Safety and tolerability of chikungunya virus-like particle vaccine in healthy adults: a phase 1 dose-escalation trial

Lee-Jah Chang, Kimberly A Dowd*, Floreliz H Mendoza, Jamie G Saunders, Sandra Sitar, Sarah H Plummer, Galina Yamshchikov, Uzma N Sarwar, Zonghui Hu, Mary E Enama, Robert T Bailer, Richard A Koup, Richard M Schwartz, Wataru Akahata, Gary J Nabel, John R Mascola, Theodore C Pierson, Barney S Graham, Julie E Ledgerwood, and the VRC 311 Study Team*

Lancet 2014; 384: 2046–52

Published Online August 15, 2014 http://dx.doi.org/10.1016/S0140-6736(14)61185-5

See Comment page 2008

*Contributed equally

Vaccine Research Center (L-J Chang MD, F H Mendoza RN, J G Saunders BSN, S Sitar MSc, S H Plummer NP, G Yamshchikov MSc, U N Sarwar MD, M E Enama PA-C, R T Bailer PhD, R A Koup MD, R M Schwartz PhD, W Akahata PhD, G J Nabel MD, J R Mascola MD, B S Graham MD, J E Ledgerwood DO), **Viral Pathogenesis Section, Laboratory of Viral Diseases** (K A Dowd PhD, T C Pierson PhD), **and Biostatistics Research Branch, Division of Clinical Research** (Z Hu PhD), **National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD, USA**

Correspondence to: Dr Julie E Ledgerwood, Vaccine Research Center, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD 20892, USA **ledgerwood@mail.nih.gov**

Summary

Background **Chikungunya virus—a mosquito-borne alphavirus—is endemic in Africa and south and southeast Asia and has recently emerged in the Caribbean. No drugs or vaccines are available for treatment or prevention. We aimed to assess the safety, tolerability, and immunogenicity of a new candidate vaccine.**

Methods **VRC 311 was a phase 1, dose-escalation, open-label clinical trial of a virus-like particle (VLP) chikungunya virus vaccine, VRC-CHKVLP059-00-VP, in healthy adults aged 18–50 years who were enrolled at the National Institutes of Health Clinical Center (Bethesda, MD, USA). Participants were assigned to sequential dose level groups to receive vaccinations at 10 μg, 20 μg, or 40 μg on weeks 0, 4, and 20, with follow-up for 44 weeks after enrolment. The primary endpoints were safety and tolerability of the vaccine. Secondary endpoints were chikungunya virus-specific immune responses assessed by ELISA and neutralising antibody assays. This trial is registered with ClinicalTrials.gov, NCT01489358.**

Findings **25 participants were enrolled from Dec 12, 2011, to March 22, 2012, into the three dosage groups: 10 μg (n=5), 20 μg (n=10), and 40 μg (n=10). The protocol was completed by all five participants at the 10 μg dose, all ten participants at the 20 μg dose, and eight of ten participants at the 40 μg dose; non-completions were for personal circumstances unrelated to adverse events. 73 vaccinations were administered. All injections were well tolerated, with no serious adverse events reported. Neutralising antibodies were detected in all dose groups after the second vaccination (geometric mean titres of the half maximum inhibitory concentration: 2688 in the 10 μg group, 1775 in the 20 μg group, and 7246 in the 40 μg group), and a significant boost occurred after the third vaccination in all dose groups (10 μg group p=0·0197, 20 μg group p<0·0001, and 40 μg group p<0·0001). 4 weeks after the third vaccination, the geometric mean titres of the half maximum inhibitory concentration were 8745 for the 10 μg group, 4525 for the 20 μg group, and 5390 for the 40 μg group.**

Interpretation **The chikungunya VLP vaccine was immunogenic, safe, and well tolerated. This study represents an important step in vaccine development to combat this rapidly emerging pathogen. Further studies should be done in a larger number of participants and in more diverse populations.**

