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Status of research and development of vaccines for chikungunya

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ABSTRACT

Chikungunya virus (CHIKV) is an arthritogenic alphavirus that during the last decade has significantly expanded its geographical range and caused large outbreaks of human disease around the world. Although mortality rates associated with CHIKV outbreaks are low, acute and chronic illnesses caused by CHIKV represent a significant burden of disease largely affecting low and middle income countries. This report summarizes the current status of vaccine development for CHIKV.

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 identified

linear and conformation-dependent epitopes in the E1/E2 glycoproteins, particularly in the region of the exposed trimer spike, that are targets of strongly neutralizing antibodies. It has also been suggested that early production of neutralizing IgG3 antibodies in particular may protect against chronic arthralgia in humans [12]. Significantly, passive immunization experiments in mouse models using neutralizing serum [13] or monoclonal antibodies, convalescent human serum, or post-vaccination NHP serum have demonstrated protection against viremia and/or disease, suggesting that neutralizing antibodies are a likely correlate of protection. An ongoing phase I/II clinical trial (clinicaltrials.gov NCT02230163) is investigating the use of anti-CHIKV hyperimmune intravenous immunoglobulin for therapy of neonates at risk of exposure to CHIKV during childbirth. However, only limited enrollment (4 of a planned 40 subjects) has been reported to date [14].

Although CMI is likely to be important for developing durable protective immunity following vaccination, specific roles for cellular responses in protection or resolution of disease are not well defined [11]. CD8T cells have been shown to play a role in controlling natural acute infections in humans, but adoptive transfer of T lymphocytes in mouse models has suggested that cellular responses are not necessary for protection [13]. There is some evidence from studies in immunocompromised mouse models showing involvement of CD4T cells in pathology of chikungunya disease, leading to a suggestion that a vaccine that induces a T-cell response in the absence of a robust antibody response could contribute to immunopathology [15]. More work is needed to clearly define the role of CMI in protection and/or immunopathology.

2.2. General approaches to vaccine development for CHIK for low and middle income country (LMIC) markets

At present there does not appear to be a strong consensus regarding the potential deployment of a licensed chikungunya vaccine in LMIC, although it would most likely be either as part of outbreak response or in vaccination campaigns and/or as part of a standard immunization schedule in endemic areas. Candidate vaccines could be expected to be used in adult and pediatric populations. Vaccine developers/manufacturers in LMIC, primarily in India, have focused on the development of inactivated candidates, which will most likely require multiple doses and subsequent boosting to develop and maintain immunity (see Section IV) but may have better thermostability and be more amenable to a controlled temperature chain than live attenuated or vectored candidates. However, other vaccine candidates include potential single-dose formulations that may be more appropriate for use in outbreak response scenarios or targeted vaccination campaigns. Each of the different vaccine approaches under development has potential advantages and limitations for LMIC use in terms of e.g. dosing requirements, cost of production, stability, and durability of immunity. For this reason, definition of preferred product characteristics of a chikungunya vaccine, particularly consensus on the optimal vaccination strategy, would be helpful in product development planning and supporting the investment case.

As described in Section I above, the burden of disease associated with chikungunya epidemics, and with endemic transmission in some areas, is significant even compared to other arboviral diseases such as dengue, so an effective chikungunya vaccine can be expected to provide significant public health benefit.

3. Technical and regulatory assessment

Many of the chikungunya vaccine candidates under development utilize platforms or approaches that have precedents for regulatory approval. The most probable path forward for vaccine candidates is demonstration of field efficacy via traditional clinical trials. However, due to the unpredictable, focal and periodic nature of chikungunya outbreaks, Phase II/III randomized controlled trials in humans to demonstrate vaccine efficacy are likely to be logistically challenging. Endpoints for clinical efficacy studies would include prevention or reduction of symptomatic illness and induction of neutralizing antibodies. Licensure based on neutralizing antibody titer as a correlate of protection may be plausible and the majority of vaccine candidates appear to be focused towards induction of antibody responses against viral structural proteins, particularly E1 and E2. No specific minimum protective titers have been robustly established, although one passive protection study in A129 mice reported $PRNT_{50} \geq 35$ as protective [13]. It has also been suggested that the United States Food and Drug Administration's (FDA) Animal Rule may represent a path to licensure for chikungunya vaccines [16]. However, this seems unlikely given the scope and application of the Animal Rule ("serious or life threatening conditions" that are "lethal or permanently disabling") and the limitations of many current models to mimic the outcomes of human infection.

