FDA Briefing Document

Vaccines and Related Biological Products Advisory Committee Meeting

November 8, 2019

Development of Chikungunya Vaccines: Demonstration of Effectiveness

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1. Overview

First described in Tanzania in 1955 [1, 2], Chikungunya (CHIK) had been mainly confined to localized outbreaks in Africa and Asia. However, in 2007, cases were identified in Italy and France, and subsequently 17 countries or territories in the Caribbean, Central America and South America. By 2014, a total of 10,201 suspected cases had been reported in Puerto Rico, [3] along with a total of 272 imported cases and 11 locally acquired cases reported in the US state of Florida [4].

Although CHIK disease is typically self-limited, a substantial number of patients are hospitalized with severe fever, arthralgia, rash, malaise and weakness. Severe manifestations, although rare, include meningoencephalitis, myocarditis, multiorgan system failure, and death [5-8]. Additionally, a chronic phase characterized by polyarthralgia (12% to 75%) [9-15] results in significant health and economic burdens.

Given lack of a preventive vaccine or directed anti-viral treatment for CHIKV disease, several CHIKV vaccine candidates are currently in development and have been tested in phase 1 or 2 clinical trials. As delineated in subsequent sections, vaccine effectiveness can be demonstrated using several approaches, recognizing that randomized controlled trials (RCTs) that use clinical disease endpoints represent are considered to be the most robust assessment of effectiveness. However, challenges to conducting prospective RCTs are recognized, including unpredictable size, location and duration of outbreaks and poor infrastructure for implementation of clinical trials. Therefore, FDA is working with manufacturers developing CHIKV vaccines to determine how to respond to the logistical challenges of clinical trial design while maintaining a rigorous evaluation of vaccine effectiveness.

Identified safety concerns pertaining to vaccine development include occurrence of vaccine-related arthralgia after receipt of a live-attenuated CHIKV vaccine [16], and a theoretical risk of vaccine-associated enhanced disease with subsequent wild-type CHIKV infection, presumably due to poorly neutralizing or non-neutralizing antibodies, known as antibody-dependent enhancement (ADE). While ADE has not been reported

to date in associated with CHIKV in humans, this phenomenon has been described *in vitro* and *in vivo* for some infectious diseases, including dengue [17, 18], rabies [19], respiratory syncytial virus disease [20, 21], Ebola [22], measles [23], and the closely related Ross River alphavirus [24].

During the November 8, 2019, Vaccines and Related Biological Products Advisory Committee (VRBPAC) meeting, it is expected that vaccine manufacturers will describe their respective approaches to demonstrating the effectiveness of their Chikungunya vaccine candidates. To frame the discussion, an overview of the current epidemiology of CHIK disease will be provided to inform the feasibility and potential design of clinical trials, as well as currently available animal models that might be used in conjunction with clinical studies to evaluate vaccine effectiveness.

The committee will be invited to advise on the types of pre- and potentially post-licensure data that should be generated to demonstrate vaccine effectiveness. The committee will not be asked to select a licensure pathway for Chikungunya vaccines but rather will be tasked with discussion and recommendations on scientific issues that will inform FDA's determination of which licensure pathway(s) would be feasible according to the requirements outlined in relevant FDA regulations. Although safety considerations are acknowledged as an important factor to address in both pre- and post-market settings, this aspect of vaccine development is not expected to be the focus of the VRBPAC discussion.

2. Chikungunya Clinical Disease and Epidemiology

CHIKV is an arbovirus belonging to the alphavirus genus of the family *Togaviridae*. Three distinct genotypes of the virus have been identified: The West African, the East/Central/South African (ECSA), and the Asian genotypes [25]. The Indian Ocean Lineage (IOL), which is derived from ECSA and forms a monophyletic group within the ECSA lineage, is considered the fourth genotype [25]. All these genotypes represent the same serotype based on current serotyping methods. CHIKV is primarily transmitted through the bite of infected *Aedes* mosquitos. Rarely, CHIKV is transmitted

from mother to newborn around the time of birth [26, 27]. While theoretically possible, human-to-human transmission through blood products or human milk has not been reported to date.

