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Advancing chikungunya vaccine development through regulatory science

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ABSTRACT

The escalating global spread of chikungunya virus, exemplified by the 2025 local outbreak in Guangdong Province, China, underscores the urgent need for effective vaccination strategies. This paper discusses advancements in chikungunya vaccine development through the lens of regulatory science. We reviewed recent progress in vaccine platforms, including the live-attenuated IXCHIQ® and VLP-based Vimkunya®, as well as the emerging mRNA candidates, highlighting their immunogenicity and safety profiles. We further addressed unique challenges in chikungunya vaccine development, such as viral genetic diversity, intermittent outbreaks, and ethical and practical barriers to conducting traditional efficacy trials. To overcome these, we proposed innovative regulatory strategies to accelerate approval, including: (1) surrogate endpoints based on neutralizing antibodies supported by animal challenge models; (2) streamlined chemistry, manufacturing, and controls and nonclinical/clinical study requirements through platform technology leveraging; and (3) integrated lifecycle risk management with enhanced post-marketing surveillance. Drawing on experience with platform-based vaccine regulation, we emphasize the importance of regulatory agility, international collaboration, and science-driven policy to facilitate the rapid development and deployment of safe, effective, and broadly protective chikungunya vaccines against future arbovirus threats.

KEYWORDS: Chikungunya vaccine; Regulatory science; Platform technology; Accelerated approval; Lifecycle risk management

1. Introduction

Chikungunya virus (CHIKV) is an alphavirus transmitted primarily by *Aedes (Ae.) aegypti* and *Ae. albopictus* mosquitoes, and represents a growing global public health threat[1–5]. In recent years, the global epidemiology of CHIKV has expanded considerably, driven by viral adaptive evolution, climate change-driven vector habitat expansion, and increasing international travel and trade[6]. This trend was starkly illustrated in July 2025 when an outbreak occurred in Foshan, Guangdong Province, China, resulting from imported cases from Southeast Asia. As of 27 December over 11 000 local cases had been confirmed[7]. Concurrently, the Americas, Africa, and Europe faced ongoing CHIKV transmission, underscoring the virus's potential for spread beyond traditional endemic regions and into subtropical and temperate zones[8,9].

The development of effective chikungunya vaccines faces several formidable challenges: (1) substantial genetic diversity across its main genotypes, which complicates broad cross-neutralization; (2) the high burden of chronic sequelae, highlighting the need for durable immune responses—including robust T-cell immunity; (3) intermittent and unpredictable outbreak patterns that hinder the execution of traditional randomized controlled efficacy trials; and (4) ethical constraints on the use of placebo controls during epidemics. Notably, CHIKV's intermittent outbreak pattern poses unique regulatory challenges, making traditional efficacy trials difficult or unethical and creating a critical evidence-generation gap[10–12]. These challenges underscore the critical need for innovative regulatory strategies to accelerate vaccine development and approval without compromising scientific rigor or safety.

This paper explicitly identifies key regulatory gaps and proposes

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tailored regulatory strategies to accelerate chikungunya vaccine development while maintaining a robust benefit-risk standard. We reviewed approved vaccines and emerging candidates, highlighting their immunogenicity and safety profiles. Furthermore, we discussed strategic regulatory innovations—including the use of neutralizing antibodies (NAbs) as fit-for-purpose surrogate endpoints supported by animal challenge models, streamlined development pathways leveraging platform technologies, and integrated lifecycle risk management with enhanced post-marketing surveillance and explicit post-authorization commitments—that can facilitate the timely availability of safe, effective, and broadly protective chikungunya vaccines[13]. By emphasizing regulatory agility, international collaboration, and evidence-based policy, we aims to support the rapid development and deployment of vaccines against CHIKV and future arbovirus threats.

2. Viral and immunological characteristics: Informing vaccine design

2.1. Virology basics

CHIKV is a positive-sense single-stranded RNA virus belonging to the genus *Alphavirus* in the family Togaviridae. Its approximately 11.8 kb genome encodes nonstructural proteins (nsP1-nsP4) and structural proteins (capsid C, envelope E1/E2/E3, and 6K) (Figure 1A)[14]. The envelope glycoproteins E1, E2 and E3 assemble into trimeric spikes on the viral surface[15].

Based on the *E1* gene sequence, CHIKV is classified into three genotypes: West African (WA), Asian and East/Central/South African (ECSA). The ECSA genotype, particularly the Indian Ocean lineage (IOL), has contributed to global spread due to an adaptive mutation (E1-A226V) that enhances infectivity in *Ae. albopictus* mosquitoes by approximately 40-fold[15–17]. In contrast, the E2 protein is highly conserved across lineages and serves as the primary target for neutralizing antibodies (NAbs) (Figure 1B)[18].

Viral infection begins with mosquito inoculation, followed by replication and subsequent dissemination to target tissues including synovium, skeletal muscle, and lymphoid tissue[19]. Pathological mechanisms include: (1) direct cytopathic effects causing cell lysis; (2) inflammatory cytokine storms (*e.g.*, IL-6, TNF-α) *via* activation of mononuclear phagocytes; and (3) potential autoimmune responses due to structural mimicry between E2 and host joint components[19–22].

