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Chikungunya Fever: A Decade of Progress in Epidemiology, Pathogen Diagnosis, Prevention, and Vaccine Development

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ABSTRACT

Chikungunya fever is an acute infectious disease caused by the bite of Aedes mosquitoes carrying the Chikungunya virus. This disease has a high incidence rate and significantly impacts public health. Due to climate change and human activities, the infection and global spread of this virus have attracted widespread attention in recent years. Despite a solid research foundation, challenges remain in diagnosis, treatment, and prevention strategies. This article aims to review the latest developments in Chikungunya virus and vaccine research from 2014 to 2024. It provides an overview of the epidemiological characteristics and pathogenic features of Chikungunya fever and systematically analyzes existing treatment and prevention strategies, with a particular focus on progress in vaccine development, including the clinical efficacy of marketed vaccines and recent advancements in research pipelines. The goal is to provide technical support for the prevention and control of Chikungunya fever.

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Abbreviations: CHIKV, Chikungunya virus; ECSA, East-Central-South-African; NSAIDs, Nonsteroidal Anti-inflammatory Drugs; NsP, Non-structural Protein; qRT-PCR, quantitative Reverse Transcription Polymerase Chain Reaction; VLPs, Virus-Like Particles.

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Introduction

Chikungunya fever is an acute viral disease caused by the Chikungunya virus (CHIKV), primarily transmitted through mosquito bites. Its significant symptoms include high fever and severe joint pain. In recent years, global climate change and increased population movement have contributed to the continuous geographic expansion of Chikungunya fever, making it a significant threat to global public health. According to the literature, the spread of CHIKV often occurs alongside the co--circulation of other mosquito-borne viruses, particularly dengue and Zika viruses, creating complex public health challenges [1,2].

Over the past decade, significant progress has been made in research on Chikungunya fever, particularly in vaccine development. Although there are currently no specific antiviral drugs or widely available vaccines for CHIKV, multiple candidate vaccines are actively being developed using various technological approaches, including live attenuated vaccines, virus-like particle vaccines, and mRNA vaccines[3]. These advancements offer hope for future vaccination efforts and improved disease control.

Climate change is considered a significant factor driving the spread of CHIKV. Changes in climatic conditions, such as temperature and precipitation, can influence mosquito breeding and the virus's transmission capacity. Studies have shown that the spread of Chikungunya fever is closely linked to climatic factors, particularly in temperate regions, where climate change may lead to the northward expansion of CHIKV transmission [4,5]. This implies that outbreaks of Chikungunya fever could occur in previously unaffected areas, placing additional pressure on public health systems.

Moreover, the clinical manifestations of Chikungunya fever often resemble those of other mosquito-borne viral infections, frequently leading to misdiagnosis and missed cases [6,7]. Therefore, enhancing awareness and diagnostic capabilities regarding Chikungunya fever is crucial for controlling outbreaks. As countries intensify their efforts in vaccine development and virus detection, the future control of Chikungunya fever is expected to improve significantly.

With climate change and increased international travel, the globalization of Chikungunya fever is becoming increasingly evident, posing significant challenges to public health. Consequently, Chikungunya fever is emerging as a prominent research focus. By reviewing literature from 2014 to 2024, this article systematically examines

the pathogenic characteristics, treatment and prevention strategies of Chikungunya fever, as well as the latest developments in vaccine research, providing valuable technical support for future studies and control efforts.

Overview of Chikungunya Fever and Pathogen

1. Epidemiological Characteristics

The epidemiological characteristics of Chikungunya fever indicate that the disease has experienced several large-scale outbreaks over the past few decades. Since the outbreak in India in 2005, the spread of Chikungunya fever has rapidly increased, affecting multiple countries worldwide. Since the disease was first reported in the United Republic of Tanzania in 1952, CHIKV has been known to circulate in sub-Saharan Africa, causing sporadic outbreaks[8]. In 2004, an East-Central-South--African (ECSA) CHIKV strain emerged in Kenya and subsequently spread to the Indian Ocean islands, causing unprecedented outbreaks, particularly on Réunion Island [9,10]. The severity of this outbreak led to the emergence of a fourth phylogenetic lineage, known as the Indian Ocean lineage [11].