Following the bite of a mosquito infected with CHIKV, most individuals will present with symptomatic disease after an incubation period of 3-7 days (range: 1−12 days). Serosurveys indicate that between 3.2% - 27.7% of persons with antibodies to CHIKV have asymptomatic infections [28, 29]. The distinct feature of the disease is debilitating polyarthralgia, which may persist for months or even years [9-15]. Although CHIK is known as a relatively benign disease, rarely, severe manifestations, such as meningoencephalitis, myocarditis, and multiorgan system failure, do occur, particularly in neonates and elderly patients with co-morbidities [5-8]. While mortality associated with CHIK is uncommon (about 1 in a 1,000) [5, 30], the high attack rate of acute debilitating polyarthralgia (approximately 95%) [28, 29, 31] and subsequent chronic polyarthralgia (12% to 75%) [9-15] result in significant health and economic burdens.

Manifestation of CHIK is divided into three phases: acute, subacute (convalescent), and chronic phase. Acute disease typically lasts for 3 −10 days and is characterized by sudden onset of high fever (typically greater than 102°F [39°C]) and severe joint pain [30, 32, 33]. Other signs and symptoms include headache, diffuse back pain, myalgias, nausea, vomiting, polyarthritis, rash, and conjunctivitis. The convalescent phase of the disease spans from day 10 to 3 months post-infection and is typically characterized by the improvement of the presenting symptoms. However, a relapse of symptoms can occur, with some patients complaining of various rheumatic symptoms, including distal polyarthritis, exacerbation of pain in previously injured joints and bones, and hypertrophic tenosynovitis in wrists and ankles. Relapses of the symptoms most commonly occur between 2 – 3 months after the illness onset. Other consequences of infection commonly encountered during this phase include high rates of depressive symptoms, fatigue, and weakness [34]. The chronic phase is defined by symptoms that persist for more than three months. The frequency of persistent symptoms varies substantially by study and the duration of follow-up. Studies from South Africa show that

12%−18% of patients have persistent symptoms at 18 months and up to 2 to 3 years [11, 12]. In studies in India, 49% of patients had persistent arthralgia at 10 months [13]. In studies in La Réunion as many as 93% of patients complained of persistent symptoms 3 months after disease onset, and the proportion of patients with persistent symptoms decreased to 57% at 15 months and to 47% at 2 years [14, 15].

The most common persistent symptom is inflammatory arthralgias in the same joints that were affected during the acute stages. Usually, there is no significant change in laboratory tests or x-rays of the affected areas. However, some individuals go on to develop destructive arthropathy/arthritis resembling rheumatoid or psoriatic arthritis [35]. Risk factors for chronic disease are older age (> 45 years), pre-existing joint disorders, and more severe acute disease [14, 36].

Between 1952 and 2004, CHIK had been mainly confined to localized outbreaks in Africa and Asia. In May 2004, an outbreak of CHIK originated in the Kenyan coast and rapidly spread east and south reaching unprecedented magnitude [14, 37-40]. In 2007, the first reported outbreak of local transmission outside tropical countries occurred in Italy and involved 175 laboratory-confirmed cases [41, 42]. In December 2013, the first local transmission of CHIKV in the Western Hemisphere was reported in the French side of Saint Martin Island [43-45]. Since then, the virus has spread to 17 countries or territories in the Caribbean, Central America and South America, where hundreds of thousands of laboratory-confirmed cases have been reported [46]. In May 2014, the first locally acquired, laboratory-confirmed case of CHIK was reported in Puerto Rico, and by August 2014, a total of 10,201 suspected cases had been reported there, with approximately 70% confirmed by laboratory diagnosis [3]. In June 2014, the first locally acquired case of CHIK in the southern U.S. state of Florida was confirmed, and a total of 272 imported cases and 11 locally acquired cases had been reported there by October 14, 2014 [4].