2.2. Immunological profile and challenges

Unlike other arboviruses such as dengue virus (DENV), CHIKV is a single-serotype virus with demonstrated cross-antigenicity across genotypes. Infection or vaccination induces NAbs primarily targeting the E2 protein (Figure 1B), with monoclonal antibodies (*e.g.*, C9, IM-CKV063) showing cross-genotype efficacy in animal models[23]. This immunological feature provides the foundation for broad-spectrum vaccine development, as evidenced by the approved vaccines IXCHIQ® and Vimkunya®.

However, chikungunya vaccine development still faces certain unique challenges:

Cross-neutralization limitations: CHIKV has significant genetic

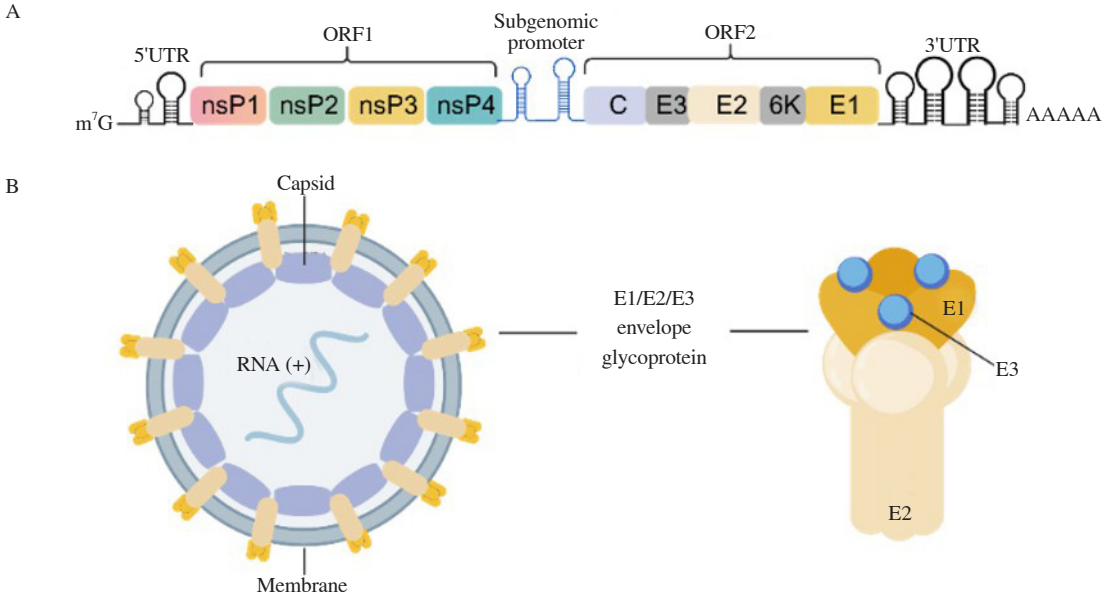

Figure 1. Schematic of the CHIKV genome and virion structure. (A) Linear genome organization (~11.8 kb) encoding nsP1-nsP4 and structural proteins (C, E3, E2, 6K, E1). (B) Virion architecture: a ribonucleoprotein core containing the positive-sense RNA genome, surrounded by a spherical capsid (capsid, light purple) and a lipid bilayer membrane structure derived from the host cell (membrane, light gray-blue), studded with trimeric spike envelope glycoprotein complexes (E1/E2/E3 envelope glycoproteins, yellow and blue). Key components are labeled in the figure.

diversity, and the NAb responses induced by different genotypes vary. Vaccines designed for West African genotypes (such as Vimkunya®) have weaker neutralizing ability against the IOL lineage, while antibodies induced by the ECSA/IOL lineage have approximately 30% lower neutralizing potency against the Asian lineage[24].

Immune evasion: Viruses can evade the host immune response using non-structural proteins. For example, the nsP2 protein inhibits interferon signaling pathways, while nsP1 downregulates host antiviral proteins like Tetherin (BST-2), facilitating immune escape[25].

Persistence and T−cell immunity: Viral RNA persists in joint tissues has been shown to contribute to chronic arthritis. This supports assessment beyond NAbs (including cellular immunity) and follow-up that is relevant to longer-term outcomes[26,27].

Clinical trial implementation: Intermittent outbreaks with short epidemic cycles and geographic clustering complicate traditional randomized controlled trials (RCTs), while ethical concerns regarding placebo use during epidemics present additional challenges[10,11].

These virological and immunological characteristics highlight both the opportunities and obstacles in chikungunya vaccine development, informing the design of next-generation vaccines that must balance genotype coverage with safety across diverse populations.

3. Vaccine platform progress

The escalating global threat of arthropod-borne viruses has prompted the international community to establish a comprehensive control system integrating long-term strategic planning, global initiatives, emergency response mechanisms, and coordinated vaccine development and policy implementation. This system strengthens global preparedness and provides a robust foundation for combating chikungunya and other *Aedes*-borne arboviral diseases, while guiding future research, policy-making, and vaccination campaigns.

The World Health Organization (WHO) has gradually developed a layered global framework since 2017. The Global Vector Control Response (GVCR, 2017-2030) aims to significantly reduce the burden of vector-borne diseases by 2030 through integrated vector management. In 2022, the WHO launched the Global Arbovirus Initiative, designating dengue, chikungunya, Zika, and yellow fever as priority pathogens and promoting international collaboration and research agendas. With increasing epidemic risks, the WHO further initiated the Global Strategic Preparedness, Readiness and Response Plan (SPRP) in October 2024, allocating USD 55 million over a one-year period to strengthen global outbreak readiness across five pillars: emergency coordination, surveillance, community protection, clinical care, and access to countermeasures, while emphasizing innovation, new technologies, and improved vector control strategies in collectively combating *Aedes*-borne arboviral threats[28–30].

