Do we need a vaccine against chikungunya?

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During the last decade, the chikungunya (CHIKV) virus has expanded its range of activity, conquering new territories and becoming an important global health threat. In particular, the challenge represented by the recent emergence of CHIKV in the Americas has strengthened the need of a safe and effective vaccine. Although research on vaccines against CHIKV has been slow, a few vaccine candidates have been tested over the years. Inactivated and attenuated vaccine candidates have shown promising results in phase I/II trials, and engineered vaccines have proven to be safe and immunogenic in mouse and/or non-human primate models. Recently, a vaccine based on virus-like particles (VLP) has been successfully tested in a phase I trial. However, large phase I/II controlled trials, which are needed in order to provide evidence of vaccine efficacy, may be planned only under certain conditions. First, they should be conducted during epidemic periods, when a large number of cases occur, in order to ensure an adequate study power. Second, they are expensive and investments returns are not always guaranteed. To overcome this problem, public/private partnership and government support, the identification of target population groups for vaccination and the commitment of donor agencies are key factors for supporting both the development and the availability of vaccines against neglected tropical diseases like chikungunya.

Keywords: Chikungunya virus, Vaccine, R&D

During the last decade, following the route traced years before by the dengue virus, another arbovirus, called ‘chikungunya’ (CHIKV), has become an important global health threat, expanding its range of activity eastwards and westwards, from eastern Africa to south-east Asia and finally to the New World.^{1,2}

The CHIKV, which belongs to the alphavirus genus of the *Togaviridae* family, is transmitted to humans by *Aedes* spp. (i.e. *Aedes aegypti* and *Aedes albopictus*) mosquitoes. Three distinct clades of the virus have been identified: the west African, the east/central/southern African (ECSA) and the Asian genotype.^{1–3} Since its identification in Tanzania in 1952,⁴ sporadic cases and outbreaks of chikungunya fever have been reported in sub-Saharan Africa and in south-east Asia.^{1–3} Chikungunya re-emerged on coastal Kenya in 2004 and caused a series of outbreaks on south-west Indian Ocean Islands in early 2005, which were followed by an epidemic in the Indian subcontinent in 2005/2006.^{5,6} In the summer of 2007, an outbreak of chikungunya fever was identified in the north-east of Italy.⁷ The large epidemic of chikungunya fever started in 2004 was caused by the ECSA genotype.^{2,8,9} A variant of this

viral genotype, presenting a substitution of the aminoacid alanine with valine in the position 226 of the envelope surface glycoprotein E1 (A226V) was selected during the course of the epidemic as a consequence of the increased viral fitness for *A. albopictus*, the so-called ‘Tiger’ mosquito.¹⁰ This virus variant emerged in areas where *A. albopictus* is predominant, such as La Reunion and the Kerala district in India.^{11,12} The same variant caused the outbreak propagated by the tiger mosquito in north-eastern Italy.⁷

Despite its rapid and large spread in the old world, local transmission of CHIKV had been never reported in the Americas up to December 2013, when autochthonous cases of chikungunya were confirmed on Saint Martin island, French West Indies; thereafter, outbreaks of chikungunya fever were reported on other Caribbean Islands,^{13,14} in French Guiana¹⁵ and in other countries of Latin America, causing more than one million cases (<http://www.who.int/mediacentre/factsheets/fs327/en/>).

The challenge represented by the recent emergence of CHIKV in the new world, which represents the last step of an uncontrollable expansion of its geographical range of activity, strengthens the demand for more efficient interventions against this arbovirus. To this regard, even though the implementation of mosquito control programmes is a key element for the containment of CHIKV outbreaks, making a safe and effective vaccine available is an

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obvious public health priority. Preventing chikungunya fever is particularly important, since it may cause long-lasting joint pain which is difficult to control with therapeutic drugs.

'Old' and 'New' CHIKV Vaccine Candidates

Although research on vaccines against CHIKV has been rather slow, a few vaccine candidates had been already tested on humans before the 2004 epidemic.

