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Current landscape with an analytical outlook: Chikungunya virus vaccine development

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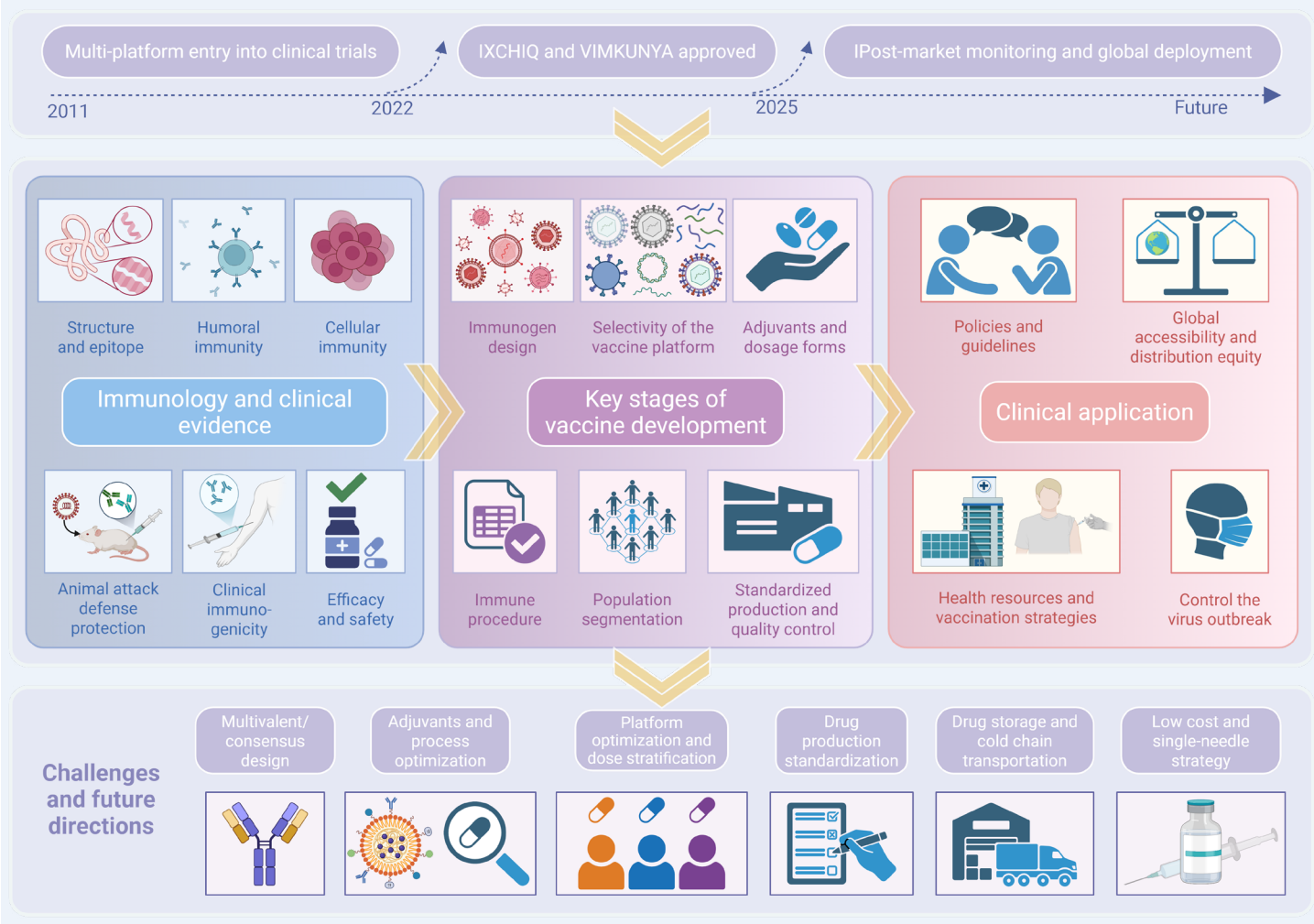
GRAPHICAL ABSTRACT



PUBLIC SUMMARY

- The recent regulatory approval of the first chikungunya vaccines marks a pivotal milestone in public health.
- Key challenges persist in ensuring durable, broad immunity and addressing safety for global deployment.
- Next-generation vaccine platforms are crucial to overcome these hurdles and achieve equitable protection.

REVIEW

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Chikungunya virus (CHIKV), a mosquito-borne alphavirus primarily transmitted by Aedes species, continues to pose a significant global health threat due to its rapid transmission potential and debilitating arthralgia. In response to the escalating incidence and expanding geographic range, notable progress has been achieved in vaccine development. Two vaccines have received regulatory authorization: IXCHIQ (VLA1553; live-attenuated; FDA approved 9 Nov 2023; U.S. license suspended 22 Aug 2025), and VIMKUNYA (recombinant VLP; FDA accelerated approval 14 Feb 2025; commercial launch Mar 2025). These approvals represent major milestones in CHIKV prevention efforts. However, several challenges persist, including limited durability of immune protection, safety concerns in vulnerable populations, antigenic drift among circulating lineages, and the need for thermostable, globally deployable formulations. In this review, we systematically evaluate diverse vaccine platforms, including live-attenuated, inactivated, VLP, nucleic acid, and viral vector-based candidates, through a comparative analysis of immunogenicity, safety, and scalability. Furthermore, we provide strategic insights into overcoming major barriers in CHIKV vaccinology, including the risks of antibody-dependent enhancement (ADE), the challenge of achieving durable immunity, and the practical limitations of cold-chain dependency. By integrating advances in structural vaccinology and broadly neutralizing antibody development with clinical and regulatory perspectives, this review proposes a roadmap for next-generation CHIKV vaccines aimed at promoting equitable global deployment.

INTRODUCTION

Chikungunya virus (CHIKV) is a mosquito-borne alphavirus first identified in Tanzania in 1952.[1] Since then, it has caused numerous outbreaks across Africa, Asia, the Indian Ocean islands, the Americas, and more recently, Europe.[2] Its name is derived from the Makonde word meaning "that which bends," referencing the severe arthralgia commonly experienced by infected individuals. Over the past decade, CHIKV has spread to 119 countries and territories (as of December 2024), facilitated by global travel and the widespread distribution of *Aedes* mosquitoes.[3,4] Recent estimates suggest that CHIKV causes approximately 35 million infections annually (95% CI: 20,900,000–56,500,000), with the highest burden observed in Southeast Asia, Africa, and the Americas.[5] Although CHIKV typically has low mortality, it results in considerable morbidity, with up to 60% of patients developing long-term rheumatic symptoms that can persist for months or even years.[6]

The primary vectors of CHIKV are *Aedes aegypti* and *Aedes albopictus*, both of which thrive in tropical, subtropical, and even some temperate regions. Of note, both species are now widespread globally and exhibit strong anthropophilic behavior. Moreover, these mosquitoes commonly breed in urban water containers, such as buckets, flower pots, and discarded tires, making vector control particularly difficult. Climate change is further expanding their geographic distribution, facilitating the reemergence of CHIKV in parts of Europe and North America.[7] Recent outbreaks in Brazil, India, the Americas, and several French overseas territories, have demonstrated efficient urban transmission, especially in areas with limited vector control infrastructure.[8,9] Most recently, an ongoing outbreak in subtropical regions of China, particularly Guangdong Province, has raised considerable public concern, with 4208 confirmed cases reported in a single cluster in Foshan City in July 2025.[10,11]

The clinical spectrum of CHIKV infection often closely resembles that of dengue fever, with patients typically presenting with an abrupt onset of fever, rash, headache, myalgia, and polyarthritis.[12] Clinical distinction between CHIKV and other Aedes-borne arboviruses is unreliable and therefore laboratory confirmation (PCR or specific serology) is required.[13] In many endemic settings limited laboratory access leads to under detection and reliance on variable clinical case definitions. Although PAHO/WHO provide standardized case definitions (2023),[14] implementation varies by country, producing heterogeneous surveillance data. In certain cases, post-viral chronic inflammatory arthritis may develop, mimicking rheumatoid arthritis and leading to long-term disability.[6] With increased global attention to arboviruses in recent decades, surveillance data and case reports have expanded the recognized manifestations of CHIKV infection. Atypical presentations now documented include neurological complications such as Guillain-Barré syndrome, encephalitis, seizures, confusion, and even stroke, which may be accompanied by cardiorespiratory failure, hepatic dysfunction, renal impairment, and muscular complications.[15] These severe and persistent symptoms contribute to the substantial economic burden of CHIKV outbreaks, particularly in low- and middle-income countries.[16,17] The impact includes increased outpatient healthcare costs, productivity losses, and strain on already limited healthcare infrastructure. Furthermore, the burden of disease, as measured in quality-adjusted life years, is estimated to be comparable to that of dengue fever in co-endemic regions.

Nevertheless, existing economic estimates of CHIKV burden exhibit significant limitations. A recent systematic review highlights the sparsity and high heterogeneity of cost-of-illness studies, which vary considerably in design, population, healthcare setting, and cost inclusion criteria, complicating cross-study comparison.[18] For instance, divergent methodologies for quantifying outpatient visits, hospitalizations, and productivity losses yield widely varying burden estimates. Such methodological inconsistencies necessitate cautious interpretation of published economic figures.

Despite its global health threat status, CHIKV remained without a licensed vaccine for decades. This changed with the recent approval of IXCHIQ (Valneva, 2023) and VIMKUNYA (Bavarian Nordic, 2025), representing pivotal milestones in public health preparedness.[19] However, several challenges persist, such as the high reactogenicity of certain live-attenuated vaccine platforms in older adults and immunocompromised individuals,[20] uncertainty regarding the durability of vaccine-induced immunity, and the limited availability and high costs of novel vaccines in low-resource settings. Furthermore, the World Health Organization (WHO) in 2023 has emphasized the need to prioritize CHIKV vaccine deployment in outbreak response strategies, given the virus's potential for explosive transmission, the presence of non-human primate reservoirs in Africa, and an increasing force of infection.[21] These factors underscore the urgent need for next-generation CHIKV vaccines capable of providing durable and broad protection against both current and emerging variants.

This review begins by examining the immunogenic properties of structural proteins of CHIKV and outlines global progress across diverse vaccine plat-

forms, including live-attenuated, inactivated, virus-like particle (VLP), protein subunit, nucleic acid, and viral vector-based approaches. In parallel, we explore the role of neutralizing antibodies and their contribution to protective immunity. Furthermore, strategies aimed at enhancing vaccine efficacy through next-generation design principles are discussed. A comprehensive understanding of these platforms and immunological optimization strategies is essential for addressing current challenges in CHIKV vaccine development and achieving durable, broad-spectrum protection against future outbreaks. The insights presented herein aim to inform the design of more effective vaccines and support global efforts toward CHIKV prevention and control.

MATERIALS AND METHODS

Sources and search strategy

We searched the Web of Science Core Collection and Scopus using predefined strings combining terms for chikungunya/CHIKV, vaccines/platforms (e.g., live-attenuated, inactivated, VLP, DNA, RNA/mRNA, vectors), and development stages or readouts (trials, preclinical, immunogenicity/neutralization). We also queried ClinicalTrials.gov and WHO ICTRP for interventional vaccine studies and retrieved regulatory/policy documents (assessment reports, labels, safety updates) for authorized or advanced candidates; records were exported and deduplicated across sources. Full search fields and time windows are provided in the Supplement.

Eligibility criteria

We included peer-reviewed preclinical studies, phase I–III clinical trials, and relevant regulatory/policy reports directly addressing CHIKV vaccines. We excluded duplicates, opinion pieces without primary data, and non-vaccine topics (e.g., vector control or diagnostics alone).

Study selection and screening

Two reviewers independently screened titles/abstracts and full texts with disagreements resolved by consensus.

