Commentaries

A vaccine against an explosively spreading virus

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Invited Commentary

Chikungunya virus (CHIKV) is a member of the alphavirus genus of the *Togaviridae* family, that is transmitted to humans through *Aedes Aegypti* and *Aedes albopictus* mosquito bites. CHIKV has long remained endemic in continental areas of Africa and Asia, but in recent years it has acquired a marked spreading potential, causing outbreaks in most continents, including Southern Europe and, more explosively, the Americas.^{1,2} The establishment and adaptation of *A. albopictus*, the 'tiger mosquito', to temperate climates together with the frequency and rapidity by which viremic subjects move from endemic regions of Africa and Asia has generated major concerns about several European and American countries' vulnerability to the virus. The disease spread can also be notable in countries with health systems apparently prepared to the challenge: in the first European CHIKV outbreak of summer 2007, a single viremic traveler from India visiting relatives for a few hours in a small village in the province of Ravenna, Italy, caused an epidemic affecting more than 200 subjects before being defeated by intensive disinfection and the advent of a cooler fall season.³

The disease caused by CHIKV is essentially a polyarthrititis accompanied by fever and rash. The arthralgia is usually severe and long lasting. While it is rarely lethal, complications and sequelae may cause even death in old and debilitated subjects. There is no specific therapy or prevention measure but it is known from studies in experimental models and in patients that the rise of virus-neutralizing antibodies may protect them from disease or make it less severe. Overall, a CHIKV vaccine appears to be an ideal preventive weapon. The first vaccine tested in humans was a live, attenuated one but did not progress to a large efficacy trial, possibly due to the potential reversion of the virus to pathogenicity.⁴ Among other approaches, the generation of vaccines constituted by virus-like particles (VLP), i.e. self-assembled major capsidic and pericapsidic immunogenic determinants of the virus has major promises because of its safety, lack of pathogenicity reversion and less immunoescape potential expected to be

associated with an inactivated vaccine. However, in the absence of strong adjuvants, the immunogenicity of this kind of vaccine remains problematic.

The report by Chang and collaborators is now a good step toward the objective of a safe and efficacious CHIKV vaccine.⁵ In a Phase 1 clinical trial, five, ten, and eight healthy, 18-50 year-old adults received priming and booster injections of 10, 20, and 40 µg of the vaccine, respectively, and were appropriately monitored for vaccine safety, tolerability and immunogenicity. The vaccine proved to be safe and well tolerated, with no severe adverse events. Importantly, high titers of neutralizing antibodies at each vaccine dose were detected in boosted subjects.

These results are promising but, as usual for a Phase 1 trial, both safety and immunogenicity data need to be expanded in subsequent clinical investigations with a higher number of subjects, particularly those living in endemic areas who are at risk of CHIKV disease and constitute the main vaccination target. VLP are known to possess some intrinsic adjuvanticity and carrier effects, nonetheless, the possibility of using the lowest vaccine dose by the insertion of adjuvants is probably warranted and is indeed discussed by the authors. Future clinical trials may also help establish whether neutralizing antibodies are in fact the true correlate of protection from CHIKV disease.

This trial was funded by a public US Institution (the NIH) with exclusive intramural grants. It is an example of a public intervention for starting the generation of an important public health new tool when, as happens for infections where the vaccine is likely to target restricted and numerically unpredictable populations, the private vaccine manufacturers do not enjoy engagement. Until which stage of the long and tremendously expensive clinical efficacy trials will the NIH be supportive? Or is a public-private effort being planned?

References

- 1 Johansson MA. Chikungunya on the move. *Trends Parasitol.* 2015;31(2):43–5.
- 2 Rezza G. Dengue and Chikungunya: long-distance spread and outbreaks in native areas. *Path Global Health.* 2014;108:349–55.
- 3 Rezza G, Nicoletti L, Angelina R, Romi R, Finarelli AC, Panning M, *et al.* Infection with Chikungunya virus in Italy: an outbreak in a temperate region. *Lancet.* 2007;370:1840–6.
- 4 Weaver FC, Osorio JE, Livengood JA, Chen R, Stinchcomb DT. Chikungunya virus and prospects for a vaccine. *Expert Rev Vaccines.* 2012;11:1087–101.
- 5 Chang L, Dowd KA, Mendoza FH, Saunders JG, Siter A, Plummer SH, *et al.* Safety and tolerability of chikungunya virus-like particle vaccine in healthy adults: a phase 1 dose-escalation trial. *Lancet.* 2014;384:2046–52.

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