Review

Chikungunya Virus Vaccine: An Update Review

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Abstract: Chikungunya virus (CHIKV), a single-stranded RNA virus transmitted by Aedes mosquitoes, poses a significant global health threat, with severe complications observed in vulnerable populations. The only licensed vaccine, IXCHIQ, approved by the USFDA, is insufficient to address the growing disease burden, particularly in endemic regions lacking herd immunity. Monoclonal antibodies (mAbs), explicitly targeting structural proteins E1/E2, demonstrate promise in passive transfer studies, with mouse and human-derived mAbs showing protective efficacy. The article explores various vaccine candidates, including live attenuated, killed, nucleic-acid-based (DNA/RNA), virus-like particle, chimeric, subunit, and adenovirus vectored vaccines. RNA vaccines emerge as promising candidates due to their rapid response capabilities and enhanced safety profile. The review underscores the importance of E1 and E2 proteins as immunogens, emphasising their antigenic potential. Several vaccine candidates, such as CHIKV/IRES, measles vector (MV-CHIK), synthetic DNA-encoded antibodies, and mRNA-lipid nanoparticle vaccines, demonstrate encouraging preclinical and clinical study results. In addition to identifying potential molecular targets for antiviral therapy, the study looks into the roles played by Toll-like receptors, RIG-I, and NOD-like receptors in the immune response to CHIKV. It also offers insights into novel tactics and promising vaccine candidates.

Keywords: chikungunya; prevention; vaccines; epidemiology; RNA vaccines

1. Introduction

The Chikungunya virus (CHIKV), a compact enveloped virus measuring around 60–70 nm, is a single-stranded RNA virus spread through *Aedes* mosquitoes [1]. Moreover, CHIKV infection can also cause neuropathology, especially in infants and the elderly, which can be fatal [2]. Currently,

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real-time PCR identification of viral RNA and serological analysis for the existence of IgM and IgG antibodies forms the basis of laboratory diagnosis of CHIKV infection [3]. Treatment of CHIKV infection involves anti-inflammatory drugs and analgesics, which are inadequate [4]. Despite its increased global and national disease burden, IXCHIQ is the only licensed vaccine and effective antiviral therapy approved by the US FDA to treat or prevent CHIKV infection [5]. The lack of herd immunity in developing countries, which are endemic to CHIKV infection, presents an imminent risk for the spread of large-scale outbreaks. Therefore, it is essential to understand the development of anti-CHIKV immunity through vaccination or passive immunisation techniques [6]. CHIKV is an enveloped alphavirus that enters host cells via receptor-mediated internalisation. The RNA genome of CHIKV encodes four non-structural proteins (nsP1 to nsP4) that are required for virus replication and three structural proteins (Capsid, E1 and E2) together with two small cleavage products (E3 and 6K). The E1 and E2 glycoproteins regulate the entry of viruses into host cells; E1 is involved in the fusion of the virus with the cell membrane, whereas E2 interacts with the receptors on cells and aids in cell attachment [4,7,8]. The E2 glycoprotein has been identified as the primary target for the anti-CHIKV antibody response throughout the illness [3].

Therapeutic monoclonal antibodies (mAbs) offer potential value as an alternate therapy for pre- and post-exposure protection [9]. At present, research on mAb-based passive therapy for arboviruses is at an early stage; a few therapeutic studies on CHIKV mAbs have shown that neutralising antibodies are protective in passive transfer studies and mainly target CHIKV structural proteins E1/E2 [9,10]. Neutralising antibodies raised against E2 protein have shown protection in animal models and murine monoclonal antibodies against E2 [9,10]. Besides mouse monoclonal antibodies, few reports have shown the development of human monoclonal antibodies and their role in protection against CHIKV infection. Scientists also developed Env-specific anti-CHIKV monoclonal antibodies for prophylactic and therapeutic measures against CHIKV infection [3,11]. There is enough evidence in the literature regarding immunogenic epitopes recognised by protective monoclonal antibodies. Using this knowledge, a reverse vaccinology approach can be successfully employed to design a safe and effective anti-CHIKV vaccine [11,12]. Besides the development of monoclonal antibodies, vaccination is another approach for controlling CHIKV infection. Various vaccine candidates are currently being explored for mediating immunity to CHIKV, such as using different types like live attenuated virus, killed vaccines, nucleic-acid-based (DNA/RMA) vaccines, virus-like particle vaccines, chimeric vaccine, subunit vaccines and adenovirus vectored vaccines [13,14]. Live-attenuated vaccines effectively trigger immune responses but carry the risk of virus reversion [15]. Virus-like particle vaccines are safer but mainly elicit humoral responses and are costly. RNA-based vaccines, proven effective during the COVID-19 pandemic, offer a rapid response to emerging infections [13,16]. RNA vaccines can induce robust immune responses with improved safety, making them promising candidates for CHIKV vaccines [17]. RNA vaccine candidates include non-replicating RNAs (nrRNAs) with synthetic modifications, self-amplifying RNAs (saRNAs) and trans-amplifying RNAs (taRNAs), which are derived from positive-sense viruses [13].

