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Status of research and development of vaccines for chikungunya

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ABSTRACT

This manuscript title is being submitted in response to a request received for the Special Issue of Vaccine on WHO Pipeline analyses of emerging vaccine candidates against global infectious diseases.

1. About the disease and pathogen

Chikungunya fever, a mosquito transmitted disease caused by chikungunya virus (CHIKV), is an acute febrile illness characterized by severe, debilitating polyarthralgia, that often progresses to a chronic stage, with reports of over 60% of those affected suffering from joint pain three years after infection. Unlike similar arboviral diseases such as dengue, infection with CHIKV is rarely asymptomatic with less than 5–25% of patients reported as having seroconverted without symptoms during recent large epidemics. Disease occurs across all age groups with similar frequencies and is associated with fever and severe myalgia (90% of patients), polyarthralgia and polyarthritis (95%), and rash (50%). Severe but rare manifestations include encephalopathy, encephalitis, myocarditis, hepatitis, multi-organ failure and death. These are typically associated with older age and pre-existing morbidities such as cardiovascular or neurologic disease, respiratory disorders, or diabetes. Neonates and young children may also experience higher incidence of severe chikungunya disease. Following the acute phase of febrile disease, roughly half of patients experience chronic joint pain that may persist or recur in cycles over several years. Chronic symptoms can be similar to those of seronegative rheumatoid arthritis, frequently resulting in persistent incapacitation, often requiring long-term treatment using non-steroidal anti-inflammatory and immunosuppressive drugs. There are no antiviral treatments currently available [1,2].

CHIKV is an enveloped, positive-sense single stranded RNA alphavirus in the family *Togaviridae*. Like most alphaviruses, CHIKV has the ability to infect and replicate in both vertebrates and invertebrates, allowing for maintenance of the virus in enzootic cycles between its non-human primate reservoir and arboreal mosquitoes, with occasional transmission to human populations. However, unlike most alphaviruses, CHIKV utilizes an urban cycle resulting in sustained transmission between humans and anthropophilic mosquitoes causing widespread epidemics with attack rates reaching 90%. Over the past decade CHIKV has emerged as a major cause of vector-borne disease with transmission reported in more than 100 countries and territories worldwide. Globally, there are an estimated 1 million cases per year including periodic large-scale epidemic outbreaks throughout the world and low-level endemic transmission in Africa and Southeast Asia [3,4]. Large epidemics occur episodically and unpredictably and tend to be explosive. For example, in 2004, CHIKV reemerged in Lamu Island, Kenya, resulting in 1300 documented clinical cases and potentially infected over 70% of the population. In 2005, CHIKV infected 63% of Union of the Comoros' population resulting in 225,000 cases. In 2006, there were 266,000 cases on the island of La Réunion (approx.

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1/3 of population) with the first significant reports of neurological symptoms and fatal cases. Similar large epidemics, with over 1 million estimated cases, occurred in southern India during 2005–2006. An ongoing epidemic spreading throughout the Americas began in December of 2013 and, as of May 2015, has resulted in over 1.4 million suspected cases across 50 countries and territories, with 178 associated deaths [5].

While the estimated case fatality rate is low (~0.1–5% reported in recent epidemics) compared to some other arboviral diseases of global importance, the economic and disease burden due to the severe morbidity of chikungunya fever appears substantial, although only a few studies to evaluate costs of chikungunya disease have been performed and additional data are needed. The La Reunion outbreak in 2006 resulted in an estimated US$50–55 million in medical costs [6] and 55,000 DALYs when accounting for acute and long term disease [7]. A recent prospective cohort study of acute febrile illnesses in children at study sites in several Southeast Asian countries determined that CHIKV infection was responsible for approximately 3-fold higher number of cases compared to dengue viruses [8], although this may be an overestimate due to the limited confirmatory testing performed on anti-CHIKV IgM positive samples. Similar hospital-based studies during 2008–2009 in India identified CHIKV as the cause of almost 50% of acute febrile illnesses in the southern state of Karnataka [9], an area greatly affected by the 2005–2006 epidemics.

Four lineages of CHIKV currently circulate throughout the world: the East, Central, and Southern African (ECSA) lineage, the West African lineage, the Asian lineage, and the Indian Ocean lineage (IOL). While the ECSA and Asian lineages are typically transmitted by the urban vector, *A. aegypti*, the IOL is characterized by acquired adaptive mutations in the E1/E2 proteins allowing for sustained transmission by the more widespread *A. albopictus* urban mosquito. It was thought that IOL CHIKV may become predominant due to this adaptation and its association with large outbreaks in 2005–2008. However, the ongoing outbreak in the Americas (associated with strains belonging to the Asian lineage), and the emergence and spread of Asian and ECSA lineages in the South Pacific since 2011, highlight the epidemic potential of all CHIKV variants. Animal studies suggest that there is no major difference in virulence between CHIKV strains representing the different lineages. Recent reports from Southeast Asia [10] and the Americas have described higher than typical rates of subclinical CHIKV infection leading to suggestions that there may be lineage- or strain-specific differences in virulence, although pre-existing immunity in Asia may also have influenced subclinical infection rates.