The species of *Aedes aegypti* was the principal vector involved in the outbreaks in tropical regions. However, during the outbreaks in Asia, the Indian Ocean, Europe, and the Caribbean, *Aedes albopictus* was identified as the principal vector. The change in

the vector species occurred when CHIKV acquired a mutation that enhanced its infectivity in *Aedes albopictus* [7, 39, 47]. The adaptation of the mutated CHIKV in *Aedes albopictus* will potentially enhance transmission of CHIKV in more temperate regions. In response to this fast emerging infectious disease, the World Health Organization (WHO) and the Centers for Disease Control and Prevention (CDC) have started epidemic surveillance for CHIK and have been tracking outbreaks and reporting on their websites [48, 49] .

As of May 2018, CHIKV infection has been reported in different countries on all continents except for Antarctica [48]. The most recent CHIKV outbreaks were reported in seven states in Sudan in October, 2018, and in Congo in May 2019 [49] .

3. Development of CHIKV Vaccines

Natural CHIKV infection may lead to long-term protective adaptive immunity. Anti-CHIKV IgM and IgG antibodies have been detected in the sera of infected patients during the acute phase of the infection [50, 51]. Long intervals (up to decades) between epidemics in small rural populations is thought to be likely attributed to long-term protective immunity elicited by CHIKV infection [52, 53]. However, it is unclear whether these long intervals reflect local circulation of a single genotype or the capacity of the immune response to natural infection by one genotype to confer cross-protection against heterologous genotypes.

Animal studies have demonstrated that CHIKV infection [54, 55] or vaccination with investigational CHIKV vaccines [56-58] induces protective immunity against CHIK and that protection in these animal models is primarily mediated by neutralizing antibodies. Human studies have suggested that serum neutralizing antibodies elicited by CHIKV infection correlate with viral clearance and long-term protection against subsequent infection and disease [38, 39]. CHIKV surface viral glycoproteins have been demonstrated to be key targets for protective neutralizing antibodies against CHIKV [50, 59-61]. Passively transferred human or mouse anti-CHIKV antibodies appear to mediate protection in mouse models of infection [40, 41].

T cells are important effector cells during viral infection. Both CD4+ and CD8+ T cells can eliminate virus-infected cells. Studies have demonstrated that the innate immune system is strongly activated within the first days after natural CHIKV infection in humans and leads to a robust and long-lasting CD4/CD8 response against several viral proteins [62-65]. However, studies in mice have also suggested that neither CD4+ nor CD8+ T cell subsets appear to have a role in control of CHIKV replication and dissemination [54, 55, 66]. Thus, the role of T cells in prevention of CHIK in humans remains to be elucidated.

Currently, there is no licensed vaccine available to prevent CHIK. Vaccine candidates in development include inactivated viruses, live-attenuated viruses, chimeric viruses, replication-defective vectored vaccines, recombinant DNA or mRNA vaccines, subunit vaccines, and virus-like particle (VLP) vaccines [67, 68]. While most of these investigational vaccines have demonstrated immunogenicity and/or protection against lethal challenge in animals [67, 68], only a few have advanced into clinical trials in humans [16, 69-73].

4. Approaches to demonstrating CHIKV Vaccine effectiveness

In the U.S., “traditional approval”, accelerated approval, and “animal rule” approval are potentially available pathways for CHIKV vaccine candidates and can be applied, provided the regulatory requirements for the particular pathway are met. Vaccine effectiveness can be demonstrated using several approaches. While field efficacy trials using a clinical disease endpoint for demonstrating vaccine efficacy represents the gold standard, under certain situations, clinical studies using an immunologic biomarker or animal efficacy studies may be used as the primary basis to support vaccine effectiveness. The following sections will discuss these approaches and the uncertainties and practical issues associated with each.

4.1 Demonstration of Vaccine Effectiveness Based on Studies Using Clinical Disease Endpoints or Scientifically Well-Established Immunologic Markers ("Traditional Approval")

Under FDA's "traditional approval" licensure pathway, demonstration of vaccine effectiveness can be based either on a clinical disease endpoint or, alternatively, a scientifically well-established marker of protection, e.g., an immunogenicity endpoint that is applicable to the candidate vaccine. Under this scenario, several clinical trial designs may be considered for providing evidence of CHIK vaccine effectiveness.