E1 plays an important role during membrane fusion, and E2 is responsible for receptor binding. Therefore, E1 and E2 proteins are often selected as immunogens in vaccines. This indicates that CHIKV E2-E1 has an attractive antigenic potential [18–20]. Humoral immunity plays an important role in virus clearance. The viremia can be rapidly cleared in wild-type mice when infected with an attenuated CHIKV strain but not in B cell deficient (μMT) mice. This indicates the direct cleanup effect of virus specific antibodies [14]. Charalambos D. Partidos et al. have developed a live-attenuated CHIKV vaccine (CHIKV/IRES) that is highly attenuated yet immunogenic in mouse models and is incapable of replicating in mosquito cells [21]. They sought to decipher the role of adaptive immunity elicited by CHIKV/IRES in protection against CHIKV and o'nyong-nyong virus infection [21]. Maternal transfer of immunity is crucial for offspring survival [22]. Muthumani K. et al. demonstrated that administering synthetic DNA-encoded antibodies via injection rapidly provided immunity against CHIKV in mice, effectively neutralised various virus strains in vitro and safeguarded mice from lethal infection [23]. Ramsauer K. et al. developed a Chikungunya vaccine using a measles vector (MV-CHIK) that effectively triggers immune responses, even in individuals

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with existing measles immunity. Clinical trial results showed promising outcomes in terms of safety, tolerability, and immunogenicity [24]. Parida M. M. et al. found that Toll-like receptors (TLRs) are crucial in CHIKV's impact on neuronal cells. TLRs are vital proteins in the innate immune system across species, including humans [25]. David B. Weiner et al. formulated a synthetic DNA vaccine to create targeted immunity against CHIKV expressing its envelope glycoprotein. It successfully induced robust immune responses in mice and Rhesus Macaques [26]. Yu Wei et al. developed an mRNA-lipid nanoparticle (mRNA-LNP) vaccine expressing the CHIKV E2-E1 antigen [14]. Their research revealed that this vaccine not only triggered a more potent neutralising antibody response but also elicited stronger cellular immune responses, particularly CD8+ T cell responses, in comparison to recombinant protein antigens, showcasing its enhanced efficacy over recombinant protein CHIKV vaccine candidates [14,27]. Polyclonal and monoclonal antibodies are immunotherapeutics that provide immunity against CHIKV infection. Advances in monoclonal antibody technologies have resulted in diverse antibodies targeting various epitopes of E1 and E2 envelope glycoprotein [11,28]. Recent progress in anti-CHIKV monoclonal antibodies, especially those showing efficacy in preclinical models or clinical trials, suggests their potential for a new therapeutic approach [11,28]. These antibodies, directed at different CHIKV epitopes, also contribute to the design of subunit vaccines [11,28]. The research explored the impact of chikungunya and mayaro viruses on cellular immune responses by identifying genes that initiate antiviral pathways, such as Toll-like, RIG-I, and NOD-like receptors, and also induce Eotaxin and IL-6, revealing potential molecular targets for antiviral therapies addressing inflammatory responses [29]. Other immune-regulating and pathogenic pathways, such as NFKB, T-cell receptor, TGF beta, MAPK, PI3K-Akt, B-cell receptor, Natural Killer cell-mediated cytotoxicity, and Apoptosis, could serve as potential alternative antiviral targets or biomarkers for CHIKV infection [30–33].

2. Epidemiology of Chikungunya

The CHIKV virus poses a significant health threat to both individuals and their communities. Its impact includes acute symptoms such as arthralgia, rash, fatigue, fever, and myalgia [34]. Regions with a high prevalence of dengue, like urban centres in Africa and Asia, experience dual outbreaks of CHIKV [35]. For instance, in Lamu, Kenya, over 70% of the island's population was affected in the first outbreak, followed by another outbreak in the Union of Comoros in January 2005, where more than 63% of the population totalled 225,000 [36]. India experienced its initial chickenpox outbreak in 1963; the second significant outbreak occurred in 2006. During the 2006 epidemic, the national burden of CHIKV was estimated at 25,588 daily, with Karnataka contributing 55% to the national burden [37]. In 2015, 43.15% of clinically diagnosed dengue patients were positive for the CHIKV virus, surpassing the confirmed dengue cases in laboratories [38]. CHIKV can impact life quality by causing post-infection symptoms like rheumatism, which affects joints and exacerbates pre-existing chronic inflammatory rheumatism. In France, 57% of individuals experience rheumatic pain 15 months after CHIKV infection [39]. In 2014, 38 million Americans experienced chronic inflammatory rheumatism [40]. During this epidemic, Viremic travellers introduced CHIKV into non-endemic countries, leading to local transmission in several nations, such as Italy, France, New Caledonia, Papua New Guinea, Bhutan, and Yemen [41]. Three different genetic forms of the CHIKV virus are identified: West African, East/Central/South African (ECSA), and Asian variants. Since 2004, an epidemic has spread in tropical and sub-tropical areas worldwide, including Africa, Asia, Europe, the Pacific islands, and the Americas. The outbreaks are linked to ECSA or Asian genotype viruses, and occasionally both, depending on the region [42]. CHIKV virus emerged as a worldwide health concern over the past two decades. While its mortality rate is low, there is a higher incidence of long-term disability, posing a significant health risk [43].

3. Immunology of Chikungunya Virus

A vaccine must trigger both humoral and cell-mediated immune responses to prevent reinfection fully. T-cell epitope-based vaccine design identifies virus-specific immune triggers for targeted vaccine development [44,45]. Immunoinformatics aids in identifying key virus epitopes,

