquito-borne Zika virus transmission and associated disease, including the U.S. with cases of local transmission in Florida and Texas.³ Transmission to humans is primarily by mosquito, but sexual transmission through genital secretions and semen, and transfusion-associated transmission, have been reported.⁴ The broad distribution of Zika virus in the Americas and the ongoing risk of infection during pregnancy underscore the crucial need for a safe and effective vaccine.

Long-term public health goal: To prevent CZS through deployment of a safe and effective vaccine(s) against Zika virus.

The USG has committed to a focused, multidisciplinary and multiagency effort to rapidly design, develop, produce and evaluate Zika virus vaccines. Based on experience with Congenital Rubella Syndrome (CRS), it is expected that evidence demonstrating that a vaccine can prevent CZS will take years of clinical study to obtain, and will likely depend on post-licensure studies conducted after licensed Zika virus vaccines are in widespread use.⁵ Development of a safe and effective vaccine candidate for use in the near term will require a series of parallel and iterative steps. This includes the demonstration of scalable and reproducible manufacturing, safety and efficacy in standardized animal models, acceptable toxicity in preclinical models, and safety and immunogenicity in Phase 1 clinical studies. These initial studies will need to be followed by appropriately powered ones to develop a robust safety,

¹ From the Department of Health and Human Services, the following operating and staff divisions are included in the coordination efforts and have contributed to the Strategy development: National Institute of Allergy and Infectious Diseases (NIAID), including NIAID's Vaccine Research Center (NIAID/VRC), Division of Microbiology and Infectious Diseases (DMID), Laboratory of Infectious Diseases (LID) and Viral Diseases Lab of the Division of Intramural Research (DIR); the Office of the Assistant Secretary for Preparedness and Response (ASPR); Biomedical Advanced Research and Development Authority (BARDA); Centers for Disease Control and Prevention (CDC); and Food and Drug Administration (FDA). Similarly, from the Department of Defense, Walter Reed Army Institute of Research (WRAIR) and U.S. Army Medical Research and Materiel Command has been involved and has contributed to Strategy development.

² Moore *et al.* JAMA 2017; 171(3):288-295. March 2017.

³ World Health Organization (WHO), [Zika Virus and Complications](http://www.who.int/emergencies/zika-virus/en), www.who.int/emergencies/zika-virus/en, accessed on March 31, 2017.

⁴ Motta *et al.* N Engl J Med 2016; 375:1101-1103. September 15, 2016.

⁵ Marston *et al.* N Engl J Med 2016; 375:1209-1212 September 29, 2016.

immunogenicity, and efficacy database that demonstrates clinical benefit in adults. Vaccines will be evaluated based on their safety, tolerability, immunogenicity and efficacy against disease and infection in adults, in pursuit of FDA licensure. The USG strategy includes consideration of making sufficiently characterized investigational vaccine available prior to licensure through expanded access under an Expanded Access (EA) Investigational New Drug Application (IND) or Emergency Use Authorization if the epidemiological circumstances warrant.⁶ Data assessing the impact of vaccine candidates on the incidence of CZS will be accumulated as vaccines are used in clinical trials, in any pre-licensure use registry, and following any licensure for the prevention of Zika virus infection in adults and (if appropriate) children.

The overarching USG Goal for Zika vaccine development is to protect individuals from disease as soon as practical by developing licensed vaccine(s) against Zika virus. In mid-2016, the USG defined the following three **Aims** to support achievement of this Goal:

- 1) Evaluate vaccine candidates for evidence of safety and immunogenicity. If disease incidence remains high, promising vaccines will be assessed beginning in 2017 for clinical efficacy in preventing documented infection or clinical disease, and to identify immune correlates of protection.
- 2) Provide access to investigational Zika vaccine(s) through the most appropriate regulatory mechanisms (as determined by the US FDA), potentially through Emergency Use Authorization or expanded access (to populations at highest risk) assuming the following inclusive conditions:
 - a. Sufficient preliminary evidence of safety and effectiveness is obtained and determined to be adequate by the US FDA.
 - b. Deployment would serve an unmet important public health need.
 - c. It would not interfere with obtaining data to support licensure of the provided vaccine or other vaccine candidates.
- 3) Work with industry partners to develop a vaccine towards FDA licensure for usage as soon as possible, potentially as early as 2020.