At the research and policy level, CHIKV was listed by the WHO as a priority pathogen for vaccine development in 2018. The Coalition for Epidemic Preparedness Innovations (CEPI) included it in its core funding portfolio in 2019 to support multi-platform vaccine development[6,31]. Significant progress has been made in recent years[10]. Valneva's live-attenuated vaccine IXCHIQ® received the U.S. Food and Drug Administration (FDA) accelerated approval (November 2023) and European Medicines Agency (EMA) authorization (June 2024) for adults at increased risk; in 2025, following safety reviews in older adults, EMA restricted the vaccine's use to individuals at high risk of exposure, whereas FDA ultimately suspended the license in August[32–38]. Bavarian Nordic's virus-like particle (VLP) vaccine Vimkunya® was approved in 2025 in both the U.S. and Europe[39,40]. Other platforms, including mRNA vaccines (*e.g.*, Moderna, CureVac candidates) and viral-vectored vaccines, are advancing in preclinical and early clinical stages[41–45], illustrating a diverse and promising vaccine development landscape (Table 1). Concurrently, the WHO Strategic Advisory Group of Experts on Immunization (SAGE) established a dedicated Chikungunya Vaccine Working Group in Q2 2025, with plans to issue a comprehensive policy and position paper in 2026. This initiative will systematically evaluate evidence on vaccine safety, effectiveness, immunization strategies, cost-effectiveness, and equity, facilitating the translation of scientific advances into global immunization policy and practice[46].

Each vaccine platform presents distinct advantages and limitations (Table 1). Traditional inactivated platforms are safe and accessible but often limited in immunogenicity. Live attenuated vaccines, while effective, carry a risk of reversion to virulence. Modern platforms (*e.g.*, mRNA, VLPs, viral vectors) enable rapid response to emerging infectious diseases and cross-indication development. Their deployment, however, faces technical challenges such as stability and long-term immune durability, and therefore requires rigorous validation. The parallel development of multiple platforms, coupled with advancements in adjuvants, delivery systems, saRNA, and circRNA technologies, holds promise for accelerating the development of safe, effective and accessible vaccines[47–50].

3.1. Licensed vaccines

3.1.1. Live attenuated vaccine

IXCHIQ® (VLA1553) (Figure 2A), which received FDA accelerated approval in November 2023 and EMA marketing authorization in June 2024, is based on the ECSA genotype wild-type strain (LR2006-OPY1). It was developed *via* reverse genetics, attenuating viral replication and host adaptability.

Preclinical studies in C57BL/6 mice showed that a single immunization induced high levels of IgG, NAbs, and $CD8^+$T-cell responses, with challenge tests demonstrating complete suppression of viremia or footpad swelling. A phase ||| clinical trial

Table 1. Progress and comparison of chikungunya vaccines.

Vaccines	Vaccine platform	Development progress	Advantages	Limitations
IXCHIQ® (Valneva)	Live attenuated vaccine	US: Accelerated approval[32]; license suspended due to safety signals in older adults[36]. EU: Marketing authorization[33,34]; use restricted to high-risk exposure groups[38].	Mimics natural infection; induces both humoral and cellular immunity.	Potential reversion to virulence in certain populations (*e.g.*, immunocompromised individuals, pregnant women); stringent cold-chain requirements.
Vimkunya® (Bavarian Nordic)	VLP vaccine (alum-adjuvant)	US: Accelerated approval[39]; EU: Marketing authorization[40].	Mimics viral structure; induces robust immune response; elicits mild to moderate reactions.	Complex manufacturing process; immune response in specific populations and long-term protective effectiveness require further validation.
BBV87 (Bharat Biotech)	Inactivated vaccine (alum-adjuvant)	Phase Ⅱ/Ⅲ clinical trials[51].	High safety profile; mature, readily scalable manufacturing; good stability; suitable for varied settings.	Immunogenicity may be suboptimal; typically requiring adjuvants and multiple doses.
Viral vector vaccines (Paul-Ehrlich-Institut & IDT Biologika)	Viral vector vaccine	Phase Ⅱ clinical trial ongoing[43].	Mimics natural infection; induces strong immune response, both humoral and cellular immunity; rapid development timeline with swift response capabilities.	Complex manufacturing process and advanced technology needs; effectiveness may be lower in elderly individuals.
mRNA-1388 (Moderna)	mRNA vaccine	Phase Ⅰ clinical trial[41].	High immunogenicity; rapid development, induces both humoral and cellular immune responses; immunogenicity and tolerability demonstrated in early-phase.	Long-term immune durability and safety require more clinical data; ultra-low-temperature cold-chain requirements.

(NCT04546724) enrolled 4 128 healthy subjects and reported a 98.9% seroconversion rate 28 days post-vaccination, maintained at 96.3% after 6 months. At Month 24, 97% participants maintained NAb titers above the seroresponse threshold (≥150)[27,32,33]. Based on these findings, the FDA and EMA approved the vaccine but required post-marketing studies to confirm efficacy and safety in endemic areas[32,33]. In the EU, the indication was subsequently extended to adolescents aged ≥12 years in March 2025, supported by interim 6-month data from the phase Ⅲ VLA1553-321 study, showing a 98.8% seroresponse at Day 29 in baseline seronegative participants and persistence through Month 6, with no new safety concerns identified[34].