4.1.1 Clinical Efficacy Field Trial

Randomized controlled field efficacy trials that are based on clinical disease endpoints and conducted in people at risk of contracting disease are the gold standard for providing direct, conclusive evidence of vaccine effectiveness. Challenges to conducting an RCT include the recognition that outbreaks of CHIK disease are unpredictable and the duration of outbreaks can be relatively short.

The feasibility of conducting clinical field efficacy trials may change over time. For example, the scope and frequency of CHIK outbreaks have increased significantly in recent years with the adaptation of CHIKV to *Aedes albopictus* mosquitos, which are found in more temperate regions, such as Europe and the Americas, where populations are naïve to the virus. Thus, given the high attack rates and rates of symptomatic infection (up to >90%) associated with CHIK outbreaks [74], the feasibility of conducting a well-designed clinical disease endpoint efficacy trial in an immunologically naïve population may be feasible and may be further explored. While outbreaks are unpredictable, adequate preparation of potential study sites, close monitoring of CHIK disease activity through ongoing surveillance to identify outbreaks early and use of master protocols could facilitate a successful clinical disease endpoint efficacy study. A recent report by the WHO proposed clinical endpoints (e.g., laboratory confirmed CHIK disease), statistical success criteria (e.g., VE % > 30% assuming a two-sided type 1 error rate of 0.05), randomization schema (e.g., 2:1 vaccine to placebo), and

associated suggested sample sizes (e.g., N = 1200) that might be feasible [75]. Cooperation among vaccine developers, local governments, public health authorities, and regulatory authorities will be crucial for successful field efficacy trials.

4.1.2 Human Challenge Study

With some pathogens, challenge studies in human subjects may provide evidence of effectiveness of a vaccine candidate directed against that pathogen. Human challenge studies can be ethically justified in adults who have provided appropriate informed consent when there is assurance that the challenge infection will be self-limited or interrupted with appropriate therapy, and that complications can be easily and fully managed without sequelae. In 1998, an FDA VRBPAC agreed that human challenge studies in subjects from cholera non-endemic areas could suffice to demonstrate effectiveness of a cholera vaccine for use in travelers to affected regions. This agreement was influenced by the disappointing efficacy of a cholera vaccine in a large field efficacy trial in a cholera endemic area [76]. Subsequently, FDA licensed a cholera vaccine, Vaxchora, based on a challenge study conducted in a non-endemic region, for individuals traveling to cholera-endemic regions, with the nature of the study population and study design reflected in the product labeling, accordingly.

Most cases of CHIK eventually resolve without permanent sequelae; however, infected individuals may develop persistent debilitating arthralgia, for which no treatment is available. It has been reported that up to 75% of patients experience persistent or recurrent arthralgia as long as 15 months after initial infection [14], and 12% of patients with serologically proven CHIKV infection have described joint stiffness, swelling and pain up to 3 years after initial infection [11]. Epidemic studies have demonstrated that persistent arthralgia is associated with older age [13, 14] and may also be associated with specific virus strains or genotypes [7, 77-81]. While persistent arthralgia and other long-term yet-uncharacterized sequelae of infection could present a risk to volunteers enrolled in a CHIK challenge study, stringent eligibility criteria combined with rigorous strain selection and informed consenting procedures might render this approach feasible. It is unknown whether the risk of long-term sequalae from human challenge

studies with CHIKV can be mitigated by carefully selecting the study population and virus strains (or attenuated strains) used for challenge.

4.1.3 Immunogenicity Study

As stated above, under FDA's "traditional approval" pathway, if a scientifically well-established immune marker that predicts protection (e.g., antibody threshold) is available, immunogenicity studies can be conducted using an immune marker as an immunogenicity endpoint in lieu of a clinical endpoint to infer vaccine effectiveness. In these situations, immune markers that predict protection have typically been previously established in vaccine clinical efficacy trials and/or epidemiologic studies. For example, yellow fever vaccine (YF-VAX®) was approved based on demonstration of protective neutralizing antibody responses post-vaccination [82-84]. Antibody to hepatitis B surface antigen above a certain threshold (i.e., anti-HBsAg IgG titer ≥10 mIU/mL) has been established as a threshold predictive of protection and has been used to support traditional approval of hepatitis B vaccines. Effectiveness of a vaccine may also be demonstrated by non-inferiority of a clinically relevant immune response compared to a licensed vaccine. For example, the Japanese encephalitis virus (JEV) vaccine (IXIARO®), was approved by FDA based on non-inferiority of both the proportion of subjects with anti-JEV neutralizing antibody titer ≥ 1: 10 and geometric mean anti-JEV neutralizing antibody titer compared to the licensed JEV vaccine, JEVax®. This non-inferiority approach would only be applicable in situations where another CHIK vaccine had been previously licensed in the US based on demonstration of efficacy.