The trend of CHIKV spread over the past decade indicates that the virus has expanded its transmission from its initial African regions to multiple areas globally, particularly in Asia and the Americas. In December 2013, the Asian lineage strain was first reported on the Caribbean island of Saint Martin, triggering another significant outbreak. The virus subsequently spread to over 50 countries in South America, with conservative estimates of infections reaching 1 million[12]. In 2014, the ECSA lineage strain was reported in northeastern Brazil, where it remains the most prevalent strain[13].

Reports indicate that despite a decline in prevalence in some countries, the emergence of new variants and the expansion of transmission ranges due to climate change continue to pose a serious global threat [14]. Since 2020, significant changes have occurred in the regions where CHIKV is prevalent, particularly in Southeast Asia and South Asia, where new trends in the transmission patterns of viral variants have emerged. The transmission capacity and pathogenicity of these variants may influence the development of public health strategies.

CHIKV is primarily transmitted by Aedes aegypti and Aedes albopictus mosquitoes. These species are widely distributed across tropical and subtropical regions, and climate change is exacerbating their spread, resulting in an expanding range of CHIKV transmission. In particular, warm and humid environments increase mosquito breeding rates, thereby enhancing opportunities for virus transmission. Studies have demonstrated that changes in temperature and precipitation directly affect mosquito survival rates and breeding cycles, influencing the dynamics of CHIKV

transmission [15]. Consequently, the impact of climate change on mosquito transmission capacity has become a critical factor in studying CHIKV epidemiology.

2. Pathogenic Characteristics

CHIKV belongs to the genus Alphavirus in the family Togaviridae and is a single-stranded positive-sense RNA virus with a genome of approximately 11.8 kb, encoding two main structural proteins: the capsid protein (C) and glycoproteins (E1 and E2)[16,17]. A schematic diagram of the viral genome structure of CHIKV is shown in Figure 1.

The viral particles of CHIKV are spherical, with a diameter of approximately 70-100 nanometers, surrounded by a lipid bilayer envelope adorned with glycoproteins that facilitate binding to host cell receptors and mediate viral entry into cells. Based on differences in the viral genome, CHIKV can be classified into several subtypes, including East African, Central African, South African, and Asian types, with the Asian subtype playing a significant role in global transmission [16]. The genetic diversity of the genome enables CHIKV to adapt to various