Presumptive diagnosis is typically clinical with confirmatory laboratory tests performed using serum samples. If samples are collected within 5 days of fever onset, reverse transcription polymerase change reaction (RT-PCR) can be used to detect viral genome. For RT-PCR negative samples collected 5 or more days after onset, enzyme-linked immunosorbent assays (ELISAs) can be performed to detect anti-CHIKV IgM antibodies. Several IgM-ELISA kits are commercially available. Since other alphaviruses belonging to the same antigenic complex as CHIKV, such as Mayaro, o'nyong-nyong, and Ross River viruses, co-circulate in areas where CHIKV transmission has occurred, there is potential for cross-reactivity when performing ELISAs. Confirmatory serological testing via plaque reduction neutralization test (PRNT) for ELISA-positive, RT-PCR-negative samples is performed at reference laboratories.

To date, vector control has been the primary response to chikungunya outbreaks but effectiveness has not been extensively evaluated and may face challenges due to insecticide resistance in *Aedes* spp. vectors.

2. Overview of current efforts

2.1. Biological feasibility for vaccine development

There are no licensed vaccines for chikungunya. However, several other alphavirus vaccine candidates have been evaluated in human clinical trials or licensed for veterinary use, including for Ross River virus (RRV) and Venezuelan equine encephalitis (VEEV) among others. The RRV candidate and the veterinary vaccines are based on an inactivated-virus platform, and a live, attenuated VEEV vaccine has been used for special immunization in the United States under an investigational new drug (IND) approval. Protective immunity induced by each of these vaccines is believed to be associated with induction of neutralizing antibodies directed towards the envelope glycoproteins.

All CHIKV lineages appear to comprise a single serotype and it appears that long-lasting cross-protection between lineages is afforded, so a single vaccine can be expected to protect against all CHIKV strains. A formalin inactivated chikungunya vaccine candidate was developed by the US military in the 1960s. Due to concerns about cost and safety of bulk production of CHIKV at BSL3, a live, empirically attenuated candidate, TSI-GSD-218 (strain 181/clone 25, derived from Asian lineage strain AF15561) was subsequently developed during the 1980s-90s by the US Army Medical Research Institute for Infectious Diseases (USAMRIID) and evaluated in Phase I/II clinical trials. This vaccine displayed strong immunogenicity (>98% seroconversion) and was generally well tolerated with only mild effects, including transient arthralgia in approx. 10% of recipients. Further development of this vaccine was discontinued, primarily due to low priority of chikungunya to the military coupled with significant perceived challenges for further development and clinical efficacy trials. The live, attenuated virus was provided to other vaccine developers following resurgence of chikungunya in the mid-2000s. Reversion to virulence is a concern for this vaccine as subsequent studies showed attenuation was mediated by only two point mutations.

Several animal models are available to study chikungunya disease and to assess vaccine efficacy. The model that most closely mimics the human disease is cynomolgus macaques, which are a natural reservoir of the virus and show a dose dependent pathophysiology. Low infecting doses (10^1 pfu) result in viremia, fever and rash while higher doses (>10^6 pfu) can also result in joint swelling and meningoencephalitis, similar to severe disease seen in humans. Immunocompetent mice (e.g. C57BL/6, ICR, or CD1) do not mimic the human disease and show an age-dependent susceptibility. Suckling mice are susceptible to a neuroinvasive disease. Disease in mice greater than 3–4 weeks of age is characterized by transient viremia and swelling at the site of inoculation, typically the footpad. Those two parameters are typically used as endpoints to assess protection in challenge studies. Immunocompromised mice, particularly IFN-α/β receptor knockouts (e.g. A129) exhibit more severe disease, including mortality, and may more accurately mimic the cell/tissue tropism of CHIKV infection in humans.

The current understanding of protective immune responses to CHIKV infection has been derived from animal models as well as limited human data following natural infection [11]. The humoral immune response seems to play a more important role in controlling CHIKV infection than cell mediated immunity (CMI). Following CHIKV infection in humans and nonhuman primates (NHPs), the incubation period is typically 3–7 days (range 1–12 days) and IgM antibodies can be detected approximately 2–3 days after onset of symptoms, followed by production of IgG antibodies at approximately 1–2 weeks. Neutralizing antibodies offer protection against CHIKV infection/disease in humans and in animal models and persist for many years after infection in humans. Epitope mapping studies with human sera and monoclonal antibodies have

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