Funding **Intramural Research Program of the Vaccine Research Center, National Institute of Allergy and Infectious Diseases, and National Institutes of Health.**

Introduction

Chikungunya virus is an arthropod-borne virus of the *Alphavirus* genus of the Togaviridae family and is represented by three clades (west African; east, central, and South African; and Asian), with a high amount of aminoacid homology.[1–3] The virus is transmitted through the bite of an infected *Aedes aegypti* or *Aedes albopictus* mosquito and has been documented in about 40 countries.[3–15] Chikungunya virus is endemic to tropical and subtropical regions of Africa and south and southeast Asia. In 2013, the virus spread to the Americas and is responsible for a rapidly spreading epidemic in the Caribbean. As of June 13, 2014, 19 Caribbean or South American countries or territories have been affected, with an estimated 165 990 suspected chikungunya virus cases.[16–18]

Chikungunya virus causes an acute infection associated with severe morbidity lasting several weeks, although symptoms can persist for months. The incubation period ranges from 2 days to 12 days,[14,19] and the acute symptoms include fever, myalgia, arthralgia, headache, rash, nausea, and fatigue.[20] The hallmark symptom of chikungunya virus infection is severe polyarthralgia, with subacute or chronic arthritis presenting as a long-term sequela in some patients.[3,11,13–15] After presentation with acute-onset arthritis, the virus can be identified on PCR[21] and virus can be detected in the joints of infected patients.[22,23] Therefore, chikungunya-virus-associated arthritis is regarded as a direct consequence of viral infection and the related pro-inflammatory innate immune response, rather than a byproduct of adaptive immune responses.[21,24] Neurological complications (encephalitis and meningoencephalitis) have also been reported in rare cases.[7,15,25–27] Although rarely fatal, deaths have occurred, primarily in the elderly and in those with comorbid disorders.[8,11,13,28]

Characterisation of the chikungunya virus adaptive immune response shows that IgM antibodies are present as early as 2 days after the onset of symptoms and persist for weeks to months, whereas IgG is generally detected as the virus is cleared and persists for many years.[29,30] The antibody response against chikungunya virus is primarily of the IgG3 isotype.[29] These IgG3 antibodies are neutralising, associated with viral clearance, and associated with a low risk of prolonged arthralgia when they are induced early in the course of infection.[30] Therefore, the adaptive immune response seems to play a part in controlling the arthritis, further implicating the direct role of viral infection as the cause of the joint inflammation.[31] Neutralising antibodies also prevent virus reinfection, which further suggests that antibody-mediated protection occurs.[6,8,15]

Confirmation and diagnosis of chikungunya virus can be made by serology or detection of viral RNA by RT-PCR during acute infection, but access to rapid testing is not widely available. Because of the durable IgG response to chikungunya virus, assays of greatest potential for diagnosis of acute infection are an IgM-based serological test or direct detection of viral nucleic acid.

No vaccine is available for the prevention of chikungunya virus infection and no specific treatment exists. A live attenuated vaccine candidate has been assessed in a phase 2 clinical trial,[32] but did not advance to efficacy testing.[33] Other vaccine strategies under investigation include a formalin-killed vaccine candidate,[34,35] a chimeric alphavirus vaccine candidate,[36] a virus-like particle (VLP)-based vaccine,[37,38] vaccines based on modified vaccinia Ankara and measles vector,[39,40] and DNA candidate vaccines.[41,42]

The Vaccine Research Center (VRC) chikungunya virus candidate vaccine described herein is a VLP that was chosen because VLPs are highly immunogenic, have a proven safety record, and typically elicit high titre neutralising antibodies needed to protect against chikungunya virus.[1] Additionally, there are few containment requirements for manufacturing because live virus production is not needed. The VRC chikungunya VLP candidate vaccine protects non-human primates from infection and illness, and protective immunity is based on the neutralising antibody.[1]

In this phase 1 study of the VRC chikungunya VLP vaccine in healthy adults, we aimed to assess the safety, tolerability, and immunogenicity of this new candidate vaccine.