Data extraction

We extracted: study design/setting; population; vaccine platform/type; dose/schedule; assay and timepoints; immunogenicity (e.g., GMTs, seroresponse); safety (overall AEs, ≥grade-3 AEs, SAEs); durability; manufacturing/cold-chain notes; regulatory status; and key limitations.

Synthesis, effect-size reporting, and clinical interpretation (no cross-trial pooling)

Owing to heterogeneity in assays, endpoints, populations, and follow-up, we conduct a narrative synthesis and do not pool or rank across trials. Where outcomes are methodologically comparable within a study, we report: (i) baseline-adjusted geometric mean titer (GMT) ratios (post/baseline) with 95% CIs; (ii) seroresponse rates (e.g., ≥4-fold rise or study-defined threshold) with 95% CIs; and (iii) safety as absolute risks and risk differences (overall AEs, ≥grade-3 AEs, SAEs) with 95% CIs; durability is described as within-study change in GMT or seroresponse over time. We preferentially transcribe author-reported estimates; where raw numerators/denominators are available, we compute RDs/RRs with standard 95% CIs (exact or continuity-corrected for sparse cells) and summarise GMTs on the log scale. We do not compare effect sizes across non-commensurable assays or infer non-inferiority/superiority between platforms.

Clinical interpretation anchors (no validated correlate claimed)

Because no universally accepted correlate of protection exists for CHIKV, we adopt interpretive anchors rather than categorical judgments: neutralization readouts are interpreted relative to each assay's LLOQ and predefined fold-rise criteria within the same study; durability emphasizes direction and magnitude of change at reported time windows; safety prioritizes absolute risks and risk differences. These guardrails aim to maximize transparency and auditability while avoiding false precision.

VIROLOGY AND IMMUNOLOGICAL BASIS OF VACCINE DESIGN

Molecular structure of CHIKV and key antigenic targets

CHIKV, a member of the Alphavirus genus within the family Togaviridae, is an enveloped, spherical arbovirus approximately 60–70 nm in diameter.[22] The virion is encapsulated by a lipid bilayer, beneath which lies a T=4 icosahedral nucleocapsid assembled from 240 copies of the capsid protein. Its single-stranded, positive-sense RNA genome, ~11.8 kb in length, contains a 5′ cap structure of 7-methylguanosine and a 3′ poly(A) tail, mimicking eukaryotic mRNA to facilitate efficient translation. The 5′ two-thirds of the genome encode four nonstructural proteins (nsP1–nsP4) responsible for viral RNA replication and transcription, whereas the 3′ one-third is transcribed as a subgenomic RNA to express five structural proteins: capsid, E3, E2, 6K/transframe (6K/TF), and E1 (Figure 1A).[23,24] These structural components collectively govern virion assembly, receptor engagement, and membrane fusion, which are pivotal for viral entry and infectivity.

The CHIKV surface consists of heterodimeric E1–E2 glycoproteins arranged into trimeric spikes; E2 primarily mediates receptor binding, while E1 drives low-pH-triggered membrane fusion. During maturation, p62 is cleaved by furin into E3 and E2, followed by major conformational rearrangements under acidic conditions. These features dictate that neutralizing antibody epitopes are concentrated within domains of E2, near the E1 fusion loop, and across inter-subunit quaternary epitopes (Figure 1B).[25,26] Multiple studies using human and murine monoclonal antibodies have demonstrated that domain A of E2 harbors immunodominant epitopes relevant for neutralization. Antibodies such as CHK-152, C9, and IM-CKV063 block viral attachment, interfere with E1–E2 conformational transitions, or inhibit budding. Escape mutations and cryo-EM mapping place these epitopes on the exposed outer face of domain A.[29,30] Domain B sits at the "crown" of the spike, close to the receptor footprint, and contains residues critical for cross-reactive antibodies. Near-germline human antibodies targeting this domain can potently neutralize multiple arthritogenic alphaviruses. However, these epitopes represent immunodominant rather than inherently broad-spectrum determinants, highlighting the need for rational immunogen design.[31,32]

E1 glycoprotein is composed of three domains: DI, DII, and DIII. DII contains the conserved fusion loop and a hinge region that are essential for membrane fusion within the acidic endosomal environment. Antibodies targeting the E1 fusion machinery stabilize the prefusion conformation and prevent the low-pH rearrangements essential for membrane fusion.[33] Some of the most potent neutralizing antibodies span both E1 and E2 subunits, disrupting inter-subunit coupling and spike dynamics. Structural studies have elucidated the spatial organization of these composite epitopes and their neutralizing mechanisms.[31] Mechanistic analyses indicate that potent neutralizing antibodies act through multiple pathways: blocking receptor-dependent attachment and internalization, stabilizing prefusion E1–E2 complexes to inhibit acid-triggered fusion, and interfering with budding and egress. These mechanisms map directly to epitopes on E2-DA, E2-DB, E1-DII, and inter-subunit interfaces.

Host immune responses and correlates of protection

Following natural CHIKV infection, the host mounts a rapid and robust antibody response. An IgG3-dominant profile is commonly observed during the acute phase and is associated with stronger neutralizing activity and more favorable outcomes.[34] A study in India showed that the appearance of neutralizing antibodies and early IgG class switching correlated with reduced progression to chronic arthritis, underscoring that antibody quality and subclass distribution, influence outcomes.[35]

A 19-year follow-up study in Thailand demonstrated that survivors maintained neutralizing titers against multiple CHIKV genotypes, suggesting long-term, cross-genotype protection in a significant proportion of individuals.[36] Supporting this, memory B cells targeting domain B of the E2 protein persist for decades and exhibit cross-neutralizing activity against CHIKV and related alphaviruses such as Mayaro virus (MAYV).[37] Although IgM has been detected in some individuals with chronic arthralgia more than two years after infection, long-term serological protection is primarily mediated by IgG memory.[38] Importantly, IgM may persist for >2 years in individuals with chronic arthralgia, cautioning against its sole use as a marker of recent infection.[38,39]

Neutralizing antibody titers are widely used as correlates of protection,[40] yet methodological variability in assays (e.g., $PRNT_{50}$ thresholds ranging from 10 to 150) undermines cross-study comparability.[41] To address this, the WHO

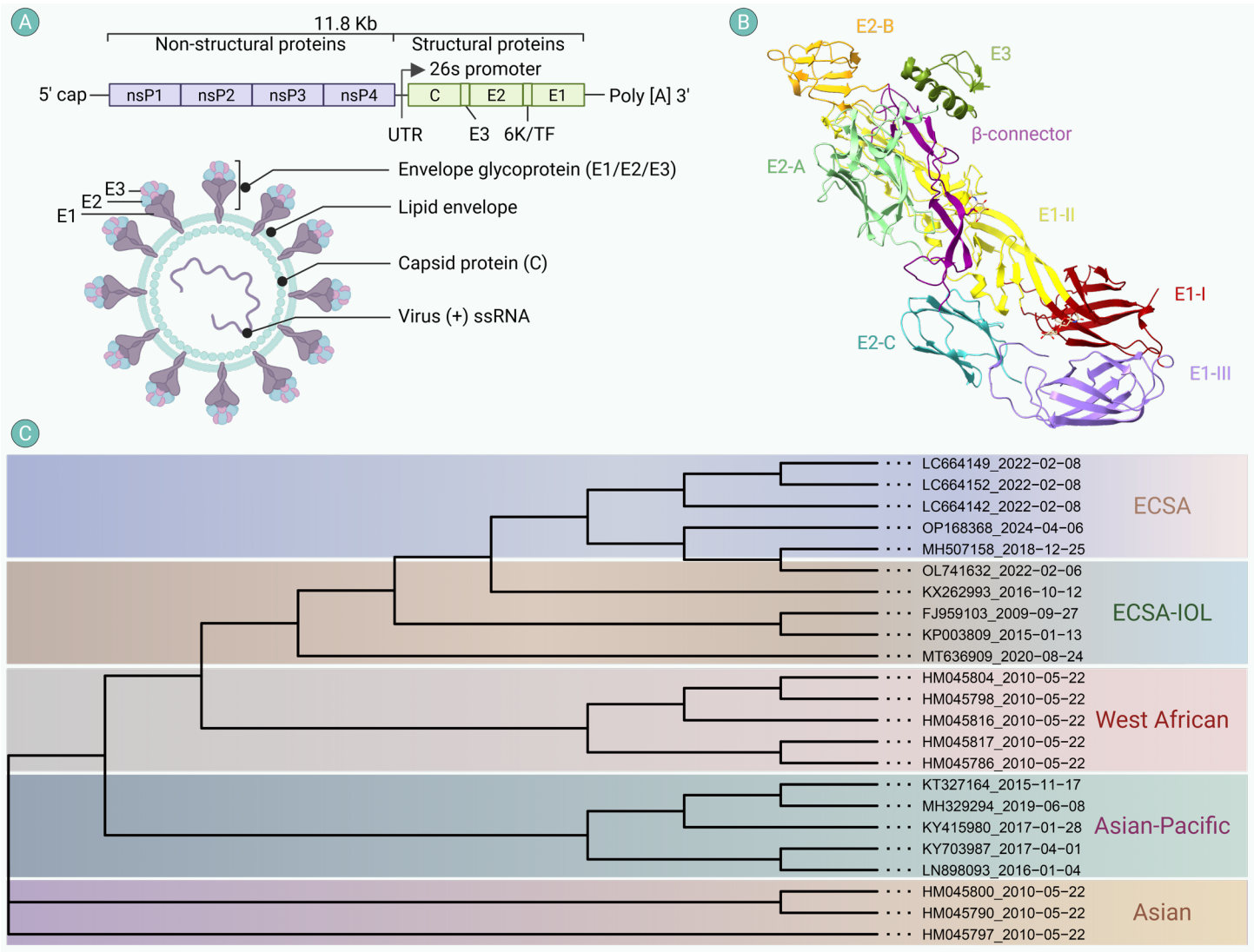

Figure 1. Structural composition and phylogenetic relationships of CHIKV lineages (A) The CHIKV virion contains an ~11.8 kb single-stranded positive-sense RNA genome, encapsulated by an icosahedral capsid and enveloped by a host-derived lipid membrane. Its surface features heterotrimeric spikes composed of glycoproteins E1 (domains I–III), E2 (domains A–C), and auxiliary protein E3. Non-structural proteins (nsP1–nsP4) are translated from the 5'-capped genomic RNA, while the structural polyprotein is expressed from the 26S subgenomic RNA via the junction region promoter. The 6K/TF peptide connects E2 and E1. (B) Overall structure of the CHIKV envelope glycoprotein complex (E1–E2–E3), with major domains indicated (PDB 3N42; PDB 2XFC).[26–28] (C) Phylogenetic tree depicting the evolutionary divergence of CHIKV lineages from the ancestral Asian genotype to the emerging ECSA and ECSA-IOL clades and the more recent West African lineage. To construct a genetic relationship diagram for different genotypes, we downloaded complete CHIKV sequences from the Chikungunya Virus Database (https://nmdc.cn/gcpathogen/chikv) and randomly selected up to five sequences from each genotype. Sequences were aligned using MAFFT (v7.526), and the phylogenetic tree was constructed using IQ-TREE2 (v2.4.0). The tree was visualized using ggtree (v3.12.0).

has established an international anti-CHIKV IgG standard to enable reporting in IU/mL and improve harmonization.[42] In addition to the magnitude and quality of neutralizing responses, population- and age-specific differences significantly shape the durability of immunity. Long-term cohort data from northeastern Thailand revealed that only 39% (44/111) of individuals infected during the 1991 outbreak retained detectable neutralizing antibodies 19 years later, demonstrating substantial attrition at the population level despite some older adults maintaining higher titers.[36] Age-stratified serological analysis in India further showed that adults exhibited higher IgG titers and distinct subclass profiles, likely reflecting repeated exposures, while children had lower levels, underscoring the risk of overestimating protection if adult thresholds are applied to younger groups.[43] Similarly, a cohort study in the Philippines demonstrated that pre-existing neutralizing antibodies were strongly associated with reduced risk of symptomatic infection, yet many children and adolescents lacked baseline antibodies, highlighting their increased vulnerability during inter-epidemic periods.[44] Pediatric studies in Kenya confirmed that seropositivity and seroconversion rates varied across settlements, influenced by both age and local environment, suggesting that immune durability is highly context-dependent.[45]

In parallel with antibody responses, CHIKV infection elicits robust cellular immunity. During the acute phase, $CD8^+$ T cells are activated and express cytolytic markers such as CD69, granzyme B, and perforin. However, MHC class I downregulation in chronically infected tissues may contribute to immune evasion.[46] Notably, long-term T cell memory is skewed toward $CD4^+$ subsets, with up to 87% of individuals retaining CHIKV-specific $CD4^+$ memory responses for at least six years, compared to only ~13% for $CD8^+$ T cells.[47] In addition, recent evidence highlights the role of tissue-resident memory T cells (TRM) in skin and joints, where they may provide local protection or contribute to chronic pathology, a factor not fully captured in earlier systemic studies.[46] Moreover, $CD4^+$ Th1 cells play key roles in promoting B cell activation, IgG2c production, and IFN-γ–mediated viral clearance. In murine models, the absence of $CD4^+$ T cells impairs both antibody development and viral control.[46] Although certain structural proteins such as 6K and capsid are weakly immunogenic in terms of neutralizing antibody induction, they elicit strong T cell responses and contribute to long-term immunity.[46,48] These findings underscore the importance of incorporating T cell epitopes in vaccine formulations to achieve comprehensive and durable protection.