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expediting research, and saving resources [2]. CHIKV's proteome to predict immunogenic regions for vaccine development and potential drug targets for treatment, aiming to guide future lab efforts against CHIKV. (5-II) The protection afforded by antibodies could be attributed to their capacity to neutralise CHIKV directly and to induce other protective immune responses, such as antibody-dependent and complement-mediated cellular cytotoxicity [21,46]. Effective protection against persistent arthritis in natural CHIKV infection involves crucial contributions from IgG antibodies, particularly IgG3 for neutralisation, while IgM complements IgG in immune responses; however, a discrepancy in IgG levels poses a challenge to achieving optimal protection [3,47]. IgM antibodies offer short-term protection in the early phase, and neutralising antibodies is vital in preventing symptomatic CHIKV infection by identifying specific epitopes on CHIKV glycoproteins [48,49]. The presence of circulating CD8+ T cells was associated with the acute phase of infection, whereas CD4+ T cell responses develop at a later stage of infection [21]. Humoral immunity has been identified as a potential immune correlate of protection against CHIKV infection. Many CHIKV vaccine candidates are currently being developed to generate long-term humoral responses. Clinical trials on these various vaccine candidates demonstrate the role of humoral immunity in CHIKV infection management [50]. A single dose of the live-attenuated CHIKV/IRES vaccine effectively triggered T cell activation, reaching its peak on the 10th day post-immunization. It induced memory CD4+ and CD8+ T cells producing proinflammatory cytokines (IFN-γ, TNF-α, and IL-2) upon CHIKV/IRES restimulation [21]. Passive immunisation with anti-CHIKV/IRES immune serum provided protection, establishing a minimum protective neutralising antibody titer. The CHIKV/IRES vaccine generates both humoral and cellular immune responses, with humoral immunity being the primary mediator of protection during the acute phase of CHIKV infection, followed by the activation of adaptive immunity [51]. CHIKV/IRES elicit a strong neutralising antibody response consisting of all IgG isotypes detected in the serum [21]. Parida M. M. et al. showed increased activity in specific genes and cytokines significant up-regulation of TLR3, TRAF-6, TICAM-1, MCP-1, CXCL-10, IL-6, IL-4, ISG-15, MX-2, IFN-β, OAS-3 genes related to the immune response in mice brains infected with a virus, resulting in the clearance of the virus by day 9–10 [52]. Using Poly I: C, a compound that activates immune responses, protected mice from the virus by enhancing the activity of certain genes, suggesting its potential as a preventive treatment against the virus [53,54]. Type I IFN is vital for regulating viral replication. Still, it is not adequate for the full elimination of CHIKV, as the virus persists in tissues even after IFN levels normalise, emphasising the crucial role of adaptive immunity, where T cells and antibodies, particularly those from memory B cells, play a significant role in providing long-term protection [55,56]. The highest levels of certain proteins (CCL-2, KC, CCL-4, RANTES, IL-6, IL-10, CSF-3) in the bloodstream and gene expression (CCL-2, CXCL-10, CXCL-11) along with IFNγ, IL-10, STAT-1, SOCS-1, and CSF-3 suggest a strong immune response during the peak viral load [57]. When symptoms appeared, there were elevated levels of IL-2, IFNg, IL-17, CCL-3, IL-1b, eotaxin, IL-9, and CSF-2 in the blood, and an increase in the expression of genes linked to pro-inflammatory responses in the affected tissues, mainly favouring Th1 immune cells [52,57]. Chemokines like CXCL-10, CXCL-11, CCL-2, and CCL-5 showed increased levels initially but decreased significantly during symptoms. CCL-3 peaked during symptoms. Receptors like CXCR-3 and CCR-2 were upregulated during incubation, with CCR-2 peaking during this phase and CXCR-3 during symptoms [57–59]. The increased expression of T cell and macrophage surface markers aligned with higher CXCR-3 and CCR-2 levels, suggesting their role in immune cell movement to the infection site [57,59]. Th1 cytokines like IFN-γ peaked during incubation and stayed steady through the symptomatic period. Additionally, IL-2 and TBX-21, crucial for CD4 cell commitment to Th1, peaked during symptoms. IL-15, IL-18, and IL-12, other Th1-stimulating cytokines, peaked early and declined sharply by the symptomatic phase [57,60,61]. (6-II) During the incubation phase, there was a high level of Th2 cytokines (IL-4, IL-10, IL-6), which decreased significantly when symptoms appeared [57,60–62]. During the symptomatic phase, there was a peak expression of pro-inflammatory cytokines such as NoS-2 (iNoS), TNF-α, Il-1α, IL-1β, and COX-2 (PTGS-2), CCL-3, which were significantly up-regulated [57,63,64]. Cell surface antigens such as CD3, CD4, CD8, ICOS, CD40Lg, H2Ea, and H2Eb1 were notably increased during the symptomatic phase compared to the

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incubation period, indicating a surge in T cell presence [57,65,66]. The MHC class II marker H2Eb1 showed higher levels during recovery than in the symptomatic phase, while other T cell antigens decreased slightly during recovery [57,67].

A recent study found that during peak viral load (Day 3PI), there were high levels of CCL-2, IL-6, and IL-10 locally and in the bloodstream, similar to what was observed in human studies. In mouse models, CCL-2 seems to play a role in attracting immune cells (monocytes/macrophages) to the infection site [68,69]. Additionally, there was an increase in Keratinocyte chemoattractant (KC), similar to human IL-8, at peak viral load [70]. These findings suggest that during peak virus levels, a response triggers both inflammatory and counter-inflammatory responses to IFNγ, with IL-10 likely playing an essential immunomodulatory role [57]. Identifying CXCL-10 as a potential biomarker for CHIKV severity in humans and its relevance as a drug target emphasises the usefulness of a mouse model in studying CHIKV infection [58,64,71]. Additionally, results indicate a strong IFNγ program associated with upregulating specific genes during peak virus load. This activation of the STAT-1 pathway differs across diseases like rheumatoid arthritis, inflammatory myopathies, and osteoarthritis due to variations in IFN expression [72–74]. Elevated CD3+ CD8+ cells in early disease stages imply a role for activated cytotoxic T lymphocytes in clearing CHIKV-infected cells. The study suggests tissue-specific functions for CD40L expression and highlights the potential influence of CD40-CD40L interaction on immune response [75–77]. It also discusses the suspected involvement of activated T cells with skeletal muscles in idiopathic inflammatory myopathies [78,79]. Additionally, it confirms earlier findings of peak CCL-2 and IL-6 levels during peak viral load, highlighting an early innate immune response while indicating consistent local high expression of IFNγ and TNF-α during incubation and symptomatic phases, suggesting their role in antiviral/pro-inflammatory response [68,69,80]. Notably, unlike the therapeutic effect seen in IIM, alphavirus infections show increased viral titres and worsened myositis with anti-TNF drugs [57,81].