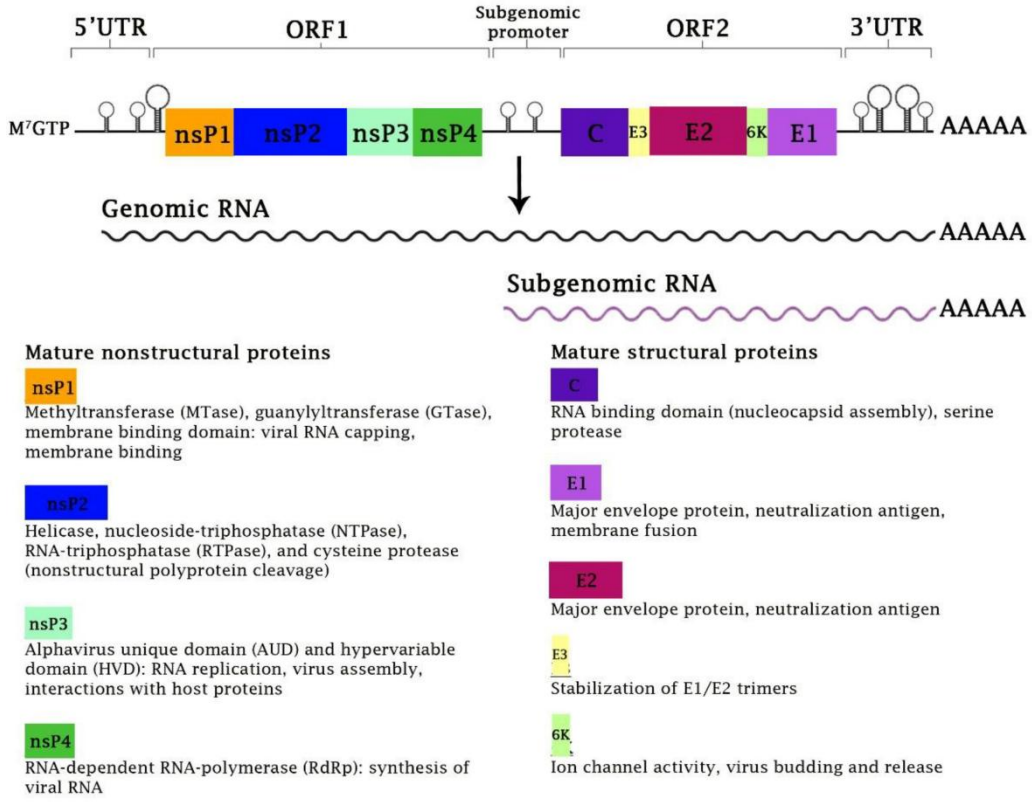

Figure 1: Schematic diagram of the viral genome structure of CHIKV and the main proteins encoded[17]

environments and hosts, thereby influencing its pathogenicity and transmission capacity.

CHIKV enters host cells by binding to receptors on their surface, primarily through the binding properties of glycoprotein E2, and subsequently gains entry via endocytosis. The virus replicates within host cells, utilizing the host's cellular machinery for assembly and release. CHIKV also evades the immune system by modulating the host's immune response; for example, it can interfere with interferon production, thereby inhibiting the host's antiviral defenses[18]. Additionally, the inflammatory response triggered by CHIKV infection may result in chronic symptoms such as joint pain, which can significantly impact patients' quality of life. Understanding these pathogenic mechanisms is essential for developing effective vaccines and treatment strategies against CHIKV.

Treatment, Diagnosis, and Prevention

1. Treatment Strategies

Emergency treatment for Chikungunya fever primarily involves supportive care and symptom relief, emphasizing rest, fluid replacement, and pain relief. Nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly used to reduce pain and fever in patients. Studies have demonstrated that NSAIDs such as ibuprofen and naproxen effectively relieve joint pain and significantly improve patients' quality of life [19].

However, the use of NSAIDs has some limitations, including potential gastrointes--tinal discomfort and renal impairment, especially in elderly patients or those with underlying conditions[16,20]. In dengue--endemic areas, or among travelers to these regions, acetaminophen is the preferred first-line medication for treating fever and joint pain to reduce the risk of dengue hemorrhage.

Moreover, NSAIDs do not act directly on the virus itself, so their effectiveness in controlling the progression of viral infections is limited.

The development of antiviral drugs specifically targeting Chikungunya fever is ongoing, and currently, no approved specific antiviral treatments exist. Researchers are continuously exploring new therapeutic approaches, including small molecule inhibitors, monoclonal antibodies, and RNA interference technology. For example, small molecule inhibitors targeting CHIKV non-structural proteins have demonstrated promising antiviral effects; inhibitors targeting CHIKV non-structural protein 1 (NsP1) have shown antiviral activity by inhibiting viral replication [21,22]. Although these new drugs have shown potential in laboratory studies, clinical trials are necessary to confirm their safety and efficacy.

2. Diagnosis

Early and accurate diagnosis is essential for effective clinical treatment. However, because the symptoms and signs of CHIKV

infection are non-specific, laboratory-based diagnosis is critical. Diagnosing CHIKV based solely on clinical symptoms is particularly challenging in regions where other mosquito-borne viruses, such as dengue and Zika, are co-circulating.

Laboratory tests for CHIKV infection can be performed using various methods, including virus isolation, serological assays [23], and RNA detection through quantitative reverse transcription polymerase chain reaction (qRT-PCR) [24,25]. Among these, qRT-PCR is more commonly used technique to detect viral RNA, especially during the acute phase of infection.

Importantly, the selection of the testing method should be carefully considered based on the test's purpose and the timing of specimen collection, as shown in Figure 2.

