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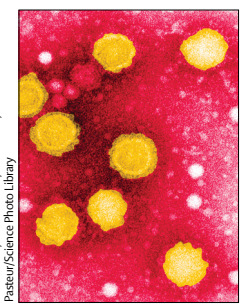
# Fighting back against chikungunya



O Schwartz, M Souriseau, Mc Prevost, Institute Pasteur/Science Photo Library

Published Online
March 2, 2015
http://dx.doi.org/10.1016/S1473-3099(15)70079-4

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Chikungunya is a mosquito-borne disease that leaves the afflicted patient with incapacitating arthritis that can last for several months or even years.[1] Since the start of the largest ever outbreak of chikungunya virus infecton in 2005 in the Indian Ocean, there has been a resurgence in chikungunya cases that continues to this day.[1] Adaptation of chikungunya virus to the globally distributed Asian tiger mosquito (*Aedes albopictus*) has led to autochthonous cases in both Europe and the Americas.[2] In the year after chikungunya virus first appeared in the Caribbean, an estimated 1 million cases were reported, with concerns that the virus could spread extensively throughout the Americas.[3] Despite the emerging importance of chikungunya virus, no specific treatment or vaccine is available for infected individuals. In *The Lancet Infectious Diseases,* Katrin Ramsauer and colleagues[4] report promising results from a randomised, phase 1, active-comparator trial assessing the immunogenicity, safety, and tolerability of a live recombinant measles-virus-based chikungunya vaccine.

Ideal vaccine candidates need to be safe, induce humoral and cellular immunity, and should provide long-lasting protection with one or just a few doses. Ramsauer and colleagues' use of the attenuated measles virus Schwarz strain is a good technique. The measles virus vaccine is one of the safest on the market and has been mass-produced at low cost in many countries since the early 1960s. The vaccine has stood the test of time and meets all the above criteria by being extremely safe and effective.[5] Furthermore, measles virus is an ideal vaccine vector because it is easy to manipulate via reverse genetics, insertion of foreign sequences is well tolerated, and the resulting recombinant viruses are highly stable.[6] Being an RNA virus, replication is limited to the cytoplasm of cells, thereby increasing its safety. These properties make measles virus an obvious choice as a vaccine vector for various illnesses, such as those caused by Nipah virus, West Nile virus, respiratory syncytial virus, HIV, dengue virus, and severe acute respiratory syndrome coronaviruses.[5–9]

In Ramsauer and colleagues' clinical trial, 42 healthy adults (aged 18–45 years) were assigned to receive three different doses (low, medium, or high) of the recombinant measles-virus-based chikungunya candidate vaccine, with a booster immunisation at either 28 or 90 days after the initial vaccination. All doses of the candidate vaccine were effective, albeit with varying rates of seroconversion after the primary immunisation (44% in the low-dose group, 92% in the medium-dose group, and 90% in the high-dose group). However, 100% of participants had seroconverted after the second vaccination. Pre-existing antibodies against measles did not interfere with immunogenicity of the candidate vaccine[10]—an important feature of this vaccine candidate in view of the high compliance rate for measles virus vaccination (around 84% worldwide). The safety profile of the candidate vaccine was deemed acceptable, with seven severe adverse events recorded in six patients (17% of participants receiving vaccinations). This proportion accords with the 5–15% of patients who develop systemic reactions after a monovalent measles vaccination. The adverse events reported included nasopharyngitis, oropharyngeal pain, headache, injection-site pain, influenza-like illness, and musculoskeletal pain. Despite the generally acceptable tolerability profile, one in six patients is a fairly concerning figure and this aspect will need to be carefully followed up in future trials.

So far, this candidate vaccine is only the third chikungunya vaccine to be studied in a phase 1 setting. Strategies used for the other two vaccines differed slightly from those used in the present study. Investigators of the first study used a live-attenuated virus as a means of vaccination, whereas the investigators of the other study chose to produce a virus-like particle vaccine (VRC-CHKVLP059-00-VP).[11,12] The other candidates also yielded positive results by inducing long-lasting immunity while generating few adverse effects. Unfortunately, despite entering phase 2 trials, the first vaccine fell victim to a lack of funding and marketable interest,[13] and no follow-up information is available about the second candidate. Although the present phase 1 trial has only recently been published, preparations for a phase 2 trial are probably underway. Several other vaccine candidates and strategies that have yielded promising preclinical data, such as use of the picornavirus internal ribosome entry site or subunit, genetic, or recombinant modified vaccinia virus Ankara-based vaccines.[14,15]

The road towards development of a vaccine approved by the US Food and Drug Administration is long and winding, but with two potential candidates in the pipeline, we might be on the right track in the fight against chikungunya.

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We declare no competing interests.