A number of animal studies, including anti-CHIKV antibody adoptive transfer studies, have demonstrated that protection is primarily mediated by anti-CHIKV neutralizing antibodies [54, 56, 58, 61, 85-89]. Human epidemiological studies also suggest that neutralizing antibodies against CHIKV are protective [50, 51, 53, 78]. However, there is currently no scientifically well-established marker of protection for CHIKV. Thus, if use of the traditional approval pathway were to be considered, demonstration of effectiveness would likely need to be based on an endpoint such as prevention of CHIKV disease.

4.2 Demonstration of Vaccine Effectiveness Based on Studies Using Immunologic Markers that Are Reasonably Likely to Predict Clinical Benefit (Accelerated Approval)

In the US, products for serious or life-threatening illnesses providing meaningful benefit over existing treatment can be approved under the accelerated approval provisions. For a CHIKV vaccine, approval under these provisions would be based on adequate and well-controlled clinical trials establishing an effect of the product on a surrogate endpoint (e.g., immunological marker) that is *reasonably likely* to predict clinical benefit. Due to some uncertainty regarding the ability of the immune marker to predict protection, accelerated approval is subject to the post-licensure requirement that the applicant conduct adequate and well-controlled clinical trials with due diligence (usually underway at the time of licensure) in order to verify and describe the clinical benefit, (e.g., evaluating the effect of the vaccine on a clinical disease endpoint).

One potential approach to identifying an immune marker reasonably likely to predict clinical benefit of a CHIKV vaccine could involve sero-epidemiologic studies in CHIK-endemic regions. For example, in a prospective longitudinal study conducted in the Philippines, >800 subjects 6 months of age and older underwent active surveillance for symptomatic CHIKV infection, and CHIKV-neutralizing antibody titers were determined at various time points over 12 months starting at study entry [81]. Among 19 subjects who had laboratory confirmed symptomatic CHIKV infection (all relatively mild), none had a baseline CHIKV-neutralizing antibody titer of 1:10 or higher as determined by plaque reduction neutralization test (PRNT), and only a few of the 87 subjects with asymptomatic CHIKV infection, as determined by a 8-fold or greater increase in CHIK-neutralizing antibody titer during the surveillance period, had a baseline titer of 1:10 or higher. While the applicability of these study observations is limited by factors including unusually mild disease manifestations among the symptomatic cases, an unusually high percentage of asymptomatic infections, and uncertainty about the validation status of the serologic and diagnostic assays, the study shows that this approach is feasible and could potentially contribute to identification of an immune marker to support accelerated approval.

Another approach could involve passive transfer of individual or pooled sera, or purified IgG, from CHIKV vaccine-immunized human subjects to non-human primates (NHPs) in CHIKV challenge models. Such studies might be relevant to either "accelerated approval" or "animal rule" licensure (see below). Since persistent or recurrent polyarthralgia and polyarthritis are the most common morbidities associated with CHIK, an animal model that demonstrates acute polyarthralgia or polyarthritis associated CHIK, rather than being limited to evaluating viremia and fever, will greatly enhance the value of the model to assess the capacity of passively transferred human anti-CHIKV to predict a clinical benefit. However, NHPs are relatively resistant to CHIKV infection, such that challenge doses of CHIKV equivalent to natural infection (approximately 10^3 PFU) in any animal model cannot reproduce the polyarthritis observed in humans [90]. Although higher challenge dose (~10^7 PFU) induces joint inflammation and effusions in NHPs, the dose is not physiologic and causes more severe complications and mortality than with natural human infection [90]. In addition, it is unclear whether the pathogenic mechanism(s) of polyarthritis associated with CHIKV infection in humans is caused by persistent infection [36, 91, 92], and/or autoimmunity [93-95].