3. Prevention and Control Strategies

Chikungunya fever mainly spreads through mosquitoes, particularly Aedes aegypti and Aedes albopictus. Therefore, controlling mosquito populations is a crucial preventive measure against the disease. The most common methods of mosquito control include spraying insecticides and using physical barriers such as mosquito nets. In some regions, regular mosquito monitoring

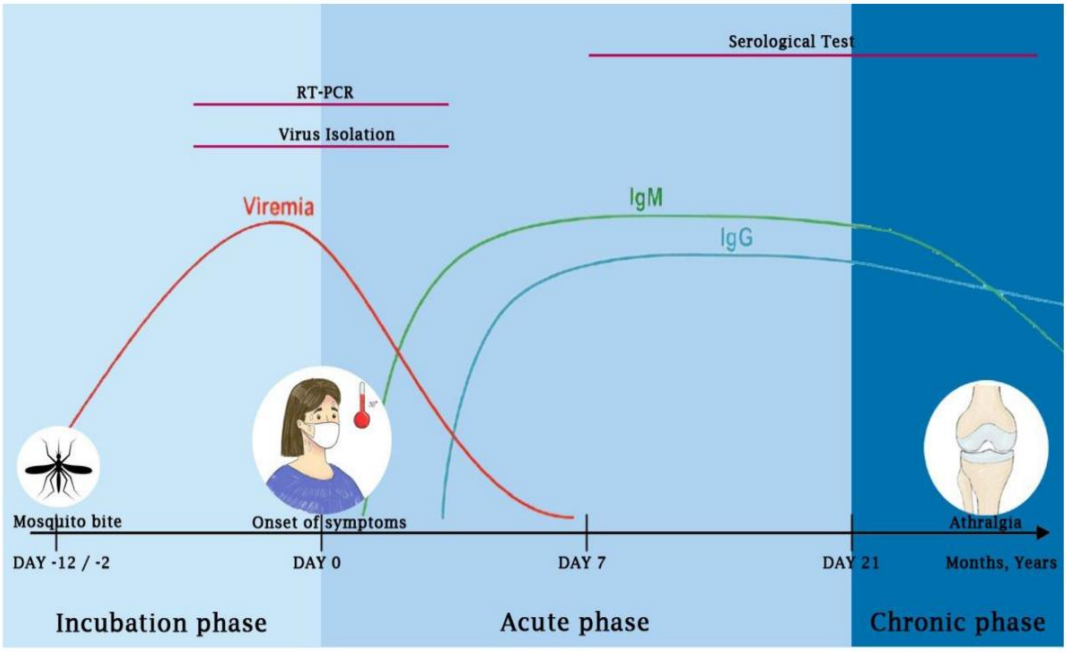

Figure 2. Course of CHIKV infection and its association with different in vitro diagnostic methods[17].

RT-PCR and virus isolation are best performed during the onset of febrile illness when viremia reaches its peak. Serological tests for detecting IgM and IgG are best conducted 7th days after the onset of symptoms.

and control activities have effectively reduced the incidence of Chikungunya fever[26].

Environmental management is a crucial component in preventing Chikungunya fever. Measures such as eliminating standing water and improving drainage systems help reduce mosquito breeding sites and lower transmission risks. Additionally, community--based interventions are important preventive strategies. These include educating residents about Chikungunya fever through community health workers. In some countries, joint educational campaigns by governments and communities have enhanced public awareness and participation in mosquito control, yielding significant results[27].

Personal protective measures should not be overlooked. Using insect repellents is one of the simplest and most effective ways to prevent infection, as they significantly reduce the risk by effectively deterring mosquito bites.

In summary, a comprehensive approach that includes mosquito control, environmen--tal management, and personal protective measures is an effective strategy for preventing Chikungunya fever. In the future, the introduction of new vaccines will further enhance preventive strategies, providing greater assurance in controlling the spread of Chikungunya fever.

Current Status of Chikungunya Vaccine Development

Vaccines, as the most effective preventive measure against viral diseases with a favorable risk-benefit ratio, must elicit both humoral and cell-mediated immune responses to fully prevent reinfection. Since the 1970s, researchers have continuously explored various vaccine platforms to combat this tropical infectious disease, achieving significant progress in vaccine development in recent years[28]. However, the extensive genetic diversity resulting from the virus's wide variation presents challenges in developing a vaccine that provides broad strain coverage.