However, in May 2025, following reports of adverse events, the FDA/CDC and EMA temporarily restricted IXCHIQ® use in older adults due to higher rates of cardiac and neurological events in individuals ≥60 years[37,52]. Although EMA lifted the restriction in July with specific risk-benefit guidelines[38], the FDA updated labeling to advise against vaccination for most U.S. travelers, particularly those ≥65 years with comorbidities[35]. Subsequently, post-marketing data, including a confirmed vaccine-associated encephalitis death, led the FDA to suspend IXCHIQ®'s license in August 2025[36].

Above all, IXCHIQ® shows robust immunogenicity, particularly in generating neutralizing antibodies, supporting its potential use in populations at risk of exposure. However, post-marketing safety signals and subsequent regulatory actions highlight the need for age- and risk-stratified use, enhanced pharmacovigilance, and timely risk communication as part of lifecycle management for live-attenuated chikungunya vaccines.

3.1.2. VLP vaccine

Vimkunya® (PXVX0317) (Figure 2B), approved by the FDA and EMA in February 2025, is a VLP vaccine expressing the E1, E2, E3, and capsid proteins of the West African genotype strain (Senegal strain 37997) with an aluminum hydroxide adjuvant[53].

Preclinical data showed NAbs induction in BALB/c mice and rhesus monkeys, and passive IgG transfer protecting immunodeficient mice from lethal viral challenge. A phase Ⅲ clinical trial (NCT05072080) demonstrated a 98% seroconversion rate 22 days post-vaccination in 3 254 individuals aged 12-65 years, maintained at 86% after 6 months. The seroprotection rate in elderly individuals (>65 years) reached 87% at Day 22[53]. Based on the findings, the FDA and EMA granted approval but required post-marketing studies to verify clinical benefits[39,40].

As a non-replicating vaccine, Vimkunya® offers an improved safety profile, with most side effects being mild to moderate. It is suitable

