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First phase 3 trial of a chikungunya vaccine candidate finds it is generally safe and provokes an immune response

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The VLA1553 vaccine candidate for chikungunya disease was generally well tolerated and produced an immune response in 99% (263/266) of participants, according to a phase 3 randomized controlled trial published in *The Lancet*.

Because the study, VLA1553-301, was not conducted in regions where chikungunya is endemic, researchers were unable to investigate whether the vaccine protects against subsequent disease. Instead, the study tested for an immune response at levels that are thought to protect against the disease if infected with the virus.

Chikungunya is a mosquito-borne disease caused by the chikungunya virus (CHIKV), which is endemic in some regions of Africa, Asia, and the Americas. It causes a fever in patients roughly four to eight days after they have been bitten by an infected mosquito. Symptoms include headaches, fatigue, nausea, and severe muscle and joint pain. The joint pain is often debilitating and usually lasts for a few days but may be prolonged, lasting for weeks, months or even years. Serious disease and death is rare, but older people and newborn babies are most at risk. Currently, there are no approved vaccines to prevent the disease caused by CHIKV infection nor are there effective antiviral treatments for the disease.

Lead author of the study, Dr. Martina Schneider, Clinical Strategy Manager at Valneva, says, "This could be the first chikungunya vaccine available for people living in endemic regions, as well as for travelers to endemic areas or areas at risk for an upcoming outbreak. Our promising results showed good persistence of antibody levels after vaccination, which is important considering that chikungunya outbreaks may recur suddenly. As age is a risk factor for severity and mortality of chikungunya disease, the strong immune response observed in older participants might be particularly beneficial."

Study author Katrin Dubischar, Program Director, Chikungunya Vaccine at Valneva says, "At present, there is no dedicated treatment or vaccine available against chikungunya, which is a debilitating disease whose symptoms can persist on a long-term basis. Moreover, it is currently regarded as one of the viruses most likely to spread globally, and studies

have shown that climate change is driving the spread of the mosquitoes that carry it into new areas of the world. Therefore, having an effective vaccine is important for preparedness for future outbreaks."

The study enrolled 4,115 healthy adults across 43 study sites in the United States. Of those, 3,082 participants were given one dose of VLA1553 (via an injection in the arm), and 1,033 were given a placebo. All participants were included in the safety analysis but the immune response was only tested in a subgroup of 362 participants (266 given the vaccine and 96 given the placebo). Participants had their immune responses assessed one week, 28 days, three months, and six months after their vaccination. They also recorded adverse events in an electronic diary for 11 days after vaccination. Those who did experience adverse events within 21 days of vaccination (e.g. fever and joint pain, back pain, neurological symptoms, heart problems, rash, or swelling) were monitored more closely.

After a single vaccination, VLA1553 induced antibody levels at a level that is considered to protect against disease among 99% (263/266) of participants. There was no difference in immune response according to age.

VLA1553 was generally well tolerated across all age groups with most adverse events being mild or moderate. In those given the vaccine, the most common adverse events were headaches (experienced in 32% of vaccinated participants), fatigue (29%), muscle pain (24%), joint pain (18%), and pain at the injection site (13%).

After six months, there were more adverse events recorded for those given VLA1553 than those given placebo. Overall, 51% (1,575/3,082) of participants who were given VLA1553 and 31% (322/1,033) of those who received the placebo experienced at least one AE that was considered related to the vaccination. The safety profile in older adults

was similar to that of adults.

Serious adverse events were reported in 2% (46/3,082) of participants exposed to VLA1553 and 1% of participants in the placebo arm (8/1,033). Two of these were classified as related to the vaccine. One was a case of mild muscle pain in a woman with a medical history of fibromyalgia, and the other was a fever, which resulted in hospitalization. Neither of these cases resulted in death.

The rate of observed miscarriages in the population given VLA1553 was slightly higher than expected in the general population (23% versus around 11-16%). However, this could be due to natural variation in the small sample size. Two of the three miscarriages among women given VLA1553 were explained by genetic disorder or the participants' history of miscarriage. In the remaining case, no reason could be identified and the authors note further monitoring will be needed as the vaccine candidate is rolled out.

Commenting on the safety outcomes of the study, Dr. Juan Carlos Jaramillo, Chief Medical Officer at Valneva, says, "An independent Data Safety Monitoring Board (DSMB) evaluated safety data during the study and did not identify any safety concerns after evaluating all reported adverse events. The two related serious adverse events reported during the study both recovered fully and were reviewed by the DSMB who did not raise concerns or consider that there were serious risks caused by the vaccination in general."

The authors note some limitations of their study. The study did not take place in an endemic region, so participants' pre-existing immunity to the chikungunya virus is unknown, as is the safety of the vaccine in this population. In addition, the vaccine is made from a weakened version of the live virus, so is likely to be unsuitable for people with weakened immune systems, and pregnant women. They also acknowledge that to

be highly effective in controlling endemic disease, a chikungunya vaccine will also need to be administered to children. To determine safety and efficacy in this age group, there is a study in adolescents in endemic areas of Brazil currently ongoing.

Writing in a linked Comment, Dr. Kathryn Stephenson, Center for Virology and Vaccine Research at the Beth Israel Deaconess Medical Center, who was not involved in the study, said, "…the positive results of this trial are very good news for CHIKV pandemic preparedness. CHIKV and other arboviral infections continue to be global threats, spurred on by the expansion of mosquito habitats because of climate change and globalization of trade and travel. Further studies of VLA1553 in endemic regions and expanded populations, such as an ongoing trial in adolescents in Brazil (NCT04650399), will be critical to affirming VLA1553's value for CHIKV prevention, as will be real-world effectiveness studies in the context of actual CHIKV outbreaks."

More information: Safety and immunogenicity of a single-shot live-attenuated chikungunya vaccine: a double-blind, multicentre, randomised, placebo-controlled, phase 3 trial, *The Lancet* (2023). www.thelancet.com/journals/lan … (23)00641-4/fulltext

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