First, formalin-inactivated CHIKV vaccines were found able to induce neutralising antibodies with no adverse events in human volunteers.¹⁶ However, to contain production costs, to reduce risks associated with handling large quantities of un-attenuated virus prior to inactivation, and to induce a strong protective response with a single shot, the development of live attenuated vaccines was pursued.

To this regard, the US Department of Defense made considerable progress towards the development of a serially passaged, plaque-purified live chikungunya vaccine. The attenuated strain, CHIKV 181/clone 25, which was used as the vaccine seed, was selected after cell-culture viral passaging procedures. This vaccine candidate was administered to a total of 131 volunteers over a 22 years period.¹⁷ In particular, almost all the vaccinees enrolled in a phase II, randomised, double-blind, placebo-controlled, safety and immunogenicity trial developed neutralising antibodies; no volunteer developed clinically important reactions to the vaccine, but 8% of them had well-tolerated side effects, such as transient arthralgia, which is a commonly observed sign of chikungunya fever.¹⁸ Thus, the vaccine was highly immunogenic, and neutralising antibodies were still detected in 85% of the vaccinees by 12 months after vaccination; however, seroconversion rates for CHIKV were rather low (36%) among those who had been previously vaccinated with other live attenuated alphavirus vaccines, such as a vaccine against Venezuelan equine encephalitis virus, suggesting immunological interference between these vaccines.¹⁹ The theoretical risk of transmission of the attenuated CHIKV strain to *Aedes* spp. mosquitoes is considered remote because of the low and transient levels of viraemia developed by vaccines.²⁰ However, mild, transient joint pain may suggest insufficient and/or unstable attenuation; to this purpose, recent studies have indicated that the attenuation of the vaccine strain 181/clone 25 is mediated only by two point mutations (i.e. two of five non-synonymous mutations identified between the vaccine and the wild strain), due to the simultaneous expression of two E2 glycoprotein substitutions.²¹ At the end, this live-attenuated vac-

cine did not advance to efficacy testing for a series of reasons, including scarcity of funding and concerns regarding its eventual marketing.^{17,22,23}

To retain the advantages of attenuated vaccines, consisting in rapid, single-dose protection, and long-lived immunity, yet improving upon safety, novel attenuated CHIKV vaccine candidates were produced and tested, with promising results in animal models.²⁴ In particular, chimaeric vaccines, using alphavirus backbones (Venezuelan equine encephalitis virus, Eastern equine encephalitis virus and Sindbis virus), and replacing the structure genes with CHIKV corresponding genes,²⁵ were found to be highly immunogenic in mouse models. However, some residual infectivity of the vaccine strains in mosquito vectors could not be excluded.^{24,26} To overcome this problem, other genetically engineered vaccines have been successfully tested in mice^{27,28} and in non-human primate models.²⁹

At last, promising results were obtained using DNA vaccine candidates, which were found to be protective in mice and to induce neutralising antibodies in nonhuman primates.^{30,31}

Recently, a phase I, dose-escalation, open-label clinical trial on a virus-like particle (VLP) vaccine candidate has been conducted by the Vaccine Research Center of the National Institute of Health (NIH). Overall, 25 participants were assigned to three dosage groups (10, 20, and 40 µg). Antibodies were detected by ELISA in most participants after the first vaccination and were boosted at peak titres after the third vaccination. Neutralising antibodies were detected in all participants 4 weeks after the second vaccination and remained detectable 6 months after the third vaccination. No serious adverse events were reported, and only mild local (i.e. pain or tenderness at the injection site) and systemic reactogenicity (i.e. malaise, headache, nausea, myalgia) was observed in a minority of the participants. Thus, this vaccine candidate appeared to be immunogenic, safe and well tolerated.³² To this regard, it should be mentioned that immunisation with VLPs had been already tested in nonhuman primates, eliciting the production of neutralising antibodies and protecting monkeys against viraemia after high-dose challenge. Moreover, antibodies transferred into immunodeficient mice were able to protect against subsequent lethal CHIKV challenge, suggesting a humoral mechanism of protection.³³

The promising results of the NIH trial, along with the growing impact of CHIKV on global health, may trigger the interest towards developing vaccines against chikungunya. In particular, vaccine eliciting protective immunity after a single shot may represent the ideal candidate for use during ongoing epidemic events, in order to mitigate and contain the impact of the disease on the population.