CHIKV also employs multiple strategies to achieve immune evasion. For instance, recent studies using human fibroblast models have demonstrated that nsP2 disrupts MHC-I antigen presentation, thereby weakening $CD8^+$ T

cell surveillance.[49] Moreover, several investigations combining escape mutants with cryo-electron microscopy and epitope mapping have identified critical residues within the E2 domain A/B domains and the E1–E2 interface that mediate neutralization escape. These analyses revealed that different antibody combinations or epitope targets can act synergistically or complementarily.[50-52]

Identification of correlates of protection is fundamental for guiding CHIKV vaccine development and regulatory evaluation. A cohort study in the Philippines revealed that individuals with pre-existing neutralizing antibodies had a significantly reduced risk of symptomatic CHIKV infection.[44] Powers et al. also showed that neutralizing antibodies co-exist with memory B cells for years post-infection, supporting their central role in durable immunity.[37] In addition to antibody titers, qualitative aspects, such as IgG subclass distribution and affinity, also influence protective efficacy. Notably, an early IgG3-dominant response has been associated with decreased risk of chronic arthralgia, making it a potential functional correlate.[34] Moreover, both natural infection and vaccination can induce long-lasting B and T cell memory responses, with $CD4^+$ memory T cells demonstrating greater durability over time.[46] Therefore, effective vaccine candidates should aim to elicit not only strong neutralizing antibody responses but also broad cellular immunity, particularly by targeting conserved epitopes within the E2 glycoprotein and T cell–stimulatory regions shared across CHIKV genotypes, while also ensuring vaccine-induced antibodies at sub-neutralizing levels do not predispose to ADE via Fcγ receptor–mediated uptake of immune complexes by macrophages.[53]

Furthermore, the transition from a qualitative correlate (neutralizing antibodies) to a quantitative, standardized protective threshold remains a major challenge. Proposed neutralizing antibody titers associated with protection vary significantly, influenced by assay methodology (e.g., $PRNT_{50}$ vs. NT_{80}), endpoint definitions, and study populations. This heterogeneity, compounded by the lack of an international reference serum, complicates cross-trial comparisons and regulatory decision-making. Establishing a universally accepted threshold through standardized assays and correlative clinical data is therefore an urgent priority for the field.

Antigenic drift, viral evolution, and lineage diversity

CHIKV is classified into three major phylogenetic lineages: West African (WA), Asian, and East/Central/South African (ECSA). Notably, the Indian Ocean lineage (IOL) emerged as a distinct sub-lineage through adaptive evolution from the ECSA clade and played a major role in global outbreaks since 2005 (Figure 1C).[54-56] As a positive-sense RNA virus, CHIKV lacks proofreading activity in its RNA-dependent RNA polymerase, which leads to a high mutation rate and frequent antigenic drift. These mutations, primarily occurring in the surface glycoproteins E1 and E2, impact viral fitness, host adaptation, and immune escape, thereby complicating both surveillance and vaccine development.

Among lineage-defining mutations, E1-A226V, characteristic of the IOL, markedly enhanced replication efficiency in Aedes albopictus, facilitating the virus's adaptation to new ecological niches and expanding its geographic range.[57] Similarly, the E1-K211E residue is consistently found in all sequenced endemic Asian CHIKV strains but is absent from other CHIKV lineages, including all sequenced IOL isolates.[58] Adaptive mutations in the E2 protein, such as L210Q, I211T, G205S, and V264A, have been associated with altered receptor binding and increased vector competence.[56,59] While key neutralizing epitopes on E2 are generally conserved, these amino acid substitutions can reduce antibody recognition and binding affinity, thereby promoting immune evasion.[49] These findings highlight the need to continuously monitor emerging mutations that may compromise the efficacy of existing vaccine-induced or natural immunity.

Given the antigenic variability of CHIKV, the development of vaccines with cross-lineage protective efficacy is imperative. For example, the live-attenuated vaccine IXCHIQ, which has completed Phase III trials and received accelerated approval, was shown to elicit broadly neutralizing antibodies effective against WA, ECSA, and Asian strains. However, modest reductions in neutralization titers against certain IOL variants suggest that antigenic drift may partially affect vaccine performance.[60] These limitations underscore the urgency of advancing multivalent or rapidly adaptable platforms, capable of countering future evolutionary variants. Additionally, robust genotype surveillance systems, such as the CHIKVdb database (https://nmdc.cn/gcpathogen/chikv) hosted by China's National Microbial Data Center, are essential for real-time tracking of viral evolution, facilitating predictive vaccine updates and informing global outbreak preparedness.

LICENSED AND CANDIDATE VACCINE PLATFORMS

Building on evidence that CHIKV infection elicits broad and durable immunity across diverse genotypes, recent vaccine development has yielded notable progress, including the licensure of two products, IXCHIQ and VIMKUNYA, that demonstrate strong immunogenicity and substantial disease burden reduction. Alongside these, multiple platforms, including mRNA, viral vectors, and inactivated approaches, are progressing through clinical trials (Figure 2: clinical-stage candidates; Table 1: major pipeline vaccines).

Bars denote the duration of each program (VIMKUNYA, MV-CHIK, BBV87, mRNA-1388, IXCHIQ, HydroVax-005); ticks label key events (trial starts/results and approvals or label actions by FDA, EMA/EC, MHRA, and Health Canada). Arrowheads indicate activity continuing beyond the plotted period. "Program discontinued by Merck" denotes sponsor-initiated termination of the development program. Abbreviations: FDA, U.S. Food and Drug Administration; EMA, European Medicines Agency; MHRA, Medicines and Healthcare products Regulatory Agency.

Live-attenuated vaccines

Live-attenuated vaccines (LAVs) utilize replication-competent viruses that have been attenuated to prevent severe disease, aiming to elicit strong and durable humoral and cellular immune responses. Earlier LAV candidates, such as TSI-GSD-218, were hindered by safety concerns, most notably the emergence of reversion-prone sites within the structural proteins. In particular, single amino acid substitutions at positions such as E2-82 were shown to restore replication fitness, raising concerns about genetic stability during large-scale deployment.[78-80] Mechanistic lessons from first-generation LAVs reveal that attenuation relying on few loci creates a low genetic barrier, allowing fitness recovery via single-site reversions that restore entry/fusion efficiency or compensatory mutations during human transmission. Consequently, modern designs raise this barrier through defined deletions, gene rearrangements, and multi-site mutations, supplemented by process safeguards like limited production passages, deep sequencing, and serial-passaging assays to ensure stable attenuation from seed to final product.[64]

A notable example is IXCHIQ, derived from the *La Réunion* strain of the ECSA genotype and engineered with a targeted nsP3 deletion, demonstrated high immunogenicity across age groups. In adults, a single dose achieved 99% seroprotection (95% CI, 97–100) with a geometric mean titer (GMT) exceeding 4,000 by day 28.[62] In a phase 3 adolescent trial, 98.8% (247/250; 95% CI, 96.5–99.8) of baseline-seronegative participants reached protective titers, surpassing the pre-specified threshold, while all seropositive participants (52/52) achieved 100% seroprotection with GMTs increasing from 3,097 to 3,887, accompanied by fewer systemic adverse events.[61] Licensed by the US Food and Drug Administration (FDA) in November 2023 and subsequently approved in Canada and Europe, IXCHIQ is administered as a single-dose vaccine, offering rapid protection suitable for outbreak control.

Caveats on safety and follow-up are nevertheless important. While IXCHIQ's pivotal trials demonstrated high seroprotection and acceptable short-term safety, these data came from controlled trials with limited size and duration, potentially missing rare or delayed adverse events. Post-marketing surveillance and long-term follow-up are essential, especially for replication-competent vaccines.[81] Notably, IXCHIQ was licensed under the FDA's Accelerated Approval pathway, which relies on immunologic surrogate endpoints rather than demonstrated clinical protection. On 22 August 2025, the FDA announced the suspension of IXCHIQ's license in the United States due to reports of serious adverse events,[82] underscoring that even accelerated-approval vaccines may reveal safety concerns post-marketing. This highlights the continuing need for long-term surveillance and transparent risk communication.

Building on these stability principles, recent rational attenuation has produced promising candidates, including CHIKV-IRES (subgenomic

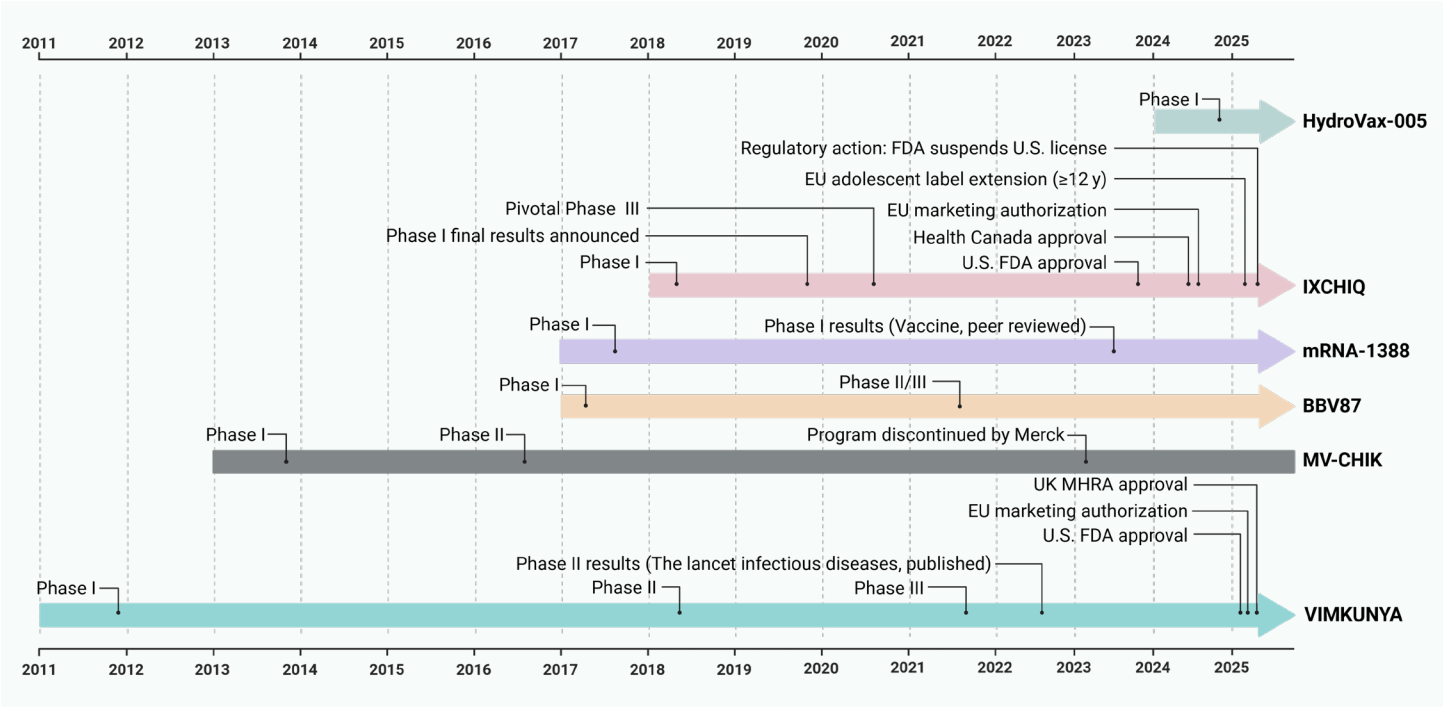

Figure 2. Clinical development timelines (2011–2025) and regulatory milestones for CHIKV vaccine candidates.

promoter replaced by an internal ribosome entry site), CHIKV-NoLS (capsid nucleolar localization sequence mutation), ΔC-CHIKV (complete capsid gene deletion), and V5040 (capsid relocation combined with stabilized E2).[12,63,64] Collectively, these rationally designed LAVs offer a blueprint for achieving both durable immunogenicity and genetic stability, reinforcing their promise in rapid-response strategies against chikungunya outbreaks.