Comparing to humans, immune competent animals are relatively resistant to CHIKV infection. Even if adoptive transfer of anti-CHIKV human sera can completely clear viremia, there remains the question as to whether CHIKV neutralizing antibody titer derived from the animal model is reasonably likely to predict a clinical benefit, e.g., recurrent polyarthritis. Furthermore, a protective titer derived from NHP challenge model with passive transfer of pooled human anti-CHIKV sera would not necessarily predict protection in individual humans with post-vaccination antibody titer equivalent to the protection titer estimated from the animal model. Following passive transfer of pooled human sera, CHIKV neutralizing antibody titer in NHP circulation would be substantially diluted and lower than in the pooled sera prior to transfer. Protection observed in the animal model might be largely driven by individual sera from those vaccinees who have protective responses (potentially with substantial over-representation of serum from individuals who have the highest neutralizing antibody titers). It is not known whether sera with high titers of anti-CHIKV neutralizing antibodies are qualitatively comparable

to sera with low titers of anti-CHIKV neutralizing antibodies. In addition, parameters other than PRNT titers, such as IgG subclasses and breadth of antibody responses, might have an impact on the ability of antibodies to protect against CHIKV. Finally, in contrast to purified IgG, human sera may also contain other factors, such as cytokines, that may drive protective immune responses, independent of the protective effects conferred by the transferred antibodies. These concerns should be considered in order to design a study that is adequate to support effectiveness of the candidate CHIKV vaccine.

4.3 Demonstration of Vaccine Effectiveness Based on Animal Efficacy Studies ("Animal Rule")

Licensure of a preventive vaccine using the "animal rule" requires that studies in humans intended to support licensure via other the approaches, (i.e., "traditional" or accelerated approval) are unethical or infeasible, and that in general, the following criteria are met: 1) there is a reasonably well-understood pathophysiological mechanism of the infectious agent and its prevention by the vaccine; 2) the effect of the vaccine is demonstrated in more than one animal species expected to react with a response predictive for humans, or in a single animal species that represents a sufficiently well-characterized animal model for predicting the response in humans; 3) the animal study efficacy endpoint is clearly related to the desired benefit in humans; and 4) the data on the immune response to the vaccine in animals and humans allows selection of an effective dose in humans. Licensure through the "animal rule" is also subject to the requirement that the applicant conduct post-marketing studies, such as field studies, to verify and describe the product's clinical benefit and to assess its safety, if circumstances arise in which a study would be feasible and ethical (e.g. in the event of an outbreak when the vaccine is used).

CHIKV is an arthritogenic virus in humans. Following infection with CHIKV, up to over 90% individuals develop acute symmetric polyarthritis, and an average 50% of infected individuals develop chronic polyarthritis lasting months or even years [94, 96-100]. However, no animal model has showed acute polyarthritis nor persistent polyarthritis

following natural infection with CHIKV, indicating that pathogenesis of CHIKV in humans may be different from animals. Theoretically, sterilizing immunity conferred by a CHIKV vaccine against CHIKV infection in animal models might provide a reasonable basis to predict a clinical benefit in humans in support of licensure. Since the pathogeneses of CHIKV in animals and humans differs, it is unknown if sterilizing immunity conferred by a CHIKV vaccine in animal models will predict a clinical benefit in humans. Taken together, an efficacy endpoint in animal studies that is sufficiently related to the desired benefit in humans may not yet have been identified.

4.4 Postmarketing Studies to Confirm Clinical Benefit for Vaccines Approved under the Accelerated Approval or Animal Rule Pathways

As described above, vaccines approved under the accelerated approval or "animal rule" provisions would require post-licensure clinical efficacy studies to verify and describe the clinical benefit of the vaccine.