1 Burt FJ, Rolph MS, Rulli NE, Mahalingam S, Heise MT. Chikungunya: a re-emerging virus. *Lancet* 2012; **379:** 662–71.
2 Tsetsarkin KA, Vanlandingham DL, McGee CE, Higgs S. A single mutation in chikungunya virus affects vector specificity and epidemic potential. *PLoS Pathog* 2007; **3:** e201.
3 Johansson MA. Chikungunya on the move. *Trends Parasitol* 2015; **31:** 43–45.
4 Ramsauer K, Schwameis M, Firbas C, et al. Immunogenicity, safety, and tolerability of a recombinant measles-virus-based chikungunya vaccine: a randomised, double-blind, placebo-controlled, active comparator, first-in-man trial. *Lancet Infect Dis* 2015; published online March 2. http://dx.doi.org/10.1016/S1473-3099(15)70043-5.
5 Hilleman MR. Current overview of the pathogenesis and prophylaxis of measles with focus on practical implications. *Vaccine* 2001; **20:** 651–65.
6 Billeter MA, Naim HY, Udem SA. Reverse genetics of measles virus and resulting multivalent recombinant vaccines: applications of recombinant measles viruses. *Curr Top Microbiol Immunol* 2009; **329:** 129–62.
7 Escriou N, Callendret B, Lorin V, et al. Protection from SARS coronavirus conferred by live measles vaccine expressing the spike glycoprotein. *Virology* 2014; **452–53:** 32–41.
8 Yoneda M, Georges-Courbot MC, Ikeda F, et al. Recombinant measles virus vaccine expressing the Nipah virus glycoprotein protects against lethal Nipah virus challenge. *PLoS One* 2013; **8:** e58414.
9 Stebbings R, Fevrier M, Li B, et al. Immunogenicity of a recombinant measles-HIV-1 clade B candidate vaccine. *PLoS One* 2012; **7:** e50397.
10 Brandler S, Ruffie C, Combredet C, et al. A recombinant measles vaccine expressing chikungunya virus-like particles is strongly immunogenic and protects mice from lethal challenge with chikungunya virus. *Vaccine* 2013; **31:** 3718–25.
11 Edelman R, Tacket CO, Wasserman SS, Bodison SA, Perry JG, Mangiafico JA. Phase II safety and immunogenicity study of live chikungunya virus vaccine TSI-GSD-218. *Am J Trop Med Hyg* 2000; **62:** 681–85.
12 Chang LJ, Dowd KA, Mendoza FH, 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.
13 Hoke CH, Jr, Pace-Templeton J, Pittman P, et al. US Military contributions to the global response to pandemic chikungunya. *Vaccine* 2012; **30:** 6713–20.
14 Roy CJ, Adams AP, Wang E, et al. Chikungunya vaccine candidate is highly attenuated and protects nonhuman primates against telemetrically monitored disease following a single dose. *J Infect Dis* 2014; **209:** 1891–99.
15 Hallengard D, Lum FM, Kummerer BM, et al. Prime-boost immunization strategies against chikungunya virus. *J Virol* 2014; **88:** 13333–43.

# Tuberculosis and vitamin D: what's the rest of the story?

Published **Online**
April 9, 2015
http://dx.doi.org/10.1016/S1473-3099(15)70163-5

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Both protein–energy undernutrition and specific micronutrient deficiencies debilitate the cell-mediated immune system important in protection against tuberculosis.[1] However, once tuberculosis develops, the disease itself induces a catabolic state resulting in negative nitrogen balance and micronutrient deficiencies. Generations of clinicians treating patients with tuberculosis believed that nutritional support was crucial to proper patient care. Why, then, has it been so difficult to prove through randomised controlled clinical trials that nutritional interventions improve tuberculosis treatment outcomes? Findings from systematic reviews[2–6] have not shown any clear, consistent benefit in terms of tuberculosis-specific outcomes, although they do show improvements in nutritional status.

In the past 30 years, researchers have discovered many roles and mechanisms of vitamin D action in both the innate and adaptive immune systems.[7] Vitamin D promotes macrophage-mediated killing of *Mycobacterium tuberculosis*,[8] an observation that has led to several phase 2 trials[2–6] of vitamin D supplementation, nearly all of which have shown no substantial benefit in terms of tuberculosis treatment outcomes. In *The Lancet Infectious Diseases*, Peter Daley and colleagues[9] report findings from another such trial, and again the findings are negative. The randomised, double-blind, placebo-controlled trial was well designed to address an important issue with use of an inexpensive, simple intervention. Study treatment was given under direct observation; randomisation involved well concealed treatment allocation; masking of the intervention between the groups was reportedly good; at baseline the study groups were reasonably matched, although pulmonary cavitation was unknown; assessment of endpoints was masked; dedicated study staff collected all patient data; smears and cultures were processed in one laboratory by one experienced technologist who was masked to treatment allocation; and withdrawals, exclusions, and dropouts were noted. Thus, the methods seem to be robust, despite the absence of a traditional CONSORT diagram or use of multivariable regression methods in the analysis. Furthermore, the trial was reasonably powered for its primary outcome of time to sputum culture conversion. Median time to sputum culture conversion was similar between participants in the vitamin D and placebo groups (43·0 days [95% CI 33·3–52·8] and 42·0 days [33·9–50·1], respectively), as were the proportions of patients with positive sputum cultures at 2 months. Does this mean that vitamin D supplementation is of no value in the management of pulmonary tuberculosis? The answer is not yet clear, but different questions should now be asked. Although vitamin D stimulates macrophage-mediated killing of