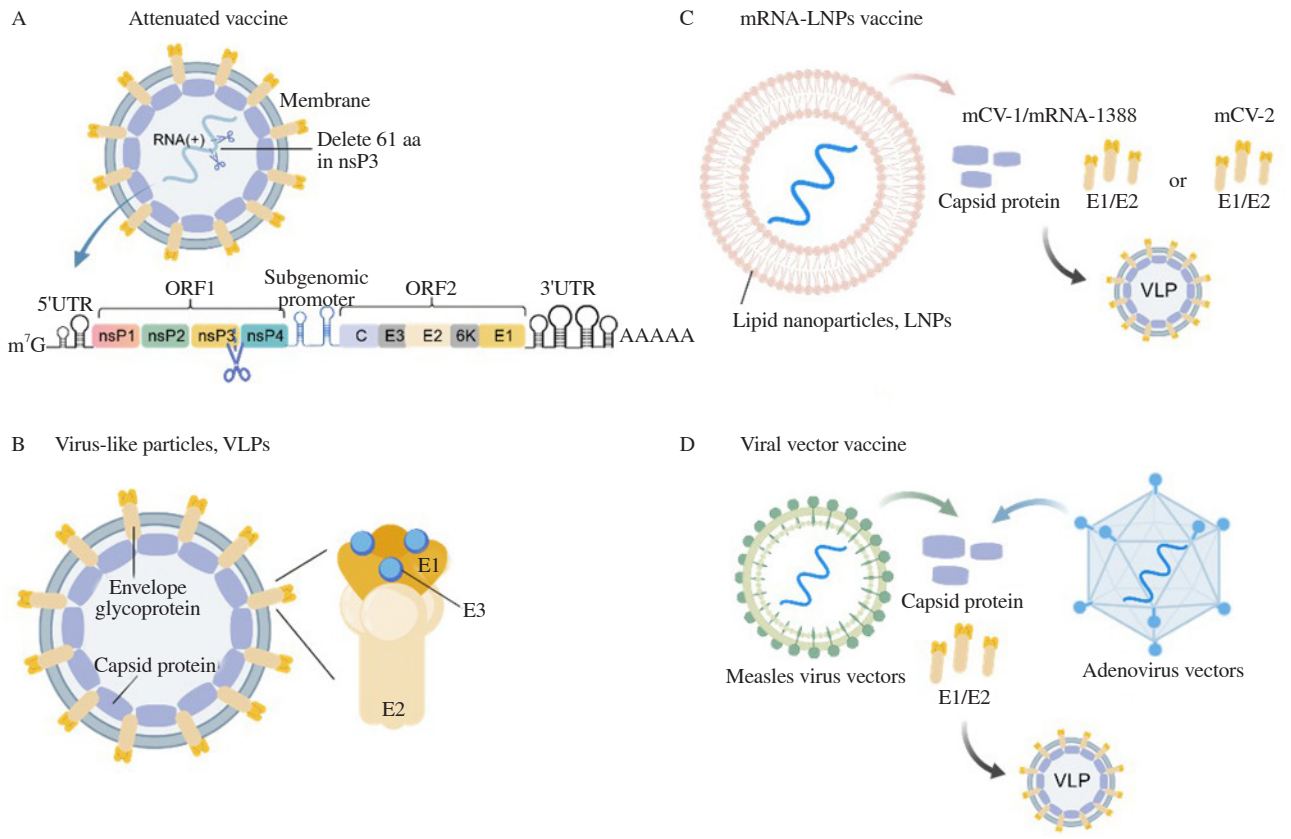

Figure 2. Chikungunya vaccine design platforms. Schematic illustration of four major vaccine platforms for CHIKV: (A) Live-attenuated vaccine: Genetic deletion of 61 amino acids from the C-terminus of nsP3 attenuates the virus while preserving immunogenicity. (B) Virus-like particle (VLP) vaccine: Recombinant structural proteins self-assemble into non-infectious particles that mimic native virions. (C) mRNA vaccine: Lipid nanoparticles encapsulate mRNA encoding chikungunya virus structural proteins, enabling endogenous antigen production and immune activation. (D) Viral vector vaccine: Replication-deficient vectors (*e.g.*, measles virus, adenovirus) deliver chikungunya virus antigen genes for *in vivo* expression.

for adolescents, the elderly, and immunocompromised individuals, making it ideal for travelers and emergency use during epidemics[54]. However, uncertainties remain regarding the durability of protection and effectiveness under outbreak conditions. Additional post-marketing surveillance and real-world data are therefore needed to further define long-term safety and clinical benefit[54].

3.2. Emerging candidates

3.2.1. mRNA vaccines

mRNA vaccines use lipid nanoparticles (LNPs) to deliver mRNA encoding viral antigens, enabling efficient *in vivo* expression and immune activation. This platform allows rapid design and large-scale production, making it highly responsive to public health emergencies. Several candidates have shown promising safety and immunogenicity in preclinical and early-phase clinical trials.

Moderna's mRNA-1388 (Figure 2C) based on the full-length structural polyprotein (C-E3-E2-6K-E1) of the West African genotype, achieved a 100% seroconversion rate with a two-dose regimen (100 μg) in phase Ⅰ trials, with sustained immune response in follow-up studies in the Philippines[41].

Researchers from the Chinese Academy of Medical Sciences developed two mRNA candidates (mCV-1, mCV-2) designed from conserved sequences of 769 viral strains. Preclinical data demonstrated broad-spectrum neutralizing activity against WA, Asian, and ECSA IOL pseudoviruses, induction of Th1 T-cell responses, and avoidance of the risk of Th2-associated vaccine-enhanced disease (VAED). A129 mice showed clearance of chronic infection and 100% survival after lethal challenge[42].

The mRNA platform supports rapid design and scalable production, but breadth of protection, durability, and longer-term safety require further clinical evidence. However, its breadth of protection requires further clinical validation.

3.2.2. Viral vector vaccines

Viral vector vaccines also play a crucial role in chikungunya vaccine development. MeV-CHIKV (Figure 2D), developed by the Paul-Ehrlich-Institut and IDT Biologika, uses an attenuated measles virus vector to express CHIKV E3-E2-6K-E1. Phase Ⅰ/Ⅱ trials have shown effective induction of NAbs and T cell responses[43]. Other viral-vectored candidates include ChAdOx1-CHIKV, which has completed a phase Ⅰ trial and advanced to clinical development, with a single dose inducing IgG and T-cell responses and generating broadly neutralizing antibodies against four CHIKV lineages, and 100% seroconversion observed in all participants[44]. MVA-CHIKV remains primarily supported by preclinical studies[45].

Viral-vectored candidates can elicit combined humoral and cellular responses. However, manufacturing complexity and performance in older adults, as well as potential anti-vector immunity, remain important considerations for clinical development and regulatory evaluation.

3.3. Platform considerations

Using chikungunya vaccine development as an example, different vaccine platforms vary in immunogenicity, safety, target populations, and accessibility (Table 1), leading to distinct regulatory considerations. Live attenuated vaccines provide durable immunity but pose risks in elderly populations, necessitating enhanced post-marketing safety monitoring and usage restrictions. VLP vaccines balance safety and broad applicability. However, regulatory assessment still emphasizes confirmation of clinical benefit, durability of protection, and real-world performance through post-marketing commitments. mRNA vaccines offer rapid development, easy antigen updates, and strong humoral and cellular immunity, but require further validation of long-term durability and integration with broad-spectrum design. Viral vector vaccines enable rapid production and induce robust immune responses, but may be affected by pre-existing anti-vector antibodies. Regulatory evaluations consider immune response profiles, safety, and accessibility to inform appropriate strategies.

4. Innovative regulatory atrategies for accelerated development

The unique epidemiological characteristics of CHIKV, marked by intermittent outbreaks, short epidemic cycles, and risks of chronic infection, pose substantial challenges to the execution of traditional randomized controlled efficacy trials. In this context, the expedited authorization of vaccines hinges on multiple factors, including phase Ⅱ clinical trial outcomes, the correlation between immunogenicity endpoints and clinical protection, the maturity of the platform technology[13], and a context-specific benefit-risk assessment accounting for disease severity. In response, global regulatory agencies such as the WHO, FDA, EMA, and National Medical Products Administration (NMPA) have promote "accelerated approval" and "lifecycle management" frameworks, promoting innovative regulatory strategies that maximize the use of platform technology to enhance development efficiency[13]. Central to this approach is the principle of ensuring timely vaccine access when potential public health benefits are deemed to outweigh risks, thereby enabling evidence-based and proportionate regulatory decision-making. Key regulatory strategies and considerations are discussed below.

