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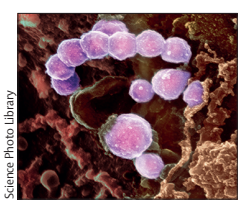
Chikungunya vaccine VLA1553 induces sustained protective antibody concentrations



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Chikungunya virus disease is one of the most neglected arboviral diseases.[1,2] Between December, 2013, and June, 2023, public health authorities reported 3·7 million suspected and laboratory-confirmed cases of chikungunya virus disease in the Americas,[3] but the total number of cases is probably much higher than this estimate because of poor notification infrastructure and is continuing to increase. Chikungunya virus has been detected in 110 countries globally to date, and is spreading as the habitat of mosquitos—responsible for the majority of transmission of the virus—expands into new regions due to climate change.[3]

Chikungunya virus disease is highly debilitating.[4] Among its several symptoms, the most prominent during an acute infection is extreme joint pain, which forces individuals to assume a characteristic stooped posture and to move slowly and carefully.[4] Although the acute symptoms of infection last approximately 2 weeks, 31–57% of patients continue to experience intense joint pain for more than 3 months after initial infection, and 22–44% develop chronic joint pain that can persists for years, and these chronic pain sequelae are very difficult to treat.[5] Chikungunya virus disease outbreaks spread quickly, all age groups can be affected and the disease has a high morbidity but a relatively low mortality rate; however, it can result in a substantial number of indirect fatalities. An excess mortality study in Brazil found an approximate four-times increase in mortality up to 84 days after infection with chikungunya virus compared with the general population.[6] The combined direct and indirect economic consequences of chikungunya virus globally are in the range of several billions of US dollars, mostly due to lost workdays,[2] but investment in countermeasures to control this disease has been disproportionately low compared with its very high medical and socioeconomic costs.

Fortunately, chikungunya virus infection induces long-lasting antibody titers and protection against reinfection, facilitating the development of highly effective vaccines. In *The Lancet Infectious Diseases*, Robert McMahon and colleagues[7] report their single-arm, multicentre, phase 3b trial assessing antibody persistence and safety up to 2 years after a single vaccination with the chikungunya virus vaccine VLA1553 (Valneva Austria, Vienna, Austria) in adults (aged ≥18 years) who participated in a double-blind, randomised, placebo-controlled multicentre, phase 3 trial in the USA.[8] The phase 3 study followed-up 4128 participants (3093 randomly assigned to VLA1553 and 1035 randomly assigned to placebo) for 6 months after a single dose of the vaccine,[8] during which time the vaccine was generally well tolerated. Severe adverse events were reported in 46 (1·5%) of 3082 participants in the vaccinated group and in eight (0·8%) of 1033 participants in the control group during the first 6 months. Two of the severe adverse events were determined to be related to the vaccine. 263 (99%) of 266 vaccinated participants who were included in an immunogenicity analysis population had protective neutralising antibody levels 28 days after vaccination, with no significant differences in the neutralising antibody titres detected between those aged 18–64 years and those aged 65 years and older.[8]

In this phase 3b follow-up study,[7] the safety and immunogenicity analyses of VLA1553 2 years after vaccination are presented (including 179 participants from the immunogenicity analysis population and 184 other participants who received VLA1533 vaccination) and show sustained neutralising antibody concentrations with a 2 year seroprotection rate of 96·8% (306 of 316 with available data; 95% CI 94·3–98·5), and the seroprotetcion rates were similar between both age groups. Ten new serious adverse

events were reported between the 6-month analysis timepoint and the 2-year follow-up date, none of which were determined to be due to vaccine. The fact that the phase 3 and 3b studies were conducted in a non-endemic area and in predominantly White populations restricts the generalisability of the results. The vaccine has demonstrated safety and immunogenicity in a population that is not representative of the population in most endemic countries, neither in terms of genetic background nor exposure to previous infections. These results presented by McMahon and colleagues, although very encouraging, still leave many questions unanswered—for instance, virological confirmation of VLA1553 vaccine efficacy against circulating strains in endemic areas and safety in people previously exposed to chikungunya virus has not been yet shown.

To further investigate the safety and immunogenicity of VLA1553 and to make it affordable, Valneva (Vienna, Austria) is collaborating with Instituto Butantan in São Paulo, Brazil, with funding from the Coalition for Epidemic Preparedness Innovations (CEPI) and the EU Horizon 2020 program, to conduct a clinical study to assess the safety and immunogenicity of the vaccine in individuals aged 12 year to younger than 18 years who have been previously infected with the chikungunya virus. The US Food and Drug Administration announced the accelerated approval of VLA1553 on Nov 9, 2023, for use in individuals aged 18 and older at risk of chikungunya virus infection on the basis of immunogenicity results and studies of correlates of protection on the condition of confirmation of clinical benefit in clinical studies.[9] In 2019, 185 054 cases of chikungunya virus disease were reported in the Americas,[10] making the conduct of such confirmatory studies difficult. However, the incidence of cases has been increasing, with 411 086 cases reported in 2023, making possibility of such a study more feasible. Immunogenicity studies conducted in endemic areas and efficacy studies will be essential for public health authorities to decide how to deploy VLA1553 in the future.

We declare no competing interests.

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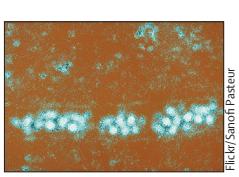
The promising prospects of a new yellow fever vaccine

In this issue of *The Lancet Infectious Diseases,* Kayvon Modjarrad and colleagues[1] report on the safety and immunogenicity of a next-generation life-attenuated Vero cell line derived yellow fever vaccine, vYF-247. The prospect of a new yellow fever vaccine is good news, and the results of this first in-human trial are highly promising. But the bar is set high if bioequivalence with the current YF-17D vaccine is the ultimate goal.

The risk of large urban yellow fever outbreaks is constantly looming in tropical Africa and South America. Uncontrolled urbanisation, increased population mobility, extreme weather conditions, expansion of the vector *Aedes aegypti,* and fragmentation of rain forest driving non-human primates—the natural reservoir of yellow fever—into human dwellings all contribute to this risk. From the beginning of 2023, 13 African countries have reported probable and documented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