1.2 USG Zika Vaccine Development Program Overview

The USG, in collaboration with academic and industry partners, is advancing a portfolio of Zika vaccine candidates based on both traditional and new technologies. Traditional technologies include purified inactivated virus (PIV) and live-attenuated chimeric virus approaches. While these have previously been used to make licensed flavivirus vaccines, they typically require significant resources and time. Nucleic acid-based DNA or mRNA approaches are also being pursued because they can be manufactured more efficiently and can potentially be produced more quickly than traditional technologies.

⁶ For full discussion of these terms, please refer to FDA.gov. Briefly, expanded access represents use of investigational products for patients with serious or immediately life-threatening diseases or conditions for which there is no comparable or satisfactory alternative. Investigators are responsible for reporting adverse events to the sponsor and ensuring that informed consent is obtained from subjects and that IRB review of the expanded access use is obtained. Emergency Use Authorization allows FDA to facilitate availability and use of medical countermeasures needed during declared public health emergencies. Under section 564 of the Federal Food, Drug, and Cosmetic Act (FD&C Act), if the statutory prerequisites (including a declaration by the Secretary of Health and Human Services) have been met, the FDA Commissioner may allow unapproved medical products or unapproved uses of approved medical products to be used in an emergency to diagnose, treat, or prevent certain serious or life-threatening diseases or conditions for which there are no adequate, approved and available alternatives.

USG-supported Zika vaccine candidates are anticipated to address different Aims, with alignment to an Aim based primarily on the vaccine's development timelines. Recognizing that all candidates are being developed as potential commercial Zika vaccines, earlier candidates are estimated to have the potential to meet the timeline for Aims 1 and 2. The selective identification of candidates in Aim 3 is based on an estimate of those most likely to achieve the Aim 3 objectives and those most promising based on prior success of the vaccine delivery platform. However, this classification of candidates is not exclusive since we anticipate that any of the candidates may meet the Aim 3 objectives as well. NIAID Vaccine Research Center (NIAID/VRC) and BARDA supported Nucleic Acid candidates are on a timeline conducive to achieving both Aims 1 and 2, provided that they demonstrate immunogenicity and preliminary evidence of safety and efficacy and that sufficient amounts of product can be manufactured. If PIV and live-attenuated virus vaccine candidates are available sooner than anticipated, they could contribute to Aims 1 and 2. All candidates have the potential to satisfy Aim 3. The timelines used to evaluate candidate alignment with specific Aims represent best-case scenarios as of August 2017.

1.3 Target Population Recommendations

Under Aim 2, the USG may seek to make available vaccine candidate(s) with adequate evidence of safety and efficacy in preventing disease caused by Zika, as determined by the US FDA, in advance of licensure under an appropriate regulatory mechanism to achieve the public health goal of preventing CZS in specific at-risk populations. However, it is essential that any pre-licensure deployment be considered in the context of the larger clinical development and manufacturing plans and should not adversely affect the ability to conduct well-controlled clinical trials. Further, in the pre-licensure period the size of the initial deployment will likely be limited in scope due to factors such as size of the at-risk populations, safety database, manufacturing capacity and delivery constraints. Moreover, pre-licensure deployment of vaccine(s) outside of clinical trials will require careful consideration by the FDA and the vaccine sponsor, taking into consideration the strength of the evidence for vaccine benefit, safety, and quality in the context of the evolving epidemic. Therefore, it is imperative to identify those individuals at highest risk of Zika infection and, thus, likelihood of having a child with CZS based upon a) geographic risk of exposure to Zika virus and b) demographics (likelihood of future pregnancy or sexual partnership with a pregnant woman).⁷

With those considerations in mind, the USG has projected potential supply requirements to protect high-risk populations in the U.S. and its Territories. The USG has defined the highest-risk population as individuals planning pregnancy (women and men) in areas with active widespread Zika transmission (e.g., Puerto Rico) and local Zika transmission (e.g., Miami-Dade and Brownsville/Cameron County Texas in summer-fall 2016) and military/USG personnel on long-term deployment to Zika endemic areas. Using statistics from the fall of 2016 (and data from the 2010 Census) as an example for planning purposes, the USG projects the need to protect between 100,000 and 175,000 individuals. This population represents a small fraction of the total population of subjects within a given geographic area, the vast majority of which would still be available for late stage, Phase 3 field trials for vaccine efficacy against Zika caused disease. The USG will continue to validate these numbers closer to any actual deployment of the vaccine, whether in IND clinical studies or under Aim 2, in collaboration with the sponsor(s), to account for changes in the Zika epidemiology and the public health need at that time.