The rise in mRNA levels of specific chemokines (CCL-2, CXCL-10, and CXCL-11) and their respective receptors (CCR-2 and CXCR-3) [82]. This points to the importance of CCR-2 in recruiting innate immune cells like blood monocytes and NK cells during the early peak of viral load [82]. Conversely, CXCR-3 is crucial in attracting CTL and Th1 cells at a later symptomatic stage. Animal models showed IFNγ-induced CXCL-10 expression and an IL-10 response, indicating potential common inflammatory pathways in acute viral myopathies [57].

During the peak of viral load, specific immune signals showed a notable increase, pointing towards a Th1 response. This response involved heightened activity of specific molecules and cells, like CXCR-3, TBX-21, and IFNγ, alongside elevated levels of cytokines such as IL-2, IFNγ, and IL-17 [58,83]. Interestingly, the presence of specific antibodies supported this immune reaction. Additionally, the study noted that NK cells played a significant role in boosting IFNγ levels early on, while T cells joined the immune response later. Specific inflammatory markers surged throughout the illness, indicating their pivotal role in chikungunya's progression [84,85]. The balance between pro and anti-inflammatory molecules appeared crucial in determining disease severity. Notably, a key chemokine, CCL-3, important for activating CD8 T cells, peaked during the symptomatic phase, hinting at its involvement in the adaptive immune response [86–88]. (6-II) Temperature influences the immune response in Aedes aegypti infected with the chikungunya virus. The study revealed that temperature-dependent variations occur in pathways such as Toll, Imd, Jak-Stat, siRNA, and apoptosis, indicating a modulation of innate immunity during CHIKV infection in *Aedes aegypti* [89].

Pattern Recognition Receptors (PRRs), including Toll-like receptors (TLR), NOD-like receptors, RIG-I-like receptors, and C-type lectin receptors, are vital components of the innate immune system, responsible for detecting various pathogen-associated molecular patterns and defending the host organism against bacteria, viruses, and fungi [29,90–92]. TLR activation leads to the expression of cytokines and other genes involved in immune response, NOD-like receptors leading to the activation of pro-inflammatory caspases, and RIG-like receptors recognise specific genetic fragments in the cytosol, typically double-stranded RNA or single-stranded RNA [29,92]. All three pathways ultimately result in the expression of immune-related genes like cytokines, chemokines, interferons,

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or ISGs [29]. Recently, a cytoplasmic sensor protein (cGAS) was identified that detects double and single-stranded DNA during viral infections, triggering an interferon type I response [93].

Understanding innate and adaptive immunity mechanisms aids in comprehending these infections' pathogenesis and identifying potential therapies due to the lack of treatment. Depletion of interferon receptors has led to more severe disease in mice. Interferon expression, particularly IFN-α, is triggered by various pathways such as RIG-I, MDA-5, and TLR upon Alphavirus infection. However, in the study, IFN-β remained unchanged, while IFN-α was expressed following MAYV and CHIKV infections [29]. The virus multiplies within cells, generating new viral proteins, with MHC class I presenting antigens to T CD8+ cells for targeted cell destruction and MHC class II activating T CD4+ cells to influence immune responses through cytokines, controlling infection and inhibiting viral replication [67,86,94]. Research indicates importance of molecular mimicry in CHIKV induced arthritis, revealing shared immune epitopes with human proteins linked to arthritis, such as FLT1, KDR, TIE1, PADI4, FCRL3, PTPN22, and CSK, and suggesting that antibodies targeting these epitopes may contribute to autoimmune responses in CHIKV infection, particularly in the context of arthritis, urging further exploration with suitable animal models [95].

Mario Perkovic et al. developed CHIKV vaccine with trans-amplifying RNA (taRNA), comprising two RNAs. One is a non-replicating mRNA encoding CHIKV nonstructural proteins, and the other is a trans-replicon (TR) RNA encoding CHIKV envelope proteins [13,96]. When amplified by the replicase, the TR-RNA induces a robust immune response with high protein expression. The vaccine elicited strong CHIKV-specific immune responses in a mouse model and protected against a high-dose CHIKV challenge infection. taRNAs as a promising and safe vaccination strategy for CHIKV infections [13]. Depleting IFN-γ-producing CD4+ T cells reduces joint swelling in CHIKV-infected mice. Still, both CD4+ and CD8+ T cells are crucial for the efficacy of a cytotoxic T-lymphocytes (CTL)-based vaccine against CHIKV, highlighting the challenge of developing a comprehensive vaccine that induces protective antibodies and appropriate T cell responses [14,97,98]. Recent scientific research indicates that mRNA vaccines hold the potential for effectively combating viruses such as HIV, Zika, dengue, and influenza by inducing robust cellular and humoral immune responses without the need for adjuvants [99–103].

4. Chikungunya Vaccine Landscape and IXCHIQ Vaccine Development

Alphaviruses, including CHIKV, have been under vaccine development for years, with CHIKV vaccines progressing from pre-clinical stages to promising clinical trial assessments [104,105]. The virus's genomic structure, with different lineages, has been crucially identified through whole genome sequencing. The complete CHIKV genome sequencing has revealed the existence of four lineages: West African (Waf), East/Central/South African (ECSA), Asian, and Indian Ocean Lineage (IOL) [106]. The historical context highlights the ongoing need to address the virus's changing nature, leading to the development of vaccines that show promise in clinical trials. The IxChiq vaccine, the first approved by the USFDA, is specifically designed to target common antigens of the CHIKV virus found in various strains [107]. Efforts are underway to create a vaccine for the disease CHIKV. Various types of vaccines, such as live-attenuated, virus-like particles, and mRNA vaccines, are in the testing phases to determine their safety and effectiveness in preventing CHIKV infection [108–111].