Inactivated whole-virus vaccines

Inactivated whole-virus vaccines employ chemically or physically treated virions that retain antigenic integrity but are replication-incompetent. By presenting the complete viral antigenic repertoire, they induce broad humoral immunity with a favorable safety profile.[83] Yet, immunogenic fidelity is highly dependent on the inactivation method. Early formalin-based CHIKV vaccines, produced in mouse brain or primate cell cultures, exhibited limited efficacy and raised safety concerns.[12,84] These shortcomings are consistent with broader experience showing that formaldehyde-induced cross-linking can disrupt conformational epitopes, skew responses toward Th2 polarization, and, in rare cases, trigger vaccine-enhanced disease, as observed with inactivated RSV vaccines.[85,86] Such historical failures underscore the need for epitope-preserving strategies. Contemporary approaches using β-propiolactone or controlled hydrogen peroxide inactivation, often coupled with potent adjuvants, have demonstrated improved antigenic preservation and enhanced immunogenicity.[87] Nonetheless, despite encouraging results in early clinical trials, no inactivated CHIKV vaccine has yet received regulatory approval.

Modern inactivated platforms employ optimized inactivation methods, such as β-propiolactone or controlled oxidative treatments, to preserve neutralizing epitopes, and pair them with adjuvants like oil-in-water emulsions, TLR agonists, or saponins to enhance durable, balanced antibody responses while avoiding Th2 bias. Adjuvants such as alum or oil-in-water emulsions (e.g., MF59, AS03) enhance local innate activation, dendritic cell maturation, antigen presentation, and depot effects, thereby promoting durable and balanced immunity.[65,88-90] The BBV87 vaccine, formulated with β-propiolactone-inactivated virions and aluminum, and administered in two 20-μg intramuscular doses, achieved potent neutralizing responses ($PRNT_{50}$: 160–586), sterilizing immunity (plasma CHIKV RNA <50 IU/mL), complete tissue viral clearance, and pathology suppression without severe adverse events, advancing to phase III trials.[65] In addition, HydroVax-005 CHIKV, which also uses aluminum hydroxide adjuvant in conjunction with its targeted oxidation inactivation technology, is currently in phase I evaluation.[66] These advances highlight that effective adjuvantation, together with epitope-preserving inactivation, constitutes the cornerstone of modern inactivated vaccine design.

Inactivated vaccines, historically constrained by poor immunogenicity and multi-dose regimens, remain challenged by antigenic drift and cold-chain demands. While modern epitope-conserving inactivation and adjuvantation strategies significantly enhance immunogenicity and safety, particularly for CHIKV in vulnerable populations, regulatory progress must not be equated with established efficacy. Robust phase II/III data are still essential to confirm durable neutralization, controlled antibody kinetics, and absence of enhanced disease across ages. Further considerations include manufacturing consistency, potential booster requirements in elderly cohorts, and scalable production during outbreaks.

Virus-like particle vaccines

Virus-like particles (VLPs) are morphologically identical to infectious viruses but lack nucleic acids, rendering them replication-incompetent while retaining high immunogenicity. They display the CHIKV structural proteins, capsid, E1, and E2, in their native conformation, eliciting neutralizing antibodies comparable to those generated during natural infection.[91,92] VLP vaccines combine genome-free safety with potent immunogenicity and versatile antigen presentation, supporting their clinical and commercial success.

VIMKUNYA, one of only two licensed CHIKV vaccines, is a single-dose, aluminum hydroxide–adjuvanted VLP formulation expressing E1, E2, and capsid proteins from the CHIKV Senegal 37997 strain. Phase 3 trials of the CHIKV VLP vaccine VIMKUNYA (40 μg, alum-adjuvanted, single IM dose) using a standardized luciferase-NT_{80} assay demonstrated rapid and durable immunity. In adults 12–64 years (n = 2,559), peak GMT at Day 22 reached 1,618 IU/mL (95% CI 1,566–1,671), 204.8-fold above placebo (95% CI 192.3–218.1; $p < 0.0001$), with 85.5% seroprotection (84.0–86.9) maintained at six months (GMT 323 IU/mL, 312–335; 3.2-fold above the protective threshold). Immunity declined with age: Day 183 seroprotection was 94.8% (12–17 y), 85.0% (18–45 y), and 84.1% (46–64 y), corresponding to GMTs of 511, 323, and 322 IU/mL, with a GMT ratio of 1.59 (95% CI 1.41–1.79; $p < 0.001$) between the youngest and oldest subgroups. In participants ≥65 years (n = 189), Day 22 GMT was 724 IU/mL (663–791), 90.5-fold above placebo, with 76% seroprotection (68.9–81.2) and GMT 233 IU/mL (215–253) at six months; in ≥75 years (n = 40), GMT was 281 IU/mL (235–337) with 73%

Table 1. Summary of major pipeline CHIKV vaccines.

No.	Vaccine Platform	Vaccine Name	Detailed Information	Immunization Route	Study Type	Immunogenicity	Safety	Durability	Developers	Ref.
1	Live-attenuated vaccine	IXCHIQ	nsP3 deletion; attenuated replication; high immunogenicity	IM	Phase 3 (Brazil, Adolescent) Phase 3 (US/EU, Adult)	~99% seroresponse at 28 days ~98–99% seroresponse at 28 days; high GMTs	Mild/moderate AEs, no SAEs	Neutralization sustained ≥12 months Antibody persistence ≥ 12–36 months	Valneva SE (Austria)	61 62
2		CHIKV-IRES	IRES replaces subgenomic promoter; robust attenuation	ID/SC	Preclinical (mice)	High nAbs; protection in challenge	No AEs in mice	≥94 days	UTMB	12
3		CHIKV-NoLS	Capsid NoLS mutation; strong safety profile	SC	Preclinical (mice)	Durable neutralizing antibodies; cross protection	No AEs in mice	≥71 days	Griffith University	12
4		ΔC-CHIKV	Entire capsid gene deleted; genetically stable	SC	Preclinical (mice)	Strong nAbs; full protection	No AEs in mice	14 days without long-term assessment	University of Chinese Academy of Sciences	63
5		V5040	Genome rearrangement; stabilized E2	SC	Preclinical (mice)	Robust nAbs; challenge protection	No AEs in mice	3 weeks without long-term assessment	Medigen	64
6	Inactivated vaccine	BBV87	β-propiolactone inactivation; high binding antibody titers	IM	Preclinical (NHP)	Two doses induced high IgM/IgG and nAbs	No AEs in NHP	15 days without long-term assessment	Bharat Biotechnology	65
7		HydroVax-005	H_2O_2 inactivation; neutralizing epitopes preserved	IM	Phase 1 (ongoing)	Unpublished	Not reported	Not assessed	Najit Technologies	66
8		VIMKUNYA	Aluminum-adjuvanted VLP; first approved for 12+, long-lasting immunogenicity	IM	Phase 3 (USA)	~98% seroresponse; high GMTs	Mild/moderate AEs, no SAEs	≥183 days	Bavarian Nordic	67
9	Virus-like particle vaccine	VLP/DNA Co-immunization	Combined VLP and DNA; potent antigen-specific immunity; superior protection	SC	Preclinical (mice)	Higher nAbs than either alone	No AEs in mice	Complete 4-week protection without long-term assessment	National Institute for Viral Disease Control and Prevention	68
10		Multivalent VLP	Multi-antigen VLP; broad neutralization; scalable production	IM	Preclinical (mice)	High-titer multivalent neutralization	Not reported	Not assessed	Texas Tech University Health Sciences Center	69
11	Recombinant protein subunit vaccine	CHIKV E2/E1 subunit vaccine	E2/E1 proteins plus QS-21 adjuvant; strong humoral immunity; balanced Th1 and Th2	SC	Preclinical (mice)	High antibody titers, weak T-cell response	No AEs in mice	Short-term protection without long-term assessment	Defense Research and Development Establishment	12
12	mRNA-based vaccine	mRNA-1388	Pre-fusion stabilized E1/E2/E3 expression; durable neutralizing antibody response	IM	Phase 1 (randomized)	All groups seroconverted; durable	Mild/moderate AEs, no SAEs	≥12 months	Moderna	70
13		mCV-1/mCV-2	Conserved-region mRNA; cross-protective neutralizing antibody response	IM	Preclinical (mice/NHP)	Broad cross-lineage neutralization with Th1-skewed immunity	No AEs, notably no Th2-associated VAED	21 days without long-term assessment	Chinese Academy of Medical Sciences	71

Table 1. *(Continued)*

No.	Vaccine Platform	Vaccine Name	Detailed Information	Immunization Route	Study Type	Immunogenicity	Safety	Durability	Developers	Ref.
14	DNA-based vaccine	pMCE321	E3/E2/E1 plasmid; dual-arm immunity; protective immunity	IM	Preclinical (mice/NHP)	Robust nAbs and T-cell responses	No AEs in mice and NHP	≥14 days without long-term assessment	University of Pennsylvania School	72
15	Chimeric/Vectored vaccine	MV-CHIK	Measles vector expressing CHIKV proteins; heterologous strain cross-neutralization; potent dual-arm immunity	IM	Phase 2 (RCT)	Two doses achieved near 100% seroconversion	Mild/moderate AEs, no SAEs	≥7 months	Themis (Merck/MSD)	73
16		ChAdOx1 Chik	Chimpanzee adenovirus vector; single-dose administration; 100% seroconversion	IM	Phase 1 (open-label)	All participants seroconverted	Mild/moderate events	≥6 months	University of Oxford	74
17		MVA-CHIKV	MVA vector; single-dose; dual-arm immunity	IM	Preclinical (mice/NHP)	High nAbs and T-cells; protection	No AEs in mice and NHP	7 weeks in mouse and 123 days in NHP	CNB-CSIC (Spain)	75
18		EILV/CHIKV	Insect-specific vector; rapid and durable protective immunity	IM	Preclinical (mice/NHP)	nAbs by day 4; cross-lineage	No AEs in mice and NHP	>1 year	University of Texas Medical Branch	76
19		DomC-Cytokine Chimera	Structural proteins plus IFN-γ/IL-21 expression; enhanced attenuation profile	SC	Preclinical (mice)	Broad-spectrum, long-lasting immunogenicity after a single dose	No AEs in mice; Reduced viremia vs control	≥71 days	Virginia Tech	77

This table summarizes key information on major pipeline CHIKV vaccines, including vaccine platforms, product names, detailed compositions, immunization routes, study type, immunogenicity, safety, durability, and developing institutions. It encompasses multiple vaccine types, such as inactivated virus vaccines, live-attenuated vaccines, VLP vaccine, recombinant protein subunit vaccine, DNA-based vaccines, RNA-based vaccines, and viral vector vaccines. The table offers comprehensive insights into the composition, technical features, and administration methods of each vaccine, serving as a valuable reference for understanding the development progress and characteristics of different CHIKV vaccine platforms. IM, intramuscular injection; ID, intradermal injection; SC, subcutaneous injection.

seroprotection (60–83), though wide CIs limit interpretability. Adverse events were predominantly grade 1–2, self-limited, with no vaccine-related serious adverse events reported. Compared to the live-attenuated IXCHIQ, it shows enhanced safety and broader suitability (≥12 years, including immunocompromised) but may induce less durable immunity.[67,93]

Relative to next-generation mRNA CHIKV vaccines (e.g., mRNA-1388), which enable rapid lineage retargeting yet remain constrained by stability, cold-chain logistics, and uncertainties in long-term safety,[70] VIMKUNYA's alum-adjuvanted VLP platform offers established manufacturing and thermostability for broad deployment. Nonetheless, its antibody titers decline over time, particularly in older adults, potentially necessitating boosters, and its efficacy against emerging variants or in previously exposed populations requires further evaluation.