While the USG has estimated the potential need to protect the highest risk populations in the U.S. and its Territories, the USG seeks to prevent CZS for those at highest risk wherever they may live. Access to the vaccine(s) for other countries in advance of licensure would be considered in partnership with vaccine sponsors and regulatory authorities

⁷ USG would not seek to vaccinate women during pregnancy, under Aim 2, at least in the near-term. The USG would want to see a clear demonstration of safety in non-pregnant adults before considering studies of immunization during pregnancy. Moreover, the benefit of immunization during pregnancy (including likelihood of generating a protective immune response in time to protect the developing fetus) would need to be balanced against the potential risk to the mother and fetus. The speed to immune protection will vary by the type of vaccine; some may achieve rapid protection (i.e., 45 days) and thus may be more appropriate to use during the course of a 9-month pregnancy.

in those countries with endemic Zika virus or outbreaks. To initiate this broader dissemination of Zika vaccine(s), USG could share data regarding safety and efficacy gathered from previous well-controlled trials and U.S. regulators could collaborate with their international peers to review data and weigh similar pre-licensure deployment and facilitate export if these vaccines were manufactured in the U.S. Finally, the USG will continue to assist its Zika partners with epidemiological data and forecasting for these endemic country markets to gauge supply needs pre- and post-licensure and make introductions of foreign governments to the vaccine sponsors.

Should licensure be achieved, the USG could work with commercial partners, the World Health Organization (WHO), Gavi and others to facilitate availability of the vaccine(s) for populations in need of protection against the Zika virus and continue to collect data regarding the prevention of CZS for clinical supplements in support of indication changes in the future.

1.4 Approach to Vaccine Development and Public Health Use

To accomplish the overall Goal and three Aims, the USG is supporting vaccine discovery, development, production, and preclinical and clinical evaluation of several investigational vaccine candidates. The USG will structure these preclinical and early stage clinical efforts to facilitate the conduct of Phase 2b efficacy studies of one or more selected candidate vaccines. During the conduct of Phase 2b studies, data will be collected to evaluate efficacy against Zika virus symptoms and Zika virus infection as measured by the presence of viral RNA in serum, whole blood or urine.⁸ As noted in Aim 2, data from a Phase 2b study could support access to investigational Zika vaccine(s) either outside of clinical trials if conditions for Emergency Use Authorization are met or under expanded access. In parallel with Aims 1 and 2, the USG will work with industry partners to facilitate development of commercial vaccine(s) licensed for broad usage under Aim 3, recognizing the primacy of achieving Aim 3 and the need to assure that implementation of Aim 2 does not interfere with achievement of Aim 3. The major long-term public health goal is to prevent CZS and all forms of Zika caused disease through usage of a safe and effective vaccine(s) against Zika virus. Data to support a vaccine indication for the prevention of CZS depends on many variables, including infection and congenital disease rates in the population; obtaining these data are likely to require post-licensure studies. The following integrated preclinical and clinical approach will be implemented to provide data to support Aims 2 and 3:

- Develop robust animal models of Zika virus infection, including adult infection and models of congenital disease. These animal models can be used to assess vaccine-mediated protection and passive immunization approaches and to establish immune correlates of protection against Zika virus challenge.
- Conduct clinical trials to assess safety and efficacy in preventing Zika virus symptoms and Zika virus infection.
- As part of efficacy studies, assess immune parameters, including neutralizing antibody levels against Zika virus, using standardized assays, to establish potential immune correlates of protection against infection in humans.

Importantly, rates of CZS are not an endpoint for planned efficacy studies. The initial trials of investigational vaccines will not include enrollment of pregnant women. Inclusion criteria will address pregnancy avoidance through counseling and contraceptives. For unexpected pregnancies, reporting will be tracked as part of safety monitoring during long term follow-up. Definitive assessment of the effects of vaccination on CZS rates would be studied in post-licensure evaluations, as part of Phase 4 post-marketing studies. In addition, it is anticipated that an effective vaccine at the population level could potentially provide herd immunity leading to a potential reduction in CZS rates.

In shaping its approach to Zika virus vaccine development, the USG is drawing from past experience addressing emerging infectious diseases coupled with current scientific, clinical and epidemiological information. However,

⁸ Should additional assays (*e.g.*, serologies) be developed with sufficient specificity and sensitivity, these could also be employed.