4.1. Accelerated approval pathways and surrogate endpoints

Whenever feasible, placebo-controlled clinical efficacy trials should serve as the foundation for vaccine licensure. However, for diseases with sporadic and unpredictable outbreaks such as chikungunya, conventional RCTs are often infeasible or ethically problematic. This necessitates the establishment of tailored clinical development pathways and regulatory processes that leverage existing knowledge while adapting to public health priorities. Following a comprehensive benefit-risk evaluation, international regulators have established accelerated approval frameworks grounded in validated surrogate endpoints, animal challenge models, and real-world evidence (RWE).

The accelerated approvals of IXCHIQ® and Vimkunya® by the FDA exemplify this strategy. Both vaccines were granted accelerated approval based on robust immunogenicity data—particularly NAb titers—corroborated by protective efficacy in animal models and well-understood CHIKV pathogenesis. According to FDA labeling, continued approval is contingent upon verification of clinical benefit through post-marketing confirmatory trials[32,39].

Validation *via* animal challenge models: Preclinical evidence played a pivotal role. IXCHIQ® demonstrated protection in murine models (suppression of viremia and footpad swelling), while Vimkunya® demonstrated efficacy in non-human primate challenge studies and passive serum transfer experiments.

Immunogenicity as a key surrogate endpoint: Although no universal protective threshold for NAbs has been established, NAbs levels informed by animal models, human immunobridging studies, and convalescent serum titers, are widely accepted by regulators as predictors of clinical efficacy.

Post-authorization efficacy studies: Given that surrogate endpoints are not fully validated, rigorous post-marketing commitments (PMCs), including post-authorization efficacy studies (PAES), are mandated to confirm effectiveness, monitor long-term safety, and identify rare adverse events. Both approved chikungunya vaccines are subject to such requirements (Figure 3).

A comparative case study of IXCHIQ® illustrates how regulatory agencies may adopt different pathways under distinct legal frameworks. While the FDA granted Accelerated Approval under 21 CFR 601 Subpart E, requiring confirmatory trials for full approval, the EMA granted standard approval under Regulation (EC) No. 726/2004 based primarily on immunogenicity and persistence data, supplemented with post-authorization measures (PAMs) to address residual uncertainties[32,33,49]. This illustrates how regulatory agencies, while aligned in their overall goals, may apply different approaches based on their respective legal frameworks and evaluation criteria.

4.2. Integrated lifecycle risk management

RWE is indispensable for continually evaluating vaccine effectiveness and safety post-licensure. Well-designed post-marketing studies and RWE generation can expand the evidence base and support vaccine use in broader populations.

Vaccination strategy-informed study design: the WHO outlines two primary use cases for chikungunya vaccines: preventive

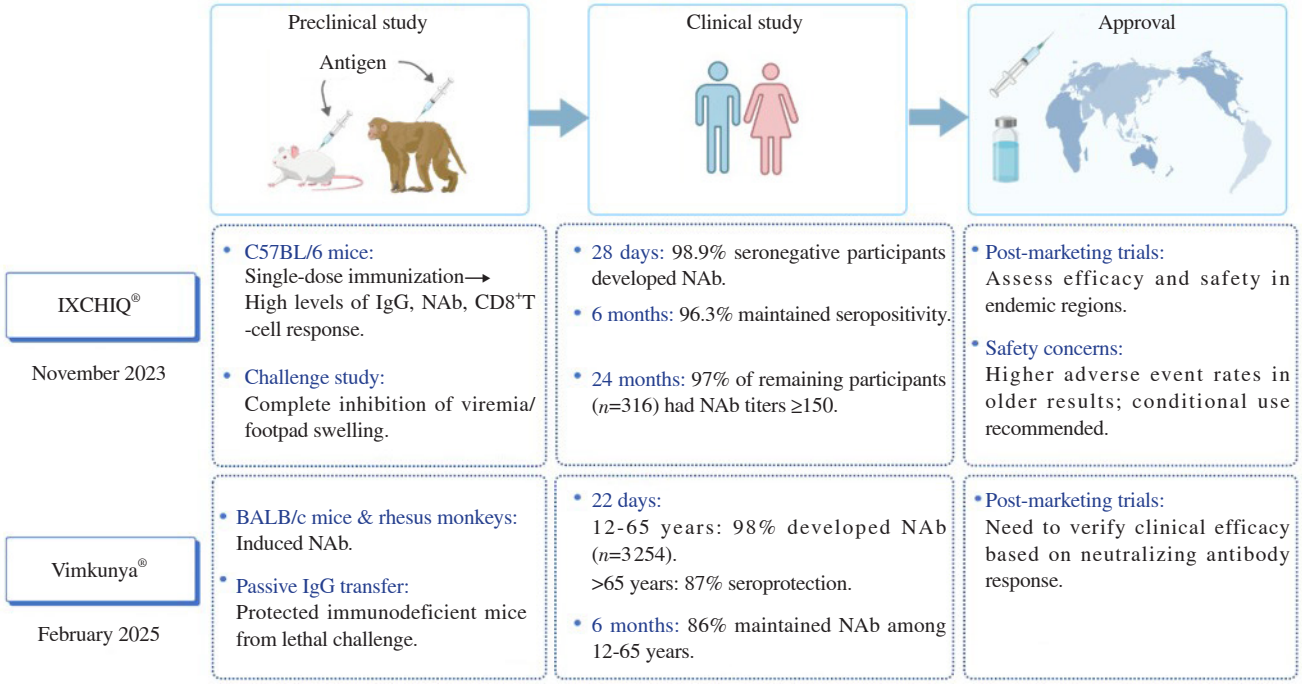

Figure 3. Characteristics of the currently marketed chikungunya vaccines. Comparative overview of the two approved chikungunya vaccines, IXCHIQ® and Vimkunya®, across preclinical, clinical, and regulatory milestones. The time points indicated below the vaccine names represent the dates of market authorization. Key data are indicated within the dashed-line boxes.