Assays employed to measure humoral immunity following vaccination have typically included ELISA and plaque reduction neutralization. The individual methodology for each assay varies widely across studies, with significant differences in key assay parameters (e.g. virus/antigen type, incubation times and temperatures, cell substrates) and endpoints (e.g. 50%, 80%, or 90% neutralization). Standardization of protocols for assessment of neutralizing and total antibody responses and/or the development of standardized antibody/antiserum reference reagents are necessary to facilitate direct comparisons of the multiple vaccine candidates in the pipeline and to establish antibody titer(s) that correlate with protection. In addition to total and neutralizing antibody titers, several studies have assessed qualitative and quantitative aspects of cell mediated immunity using T-cell based assays such as intracellular cytokine staining and ELISpot. Further studies are needed to assess the contribution of cellular immunity to protection from chikungunya disease following vaccination and if/how that will be measured in clinical studies to aid in vaccine licensure.

4. Status of vaccine R&D activities

The chikungunya vaccine pipeline appears robust [17]. More than 15 vaccine candidates based on a range of platforms (inactivated, live attenuated, live vectored, chimeric, virus-like particle [VLP], subunit protein, DNA) are currently in preclinical and clinical development and several in collaboration with industry (Table 1). Many candidates utilize CHIKV structural proteins delivered by recombinant viral or plasmid vectors or prepared as subunit/VLP antigens, and most been shown to induce strong humoral responses in mice, rabbits and guinea pigs as well as non-human primates often without exogenous adjuvants. The durability of protective immunity induced by many of these candidates is currently uncertain but detection of neutralizing antibodies 6–12 months post-vaccination in mice or NHPs has been reported for several candidates. A majority of the peer reviewed literature relating to new chikungunya vaccine candidates has emerged in the last 5 years and two candidates have recently completed Phase I testing. These and some other candidates are described below.

The first new candidate to reach Phase I trials was a VLP vaccine, which had shown strong immunogenicity and protection against CHIKV challenge in mice and NHPs. VRC-CHKVLP059-00-VP comprised VLPs expressed from VRC293 cells transfected

Table 1
Development status of current vaccine candidates (POC = proof of concept trial).

Candidate name/identifier	Developer	Type/platform	Preclinical	Phase 1	Phase 2	POC	Phase 3
TSI-GSD-218 (Thailand/1556) 2ΔE2	USAMRIID/Salk Institute for Biological Studies	Live, attenuated			**X**		
VRC-CHKVLP059-00-VP (37997)	National Institute of Allergy and Infectious Diseases (NIAID)	VLP			**X**		
Formalin inactivated (Thailand/1556)	U.S. Army Medical Research Institute of Infectious Diseases (USAMRIID)	Inactivated, whole virus		**X**			
MV-CHIK (Measles virus vector)	Themis Bioscience GmbH/Institut Pasteur	Live, vectored		**X**	2016		
Formalin inactivated, multiple Indian CHIKV isolates 2006–2010	Bharat Biotech International	Inactivated, whole virus	**X**	2016			
Formalin inactivated CHIKV181/25	Indian Immunologicals Ltd. (virus from US Army Medical Research and Material Command (USAMRMC))	Inactivated, whole virus	**X**	2016			
CHIKV-IRES (v1/v2)	Takeda Pharmaceuticals U.S.A., Inc./University of Texas Medical Branch (UTMB)	Live, attenuated	**X**				
Chimeric Alphavirus (VEEV, EEV, SINV, or EILV genetic backbones)	University of Alabama at Birmingham (UAB)/UTMB	Live, attenuated	**X**				
CHIKV-Δ5nsP3	Valneva/Karolinska Institutet (also CHIKV-Δ6K)	Live, attenuated	**X**				
TM17-2	Arbovax, Inc./North Carolina State University (NCSU)	Live, attenuated	**X**				
VSVΔG-CHIKV (VSV vectored)	Profectus Biosciences/Yale University/UTMB	Live, vectored	**X**				
Vaccinia [Ankara]-Vectored (MVA-CHIKV E1E26KE3)	Karolinska Institutet/CSIC Madrid	Live, vectored	**X**				
Vaccinia vectored (MVA-CHIKV E2E3)	University of Wisconsin-Madison/Takeda Pharmaceuticals U.S.A., Inc.	Live, vectored	**X**				
Recombinant Adenovirus (CAdVax-CHIKV)	GenPhar, Inc.	Live, vectored	**X**				
CHIKV DRDE-06 (Indian) Formalin inactivated	Defense Research and Development Organisation (DRDE), India	Inactivated, whole virus	**X**				
Formalin inactivated – Nanotherapeutics	(Transferred from Baxter U.S. in late 2014)	Inactivated, whole virus	**X**				
p181/25-7CHIKV iDNA	Medigen, Inc.	DNA	**X**				
CHIKV-Env + pnsP2; CHIKV pMCE321	Inovio Pharmaceuticals/VGX™ Animal Health/University of Pennsylvania	DNA	**X**				
rCHIK-E1/E2 (DRDE-06) *E. coli*	DRDE, India	Subunit	**X**				
rE2-CHIK	National Institute of Virology, India	Subunit	**X**				
VLP -CHIKV-S27	TI Pharma/Wageningen University	VLP	**X**				