Developing a CHIKV vaccine faces obstacles such as the virus's genetic diversity, making it challenging to create a vaccine that covers various strains. Research in Mexico and Brazil reveals numerous mutations and distinct lineages, complicating vaccine design [112]. During the CHIKV virus outbreak in Mexico from 2014 to 2016, extensive genetic variability was observed, revealing 70 non-synonymous mutations in the NSP3, E1, and E2 genes [112,113]. Understanding the spread dynamics and evolutionary history is crucial for developing effective vaccines that can combat the diverse strains of CHIKV [114,115]. The complex immune responses to CHIKV, safety concerns, regulatory hurdles, and the virus's RNA nature further complicate vaccine development [17,116]. Limited understanding of the required long-term immune response, high costs, resource limitations, and challenges in clinical trials add to the difficulties [113,116,117]. Ensuring the safety of CHIKV

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vaccines, especially in vulnerable populations, is a crucial aspect of vaccine research. Global focus and market forces tend to prioritise diseases affecting wealthier or larger populations, leading to more attention and funding than those impacting developing regions, such as CHIKV in tropical areas [116]. Despite these challenges, ongoing efforts aim to overcome these obstacles and bring a safe and effective CHIKV vaccine to the market, with promising candidates in preclinical and early clinical stages [17]. Vaccine development opportunities arise from advancements in platforms like mRNA and viral vectors, which offer innovative avenues for CHIKV vaccine research as shown in table 1 [17,118]. Increased understanding of immune responses to the infection allows for designing vaccines that induce solid and lasting protective immunity. The global collaboration among researchers and organisations and the potential public health impact of a CHIKV vaccine.

IxChiq has been chosen as a vaccine candidate against the CHIKV virus because it targets shared antigens across different virus strains, offering broad-spectrum protection [119]. Preclinical studies indicate that IxChiq can induce a robust and lasting immune response with an acceptable safety profile [120]. Given the urgent need for an effective CHIKV vaccine and the global impact of outbreaks, IxChiq emerges as a promising candidate for further development.

Clinical Studies: Ixchiq's efficacy relies on immune response data from a U.S. clinical study involving individuals aged 18 and above. The study compared the immune responses of 266 vaccinated participants with 96 who received a placebo. The antibody levels assessed were determined to be protective in non-human primates, and almost all vaccine recipients reached this protective antibody level in the study. After reconstitution, a clinical study was conducted by administering a 0.5 mL single dose of IXCHIQ through intramuscular injection. Pregnancies carry inherent risks, such as congenital disabilities and miscarriage. No sufficient and well-regulated studies on IXCHIQ in pregnant individuals exist, and the limited human data from clinical trials are insufficient to determine potential risks during pregnancy. However, a rat study administering a single human dose of IXCHIQ before mating and during gestation showed no harm to the fetus or adverse effects on post-natal development [107,121].

The safety of IXCHIQ was assessed in two clinical studies involving 3,490 participants aged 18 and older in North America. Study 1, a randomised, double-blinded, placebo-controlled trial, included 3,082 participants receiving IXCHIQ and 1,033 receiving a placebo. Study 2, a non-placebo-controlled study, involved 408 participants receiving IXCHIQ. Among the 4,523 participants across both studies, demographics included 54.7% females, 80.1% Whites, 14.0% Blacks, 1.9% Asians, and 17.2% Hispanics or Latinos. Solicited adverse reactions were collected for the first ten days post-vaccination, and unsolicited adverse events were monitored up to 6 months post-vaccination. Haematology parameters were assessed at specific intervals in a subset of participants from Study 1. These findings underscore the need for caution in comparing adverse reaction rates between different vaccines and highlight the diverse demographic representation in the studies [121,122].

Preclinical Studies: In a study involving female rats, a complete human dose of IXCHIQ (0.5 mL) was given through intramuscular injection twice – 14 days before mating and on gestation day 6. The study aimed to assess the impact on female fertility, reproductive performance, and pre- and post-natal development. No adverse effects related to the vaccine were observed in fetal development, reproductive performance, and pre- and post-natal development [121–123].

Animal Toxicology and Pharmacology: In a study involving non-human primates (NHPs), human anti-CHIKV immune sera from a Phase 1 study (NCT03382964) were passively transferred. The Phase 1 study administered a single dose of a vaccine with attenuated CHIKV, generating 8 serum pools with varying anti-CHIKV neutralizing antibody titers from Days 14 to 180 post-vaccination. In the passive transfer study, 40 CHIKV-naïve cynomolgus macaques received human anti-CHIKV immune sera (n=5 per group), while six macaques received non-immune control sera. One day post-transfer, serum samples were collected to determine pre-challenge antibody titers. Macaques were then challenged with wild-type CHIKV, and monitoring included assessing viremia and body temperature. Animals receiving postvaccination serum showed no fever post-challenge, while those receiving non-immune sera exhibited fever and viremia. Analysis indicated that a μPRNT50 titer of ≥150 was likely to predict clinical benefit in the Phase 3 study [121–124].

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Table 1. CHIKV vaccine clinical trials are registered on the websites https://www.clinicaltrials.gov and https://www.anzctr.org.au.