(endemic areas and high-risk travelers) and emergency (outbreak response). Post-marketing study designs should align with intended use. Depending on the setting, studies may include test-negative design (TND), cluster randomized trials, or large-scale observational cohorts[12,55].

Enhanced pharmacovigilance and risk management: Accelerated approval mandates robust risk management plans (RMPs), incorporating additional post-authorization safety studies (PASS), targeted monitoring (*e.g.*, for arthralgia, neurological, or cardiac events), and effective risk minimization measures (*e.g.*, label updates and educational programs). The case of IXCHIQ® underscores the necessity of vigilant post-marketing surveillance. Despite accelerated approval in November 2023, safety signals, including severe neurological and cardiovascular events in older adults, led to temporary suspensions and label revisions[35,52]. In late August 2025, the U.S. license was suspended, following a vaccine-associated encephalitis fatality[36,56,57]. This illustrates the critical balance between rapid access and ongoing safety assurance. It also highlights the need for agile regulatory responses to emerging risk data.

Concurrently, RWE supports continued evaluation of subpopulations (*e.g.*, immunocompromised individuals, pregnant women, and children) and assessment of long-term risks (*e.g.*, myocarditis with mRNA vaccines). For instance, on June 25, 2025, the FDA updated safety labeling for COVID-19 mRNA vaccines to include warnings for myocarditis and pericarditis based on a multi-agency retrospective study[58], highlighting the role of large-scale observational data in identifying rare adverse events.

4.3. Leveraging platform technologies

As a standardized, reproducible system for developing biological products, platform technology can significantly streamline chikungunya vaccine development and regulatory review by leveraging accumulated platform knowledge, reducing redundant studies, and facilitating cross-referencing of data[13]. This approach proved instrumental during the COVID-19 pandemic for the rapid authorization of variant-adapted vaccines.

Streamlined chemistry, manufacturing, and controls (CMC) and nonclinical/clinical requirements: For vaccines within a validated platform, if no major changes are introduced (*e.g.*, to LNP composition, core processes, or critical quality attributes), prior data may support simplified assessments for new CHIKV strains or regional variants. This may include reducing in certain studies by leveraging accumulated nonclinical and clinical data, thereby accelerating updates against evolving viruses.

Cross–referencing and master files: International regulatory frameworks increasingly permit the use of platform technology master files (*e.g.*, vPTMF) to centralize and cross-reference data on platform components, thereby simplifying submissions and reviews across multiple products[13].

Successful application requires balancing flexibility with predictability in product safety, efficacy, and consistency. Key considerations include platform stability across antigen sequences, scalability, thermostability, and immunogenicity profiles. Regulatory agencies, as outlined in the FDA's Platform Technology Designation

Program, encourage early engagement with developers to facilitate efficient vaccine development and review based on mature, well-characterized platforms[13].

5. Discussion and future perspectives

The persistent global spread of CHIKV[9], coupled with its significant acute and chronic disease burden, underscores the critical need for effective vaccines. While the recent approvals of IXCHIQ® and Vimkunya® mark substantial progress, several scientific and regulatory challenges remain. These include genotype-dependent variations in neutralization efficacy (reaching up to 30%), the necessity for robust T-cell responses to clear persistent infections, and safety concerns in vulnerable populations such as the elderly and immunocompromised individuals; these issues remain key hurdles[15]. Reflecting on the current vaccine landscape and ongoing regulatory dialogues, this paper emphasizes that overcoming these challenges requires a multi-faceted strategy integrating technological innovation, adaptive clinical trial designs, and agile, evidence-based regulatory frameworks (Figure 4).

5.1. Technological optimization

Next-generation chikungunya vaccines necessitate advancements in antigen design to elicit broader cross-genotype neutralization. Strategies include leveraging computationally designed immunogens based on conserved epitopes[59]. Furthermore, enhancing the induction of potent and durable T-cell immunity is paramount to address viral persistence in joint tissues[60]. Platforms like mRNA and viral vectors show inherent promise here but require further validation. Finally, improving the thermostability of vaccines[61], especially novel platforms like mRNA, is crucial to enhance accessibility and distribution in resource-limited settings where CHIKV often strikes.

5.2. Clinical and regulatory challenges

The intermittent and unpredictable nature of chikungunya outbreaks renders traditional RCTs largely infeasible and ethically complex. This reality solidifies the role of accelerated approval pathways based on animal challenge models and immunobridging using NAbs as surrogate endpoints. However, as evidenced by the IXCHIQ® case[62], this approach mandates an integrated lifecycle risk management strategy. Robust post-marketing surveillance, enhanced pharmacovigilance (*e.g.*, focused on arthralgia, neurological, and cardiac events), and timely confirmatory studies are essential to verify clinical benefit and monitor long-term safety, thereby ensuring a favorable benefit-risk profile throughout the product's lifecycle[57].