Since Akahata et al. first reported a non-replicating CHIKV VLP vaccine in nonhuman primates in 2010, which assembled structural proteins into particles that elicited high-titer neutralizing antibodies, multiple CHIKV VLP-based candidates have entered development.[94] Notable strategies include VLP/DNA co-immunization, which achieves superior humoral responses with minimal pathology, and multivalent VLP designs, offering broad neutralization across multiple arboviruses with scalable manufacturing potential.[68,69] While VLP manufacturing is more complex than subunit vaccines due to the need for precise protein assembly and rigorous purification, posing significant challenges to scalability, cost-effectiveness, batch consistency, and regulatory compliance for global implementation, innovations in bioengineering and downstream processing are addressing these barriers. Key advances include the development of optimized expression systems (e.g., glyco-engineered insect cells, yeast, and plant platforms) with enhanced protein folding and reduced inclusion body formation, as well as improved purification techniques.[95] In summary, VLP-based platforms represent a promising avenue for CHIKV vaccination, effectively balancing immunogenicity and safety. Ongoing innovations in production technology continue to address historical manufacturing constraints, enhancing their potential for scalable global use, with potential for multivalent arbovirus formulations.

Recombinant protein subunit vaccines

Recombinant protein subunit vaccines, composed of high-purity antigens formulated with adjuvants or nanodelivery systems, offer excellent safety and design flexibility, making them a valuable platform for combating emerging infectious diseases.[96] For CHIKV, these vaccines primarily target the E1 and E2 envelope proteins and are commonly produced in *Escherichia coli* or mammalian expression systems.[12] They are particularly effective as booster immunizations, increasing total E2-specific IgG titers by 5–6-fold and neutralizing antibody levels by 1.2-fold compared with homologous DNA-only regimens, while also inducing robust cellular immunity.[97]

Despite these advantages, interest in this platform has waned in recent years due to its comparatively lower neutralizing antibody titers and weak cellular immunity, often necessitating potent adjuvants or multiple-dose regimens.[98] Moreover, CHIKV can suppress MHC-I expression via the nonstructural protein nsP2, further impairing $CD8^+$ T-cell responses and compounding the limitations of protein subunit vaccines.[49] Consequently, research

efforts have shifted toward platforms capable of eliciting broader and more durable immune responses. Nevertheless, recombinant protein subunit vaccines retain significant value due to their safety, controllability, and antigen design versatility, making them particularly suitable for booster use, pediatric vaccination, and immunization of immunocompromised populations.

Nucleic acid vaccines

Nucleic acid vaccines deliver DNA or mRNA encoding pathogen antigens into host cells, enabling in situ antigen expression and the rapid induction of robust, antigen-specific immune responses, while offering high safety, scalability, and design flexibility.[99] This platform has been successfully applied to CHIKV vaccine development. Moderna's mRNA-1388, the first CHIKV mRNA vaccine to enter clinical trials, encodes the CHIKV structural polyprotein (C–E3–E2–6K–E1) within a lipid nanoparticle delivery system. Administered in two doses 28 days apart to healthy adults, it induced durable neutralizing antibodies (GMT 92.8; 95% CI 43.6–197.6) that persisted for at least one year and was well tolerated, with primarily transient grade 1–2 reactogenicity and no vaccine-related serious adverse events.[70] In parallel, a team from the Chinese Academy of Medical Sciences developed a novel CHIKV mRNA vaccine targeting conserved regions across 769 viral strains.[71] Their findings demonstrated that this vaccine not only elicited robust cellular immunity but also induced broad-spectrum neutralizing antibody responses, with GMT reaching up to 1.7×10^5. Notably, the vaccine conferred complete protection in rhesus macaque models, highlighting its potential efficacy.

For tropical deployment, current mRNA–LNP vaccines have faced stringent cold-chain needs: historically many products required frozen storage at -20 to -70 °C, which strains logistics and equity in hot, resource-limited regions.[99] The WHO therefore endorses extended controlled temperature conditions (ECTC), label-supported, time-limited storage above the usual 2-8 °C once stability is demonstrated, thereby facilitating last-mile deployment in tropical settings with constrained cold-chain capacity.[100] Encouragingly, formulation advances (e.g., lyophilization) and optimized mRNA–LNP designs (e.g., ARCoV), together with emerging circRNA–LNP vaccines and quantitative stability-prediction tools, have delivered short-term room-temperature or refrigerated stability without loss of immunogenicity, pointing to a credible route toward equitable access in endemic tropical settings.[101-104]

DNA-based CHIKV vaccines can induce both neutralizing antibodies and cytotoxic T-cell responses, support multivalent antigen formats, and allow straightforward manufacturing. Some DNA-launched attenuated virus particles have shown promising results.[12] However, their suboptimal immunogenicity in humans necessitates improved delivery systems and optimized adjuvant formulations.[12,72] Mechanistically, plasmid DNA requires nuclear entry for transcription, while mRNA is translated directly in the cytosol, which contributes to the relatively lower immunogenicity of unassisted DNA in humans.[99] Electroporation through intramuscular or intradermal consistently enhances DNA uptake and expression,[105] and together with adjuvantation, vector engineering,[106] and DNA-launched attenuated (iDNA) constructs,[107] substantially narrows this gap while preserving DNA's intrinsic stability and manufacturability, positioning optimized DNA platforms as a practical, complementary CHIKV vaccine option for hot, resource-limited settings.

Platform selection is fundamentally a trade-off among immunogenic potency, stability, and access. A preferable future paradigm is complementarity rather than substitution, for example, heterologous regimens with DNA priming and mRNA boosting, or the use of DNA templates for in-vitro transcription of mRNA, seeking to couple DNA's stability with mRNA's high expression efficiency to strengthen responses to emerging pathogens and advance global vaccine equity.

Chimeric/vectored vaccines

Chimeric and vectored vaccines employ attenuated or replication-deficient viral vectors to deliver CHIKV structural antigens *in vivo*, combining potent immunogenicity with scalable manufacturing.[108] This platform is rapidly engineerable and has demonstrated outbreak responsiveness, relatively inexpensive, scalable manufacturing, and practicality for stockpiling/less stringent cold chains, attributes validated at population scale by adenoviral vectors.[109]

Several vector platforms have advanced in CHIKV vaccine development. MV-CHIK, a measles virus–based vector expressing the full CHIKV structural polyprotein, elicited strong humoral and cellular immune responses in clinical trials. In the phase 2 study, neutralizing antibody GMT ranged from 12.9 to 174.8, with seroconversion rates of 50.0–95.9% depending on dose and schedule, approaching 96% after a booster dose. Vaccine-induced sera also cross-neutralized heterologous CHIKV strains. Safety and tolerability were comparable to the measles control vaccine (solicited adverse events: 73% vs 71%).[73] Although MV-CHIK induces robust CHIKV-specific antibodies in measles-seropositive adults, the high global coverage of measles vaccination[110] may theoretically attenuate responses by limiting vector replication/transgene expression, as suggested by an MV-vectored COVID-19 vaccine.[111] Subsequent efforts should include dose and schedule optimization within a safe range, long-term monitoring, and the use of heterologous prime-boost regimens to improve efficacy.

Likewise, ChAdOx1 Chik, a replication-deficient chimpanzee adenovirus vector encoding the full structural polyprotein, achieved 100% seroconversion against all four CHIKV lineages after a single dose and may form CHIKV-like VLP structures, potentially enhancing antigen presentation by mimicking native virion morphology. Neutralizing antibody GMTs ranged from 40 to 369.7 across lineages, peaking at day 28 and remaining detectable for up to 6 months.[74] Notably, ChAdOx1 vectors has a documented, albeit rare, association with vaccine-induced immune thrombotic thrombocytopenia (VITT), presumably via anti-PF4–mediated platelet activation. Despite this concern, its low incidence (around 3–15 per million doses)[112] is eclipsed by the high attack rate of CHIKV in endemic areas (35%–75%),[6] sustaining a favorable benefit–risk balance. Another important point is that pre-existing anti-adenovirus immunity, which is common in Southeast Asia[113] and overlaps with CHIKV endemicity,[6] may blunt immune responses. These risks can be substantially mitigated through the implementation of clear risk communication, active surveillance, early clinical management pathways, and the use of rare-serotype vectors or heterologous prime–boost regimens.

In contrast, MVA-CHIKV, based on modified vaccinia Ankara, conferred complete protection in mice after a single dose and achieved sterilizing immunity in non-human primates when co-administered with a DNA vaccine.[75] Similarly, EILV/CHIKV, an insect-specific chimeric vector expressing full-length CHIKV structural proteins, provided rapid protection within six days and durable immunity lasting at least one year in primates, inducing strong innate and T-cell responses without replication or allergy risks.[76] Another chimeric approach integrates a viral backbone with cytokine expression, incorporating DomC domain replacement and sustained IFN-γ/IL-21 secretion to achieve sterilizing protection without systemic viral dissemination.[77] Other platforms, such as venezuelan equine encephalitis virus-CHIKV and vesicular stomatitis virus–based chimeras, demonstrated high immunogenicity in preclinical studies but were discontinued due to neurovirulence, vector-associated reactogenicity, and translational limitations.[12]

Overall, vectored and chimeric CHIKV vaccines express the full structural polyprotein from attenuated or replication-defective backbones, co-activating humoral and cellular immunity, often after a single dose and they are compatible with thermostabilization and stockpiling for outbreak use. Yet "scalable" is not constraint-free: reliance on mammalian cell-culture and viral-seed campaigns, capacity-intensive upstream/downstream processing, and release testing can slow initial ramp-up and require distributed manufacturing and advance planning.[114] These challenges underscore the need for careful planning and process optimization to enable rapid and sufficient global supply.