Vaccine candidate	Clinical trial status	Intervention	Sponsored by	Collaborator	Clinical trial registration no.	Study Status	Sex	Age	Phase	Enrollment	Study design Allocation: na intervention model	Study type
Pxvx 0317	Completed	Biological: Chikv Vlp, Adjuvanted	Bavarian Nordic	Emergent Biosolutions	Nct05065983	Completed	All	Adult	2	25	Single_Group|Masking: None|Primary Purpose: Prevention	Interventional
Pxvx 031	Recruiting	Biological: Pxvx0317 Vaccine Booster|Biological: Placebo Booster	Bavarian Nordic		Nct06007183	Recruiting	All	Child, Adult, Older_Adult	3	800	Parallel|Masking: Triple (Participant, Care_Provider, Investigator) |Primary Purpose: Prevention	Interventional
Live-Attenuated Chikungunya Virus Vaccine	Completed	Biological: Vla1553|Biological: Placebo	Valneva Austria Gmbh		Nct04546724	Completed	All	Adult, Older_Adult	33	4128	Parallel|Masking: Double (Participant, Investigator) |Primary Purpose: Prevention	Interventional
Vla1553	Not_Yet_Recruiting	Biological: Vla1553	Valneva Austria		Nct06028841	Not_Yet_Recruiting	All	Adult, Older_Adult	3	75	Single_Group|Masking: None|Primary Purpose: Prevention	Interventional
Chikungunya Vaccine	Active_Not_Recruiting	Drug: Bbv87 Chikungunya Vaccine|Drug: Normal Saline	International Vaccine Institute		Nct04566484	Active_Not_Recruiting	All	Child, Adult, Older_Adult	2	3210	Sequential|Masking: Double (Participant, Investigator) |Primary Purpose: Prevention	Interventional
Live-Attenuated Chikungunya Virus Vaccine	Completed	Biological: Biological Vaccine Vla1553	Valneva Austria Gmbh		Nct04786444	Completed	All	Adult	3	409	Parallel|Masking: Double (Participant, Investigator) |Primary Purpose: Prevention	Interventional
Chikungunya And Zika Vaccines	Completed	Biological: Chik Low Dose|Biological: Chik Mid Dose|Biological: Chik High Dose|Biological: Zika Low Dose|Biological: Zika Mid	University Of Oxford		Nct04440774	Completed	All	Adult	11	120	Sequential|Masking: Double (Participant, Care_Provider)|Primary Purpose: Prevention	Interventional

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		Dose|Biological: Zika High Dose|Biological: Saline Placebo									
Vla1553	Not_Yet_Recruiting	Biological: Vla1553 Full Dose|Biological: Vla1553 Half Dose|Biological: Control	Valneva Austria Gmbh		Nct06106581	Not_Yet_Recruiting	All	Child	2	300	Parallel|Masking: Quadruple (Participant, Care_Provider, Investigator, Outcomes_Assessor)|Primary Purpose: Prevention	Interventional
Live-Attenuated Chikungunya Vaccine	Not_Yet_Recruiting	Biological: Active|Biological: Placebo	Butantan Institute	Valneva Austria Gmbh	Nct04650399	Active_Not_Recruiting		Child	3	750	Parallel|Masking: Double (Participant, Investigator)|Primary Purpose: Prevention	Interventional
Chikungunya Vaccine, Pxvx0317 Chikv-Vlp	Completed	Biological: Chikv Vlp/Unadjuvanted|Biological: Chikv Vlp/Adjuvanted|Biological: Placebo	Emergent Biosolutions	Bavarian Nordic	Nct03483961	Completed		Adult	2	445	: Parallel|Masking: Quadruple (Participant, Care_Provider, Investigator, Outcomes_Assessor)|Primary Purpose: Prevention	Interventional
Vla1553	Not_Yet_Recruiting	Biological: Vla1553		Valneva Austria Gmbh	Nct04838444	Active_Not_Recruiting		Adult, Older_Adult	3	363	Single_Group|Masking: None|Primary Purpose: Prevention	Interventional

5. Different Vaccine Platforms and Technologies Used in CHIKV Vaccine Development

Formalin-inactivated vaccines (FIV):

CHIKV vaccines were initially developed in the late 60s using a formalin-inactivated approach at the Walter Reed Army Institute of Research. The study tested vaccines derived from the African CHIKV strain 168 on mice and rhesus macaques. Different cell preparations were used, such as chik-embryo, suckling-mouse-brain, and green monkey kidney cells. The green monkey kidney cell preparation, chosen for its safety, showed good immunogenicity. The CHIKV 168 vaccine and CHIK 15562 provided homologous protection in mice, leading to the evaluation of heterologous protection in macaques using strains from Africa, Asia, and India. Vaccinated macaques demonstrated protection against homologous and heterologous challenges, marking the first successful demonstration of protective efficacy by a formalin-inactivated CHIKV vaccine in pre-clinical models [118,125,126].

Advantages and Challenges: FIV for CHIKV have proven effectiveness in pre-clinical models, a well-established research history since the late 60s, and the ability to choose suitable strains and diverse cell preparations. They demonstrate both homologous and heterologous protection, making them versatile. However, challenges include poor immunogenicity in specific preparations like chick-

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embryo, safety concerns with suckling-mouse-brain preparations, development complexity due to varied cell preparations, and the resource-intensive pre-clinical testing process. Transitioning to clinical testing is crucial for validating safety and efficacy in humans but adds complexity and resource demands [118,125,127].

Chikv Live-Attenuated Vaccines (LAV)

Initially, researchers looked into formalin-inactivated CHIKV vaccines, but concerns over safety and cost led to the development of a live-attenuated CHIKV vaccine in the 1980s. This vaccine, called CHIK 181/clone 25, underwent multiple passages and attenuation processes, proving its effectiveness in protecting mice and rhesus macaques in pre-clinical trials. Manufactured at The Salk Institute-Government Services Division (TSI-GSD), it entered clinical trials in 1986, demonstrating safety and immunogenicity in phases I and II. Notably, 98% of vaccinated individuals developed neutralising antibodies, and a small percentage experienced transient arthralgias. Despite the success of live-attenuated vaccines (CHIK 181/clone 25 & CHIKV TSI-GSD-218), challenges like biosafety concerns and adverse events have led to the exploration of alternative platforms, such as sub-unit vaccines, Virus-Like Particles (VLPs), replication-deficient viral vectors, DNA vaccines, and proteins, which are considered safer but may require adjuvants or multiple doses for enhanced effectiveness. Despite these challenges, the persistence of CHIKV outbreaks has kept the interest and efforts alive in exploring diverse vaccine platforms [128–130].