5.3. Platform technology as a catalyst for regulatory innovation

Platform technology is a cornerstone for accelerating future chikungunya vaccine development. Mature, well-characterized platforms can significantly streamline regulatory evaluation. The use of platform technology master files (*e.g.*, vPTMF) allows for the cross-referencing of nonclinical and CMC data, reducing redundant studies for new candidates within the same platform. This facilitates rapid iteration against emerging variants or new pathogens. Importantly, regulatory flexibility should be commensurate with the accumulated platform-specific data on safety and efficacy. Early and continuous dialogue between developers and regulators is strongly advised to align on evidence requirements and development planning, ensuring that the promise of platform technology is translated into safe, effective, and rapidly available vaccines[13].

5.4. A collaborative path forward

Addressing the multifaceted challenges of CHIKV will require global coordination. Priorities include standardizing neutralizing

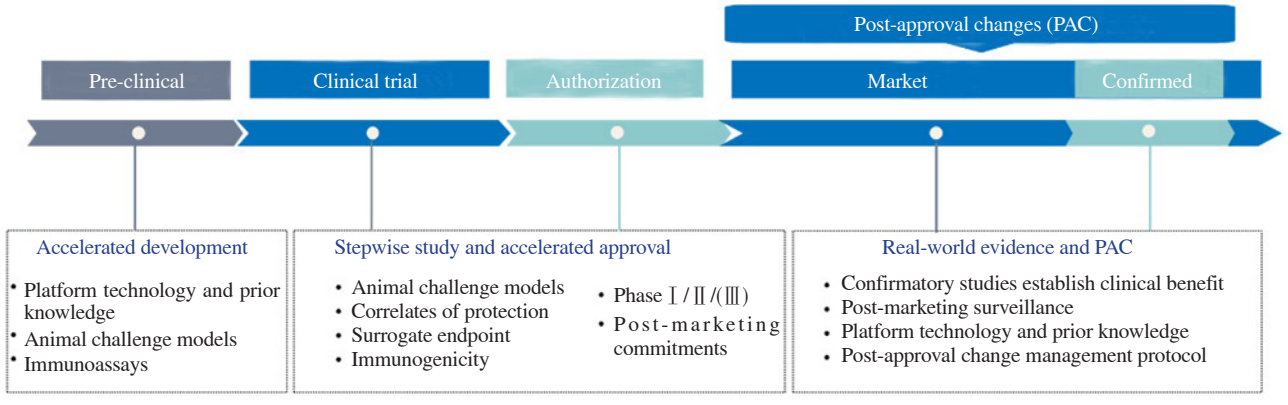

Figure 4. Perspective on regulatory strategies for accelerated vaccine development. A holistic view of innovative regulatory tools and lifecycle management approaches to facilitate chikungunya vaccine approval.

antibody assays, harmonizing regulatory expectations for platform-based vaccines, and establishing shared pharmacovigilance databases to enable faster signal detection and benefit-risk reassessment. By fostering international collaboration, advancing both technological and regulatory science, and implementing lifecycle evidence generation, we can accelerate the development of next-generation chikungunya vaccines that are broadly protective, safe, and accessible, ultimately enhancing preparedness for future arboviral threats.

6. Conclusions

The advancement and deployment of vaccines mark a critical turning point in the global fight against CHIKV, yet the persistent and evolving threat of outbreaks underscores the necessity for continued optimization in both vaccine design and regulatory preparedness. The unique challenges posed by CHIKV—including its significant genetic diversity, potential for chronic infection, and unpredictable, intermittent outbreak patterns—demand a multifaceted and agile strategy that integrates innovative vaccine platforms with science-driven regulatory frameworks.

This article proposes regulatory pathways focused on outbreak response and travel-associated risk, recommending the use of fit-for-purpose surrogate endpoints, clear post-authorization commitments for proactive pharmacovigilance and the responsible use of platform technologies within regulatory boundaries. Looking ahead, continued advances in vaccine technologies and expanding datasets will drive the evolution of regulatory systems. Priorities include global coordination to standardize NAbs assays, promote cross-institutional sharing of safety and efficacy data, and establish rapid-response networks for emerging alphavirus threats to enhance decision-making efficiency and consistency.

China is actively contributing to this global effort by advancing the standardization and application of platform technology within its regulatory framework, including initiatives to establish vaccine platform technology master files and develop corresponding technical evaluation standards. A comprehensive national strategy that integrates vector control, enhanced surveillance, vaccination campaigns, and real-world evidence generation and monitoring remains essential to mitigate the impact of regional epidemics and enhance global health security. Ultimately, mitigating the burden of chikungunya and preparing for future arboviral threats requires unwavering international collaboration. Sustained investment in technological innovation, regulatory science, and robust public health infrastructure can build a more resilient defense against the persistent threat of chikungunya and other emerging infectious diseases.

Conflict of interest statement

No potential conflicts of interest are reported by the authors. The views expressed in this article are the personal views of the authors and might not reflect the position of the regulatory authorities.

Data availability statement

No new data were created or analyzed in this study. Data sharing is not applicable to this article.

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Authors' contributions

X.L. and X.Z. drafted the manuscript, edited a summary of the legal and regulatory frameworks, S.G., S.G., Y.P., M.X. and Q.Z. commented and assisted in manuscript refinement, and T.W., M.L. supervised this paper. All authors have read and agreed to the published version of the manuscript.

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