INTERNATİONAL REGULATORY APPROACH FOR IXCHIQ®, VACCİNE FOR THE PREVENTİON OF CHİKUNGUNYA

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Discussion

The experience with IXCHIQ® states the importance of counting on a flexible legal framework that allows national regulatory authorities (NRA) a fast-track approval of vaccines, based on the public health risk and needs without compromising the quality standards, safety and efficacy.

From a regulatory perspective a conditional marketing authorization for IXCHIQ® is an example of how a flexible regulatory framework, based on public health needs and risks, can provide access to innovative vaccines without compromising the quality standards, safety and efficacy.

Phase IV, post-approval, must be considered an essential component in the regulatory life cycle of a vaccine, particularly in emerging or re-emerging with unpredictable epidemiological patterns. International regulatory convergence, the acknowledgement of stringent authorities and the alignment to the World Health Organization (WHO) recommendations, are key elements to streamline evidence generation and advocacy for a responsible use of vaccines. In this context, the Coalition for Epidemic Preparedness Innovations (CEPI) performs a strategic role as a global manager of scientific and regulatory efforts, thus contributing to minimize concerns, strengthen decision making, and improving preparedness before new public health emergencies.

Keywords: health regulation, attenuated vaccines, chikungunya virus

Epidemiological context and the need for prevention strategies.

Chikungunya is a viral disease transmitted by female mosquito bites *Aedes aegypti* and *Aedes albopictus.*

Acute infection is characterized by high fever and acute joint pain, which can last weeks, months or even years.

Other symptoms include headache, diffuse low back pain, myalgia, nausea, vomiting, polyarthritis, skin rash, and conjunctivitis. Furthermore, ocular, cardiac, and neurological complications have been described, particularly in individuals at the extremes of the age spectrum, who are at a higher risk of severe disease, hospitalization, and death.

In areas where other arbovirus coexist, such as dengue or zika, the prognosis can become complex, favoring the sub notification. Once an individual is better, the available evidence suggests, this person is likely immune to future chikungunya infections (Auerswald et al., 2018).

Developing new alternatives to prevent chikungunya infections is important due to the impact it has in a myriad of countries' public health, especially in Latin America (WHO, 2025). The aforementioned, considerably affects the quality of life and creates a high load in care, due to its chronic complications, especially the persistent joint pain, which mainly affects vulnerable age groups as children and elderly.

Even if in El Salvador there have not been any confirmed chikungunya cases since 2024 (Ministry of Health in El Salvador, 2026), some outbreaks have been confirmed in Brazil, Paraguay (European Centre for Disease Prevention and Control, 2025) and Thailand (OMS, 2025) reaffirming the importance of new regulatory frameworks that allow the evaluation, authorization and post marketing vigilance for the alternatives developed to prevent chikungunya infections.

The prevention of chikungunya is essential for endemic countries since the circulation of said virus fosters new outbreaks or expansion to new areas.

The high transmission rate of this disease, next to the lack of specific treatments, and symptoms associated to chronic joint pain, significantly reduces individuals' quality of life making prevention fundamental to reduce the incidence, limit the spreading, and prevent persistent transmission scenarios with potential regional and global impact.

Developing vaccines against chikungunya virus and the role of phase IV

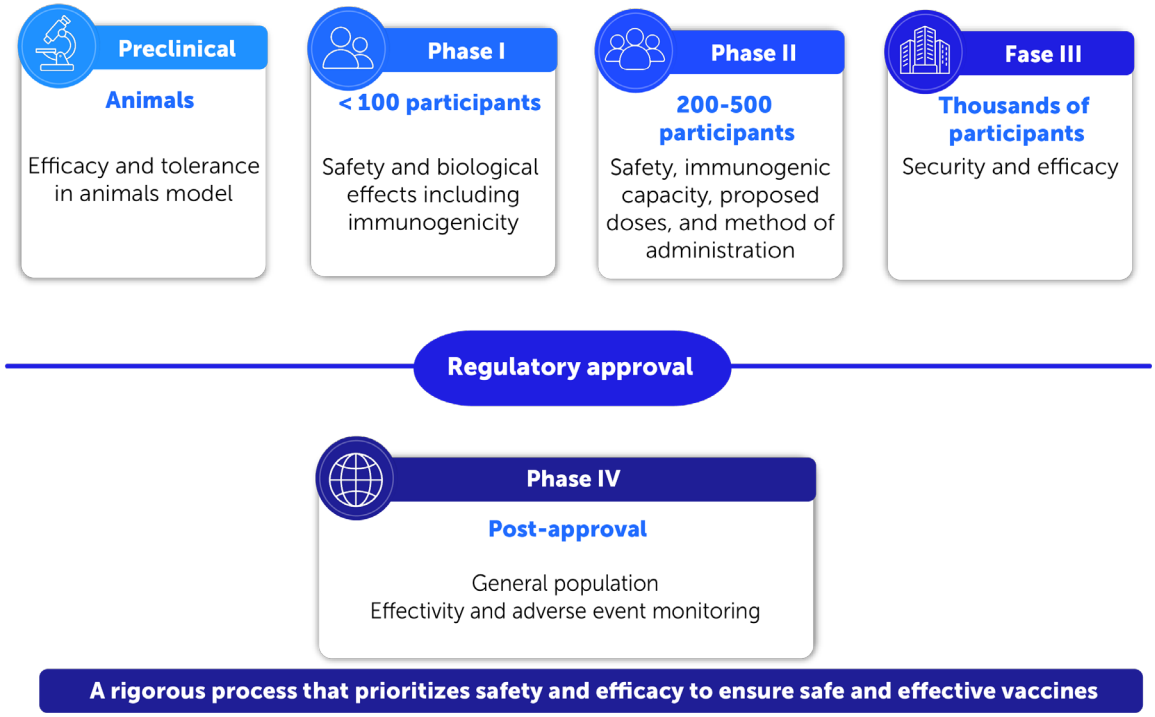
There are currently two vaccines to prevent chikungunya that have received regulatory approval or have been recommended to be used on risk populations in many countries: IXCHIQ® and VIMKUNYA®, virus-like particles vaccine (VLP) (Kling, 2026); however, these are not widely available yet nor is their use generalized.