Platform comparison: immunogenicity, safety, and scalability

We present a narrative, non-ranked comparison focusing on immunogenicity, safety, manufacturing considerations, cold-chain practicality, and current regulatory status. Because assays (e.g., $PRNT_{50}$ vs NT_{80}), study populations and follow-up windows vary across trials, we avoid cross-trial scoring or pooling and summarize platform-specific strengths and limitations descriptively. CHIKV vaccine development has advanced considerably; however, inherent limitations continue to affect each platform in distinct ways (Figure 3). While LAVs such as IXCHIQ exhibit potent immunogenicity, they are conversely burdened by notable reactogenicity, especially in seronegative recipients and require high-containment manufacturing facilities, which significantly hinder rapid scale-up.[61] These concerns were highlighted by the

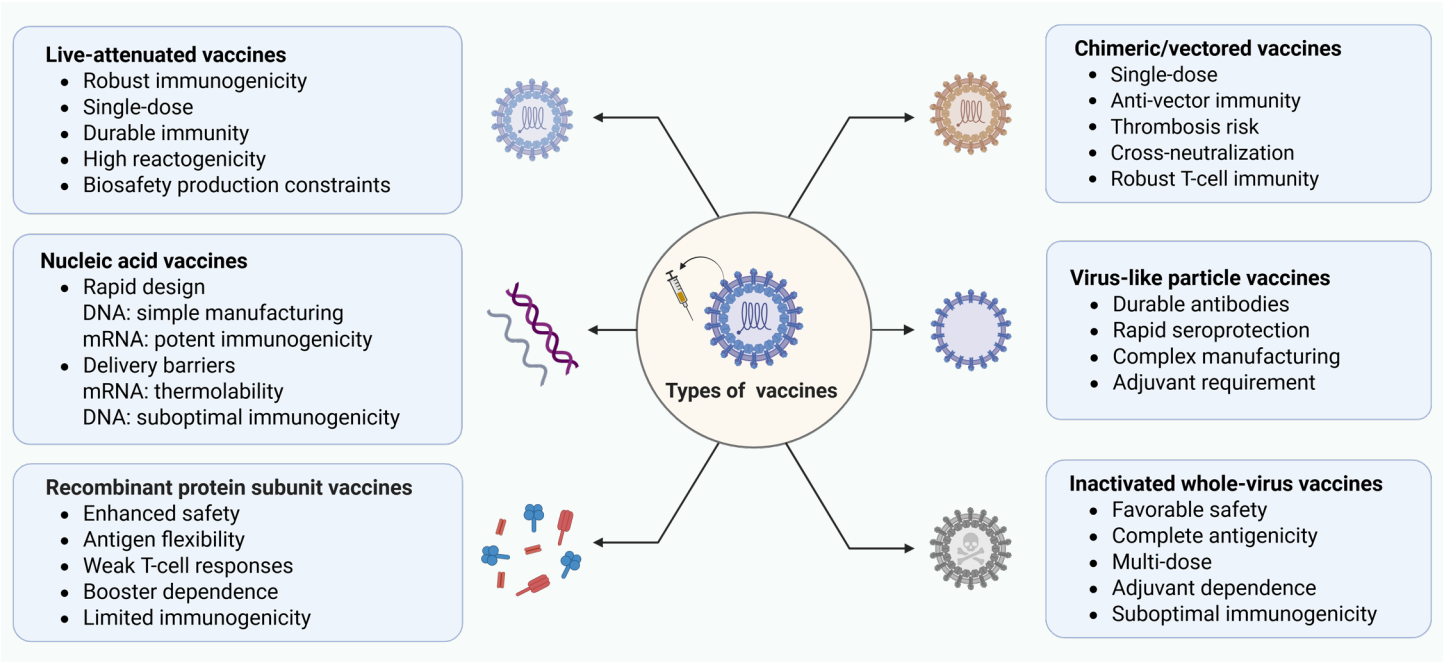

Figure 3. Comparison of CHIKV vaccine platforms Summary of key attributes of major CHIKV vaccine platforms, including their immunogenicity, dose requirements, safety profiles, manufacturing complexity, and platform-specific limitations.

August 2025 U.S. FDA license suspension[82] and cautions in older adults (≥65 years),[115] underscoring the need for age-stratified risk-benefit assessment and enhanced surveillance. In contrast, inactivated whole-virus vaccines provide a favorable safety profile; nevertheless, their dependence on strong adjuvants and multi-dose regimens to maintain neutralizing antibody titers poses challenges for patient compliance and complicates mass deployment,[65,66] and the effectiveness of candidates remains unconfirmed.[65] Meanwhile, VLP formulations achieve durable antibody responses but encounter production complexities, including intricate co-expression and purification steps. Nonetheless, the recombinant VLP vaccine VIMKUNYA secured U.S. FDA accelerated approval, leading to its marketing under confirmatory trials. Moreover, their reliance on aluminum-based adjuvants for optimal efficacy, combined with stringent cold-chain requirements, further limits global distribution.[67] By comparison, recombinant protein subunit vaccines offer superior safety control; however, they generally induce weak $CD8^+$ T-cell responses and typically necessitate repeated boosters or advanced delivery methods to reach protective immunity, potentially restricting their practical application.[49,98] On the other hand, nucleic acid platforms enable rapid antigen design and development but face significant obstacles in efficient *in vivo* delivery, endosomal escape, and mRNA thermostability, which may impede their broad adoption,[70,71] with early human data (mRNA 1388) showing acceptable tolerability but modest neutralization.[70] Lastly, chimeric/vectored vaccines can be compromised by pre-existing anti-vector immunity and vector-associated reactogenicity, potentially limiting their use in repeated or large-scale immunization campaigns.[73] Additionally, safety concerns such as thrombosis with thrombocytopenia syndrome linked to the ChAdOx1 platform could negatively affect acceptance of this vaccine modality for CHIKV.[116] Collectively, these challenges highlight the pressing need for iterative, mechanism-driven refinement to effectively balance immunogenicity, safety, and scalability. Addressing these issues is paramount to realizing effective and widely accessible next-generation chikungunya vaccines.

NEUTRALIZING ANTIBODIES AND PROTECTIVE IMMUNITY

Neutralizing antibodies (nAbs) protect against CHIKV by blocking multiple steps of the replication cycle, but viral entry is mediated by more than one host factor. Besides the primary protein receptor MXRA8, CHIKV can exploit MXRA8-independent pathways, notably phosphatidylserine (PtdSer) receptors such as TIM-1, and glycosaminoglycans (GAGs), especially heparan sulfate (HS) as attachment/entry enhancers in a cell-type–dependent manner. These alternative routes can modulate both cell tropism and neutralization sensitivity.[117-120]

Representative neutralizing antibodies map to E2-DB, E2-DA/β-connector, and E1-DII (fusion-loop-proximal) sites, as well as quaternary epitopes bridging the E1–E2 interface on trimeric spikes; these are presented as a non-graded, domain-based summary in Table 2. For example, CHK-124 binds E2-DB overlapping the MXRA8 site and relies on bivalent cross-linking to aggregate virions and block attachment, fusion, and egress; Fab monovalency markedly reduces activity. CHK-263 recognizes a conformational epitope that bridges E1 and E2, stabilizing the prefusion state and inhibiting low-pH fusion.[121] Mechanistically, E1-targeting nAbs can neutralize by stabilizing prefusion E1/E2 and preventing endosomal fusion; however, single point mutations (e.g., E1-K61T, G64S) can confer escape from CHK-166 *in vitro*/*in vivo*, illustrating that potency may trade off with escape liability depending on epitope positioning relative to conformational rearrangements.[33] Importantly, entry and immune escape are shaped by functional trade-offs. Adaptation that increases HS binding, often via acquisition of positively charged residues in E2, can enhance attachment *in vitro* yet attenuate dissemination and virulence *in vivo*, highlighting a balance between receptor avidity, vector/host adaptation, and antibody pressure.[134,135]

Beyond entry inhibition, some nAbs exert effects at later stages of the viral lifecycle by disrupting viral assembly and release, underscoring the multifaceted mechanisms of neutralization.[121,136] Structural analyses reveal that potent mAb, such as CHK-124 and CHK-263, simultaneously engage multiple viral epitopes, cross-linking or aggregating virions to reduce infectious particles, while also stabilizing fusion-related domains to prevent the low pH–induced conformational changes required for membrane fusion. Similarly, Kim et al. demonstrated that the murine mAb CHK-265 targets a conserved epitope in the E2 domain B of CHIKV, cross-linking viral spikes to inhibit budding and release. CHK-265 exhibited potent neutralizing activity across genotypes, including CHIKV, MAYV, O'nyong'nyong virus (ONNV), Ross River virus (RRV), with EC_{50} values of 10–20 ng/mL in Vero cells. However, *in vitro* evolution revealed single mutation of G170E or I175T in the E2 epitope, conferred complete escape, increasing EC_{50} by over 100-fold, highlighting a significant risk of immune evasion.[28] A thorough understanding of these diverse neutralization mechanisms is essential for the rational design of vaccines and antibody therapeutics that elicit broad, functionally diverse immune responses and effectively minimize the risk of viral immune escape.

Consistent with this broader view, broadly neutralizing antibodies that target conserved epitopes across diverse CHIKV genotypes and related

Table 2. Representative CHIKV-neutralizing monoclonal antibodies: non-graded, domain-based summary.

No.	Name	Epitope	Structural Evidence	CHIKV-LR EC_{50} ng/ml (CI)	Neutralization Mechanism	Broad Neutralization	Antibody Type	Developers	Ref.
1	CHK-102	E2-DB	No	14 (11–17)	Blocks entry; protects in vivo in combination	CHIKV ECSA, Asian, and WA lineages	Murine mAb	Pal, et al.	33
2	CHK-152	E2-DA	Cryo-EM of Fab-virion supports E2-DA binding	2 (2–2)	Inhibits low-pH fusion; in vivo protection improved by Fc-mediated effector functions	CHIKV ECSA, Asian, and WA lineages			
3	C9/IM-CKV063	E2-DA,DB,arch	Cryo-EM shows quaternary "arch" bridging adjacent E2 subunits; W64-centered site	NR	Blocks entry and inhibits budding/release	CHIKV ECSA, Asian, and WA lineages	Human mAb	Jin, et al.	29,30
4	CHK-124	E2-DB	Cryo-EM	3 (2–6)	Aggregates virions; blocks attachment; limits subsequent fusion/internalization	CHIKV, MAYV, SFV, UNAV, BEBV and GETV	IgG	Zhou QF, et al. & Fox, et al.	121,122
5	CHK-187	E2-DB	No	9 (7–11)	Inhibits entry; Fc functions	CHIKV, MAYV, ONNV, SFV, RRV, UNAV, BEBV and GETV	IgG	Fox, et al.	122
6	CHK-265	E2-DB	Cryo-EM	5 (4–7)	Blocks both entry and egress	CHIKV, MAYV, ONNV, SFV, RRV, UNAV, BEBV and GETV			
7	5F10	E2	No	NR	Reduces spread	CHIKV and ONNV	Human mAb	Warter, et al.	123
8	506.C01	E2-DB	Cryo-EM of Fab-CHIKV VLP indicates receptor-site targeting	8	Blocks interaction with MXRA8 receptor	CHIKV, MAYV, ONNV, SFV and RRV	IgG	Raju et al.	124
9	CHKV-24	E2-DA, DB	No	NR	Blocks viral entry	CHIKV	IgG	August, et al.	125
10	1.3A2, 4.6F5, 4.10C12	E2	No	NR	Blocks viral attachment to host cells	CHIKV ECSA and Asian lineages	IgG	Goh, et al.	126
11	RRV-12	E2-DB	Cryo-EM shows mAb RRV-12 has a conserved footprint on three different alphaviruses	NR	Prevents attachment to MXRA8; inhibits entry and cell-to-cell spread	CHIKV, MAYV, ONNV and RRV	Human mAb	Powell, et al.	127
12	CHE19	E2	No	NR	Inhibits viral fusion and egress	Limited	Murine mAb	Tumkosit, et al.	128
13	3E7b	E2-DB	No	4.47*	Inhibits the interaction and egress	CHIKV	IgM	Lam, et al.	129
14	DC2.271B	E2	Low-res negative-stain EM mapping to E2 interface/β-connector	0.08 (0.06-0.10)#	Inhibits the post-attachment fusion	CHIKV ECSA and Asian lineages	Human mAb	Quiroz, et al.	130
15	2H1	E2-DA	No	8 [6-10]☆	Blocks low-pH fusion	CHIKV ECSA, Asian, and WA lineages	Human mAb	Smith, et al.	52
16	3C3, 3E4, 8A4	E2	No	NR	Studies the biology of CHIK virus and pathogenesis of disease	No	IgG	Bréhin, et al.	131
17	CHK-166	E1-DII	No	154 (116–205)	Blocks viral entry	CHIKV ECSA, Asian, and WA lineages	Murine mAb	Pal, et al.	33
18	SKT05	E1-DII	Cryo-EM	NR	Blocks viral entry; Fc-mediated effector functions	Limited	mAb	Sutton, et al.	132
19	DC2.112, DC2.315	E1-DII	Conserved site within/adjacent to fusion loop	NR	Inhibits of viral egress and monocyte-dependent Fc effector functions	CHIKV, MAYV, VEEV and EEEV	Human mAb	Kim, et al.	28
20	CK-47	E1-DIII	No	NR	Inhibits viral egress	Limited	Murine mAb	Masrinoul, et al.	133
21	CHK-263	E1, E2	Cryo-EM shows cross-interface locking of E1–E2; functional multi-step block	NR	Blocks virus attachment and fusion	CHIKV ECSA, Asian, and WA lineages	IgG	Zhou QF, et al.	121
22	8B10	E1, E2	No	NR	Blocks viral entry; reduces spread	CHIKV and ONNV	Human mAb	Warter, et al.	123