Currently, the live attenuated vaccine IXCHIQ® (VLA1553) is the most promising candidate. It has completed clinical trials and received FDA approval for use in the United States, making it the only approved vaccine for Chikungunya fever. However, this alone is insufficient to address the increasing disease burden, especially in endemic areas lacking herd immunity[29]. Humoral immunity has been identified as a key immune factor in preventing CHIKV infection. Multiple vaccine development approaches exist, and literature reviews indicate that various CHIKV vaccine candidates can elicit strong humoral responses.

The specific technological approaches for development are as follows:

1. Inactivated Vaccines

The CHIKV vaccine was initially developed using formaldehyde in the late 1960s at the Walter Reed Army Institute of Research. The strain was derived from the African CHIKV 168 strain. The culture substrates explored included chicken embryos, suckling mouse brains, and Vero cells, with the vaccine formulation prepared from Vero cells showing good immunogenicity. The CHIKV 168 vaccine and CHIK 15562 provided homologous protection in mice, followed by good heterologous protection[30,31].

However, the drawback of this technological route is that large-scale cultivation of the Chikungunya virus requires a biosafety level 3 facility, which the vaccine production facilities at that time could not meet, significantly limiting subsequent vaccine translation.

2. Live Attenuated Vaccines

In the 1980s, a vaccine known as CHIK 181/clone 25 demonstrated protective effects in mice and rhesus monkeys following multiple passages and attenuation during preclinical trials. Notably, 98% of vaccinated individuals developed neutralizing antibodies, although a small proportion experienced transient joint pain. Although live attenuated vaccines such as CHIK 181/clone 25 and CHIKV TSI-GSD-218 initially showed success, the development of the CHIKV TSI-GSD-218 vaccine was eventually discontinued[32].

However, challenges such as biosafety concerns and adverse events have prompted the exploration of alternative platforms, including subunit vaccines, virus-like particles (VLPs), and replication-defective viral vectors. Genetic modification of viruses has also become a research focus, such as designing viral genomes to create attenuated live vaccines that ensure both safety and immunogenicity in vivo [33,34].

A genetically modified live attenuated Chikungunya vaccine (IXCHIQ®), also known as VLA1553, has progressed from laboratory development to market approval. Transferring VLA1553-specific serum to non-human primates has been shown to suppress plasma viremia. Identifying a protective surrogate endpoint for VLA1553 is a crucial step toward vaccine licensure. Neutralizing antibody titers against CHIKV are likely associated with protection against symptomatic CHIKV infections and subclinical seroconversion, supporting their potential use as surrogate endpoints for protection [35].

The VLA1553 vaccine achieved sero--protection levels through immunological bridging in seronegative participants 28 days post-vaccination, leading to FDA approval in 2023 for use in adults aged 18 and older in the United States. VLA1553 is also the first vaccine approved for the prevention of adult Chikungunya fever, with accelerated development based on serological surrogate protection markers. The vaccine is derived from the infectious clone of the ECSA-IOL

strain of CHIKV from Réunion Island (LR) 2006-OPY1, which has been attenuated to produce a genetically stable vaccine. A schematic diagram of the vaccine strain construction is shown in Figure 3 [36–39].

3. Recombinant Protein Vaccines

Traditionally, vaccine development requires a trade-off between immunogenicity and safety. Live attenuated vaccines typically provide rapid and long-lasting immunity but have lower safety compared to inactivated vaccines. In contrast, inactivated vaccines cannot replicate, which enhances safety but sacrifices immunogenicity, often requiring multiple doses and boosters. Although the live attenuated vaccines, such as IXCHIQ®, have been successfully marketed, they may still cause symptoms similar to actual infections, particularly in immunocompr--omised populations, including infants.