knowledge of this infection and challenges for vaccine development for Zika are evolving rapidly and there are numerous uncertainties that can impact vaccine development. Among these are the geographic distribution and magnitude of future Zika incidence; potential regional differences in congenital Zika disease; knowledge of the full clinical spectrum of Zika virus disease; potential genotypic/phenotypic changes in the circulating viruses; uncertainty in the type, scope, and duration of immunity required to protect against Zika virus infection; vaccine doses/formulations/ adjuvants required to achieve targeted immunologic responses; potential interaction/interference from pre/post exposure to other flaviviruses; clinical symptoms and congenital disease. The Zika epidemic will evolve based on numerous social and environmental factors; predictions of regional disease incidence are complex. This poses a challenge for conducting efficacy trials. To address this challenge, the USG is using the latest technologies in modeling disease epidemiology and designing a flexible clinical trial infrastructure to enable vaccine testing in regions of high Zika incidence as much as possible in the current outbreak. If traditional regulatory approval cannot be accomplished due to declining Zika disease incidence, the USG might consider accelerated approval or animal rule approval based on an adequate and well controlled surrogate endpoint of clinical efficacy in accordance with published FDA guidance.

The USG Zika virus vaccine development strategy is based, in part, on the following set of assumptions:⁹

- A vaccine that reduces the incidence of symptomatic clinical Zika disease,¹⁰ or the incidence of Zika infection (as assessed by the presence of viral RNA in serum, whole blood or urine), will substantially lower the risk of congenital Zika infection and of sexual transmission¹¹ and will also reduce the frequency of infected mosquitos in a community.
- Vaccine-elicited neutralizing antibodies (as measured by standardized *in vitro* assays) will be required for protective immunity.
- An immune correlate of protection can be identified that will provide critical scientific information and may expedite demonstration of efficacy for future vaccine candidates.
- Industry will remain committed to sharing the risk and costs of developing and advancing Zika vaccine candidates even if the epidemic wanes.
- An investigational vaccine found to be sufficiently safe and effective to qualify for FDA consideration of EUA or EA will also meet expectations of robust and reproducible manufacturability and stability to be produced at sufficient scale and cost to make product available for at-risk and/or broader populations. This assumption includes the full cost and availability of the vaccine and any specialized delivery systems.
- Close coordination and an operating model for decision-making across USG agencies will advance the Zika vaccine portfolio and increase the probability of achieving all Aims.

As experimental data have accumulated and the spectrum of CZS presentation has expanded beyond microcephaly, the first assumption above is critical to consider in more detail. A vaccine-elicited reduction in clinical disease, or reduction in infection, may correlate with reduced fetal infection, but the threshold for these protective effects may not be the same. The USG and its partners do not know the level of immunogenicity or protection needed to prevent seeding of tissue reservoirs, including placental tissue, the potential influence of prior/post flavivirus exposure on Zika caused disease risk and CZS risk, or to reduce the likelihood of mosquito-borne or sexual transmission. Elucidating these various viral loads will be essential to understand the clinical utility of a Zika vaccine as it relates to prevention of CZS in the case of maternal infection or to reduction of infection in a community.

⁹ Notably these assumptions will likely change based on new information about ZIKV, and USG will adjust its strategy as necessary according to this information.

¹⁰ Defined as: virologically confirmed Zika virus infection in conjunction with clinical signs and symptoms. According to the CDC, the most common symptoms of Zika virus disease are fever, rash, joint pain, or conjunctivitis (red eyes). Other common symptoms include muscle pain and headache.

¹¹ Protection against other possible Zika sequelae (e.g., Guillain-Barre syndrome) is not presently the focus of the vaccine development strategy.