This table compiles representative CHIKV-neutralizing antibodies, including: antibody ID/name; targeted epitopes (e.g., E2-DA/DB, E1-DII/DIII, E1–E2 interfacial or quaternary "arch" epitopes); type of structural evidence (cryo-EM, negative-stain EM, or none); potency against the CHIKV-LR strain reported as EC_{50} (ng/mL, 95% CI; NR = not reported; * denotes IC_{50}; # denotes nM; ☆ denotes VRP [SL15649] assay); primary mechanism(s) of action (attachment blockade, inhibition of low-pH fusion, inhibition of budding/release, virion aggregation, and Fc-mediated effector functions); breadth of neutralization (e.g., MAYV, ONNV, SFV, RRV, UNAV, BEBV, GETV); antibody class/source; developer/laboratory; and references. Note: EC50/IC50 values are assay-specific (e.g., PRNT50/FRNT50, VRP neutralization) and not directly comparable across studies; no pooling or ranking is performed. "Arch" refers to a quaternary epitope spanning adjacent E2 subunits. ECSA, Asian, and WA denote East/Central/South African, Asian, and West African lineages, respectively. MXRA8 is a known entry receptor.

alphaviruses represent a promising strategy. For example, Fox et al. identified a panel of monoclonal antibodies capable of cross-lineage neutralization against CHIKV, MAYV, and ONNV, which provided complete protection in a murine passive immunization model.[122] Similarly, vaccine candidates such as IXCHIQ and HydroVax-CHIKV have demonstrated cross-genotype neutralizing activity, further validating the targeting of conserved epitopes as an effective approach.[137,138] Advanced approaches include antibody cocktails targeting multiple epitopes to reduce escape, potent antibodies accessing cryptic sites with high stability, and structure-guided design of mutation-resistant epitopes for multivalent vaccines.[139,140] Collectively, these strategies emphasize targeting conserved viral structures to counteract CHIKV diversity and inform proactive vaccine development.

NEXT-GENERATION VACCINE STRATEGIES

This section outlines an evidence-informed research agenda, framing forward-looking statements as testable hypotheses and avoiding unsupported comparative claims. CHIKV vaccine development and deployment face significant challenges. Although early vaccination could prevent up to 88% of infections, heterogeneous transmission patterns complicate clinical trials and delay vaccine rollout.[5,141] Manufacturing capacity is constrained by limited infrastructure, workforce shortages, raw material scarcity, protectionist policies, cold-chain requirements, and fragmented regulatory frameworks, restricting global access.[142] Inadequate surveillance and unclear identification of high-risk populations further impede targeted vaccination efforts. The genetic diversity of CHIKV reduces cross-lineage protection and facilitates immune escape via epitope mutations and suppression of innate immunity.[74,143,144] Vaccine platforms present safety and reactogenicity concerns, particularly in vulnerable groups such as children, pregnant women, and immunocompromised individuals, for whom trial data remain insufficient.[61,67,125,145-146] Current correlates of protection rely heavily on neutralizing antibodies, often overlooking chronic disease prevention.[5] Additionally, vaccine hesitancy and inequity undermine coverage: fragmented policies and misinformation erode public trust even among affluent populations, while socioeconomic disparities delay protection for marginalized communities.[147] Furthermore, unidirectional public health communication limits effective community engagement.[148] Overcoming these barriers demands innovative clinical trial designs, regional manufacturing capacity expansion, regulatory harmonization, broader immune correlates, enhanced safety profiles, and culturally sensitive, bidirectional public health strategies.

In response to these challenges, next-generation and broad-spectrum vaccine strategies are under active development (Figure 4). Achieving cross-lineage CHIKV protection is pivotal; thus, consensus and ancestral sequence engineering have been applied in trans-amplifying mRNA vaccines encoding consensus immunogens, eliciting broad neutralization against diverse viral variants.[149] Mosaic nanoparticle vaccines co-displaying heterologous epitopes on self-assembling scaffolds have also shown promise in inducing robust humoral and cellular immunity across multiple lineages.[150] Additionally, CHIKV-specific mRNA vaccines expressing conserved structural and envelope proteins confirm broad cross-lineage efficacy,[71] collectively establishing a versatile framework resilient to antigenic diversity.

Beyond CHIKV, related arthritogenic alphaviruses such as MAYV, RRV, and ONNV share epidemiological and clinical features, motivating pan-alphavirus vaccine development. Leveraging MXRA8, the shared viral receptor, a decoy strategy employing recombinant MXRA8-Fc fusion proteins focuses neutralizing antibodies on conserved binding sites, enhancing cross-neutralization.[3] Co-presentation of E2/E1 ectodomains from multiple alphaviruses on self-assembling nanoparticles or LNP-formulated mRNAs, inspired by mosaic influenza and coronavirus vaccines, holds promise.[150,151] Even as cross-lineage strategies progress, the risk of ADE and hypersensitivity from non-neutralizing antibodies must be managed by focusing immunogens on strongly neutralizing epitopes (e.g., E2-DB), limiting immunodominant non-neutralizing surfaces, achieving durable high neutralization titers, and integrating FcγR-aware functional assays with dose-escalation and, where appropriate, Fc-engineering.[152,153]

Structure-guided antigen engineering, integrated with computational immunology and AI,[154,155] is reshaping CHIKV vaccine design by enabling precise control of antigen conformation and epitope exposure to focus responses on conserved, broadly neutralizing sites.[156,157] Recent advances, exemplified by AlphaFold 3, markedly improve interface modeling for design triage. On the PoseBusters v2 benchmark, it achieved 80.5% success (pocket-aligned RMSD < 2 Å) for protein-ligand docking without pocket specification, substantially outperforming baseline methods (15.9–35.4%). It also excelled in predicting nucleic acid structures, significantly surpassing RoseTTAFold2NA on low-homology RNA ($p = 1.6\times10^{-7}$) and DNA ($p = 5.2\times10^{-12}$) sets. Nevertheless, performance remains constrained in intrinsically disordered/highly flexible regions, multi-state (induced-fit) conformations, and large multi-component assemblies; hence, AF3 hypotheses should be coupled to physics-based refinement and orthogonal experimental confirmation (MD, cross-linking MS, cryo-EM).[158,159] In parallel, reliable protein design still hinges on principles that combine positive with negative design to avoid misfolded states, underscoring the need for evolution-guided constraints and stability engineering.[160] Fc engineering further optimizes effector functions, including ADCC and complement activation, while escape-informed immunogen design anticipates viral evasion, enhancing breadth and durability.[161] Together, these evidence-grounded strategies outline a realistic, testable pathway toward broad and durable CHIKV protection.

Advances in adjuvants and immune modulation transform vaccines from non-specific stimulants into precision tools. Novel adjuvants combine pattern recognition receptor agonists, damage-associated molecular pattern-inducing emulsions, and nanoparticle carriers to promote Th1 and $CD8^+$ T-cell responses, germinal center activity, and antigen cross-presentation. According to recent reviews of human and non-human primate datasets, saponin-based systems (e.g., AS01, Matrix-M) induced approximately 3- to 10-fold higher antigen-specific Th1-polarized $CD4^+$ T-cell frequencies and 2- to 4-fold higher germinal-center B-cell responses compared to non-adjuvanted controls. Concurrently, they elevated neutralizing-antibody GMTs by approximately 5- to 12-fold, an increase that is highly context-dependent.[162,163] Licensed systems such as AS01 and Matrix-M synergistically activate innate immunity and sustain antigen delivery, while emerging platforms facilitate mucosal priming and trained immunity through epigenetic reprogramming.[89] Genetically encoded cytokine/chemokine adjuvants can further augment $CD8^+$ priming (median increases of around 2- to 3-fold) and Tfh/GC programs in preclinical studies, potentially benefiting vulnerable CHIKV-at-risk populations.[77] While adjuvants increase immunogenicity in CHIKV candidates (e.g., alum-adjuvanted VLPs), their licensure remains challenging. Approval of adjuvanted vaccines requires comprehensive CMC documentation (including defined composition, validated potency assays, and demonstrated lot consistency), non-clinical safety assessments (biodistribution, reactogenicity, and immunopathology), and clinical evidence extending beyond neutralization to include standardized reactogenicity profiles, cellular immune durability, and real-world effectiveness with post-authorization monitoring.[164,165] Ultimately, successful adjuvant deployment for CHIKV hinges less on novel chemistry than on auditable quality systems and harmonized evidence standards, ensuring consistent benefit-risk and clinically meaningful protection across populations.

Innovative delivery platforms also address stability and distribution challenges. Techniques such as lyophilization and spray drying improve thermostability and reduce cold-chain dependency, expanding access in low-resource settings.[166] Studies on lyophilized mRNA–LNPs have showed retention of physicochemical properties and in-vivo expression for 12 weeks at 25 °C and ≥24 weeks at 4 °C; in some reports, immunogenicity is preserved for ~6 months at 25 °C with optimized cycles.[167,168] Lipid nanoparticles and other nanocarriers enable efficient targeted mRNA delivery, while long-acting formulations support sustained antigen release for robust T and B cell activation.[169-171] These technologies directly address the issues of limited vaccine stability, short-lived immunity, and logistical barriers in chikungunya control. Yet translation at scale is constrained by manufacturing and cost: the synthesis of ionizable lipids and the tight microfluidic control required for LNP assembly limit throughput and raise cost of goods, while lyophilization, though stabilizing, requires specialized equipment and extensive cycle optimization.[172,173] Addressing these economic and logistical barriers through process innovation is essential to enable equitable access and practical deployment of CHIKV vaccines in endemic regions.