Recombinant protein vaccines based on virus-like particles (VLPs) utilize viral structural proteins, such as capsid protein, E3, E2, 6K, and E1, to mimic the viral shell while lacking the genetic material necessary for viral replication. This design completely eliminates safety concerns associated with potential viral infections [37,40]. Currently, five CHIKV candidate vaccines based on the VLP approach are under development. All published CHIKV VLP candidate vaccines are produced by transiently expressing viral structural proteins from DNA plasmids or viral vectors, followed by purification of VLPs from the supernatant of transfected or infected cells. The sequences used in these CHIKV candidate vaccines are derived from four different CHIKV strains: 06-49, S27, 37997, and DRDE07 [41].

The recombinant protein vaccine based on virus-like particles (VRC-CHKVLP059-00 -VP) adheres to good manufacturing practices (GMP) and maintains excellent quality. Phase I trials confirmed the vaccine's safety, tolerability, and positive antibody response, with no serious adverse events reported[42]. To further evaluate safety and immunogenicity, Phase II clinical results (PXVX0317) demonstrated that a 20 μg dose (0.5 mL), administered via intramuscular injection into the deltoid muscle at a 28-day interval, was safe and well-tolerated, inducing stable and persistent CHIKV neutralizing antibody titers [43].

4. mRNA Vaccines

With the emergence of new vaccine platforms, the development of vaccines for Chikungunya fever is also advancing. In recent years, innovative platforms such as mRNA vaccines have progressively entered preclinical and clinical trial phases. mRNA vaccines have attracted significant attention due to their rapid development capabilities and favorable safety profiles, demonstrating considerable potential in responding to public health emergencies, such as the COVID-19 pandemic [44].

Currently, mRNA vaccines targeting Chikungunya fever have demonstrated strong immunogenicity in several clinical trials, effectively inducing the production of neutralizing antibodies, such as Moderna's mRNA-1388 [3,45].

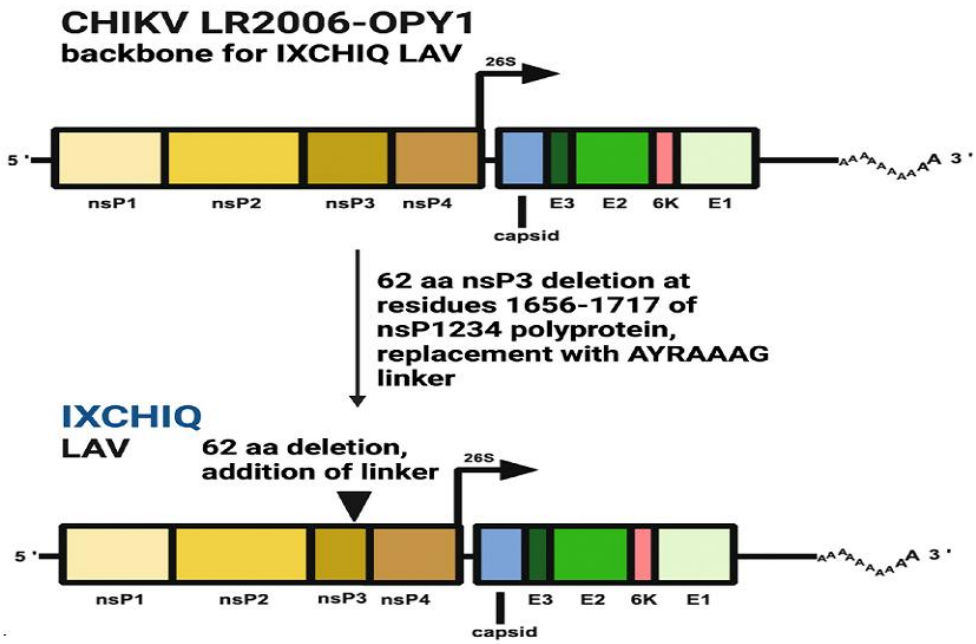

Figure 3. Design of the IXCHIQ live attenuated vaccine [37].