Advantages & Challenges: Traditional methods raise concerns regarding cost and safety, necessitating Biosafety Level 3 facilities. Newer vaccine platforms, though safer and cost-effective, may require adjuvants or multiple doses for optimal immunity. The development of live-attenuated CHIKV vaccines involves specific cloning, resulting in complete protective efficacy in animal models. Notably, the CHIK 181/clone 25 vaccine provides sterile protection in macaques, and its derivative, the CHIKV TSI-GSD-218 vaccine, demonstrates safety and immunogenicity in human trials. Challenges associated with traditional methods have led to exploring alternatives like sub-unit vaccines and viral vectors, which offer safety advantages despite potentially lower immunogenicity. Ongoing interest in vaccine development is fueled by intermittent CHIKV outbreaks, prompting continuous assessment of new platforms to address evolving challenges. [15,128,131].

Virus-like particles (VLPs)

VLPs imitate the outer shell of a virus using viral structural proteins (Capsid, E3, E2, 6K, and E1) but lack the genetic material needed for replication, ensuring their safety in vaccines. The Vaccine Research Center (VRC) at the National Institute of Allergy and Infectious Diseases (NIAID) has developed a CHIKV VLP, VRC-CHKVLP059-00-VP, composed of structural proteins from the CHIKV strain 37,997 Waf lineage. In preclinical studies with macaques, the vaccine showed immunogenicity, generating immune responses and enabling the control of CHIKV challenges. Produced under Good Manufacturing Practice, the VLP underwent a Phase I clinical trial, demonstrating safety and tolerability in 25 adults. ELISA tests revealed positive antibody responses in all doses, with neutralising antibodies induced after the first vaccination. Following Phase I success, Phase II trials involving 400 healthy adults across multiple locations aimed to evaluate further the CHIKV VLP's safety and immunogenicity [132,133].

Advantages and challenges: VLPs offer benefits and challenges in vaccine development. They are safe, lacking genetic material for replication, and mimic the virus's structure, prompting a robust immune response. The CHIKV VLP vaccine demonstrates immunogenicity in macaques, controlling viraemia and inflammation. Produced under Good Manufacturing Practices, the VLP vaccine (VRC-CHKVLP059-00-VP) maintains high quality. Phase I trials confirm safety, tolerability, and positive antibody responses with no serious adverse events reported, leading to phase II trials for broader safety and immunogenicity [133–135].

Messenger RNA (mRNA) Vaccines

mRNA vaccines, a cutting-edge advancement in vaccine technology, offer a rapid development process by utilising the genetic code of pathogens. Unlike traditional vaccines, which can take months or years, mRNA vaccines instruct the body to produce a virus-specific protein, generating an immune response without causing illness. This adaptable technology allows for quick formulation

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adjustments to target new antigens, enabling the rapid production of high-quality vaccine material. The Pfizer-BioNTech COVID-19 (BNT162b2) vaccine is a notable example of this powerful technique [14,17,136,137].

Viral-vectored vaccines (VVV)

Measles Viral Vector

Developed at the Institut Pasteur in Paris under Frédéric Tangy's leadership, serves as the basis for Viral-Vectored Vaccines (VVV). Samantha Brandler and team created a Measles viral-vectored (MVV) vaccine expressing CHIKV structural genes in 2013. The vaccine exhibited positive results in mice, demonstrating protection against CHIKV in a phase I clinical trial with 42 participants. Subsequent phase 2 trials involving 263 participants showed both low and high doses of the MV-CHIKV vaccine-induced neutralising antibodies with excellent safety and tolerability, expanding the application beyond CHIKV to include vaccines for Ebola and COVID-19 (Astra Zeneca and Johnson & Johnson) [138,139].

Advantages and challenges: Measles viral vector vaccines promise to generate robust immune responses against CHIKV infection with reasonable safety. However, challenges include determining the ideal vaccine dose and schedule, potential reliance on a booster for full effectiveness (100% seroconversion), and assessing long-term efficacy [105,138,139].

Adenoviral Vectors

ChAdOx1-Chik vaccines, utilising a chimpanzee adenoviral vector, are being explored to overcome challenges associated with pre-existing immunity to human adenovirus. The ChAdOx1-Chik vaccine has entered clinical trials to assess safety, immunogenicity, and efficacy against various CHIKV lineages. The passage underscores the significance of establishing a correlate of protection for CHIKV infection, suggesting a potential role for IgG antibodies in clearing the virus [140,141].

Advantages and challenges: Adenoviral vector vaccines, like ChAdOx1, have benefits like overcoming pre-existing immunity and generating strong immune responses without adjuvants. They show promise for cross-protection against various isolates, particularly for CHIKV vaccines. Yet, challenges include the potential reduction in vaccine efficiency due to pre-existing immunity to human adenovirus and the need to identify a protection indicator for CHIKV infection. [140,141].

6. Clinical Trial Data and Safety Profile

As Ixchiq contains a live, weakened version of the virus, it may cause symptoms that mimic an actual infection and headache, fever, fatigue, joint and muscle pain, nausea, and tenderness at injection were reported as side effects of Ixchiq vaccine when two clinical studies of 3500 participants of age 18 years and older were conducted in North America to evaluate the safety of this vaccine. In one of these studies, 1,000 participants received a placebo (Table 2). About 1.6% of vaccine recipients developed severe chikungunya-like ADR that prevented daily activities and required medical intervention, and out of these, two recipients were hospitalised. Some recipients had prolonged chikungunya-like ADR lasting at least 30 days [5,119,123].

Table 2. Clinical Trial Data and safety profile of live attenuated Ixchiq vaccine.

Study	Participants	Vaccine Recipients	Placebo Recipients	Seroresponse Rate (28 days post-vaccination)	Seroresponse Rate (6 months post-vaccination)
1	3500	2500	1000	98.9%	96.3%
2	3500	2500	1000	98.9%	96.3%

- To check the effectiveness of IxChiq, the immune response of 266 participants who received the vaccine was compared with that of placebo-taking participants (96) in a clinical study conducted in the USA in individuals 18 years of age and above [5,119,123].

FDA Approves First Vaccine to Prevent Disease Caused by Chikungunya Virus | FDA

- The vaccine demonstrated a 98.9% seroresponse rate 28 days post-vaccination. This seroresponse was sustained over time, with a 96.3% seroresponse rate observed six months post-vaccination.