Methods

Study design and participants

In VRC 311, a phase 1, dose-escalation, open-label clinical trial, we examined the safety, tolerability, and immunogenicity of a VLP chikungunya virus vaccine. Eligible participants were adults aged 18–50 years who were healthy, as defined by 40 inclusion and exclusion criteria related to clinical laboratory tests, medical history, and physical examination (appendix); with no history of chikungunya virus infection; and willing to comply with protocol schedule requirements. This study was open label: both the patients and clinicians knew what dose was being administered for all injections. There were no changes to the design after commencement of the study.

In the sera collection protocol, VRC 200, we obtained convalescent sera from two patients who had recovered

	10 μg group (n=5)	20 μg group (n=10)	40 μg group (n=10)	Overall (n=25)
Sex				
Women	2 (40%)	7 (70%)	6 (60%)	15 (60%)
Men	3 (60%)	3 (30%)	4 (40%)	10 (40%)
Age (years)				
Mean (SD)	29 (7)	34 (6)	29 (7)	31 (7)
Range	18–37	28–47	22–42	18–47
Race				
Asian	1 (20%)	1 (10%)	1 (10%)	3 (12%)
Black or African American	1 (20%)	1 (10%)	1 (10%)	3 (12%)
White	3 (60%)	8 (80%)	8 (80%)	19 (76%)
Ethnic origin				
Non-Hispanic or Latino	5 (100%)	10 (100%)	9 (90%)	24 (96%)
Hispanic or Latino	0 (0%)	0 (0%)	1 (10%)	1 (4%)
Body-mass index				
Mean (SD)	23 (2)	25 (3)	26 (5)	25 (4)
Range	22–25	21–31	20–35	20–35
Education				
High school or equivalent	0 (0%)	1 (10%)	0 (0%)	1 (4%)
College graduate	1 (20%)	3 (30%)	6 (60%)	10 (40%)
Advanced degree	4 (80%)	6 (60%)	4 (40%)	14 (56%)

Data are number (%), unless otherwise specified.

Table 1: **Baseline demographics of participants**

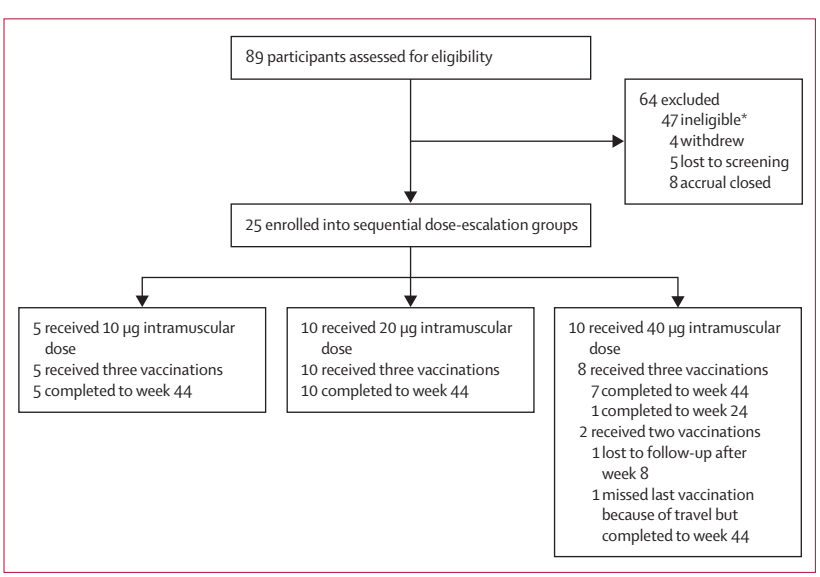

Figure: **Trial profile**

*Seven of whom did not meet several criteria. Ineligibility reasons were laboratory test (n=13), medical history (n=22), physical findings (n=10), and inability to comply with protocol requirements (n=10).