1.5 Requirements to Achieve Anticipated Outcomes

1. **Aim 1.** Completion of this Aim will require immunogenicity, safety and efficacy data, which is primarily anticipated from efficacy studies in qualified animal models (mice and nonhuman primates) and Phase 1 and 2 clinical trials preferably by the end of 2018. If a vaccine is shown to be efficacious, a key goal is to derive immune endpoints that are predictive of protection/clinical benefit. The following requirements and objectives will help to accomplish Aim 2:
 - a. Standardized and validated *in vitro* neutralization assays to assess samples from both clinical trials and preclinical animal studies
 - b. For candidates evaluated in Phase 2b efficacy studies, definition of neutralizing antibody or other serological measurements as an immune correlate of efficacy against clinical symptoms (or against infection if PCR positivity endpoint is achieved) in vaccine recipients
 - c. Animal model data demonstrating efficacy of passive transfer of key sera from clinical vaccine trials. Such data could support the use of neutralizing antibody level as a surrogate for (or correlate of) vaccine-mediated protection against Zika virus infection or CZS
2. **Aim 2.** Completion of this Aim will require that the vaccine candidate generate sufficient safety, immunogenicity and, if feasible, efficacy data to support potential use under expanded access or Emergency Use Authorization (or other appropriate regulatory mechanism) for at-risk population(s) in the continental U.S./Hawaii, its Territories, or elsewhere around the world. The following requirements and objectives will help to accomplish Aim 2:
 - a. Sponsor(s) works with FDA to consider the possible use of investigational vaccine under an appropriate regulatory mechanism, potentially expanded access or Emergency Use Authorization.
 - b. Sponsor(s) works with CDC to define recommendations for vaccination of at-risk populations.
 - c. Identification of target population (size, locality, risk-group).
 - d. Sponsor(s) work with FDA and/or other regulators to ensure that deployment would not adversely affect the broader clinical development plans toward licensure of a Zika vaccine, including ability to evaluate vaccine effectiveness in well controlled clinical trials.
 - e. Develop sufficient manufacturing capacity to support expanded use of available candidates (pre-licensure).
 - f. Demonstration of progress, capability and plans for full development of the Zika vaccine towards FDA licensure.
3. **Aim 3.** This can be achieved by working with an industry partner to develop commercial-scale vaccine manufacturing and defining a regulatory pathway to achieve licensure and access for recommended populations for a selected vaccine. While the specific licensure pathway will depend on evolving data, the USG will aim to consolidate key animal model and clinical data, especially related to vaccine immunogenicity and immune surrogate markers likely to predict clinical benefit, with the goal of supporting vaccine licensure. The following requirements and objectives will help to accomplish Aim 3:
 - a. Obtain animal model and clinical data that can guide product development through the use of immune surrogate endpoints that likely predict vaccine efficacy and clinical benefit against disease caused by Zika.
 - b. For any candidate with promising safety and efficacy data, USG could work with industry partner(s) to advance development to support FDA licensure in order to make product available for commercial marketing.

- c. If there is a requirement for USG to procure any Zika vaccine, USG could maintain close industry collaboration to facilitate commercial scale production and usage of a safe and effective licensed Zika vaccine.
- d. Establish data collection methods needed to assess the impact of a potential USG vaccine program on CZS including Phase 4 post-marketing studies and/or registries.

1.6 Critical Enablers to Success

The USG identified three enablers that are critical to achieving the Zika vaccine development Goal and Aims:

1. **Integrated Data:** An integration of clinical and nonclinical data will help identify immune correlates of protection, which can potentially be used to accelerate late-stage trials and possibly help compress timelines for subsequent candidates in the pipeline.
2. **Inter-agency Coordination:** Ongoing, effective USG-wide coordination will continue to enable decision-making, information sharing and leveraging resources. Within the parameters of the Public Health Emergency Medical Countermeasures Enterprise (PHEMCE) and under the umbrella of PHEMCE confidentiality, the Zika Vaccine Development Inter-agency Working Group (ZIG), will serve as the coordinating body for this Strategy to reduce duplication, exchange data and strategic planning, and leverage all available resources to achieve each Aim.
3. **Broader Zika Vaccine Research and Development Stakeholder Engagement:** Proactive, continued USG engagement with diverse stakeholders across the Zika vaccine research and development landscape will enable the USG to accelerate vaccine development. This includes the development of strong linkages with current corporate partners as well as vaccine companies not yet engaged in the national Zika strategy through knowledge and resource sharing (such as clinical trial infrastructure, the latest understanding of assays, endpoints, and/or trial design) and development of incentives to mitigate commercial risks and accelerate market entry.

1.7 Conclusion

USG agencies are working diligently together and with academic and industry partners to develop safe and effective vaccines against Zika virus. Since Zika virus infection of adults usually causes moderate self-limiting symptoms, the key public health goal is to prevent CZS through deployment of a safe and effective vaccine(s) against Zika virus. Full commercial-scale vaccine development usually requires many years of effort and strong industry commitment. To expedite this timeline, the USG has developed this white paper. An interim goal is to support the development and evaluation of investigational vaccine for potential use in selected populations through an appropriate regulatory mechanism, e.g., expanded access or Emergency Use Authorization, if such an emergency need arises. This white paper provides a reference point for commercial, government and academic stakeholders. Currently, the USG Zika vaccine portfolio includes candidates at different stages of development, each with its own clinical development plans and partnerships. Rigorous portfolio management and coordination across the USG agencies will optimize the likelihood of successful vaccine development and accelerate the process by supporting diverse technologies, leveraging resources, infrastructure and capacity, diminishing redundancy, establishing clear criteria for candidate evaluation, identifying knowledge gaps and overcoming unanticipated hurdles. The decision points, milestones and recommended next steps from this coordination will guide the USG efforts to develop safe and effective Zika vaccines.