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- In a placebo-controlled trial, 98.9% of vaccine recipients met the seroresponse threshold, compared to 0% of the placebo recipients [5,119,123].

For the efficacy of the IxChiq vaccine, the data from these studies suggested high seroconversion rates and a robust generation of neutralising antibodies following vaccination. This high level of efficacy was observed across different geographies and demographics, highlighting the vaccine's broad applicability. Regarding safety, findings revealed that the vaccine was generally well-tolerated, with most adverse events being mild to moderate, such as injection site pain, mild fever, and temporary fatigue [5,119,123]. IxChiq vaccine shows high efficacy and a favourable safety profile (Table 3) [107,119,144,145].

Table 3. FDA approval of Valneva's IXCHIQ brings world's first chikungunya vaccine to market - Clinical Trials Arena.

Phase	Focus	Key Findings
Phase I	Safety and immunogenicity	The Phase I trials were conducted on a few healthy volunteers, and the findings are not publicly available.
Phase II	Safety and immunogenicity	In the Phase II trials, a single dose of IxChiq, a live attenuated vaccine, developed viral resistance in 98% of those tested after 28 days, and 85% still showed resistance after one year. However, 8% of people reported transient joint pain.
Phase III	Safety and efficacy	In the pivotal Phase III data reported in 2022, IxChiq demonstrated a 98.9% (263 of 266 subjects tested for immunogenicity) seroresponse rate at 28 days with a single vaccination. 233 of 242 subjects tested for immunogenicity, seroresponse rates at 28, 84, and 180 days postvaccination were 98.9%, 98.0%, and 96.3%, respectively.

7. Public Health Implications and Regulatory Considerations

Creating a safe and efficient vaccine for the CHIKV virus is essential, as the disease disrupts life by causing increased illness, school and work absenteeism, and financial strain [146]. CHIKV displays the ability to adjust to a different mosquito vector, as noted in the Indian Ocean epidemics [147]. Mutations in A albopictus, compared to mosquitoes at higher latitudes like A aegypti, enhance infection and contribute to outbreaks in new regions, such as Europe [148]. CHIKV infection typically has a low fatality rate, but in impoverished nations like Mauritius, it reaches 2.3 per 1000, suggesting increased severity [149]. Outbreaks may lead to additional diseases like meningoencephalitis in India and fatal encephalitis in Italy and La Reunion. Long-term effects involve persistent joint pain and swelling. CHIKV outbreaks lead to increased costs in medical consultation (47%), hospitalisation (32%), and drug consumption (19%) [150]. These outbreaks result in significant economic losses, particularly in tourist destinations. It is crucial to develop a vaccine for CHIKV. This vaccine is vital in averting epidemics and endemic conditions in various regions. Effective vaccination programs also reduce the number of cases and hospital admissions. Vaccination boosts economic growth in tourist destinations by attracting more visitors, facilitating travel, and enhancing developing nations' health infrastructure and overall economy [151]. In the clinical trials of IXCHQ, it was observed that participants developed a protective antibody level against CHIKV by Day 28 after receiving a single dose of VLA1553 vaccination. This finding suggests that a single intramuscular injection of VLA1553 is effective in preventing CHIKV infection [152].

The World Health Organization (WHO) has two procedures for vaccine approval, which depend on the vaccine's quality, safety, efficacy, and performance. These procedures are the WHO Emergency Use Listing (EUL) and WHO Prequalification (PQ). In the U.S., a vaccine can be approved under the biologics licensure application (BLA) based on demonstrating its safety, purity, and potency [153]. Additionally, there is a European equivalent called compassionate use. The WHO prioritises vaccines listed in the PQ, coordinating with UNICEF and PAHO revolving funds and considering market demand. The vaccines are supplied to different countries following WHO's Strategic Advisory Group of Experts on Immunization (SAGE) recommendations. In December 2021,

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a meeting of National Regulatory Agencies (NRAs) was convened by PAHO, ANVISA, and CEPI to discuss CHIKV vaccine developments and share regulatory experiences from USFDA and EMA [153,154].

8. Future Directions and Challenges

The rapid spread of CHIKV and gaps in understanding its replication and the cause of arthritis persist, and the seasonal occurrence of Dengue and CHIKV suggests a potential need for further studies on the diseases' relationship with climate [155]. Addressing the lack of specific CHIKV treatments involves developing alternative immunotherapies such as anti-CHIKV vaccines and monoclonal antibodies. Research gaps include exploring additional functions of IgG antibodies in natural CHIKV infections and assessing protective antibody responses in different populations [114]. Protective monoclonal antibodies could serve as prophylactic measures, and their potential use with antiviral drugs is expected to grow. Understanding humoral immunity's potential and dissecting ADE mechanisms are crucial for designing effective anti-CHIKV vaccines and ensuring the safety of therapeutic interventions in clinical trials [3]. The USFDA-approved single-dose, live-attenuated CHIKV IXCHQ vaccine marks a significant step forward in preventing pandemics and endemics, but its efficacy proved for individuals aged 18 and above and potentially fatal neonatal reactions from clinical trials remains uncertain [107].

9. Conclusions

The review highlights the ongoing challenges posed by the rapid spread of CHIKV and emphasises the persistent gaps in understanding its replication and the cause of arthritis. The seasonal occurrence of Dengue and CHIKV underscores the potential importance of climate-related studies. Addressing the lack of specific CHIKV treatments requires the development of alternative immunotherapies, such as vaccines and monoclonal antibodies. Protective monoclonal antibodies hold promise as prophylactic measures, and their potential combination with antiviral drugs is anticipated to grow. The recent approval of the CHIKV IXCHQ vaccine by the USFDA represents a significant step in prevention. Yet, challenges regarding efficacy in specific age groups and potential neonatal reactions underscore the need for continued research and vigilance in pursuing effective solutions.

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