Vaccine making follows a rigorous process comprised of the following phases: pre-clinical, clinical (phases I to III), and post-approval (phase IV), progressively prioritizing safety, immunogenicity, and efficacy evaluation (Figure 1).

In the case of chikungunya, traditional efficacy clinical trials are limited by the unpredictable nature of outbreaks which brings authorities to accept alternative evaluation criteria such as immunogenicity as reasonably likely surrogate endpoint for clinical benefit.

Thus, post-approval phase IV, acquires an important role while allowing generation of evidence for its effectivity in conditions of use, the monitoring of rare adverse events, and the evaluation of vaccine performance in populations with prior exposure to the virus, particularly in endemic settings.

Figure 1. Vaccine development phases (WHO, 2020)

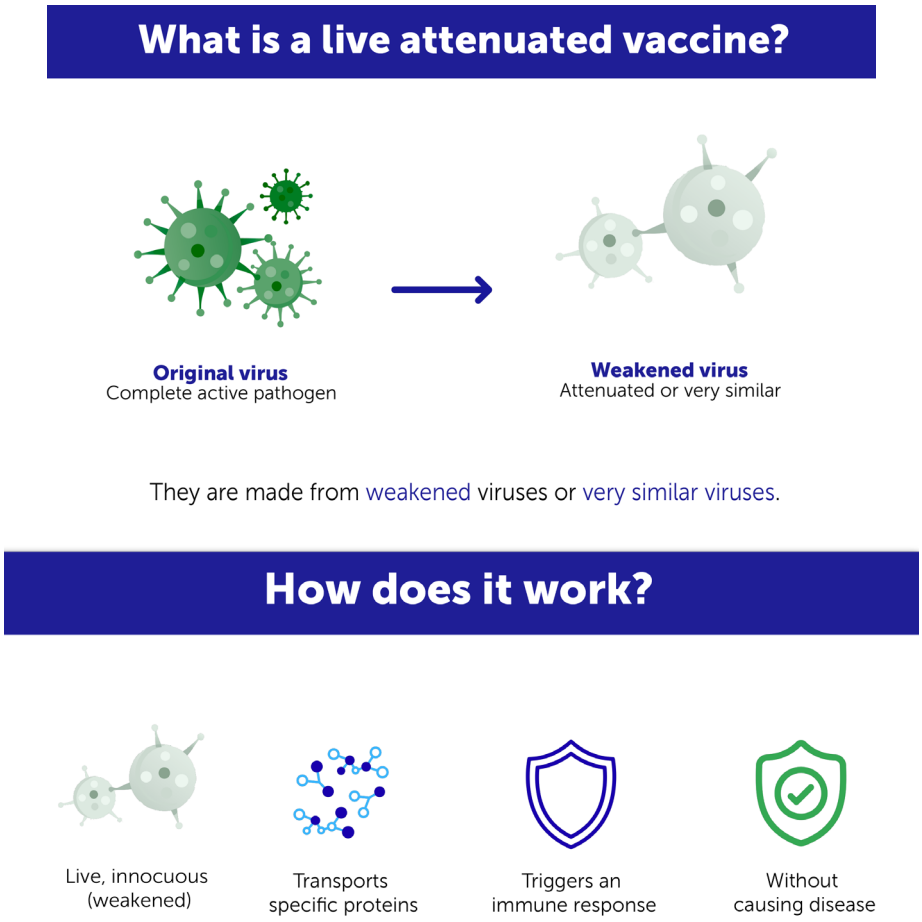


IXCHIQ®: characteristics and available evidence

IXCHIQ® is the first vaccine authorized worldwide for the prevention of chikungunya (Ly, 2024) and its indicated for individuals 12 years and older (Kang et al., 2025). It is a live-attenuated virus vaccine (Figure 2), containing a weakened strain of the chikungunya virus. Live-attenuated vaccines are developed from viruses that have been weakened, therefore, this type of vaccine may not be suitable for immunocompromised individuals.