Towards a CHIKV Vaccine: Obstacles and Opportunities

As reported above, even though affected by scarce resources, research on CHIKV vaccines has slowly progressed, and a number of vaccine candidates are now available and ready to be further tested in human studies. However, technical problems and financial constraints may represent possible obstacles for the development and licensure of safe and effective vaccines.

The randomised controlled trial model is widely considered the gold-standard for evaluating vaccine efficacy. For infectious diseases such as chikungunya, whose dynamic pattern consists of a sylvatic cycle characterised by a low level of endemicity, with sporadic human cases around the ecological niche, epidemic events represent an opportunity to test vaccine candidates in large phase II/III trials. However, phase III trials may not be feasible, because the number of cases occurring in inter-epidemics periods is low, whereas outbreaks occur sporadically and are unpredictable. Thus, obtaining reliable information on correlates of immune protection is particularly important in order to apply the so-called 'animal rule', consisting in the use of animal data instead of human trials, which are usually requested for traditional regulatory approval.³⁴ In the case of CHIKV, the level of neutralising antibodies appears to be strongly correlated with a protective immune response²² and resistance to infectious challenge in animal models.³³

Because of the width of the area at risk, the size of the susceptible population, and the availability of vaccine trial sites with adequate scientific and technical background, the current spread of CHIKV in the Americas provides now an invaluable opportunity for the evaluation of vaccine candidates.

However, beyond technical and/or scientific obstacles, R&D of a vaccine, including large and expensive clinical trials, may be jeopardised by economic considerations. In fact, since developing a human vaccine from the preclinical phase to registration requires an increasing average investment of approximately US\$200–500, or even up to 900 million,^{35,36} the development of vaccines for neglected infectious diseases, such as chikungunya fever, may be challenging because the market size might not be large enough to justify the investment.^{23,36} In fact, most R&D projects do not deliver a licensed vaccine for routine or targeted immunisation; this is mostly not because of scientific barriers, but due to financial and politico-economic obstacles.^{35,36} Moreover, not only rising costs, but also longer timelines with lower probability of market entry, are relevant obstacles to the development of vaccines against chikungunya and other neglected diseases. In this context, public/private partnerships could play a major role;³⁷ for example,

Bill & Melinda Gates and/or other foundations could be interested in funding R&D activities, and the Global Alliance for Vaccines and Immunisation (GAVI) might support vaccine markets in eligible countries.²² Finally, Government support would be also desirable in order to cut clinical trials costs.

Finally, the identification of target populations for vaccination is key to envision possible benefits of the vaccine, in terms of profits for the investors and safeguard of the affected community. To identify large, long-lasting markets for a CHIKV vaccine is difficult, due to its epidemic pattern and low case-fatality rates. The military market may be significant, when military bases with a large amount of personnel are stationed in endemic/epidemic areas. Travellers and tourists might represent another priority in terms of return of investment; to this regard, it is important to underline how, over the last decade, CHIKV epidemics mostly occurred in touristic areas, such as Indian Ocean islands and the Caribbean²². The availability of a vaccine against chikungunya would be a useful tool to protect tourists, to save local economies, and to prevent the importation of the infection in tourists' countries of origin.

Conclusions

The limited success of traditional mosquito control measures in the containment of chikungunya epidemics emphasises the need for research and development of safe and effective vaccines. Attenuated vaccine candidates which were proved to confer protection in animal models have shown the capacity to elicit the production of neutralising antibodies in human beings enrolled in phase I and II studies. New vaccine candidates based on VLPs have shown protection in animal models and promising results in phase I studies. The feasibility of large phase II/III trials in the current epidemiological context, characterised by the spread of CHIKV in the Americas, should be considered. Alternatively, the identification of neutralising antibodies as a strong correlate of protection might allow the licensure of a safe vaccine by applying the animal rule. In any case, due to the limited economic interest in the prevention and control of neglected tropical diseases, public/private partnership and Government support should be encouraged, in order to favour the development and availability of vaccines against chikungunya.

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