Shaded boxes indicate that further development of this candidate/type has been halted or is uncertain.
A small number of additional subunit or DNA vaccine candidates have been reported that are not included. Further development of those candidates also appears uncertain.

with plasmid encoding structural protein genes (C-E3-E2-6K-E1) from CHIKV strain 37997 (West African lineage). The Phase I study in healthy adults reported an excellent safety profile and strong immunogenicity for low (10 μg), medium (20 μg) and high (40 μg) dose cohorts (3 intramuscular [i.m.] immunizations each, without adjuvant, at 0, 4 and 20 weeks) [18]. Neutralizing antibodies were detected in all subjects following the second dose, titers peaked 4 weeks after the third dose (IC_{50} 4525–8745) and then declined approximately 5–20-fold by 6 months after the final dose. Titers at 6 months remained highest in the high dose group. Titers were reported to be comparable to those in convalescent sera from CHIKV-infected patients. Phase II studies (clinicaltrials.gov NCT02562482) were scheduled to begin at multiple sites in the Caribbean in October, 2015. Two other VLP vaccine candidates, based on production from baculovirus-infected insect cells expressing CHIKV structural proteins, have also been evaluated in mouse models and shown to be immunogenic and protective. VLP vaccines may face challenges with manufacturing scale-up and optimization/improvements for production are being investigated.

Phase I results were also recently reported for a vectored recombinant measles virus (MV) expressing structural proteins

(C-E3-E2-6K-E1) from CHIKV strain 06-49 (Indian Ocean lineage) [19]. In mouse studies, MV-CHIK was immunogenic ($PRNT_{50}$ titers of 450–4050; $PRNT_{90}$ = 50–450) and protective following two intraperitoneal (i.p.) doses of 10^4 pfu or a single 10^5 pfu dose. MV-CHIK was evaluated in healthy 18–45 years old (yo) adults at three different dose levels (1.5×10^4, 7.5×10^4, or 3×10^5 $TCID_{50}$) without adjuvant. Subjects received two immunizations delivered at days 0 and 28 or 0 and 90. Neutralizing antibodies (against CHIKV strain 181/25) were detected following the first immunization in all dose groups ($PRNT_{50}$ GMTs from 7 to 73) and increased following boosting ($PRNT_{50}$ GMTs from 63 to 433) with seroconversion in 100% of subjects. No significant safety problems were reported and the presence of pre-existing MV immunity had no apparent effect on neutralizing anti-CHIKV antibody responses from study volunteers. Phase II studies are planned for 2016. Additional candidates based on VSV, adenovirus or poxvirus (MVA) vectors expressing CHIKV structural proteins have been shown to be immunogenic and protective in mice following one or two doses and appear to stimulate strong cell mediated immunity to immunodominant CD8 epitopes in CHIKV structural proteins in addition to neutralizing antibodies. For one MVA-based candidate, expressing E2 & E3 proteins only, protection against CHIKV challenge in A129 mice was not strongly associated with neutralizing antibody titers suggesting that CMI was a more significant factor. Phase I trials of a VSV-based candidate are reported to have been planned for 2016.