In these vaccines, the weakened virus triggers an immune response without causing the disease itself. When an individual is vaccinated with IXCHIQ®, the immune system recognizes the weakened virus as foreign microorganisem and produces antibodies against it. Should the individual subsequently come into contact with the chikungunya virus, the immune system will be capable of fighting off the virus, protecting the person from the disease.

Figure 2. Live attenuated vaccines mechanism of action (WHO, 2025)



Phase I to III clinical trials demonstrated that IXCHIQ® induces high and sustained levels of neutralizing antibodies. Approximately 99% of previously uninfected adults and adolescents reached the target antibody level one-month post-vaccination, and these levels were maintained in roughly 97–99% of participants up to 12–24 months after vaccination (European Medicines Agency, 2024).

The observed safety profile was comparable to that of other live-attenuated vaccines, with adverse events similar to those observed with them. However, uncertainties persist regarding the duration of protection, effectiveness in populations with prior exposure to the virus, and vaccine performance in endemic settings. These limitations justify the implementation of Phase IV studies as a key condition for sustaining a long-term risk-benefit balance.

International Regulatory Scenarios and Conditional Authorizations

Given the absence of preventive alternatives and the unmet medical need, IXCHIQ® has been authorized by several reference regulatory authorities under accelerated or conditional approval mechanisms. These schemes allow for early access to the vaccine while imposing post-authorization obligations aimed at generating additional evidence, through studies in areas where the chikungunya virus circulates to evaluate its efficacy and safety, thereby ensuring responsible use and strengthening public and professional confidence in the vaccine.

These regulatory frameworks reflect an international convergence in the acceptance of alternative evidence criteria, especially in situations where traditional efficacy trials are not feasible (Table 1).

Contributions of the CEPI Approach and Regulatory Position Challenges

Technical discussions promoted by the Coalition for Epidemic Preparedness Innovations (CEPI) have highlighted the importance of coordinating international efforts for the generation of post-approval evidence. In the case of IXCHIQ®, Phase IV represents an opportunity to integrate observational studies, active surveillance, and enhanced pharmacovigilance systems, particularly in countries with active virus circulation. From a regulatory perspective, these studies not only allow for the confirmation of real-world effectiveness but also contribute to improving public opinion toward new vaccines, especially those based on live-attenuated virus platforms.

Table 1. Regulatory scenarios for IXCHIQ®

Criterion	United States (FDA)	Canada (Health Canada)	European Union (EMA)	Brazil (ANVISA)
Approval Pathway	Accelerated Approval	Notice of Compliance with Conditions (NOC/c)	Conditional Marketing Authorisation (CMA)	Conditional Sanitary Registration (Terms of Commitment)
Legal Basis	Section 506(c), FD&C Act	Food and Drug Regulations – NOC/c Policy	Regulation (EC) No 507/2006	Law No. 6.360/1976; RDC No. 55/2010; Public Consultation No. 1.282/2024
Approval Context	Unmet medical need; absence of available vaccine	Unmet medical need with preliminary evidence	Absence of chikungunya vaccine; potential benefit outweighs risks	Endemic country with high disease burden (Adult approval, April 2025)
Evidence Base	Immunogenicity as a reasonably likely surrogate endpoint	Immunogenicity and safety, with reference to international data	Immunogenicity, safety, and scientific justification of the correlate	Immunogenicity and safety, considering the epidemiological context
Post-Authorization Obligations	Adequate and well-controlled confirmatory studies	Additional studies to confirm efficacy	Effectiveness and safety studies in real-world use	Effectiveness studies in endemic areas and active pharmacovigilance
Monitoring Objective	Verify and describe clinical benefit	Reduce regulatory uncertainty	Confirm benefit-risk balance	Evaluate performance under active viral circulation

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Special Features	Manufacturer's responsibility to generate confirmatory evidence	Sovereign decision aligned with reference regulators	Centralized evaluation; PRIME support for development	Transparent process with public consultation and formal commitments

Sources: (Health Canada, 2014), (Health Canada, 2017), (European Medicines Agency, 2025), (U.S. Food and Drug Administration, 2025), (Agência Nacional de Vigilância Sanitária - ANVISA, 2025).

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