To meet the need for a CHIKV vaccine, several developers have proposed conducting studies to support licensure in CHIKV non-endemic areas, with subsequent trials evaluating effectiveness in endemic region post-licensure, to satisfy the FDA requirement to verify clinical benefit. Another approach might include conducting pre-licensure immunogenicity studies among CHIKV naïve populations in multiple potential CHIKV outbreak regions, which could be continued post-licensure to verify clinical benefit in the event of a CHIKV outbreak in one or more of those regions. If CHIKV outbreaks occurred within a reasonable time frame, the study design would both fulfill the regulatory requirements, and provide valuable information regarding duration of protection.

Alternatively, the requirement for post-licensure confirmatory trials to verify and describe a clinical benefit could be fulfilled through a well-designed observational study (e.g. a test-negative case control study). In this study design, patients seeking health care for CHIK-related symptoms are recruited into the study and tested for the disease. Vaccine effectiveness is then estimated by comparing the odds of vaccination in subjects who

have CHIKV related symptoms and laboratory-confirmed CHIKV infection to the odds of vaccination in subjects who have CHIKV related symptoms but test negative for CHIKV infection. Such a study design has been used by CDC to provide yearly estimates of seasonal influenza vaccine effectiveness [101]. Determining the acceptability of this approach would require careful consideration of sources of bias that could inflate the estimated vaccine effectiveness and a study design that would aim to curtail the impact of those factors. Ideally, the results would also be unambiguous (i.e., a well-executed, prospective study, yielding a high point estimate for vaccine effectiveness with tight confidence intervals), such that unknown and therefore uncontrolled bias would not be expected to substantially impact the overall benefit-risk assessment.

4.5 Additional Considerations for Demonstrating Effectiveness of CHIK Vaccines

Since the clinical presentation and geographic distribution of CHIK overlap with other arbovirus infectious diseases such as dengue fever, O'nyong-nyong fever, Ross River fever, and Zika, a clear case definition of CHIK (including a highly specific diagnostic assay) will be essential for demonstrating vaccine effectiveness in clinical efficacy studies. Specificity of immunogenicity assays for CHIKV versus related viruses will also be important in investigating immune markers of protection and in estimating clinical effectiveness through immunological bridging. In addition, validation of assays for quantifying anti-CHIKV antibodies will be critical for situations where immunogenicity analyses will be pivotal (e.g., licensure under accelerated approval or the "animal rule" or in deriving an antibody threshold considered predictive of protection from clinical efficacy trials or human challenge studies).

Variations in CHIKV genotype, particularly alterations in the glycoprotein gene, may translate to clinically meaningful differences. In animal studies, immunization with an investigational vaccine derived from one genotype protected animals from lethal challenge with a heterologous genotype [56, 58]. Neutralizing antibodies elicited by an investigational vaccine derived from one genotype in humans have been shown to cross-neutralize heterologous genotypes [69, 72]. However, immune sera from humans infected with CHIKV have also shown decreased neutralizing capacity against a

heterologous CHIKV genotype compared with homologous CHIKV genotype [102], lending uncertainty as to whether the immune response generated from a vaccine based on a genotype of CHIKV will induce reliable heterogenotypic cross-protection.

In addition, two CHIKV transmission waves during 2014-2015 in Bahia state of Brazil were reported to be caused by two distinct CHIKV genotypes (Asian and ECSA genotypes) [103], with serum samples from six of the eight study subjects who were hospitalized following CHIKV infection demonstrating evidence of seropositivity for both circulating genotypes [104]. It is unknown whether the infections were contemporaneous or sequential. Nevertheless, the study has raised a concern that vaccination or infection with one genotype of CHIKV may not confer cross-protection against other CHIKV genotypes. Therefore, cross-protection against known or potentially emergent genotypes not covered by a candidate vaccine would need to be addressed in the clinical development program.

Previous vaccination with an investigational Venezuelan equine encephalitis virus (VEEV) vaccine appears to interfere with neutralizing antibody response to subsequent CHIKV vaccination in humans, and *vice versa* [105]. Clinical trials with CHIKV vaccines should address whether prior exposure to other alphaviruses or pre-existing immune response to other alphaviruses interferes with anti-CHIKV antibody responses.

5. Summary

The VRBPAC is convened to obtain the committee's guidance on the type of pre-and postlicensure studies that can be conducted to demonstrate the effectiveness of CHIK vaccine candidates.

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