Although chimeric CHIK vaccines based on other attenuated alphavirus backbones have been investigated, the current leading live, attenuated candidates are rationally designed to limit potential for reversion to virulence and/or transmission by mosquito vectors, through the use of alternative RNA transcription regulation sequences (CHIK/IRES) or deletions in nonstructural (CHIKV-Δ5nsP3) or structural (CHIKV-Δ6K; TM17-2, with deletion in the E2 transmembrane domain;) genes. CHIK/IRES vaccines use an ECMV internal ribosome entry sequence (IRES) in place of the subgenomic promoter (v1) or to control capsid transcription. Both were highly attenuated in mice, stimulated humoral and CMI responses, and protected mice and NHPs against CHIKV challenge following single dose immunization (10^5 pfu i.m. or subcutaneously [s.c.] in NHPs). $PRNT_{50}$ titers in NHPs at 7 weeks post-vaccination were 160–1280 and neutralizing antibodies appear to be the primary mediator of protection. The other live, attenuated candidates also induced CHIKV-specific neutralizing antibodies and/or CD8T cell responses in C57BL/6 mice following a single dose (10^3 pfu of TM17-2; 10^5 pfu of CHIKV-Δ5nsP3 or CHIKV-Δ6K) and protected against CHIKV challenge (reduced or absent viremia, and reduced footpad swelling). Peak NT50 titers for CHIKV-Δ5nsP3 were 10^2–10^4. Data from NHP studies with these alternative candidates have not been reported. CHIK/IRES, CHIKV-Δ5nsP3 and TM17-2 have industry partners for development and are likely to proceed to clinical evaluation.

Several inactivated candidates are in development, primarily by manufacturers in India. Although little data has been published on these vaccines, a range of CHIKV strains (including wild-type isolates and the US Army live attenuated 181/clone 25), cell lines for production, inactivation and purification methods, and formulation types have been proposed some examples have been evaluated in mouse models. All require 2 or 3 doses of 10–50 μg of antigen to induce neutralizing antibodies and/or T cell responses. For example, a formalin-inactivated, alum adjuvanted vaccine, based on a Vero cell-adapted 2006 Indian isolate given as a three-dose schedule (days 0, 14 and 28) stimulated neutralizing antibodies in a dose-dependent manner, with peak PRNT50 titers ≤ 6400 in 50 μg cohort. Clinical trials of at least one inactivated candidate may begin in India during 2015–2016.

DNA vaccines, expressing CHIKV structural proteins, subgenomic replicons or full-length live attenuated CHIKVs, and subunit protein vaccines have also been evaluated in mice and/or NHPs, including in heterologous prime-boost strategies. A plasmid encoding full-length, live attenuated CHIKV 181/clone 25 induced robust neutralizing antibodies ($PRNT_{50}$ 640–10,240; $PRNT_{80}$ 320–1280) in BALB/c following a single i.m. 10 μg dose. Other plasmids expressing CHIKV structural protein genes typically required multiple doses but induced neutralizing antibodies at titers >100 and also CHIKV-specific CD8T cell responses.

5. Likelihood for financing

The recent acquisition of several leading chikungunya vaccine candidates by mid- to large-size vaccine developers/manufacturers suggests that a market is perceived to exist for these products, most likely catalyzed by the advancing geographical spread of CHIKV. Although chikungunya vaccines would have potential markets for military or traveler use, the predominant need for a vaccine is within LMIC. At least 9 countries with endemic chikungunya or that have experienced epidemics in the past 10 years are eligible for GAVI financing. Government support in many developing countries will be necessary and may only come as reactionary to control chikungunya epidemics. India is perhaps at the forefront of countries with endemic chikungunya to have government support financially and for inclusion on their routine immunization schedule should a vaccine become available. GAVI financing will ultimately depend on the cost-effectiveness of the vaccine given the burden of disease and the likelihood for host country affordability and sustainability.

Conflict of interest

CBC, CS and DWCB have no interests related to CHIK vaccine development.

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