Finally, the COVID-19 pandemic exposed critical deficiencies in vaccine

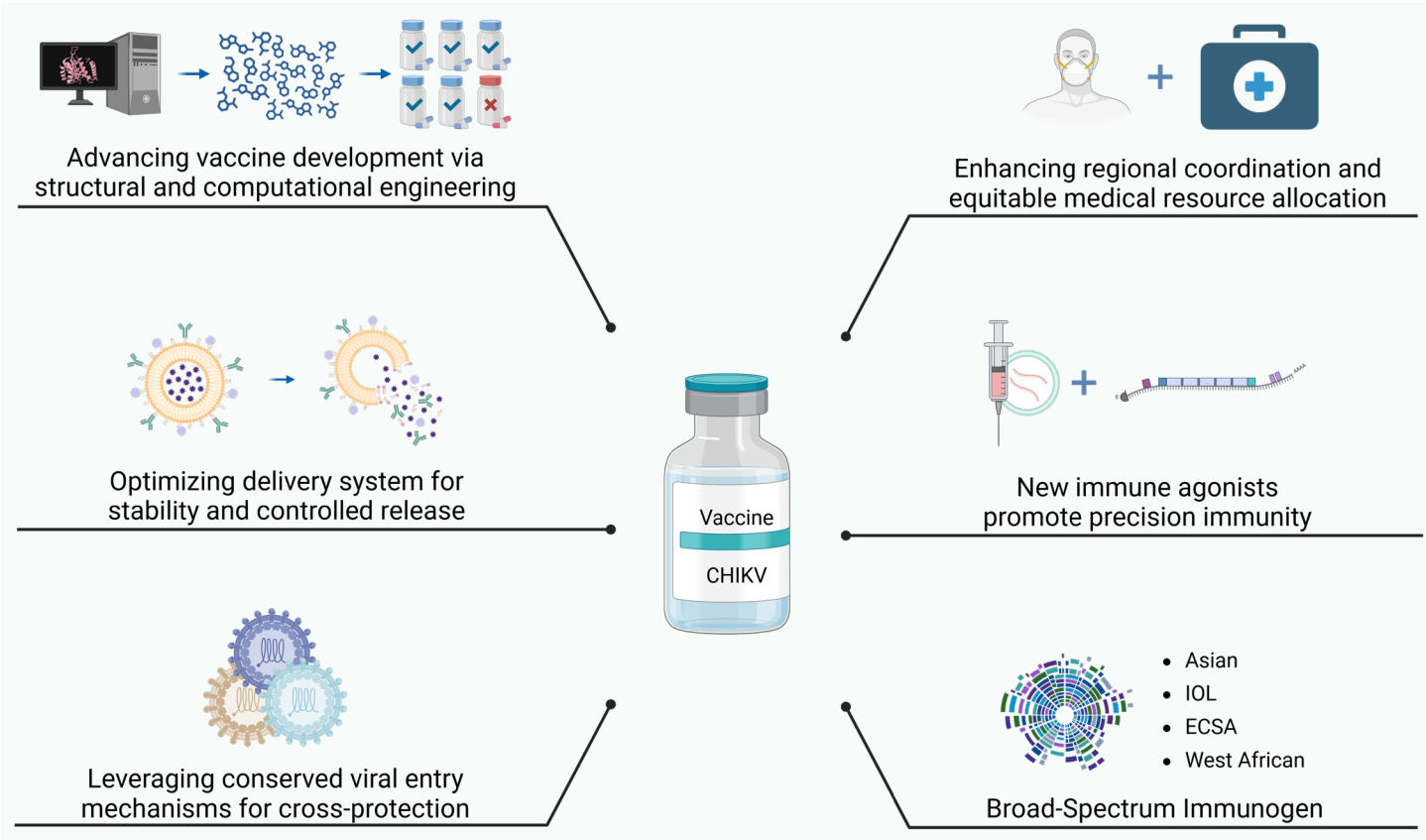

Figure 4. Strategies for broad-spectrum and next-generation CHIKV vaccines Key approaches include designing broadly protective immunogens, developing pan-alphavirus vaccines, engineering optimized antigens via structural and computational methods, using novel adjuvants for targeted immunity, optimizing delivery systems for stability and controlled release, and improving regulatory and equitable deployment pathways.

development systems and global equity, catalyzing reforms relevant to CHIKV vaccines. Vaccine rollouts have revealed high-income biases and regulatory fragmentation that delay evaluations in low-resource settings.[174] Innovative trial designs, such as geospatial cohorts and stepped-wedge studies, now provide timely effectiveness data across diverse contexts.[174,175] Streamlined licensure pathways through regional agencies (e.g., African Medicines Agency) and emergency use authorizations by WHO and European Medicines Agency accelerate access.[176-178] TRIPS-flexible licensing paired with dedicated funds enables local manufacturing capacity.[179] Embedding social vulnerability metrics into allocation frameworks further aligns equity with impact.[175] These advances are critical to optimizing dose scheduling and cold-chain logistics for chikungunya vaccine deployment in endemic tropical regions.

FUTURE PERSPECTIVES

The rapid global spread of CHIKV, along with persistent gaps in understanding its replication mechanisms and the pathogenesis of virus-induced arthritis, highlights the continued need for both basic and translational research. Although vaccines developed from a single CHIKV strain may offer partial cross-protection against other genotypes, emerging evidence indicates considerable differences in infection dynamics, immune response mechanisms, and neutralizing antibody titers across distinct viral lineages.[180] Furthermore, the seasonal co-circulation of CHIKV and dengue virus in many endemic regions suggests that environmental drivers, particularly climate change, may significantly influence outbreak dynamics.[181,182] Taken together, these challenges necessitate coupling virology with eco-epidemiology, pairing near-term vaccine deployment in high-risk settings with lineage-resolved surveillance, and standardizing immunogenicity assays to enable antigenic cartography and data-driven multivalent or engineered updates that counter strain-restricted responses, while addressing assay heterogeneity, genotype-dependent neutralization gaps, and cold-chain/affordability constraints.

In response to these threats, vaccine development efforts are increasingly exploring broad-spectrum solutions. The phylogenetic and antigenic relatedness among alphaviruses, including CHIKV, MAYV, and RRV, has stimulated interest in pan-alphavirus vaccines that aim to elicit cross-neutralizing antibodies targeting conserved epitopes on the E1 and E2 envelope glycoproteins.[3] In parallel, monoclonal antibodies are being investigated as both prophylactic and therapeutic tools, with studies exploring their combination with antiviral agents to enhance protective efficacy and achieve synergistic effects during outbreak scenarios.[183] These approaches, particularly in regions with co-circulating alphaviruses, have the potential to broaden immunity and reduce the burden of infection, provided that breadth-potency trade-offs are actively managed through rational antigen engineering and iterative antigenic cartography.

Innovations in immunogen design are further accelerating next-generation vaccine strategies. Techniques such as mosaic VLPs and chimeric antigens have demonstrated the ability to induce broad-spectrum immunity. Concurrently, AI-driven tools like AlphaFold and deep learning-based epitope prediction algorithms are facilitating the rational design of immunogens.[184,185] For example, structure-based stabilization of conformationally flexible E2 domains has shown promise in improving cross-lineage reactivity, representing a shift from traditional empirical methods toward data-driven vaccine engineering.[124] To translate these advances into public health impact, programs must establish clear milestones, including standardized neutralization assays, cross-laboratory harmonization, and regulator-accepted correlates of protection, to ensure candidates are effective across lineages and populations. AI-prioritized epitopes will furthermore require rigorous validation within these frameworks before regulatory approval.

To ensure that vaccine innovations keep pace with the changing virological landscape, the integration of real-time surveillance and proactive regulatory frameworks is essential. Although CHIKV was not included in the WHO's initial 2015 list of priority diseases with epidemic potential, it was recognized as a serious threat warranting urgent research and development.[186] Since then, WHO has underscored the need for integrated surveillance systems to

track antigenic drift, assess transmission intensity, and inform region-specific immunization strategies. Modeling based on such data is particularly critical in co-endemic regions like Brazil, India, and the Caribbean, where seroprevalence varies considerably.[6] Meanwhile, the global response to COVID-19 has significantly advanced flexible vaccine platforms, including mRNA, DNA, and viral vector technologies.[187] These platforms are now being adapted for arboviruses like CHIKV. For example, Moderna and Gennova are developing mRNA-based vaccine candidates targeting both CHIKV and MAYV. In parallel, thermostable and dry-formulated VLP vaccines are under preclinical evaluation. These formulations offer practical advantages for low-resource settings by eliminating cold-chain dependency. The ideal CHIKV vaccine should offer single-dose efficacy, long-lasting protection, broad safety, thermostability, and scalable manufacturing. Clinical trials of IXCHIQ and VIMKUNYA have shown strong immunogenicity and durable antibody responses, but challenges remain regarding reactogenicity, cost-effectiveness, and limited cross-genotype protection[62,93] —as underscored by the FDA's August 22, 2025 suspension of IXCHIQ's license.[82]

Continued progress will depend on close collaboration among vaccine developers, regulatory agencies, and global procurement organizations. Yet the path to international regulatory harmonization is substantially more complex than simple collaboration. It demands alignment of endpoints and safety datasets across agencies, mutual recognition of lot-release/potency assays to support tech transfer, and pre-agreed master protocols that can activate quickly during outbreaks—lessons shown feasible during COVID-19 but hard to sustain beyond acute emergencies.[188,189] The inclusion of CHIKV in the WHO R&D Blueprint highlights its pandemic potential and the urgent need for sustained investment and equitable access. Development and deployment timelines should therefore be anchored to empirical milestones (e.g., phase transitions, authorizations, and post-marketing safety updates) rather than calendar projections. For VLP and mRNA platforms, supply readiness, pricing for LMIC procurement, and stability at elevated temperatures are now pivotal determinants of public-health impact beyond immunogenicity metrics.

Accordingly, given the limited and heterogeneous nature of existing economic evidence, we did not perform de novo ICER modelling. Instead, we delineate a set of parameters for future evaluations, including setting-specific attack rates and age distributions; vaccine dose price ranges and stability-related delivery costs (e.g., cold chain or ECTC), accounting for wastage; duration of protection and booster requirements; QALY/DALY weights; and programmatic costs. We also summarize the reported parameter ranges where available and highlight key evidence gaps, such as genotype-specific effectiveness, long-term safety in special populations, and real-world delivery costs. These considerations serve as a bridge between the preceding regulatory and operational discussions and the subsequent priority-setting analysis.

Ultimately, CHIKV vaccine development must focus on three priorities: achieving durable and cross-protective immunity, expanding coverage against emerging strains, and delivering affordable, thermostable vaccines at scale, offering a blueprint for preparedness against future emerging viral threats. In practice, this entails defining genotype-resolved serologic targets (e.g., $PRNT_{50}$/ID_{50} across Asian/ECSA/WA lineages) and validating them as correlates, maintaining periodic antigenic mapping with pre-specified bridging criteria to guide strain updates, and aligning procurement price bands with stability specifications (for example, short-term tolerance at ≥40 °C) to ensure equitable last-mile delivery. Operationally, these scientific milestones should be paired with reliance/joint-review pathways, coordinated GMP and official lot-release plans, ECTC-ready labelling, and pharmacovigilance signal-sharing to enable rapid, multi-jurisdictional deployment.

INNOVATION AND LIMITATIONS

This review consolidates advances up to 2025 and delivers a decision-oriented synthesis across all major CHIKV vaccine platforms, alongside an evidence-based appraisal of authorized vaccines (e.g., IXCHIQ and VIMKUNYA). Integrating assay-aware immunogenicity with structural/computational insights, we link immunogen design, adjuvant/delivery, and deployability (manufacturability, thermostability, affordability) into operational steps: standardized cross-neutralization assays with reference sera; genotype-resolved serologic targets; and periodic antigenic mapping with pre-specified bridging criteria. Priority gaps include real-world durability, safety in immunocompromised populations, and lineage-resolved correlates to guide cross-lineage coverage. Notwithstanding these contributions, this review is a structured narrative synthesis based on public and regulatory sources, which limits quantitative precision. Publication bias may skew the evidence base toward optimistic efficacy estimates, a limitation acknowledged in our synthesis despite efforts to include grey literature. While our comparative framework translates evidence into testable research and implementation steps, generalizability and feasibility depend on forthcoming multicenter data, assay harmonization, and regulatory consensus across settings; they should be periodically re-evaluated against pre-specified criteria as clinical and post-authorization evidence evolves.

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X.Z., J.W., and W.Z. conceptualized and designed the review. L.Y., Y.M., and X.Z. drafted the manuscript. Y.L., B.S., Y.Z., Y.Y., Y.S., L.Z., L.L., and X.Z. contributed to figure preparation and participated in manuscript discussions. All authors contributed to and approved the manuscript.

DECLARATION OF INTERESTS

The authors declare no competing interests.

DATA AND CODE AVAILABILITY

No new data were created in this study.

SUPPLEMENTAL INFORMATION

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