Suzhou Abogen Biosciences Co., Ltd., in China has collaborated with the National Institute for Food and Drug Contol to develop an mRNA vaccine based on the wild-type gene of the CHIKV LR2006 OPY1 strain. Through codon optimization, the cDNA containing the structural protein genes C-E3-E2-6K-E1 was cloned into the plasmid ABOP-028 (GENEWIZ). Results from humoral and cellular immune assays demonstrated that the vaccine could induce high levels of neutralizing antibody titers and T cell-mediated immune responses in mice. Additionally, compared to the wild-type vaccine, the codon-optimized vaccine elicited a stronger CD^{8+} T cell response but lower neutralizing antibody titers [46].

The Jin Xia team at Fudan University developed an mRNA vaccine targeting the E2-E1 heterodimer, demonstrating that the sE2-E1 heterodimer is a more promising antigen than the sE1 or sE2 monomers. The CHIKV E2-E1-LNP mRNA vaccine outperformed the subunit vaccine sE2-E1 by inducing a strong cytotoxic T lymphocyte (CTL) response, although the CD^{4+} T cell response was weaker [47].

5. Recombinant Vector Vaccines

Adenovirus-based vaccine candidates have also shown rapid and durable immune responses. For example, the ChAdOx1-Chik vaccine, which utilizes chimpanzee adenovirus vectors, is being developed to overcome challenges associated with pre--existing immunity to human adenoviruses.

The ChAdOx1-Chik vaccine has entered clinical trials to evaluate its safety, immunogenicity, and efficacy against various CHIKV lineages[48].

Using baculovirus display technology, the CHIKV envelope proteins E1 and E2 are exposed on the surface of baculovirus particles. Employing recombinant baculo--virus as a vector vaccine offers several advantages in production and regulation, including operational safety, ease of high-titer production, non-pathogenicity in mammals, and inability to replicate.

The CHIKV E1 and E2 envelope proteins, along with their native signal and transmembrane sequences, are expressed on the surface of budding baculovirus particles. Immunization of C57BL/6 mice with adjuvant-free recombinant baculovirus induces the production of anti-E2 IgG antibodies, neutralizing antibodies, and specific IFN-γ-producing CD^{8+}T cell responses. A second immunization significantly enhances the antibody response. Mice receiving two doses of the candidate vaccine were fully protected against CHIKV challenge, exhibiting no detectable viremia or clinical signs of disease [49].

Additionally, measles virus vector vaccines have demonstrated strong immunogenicity and protective effects in non-human primates [50].

6. Combination Vaccines for Multiple Mosquito-Borne Viruses

Combination vaccines targeting the Chikungunya virus (CHIKV) and other mosquito-borne viruses, such as dengue virus and Zika virus, have been developed. The advantage of these combination vaccines lies in their ability to simultaneously prevent multiple diseases, thereby increasing vaccine acceptance and coverage [29]. For example, combination vaccines targeting CHIKV and dengue virus have demonstrated promising results in preclinical studies.

In summary, the development of vaccines for Chikungunya fever is progressing rapidly. Existing research data and clinical trial results indicate that various vaccine platforms demonstrate strong immuno--genicity and safety (as shown in Figure 4), offering new hope for controlling the spread and prevalence of Chikungunya fever. As more vaccine candidates become available, a wider range of preventive options will emerge to address the public health challenges posed by this virus.

Conclusion and Prospects

Recent studies show that the geographic range of the Chikungunya virus is gradually expanding, primarily due to climate change and human activities, with the virus's transmission patterns continuously evolving. This expansion significantly increases the risk of viral infection. Over the past decade, research on Chikungunya fever and its pathogens has advanced rapidly, particularly in vaccine development, achieving many important results. These advancements offer

new opportunities for controlling and preventing Chikungunya fever; however, global outbreak trends and challenges posed by viral mutations persist, making the effectiveness and adaptability of vaccines urgent topics for further investigation.

The actual burden of CHIKV is likely underestimated due to the lack of standardized diagnostic tests, the absence of distinctive signs and symptoms, and the overlap of clinical manifestations with other infections, especially in developing countries. CHIKV infection is typically a self-limiting disease with a low mortality rate (~0.1%). However, frequently occurring joint complications can result in persistent disabilities, significantly impacting public health. This includes a major effect on the quality of life (QOL) of infected patients and imposes substantial economic and social burdens [51,52].

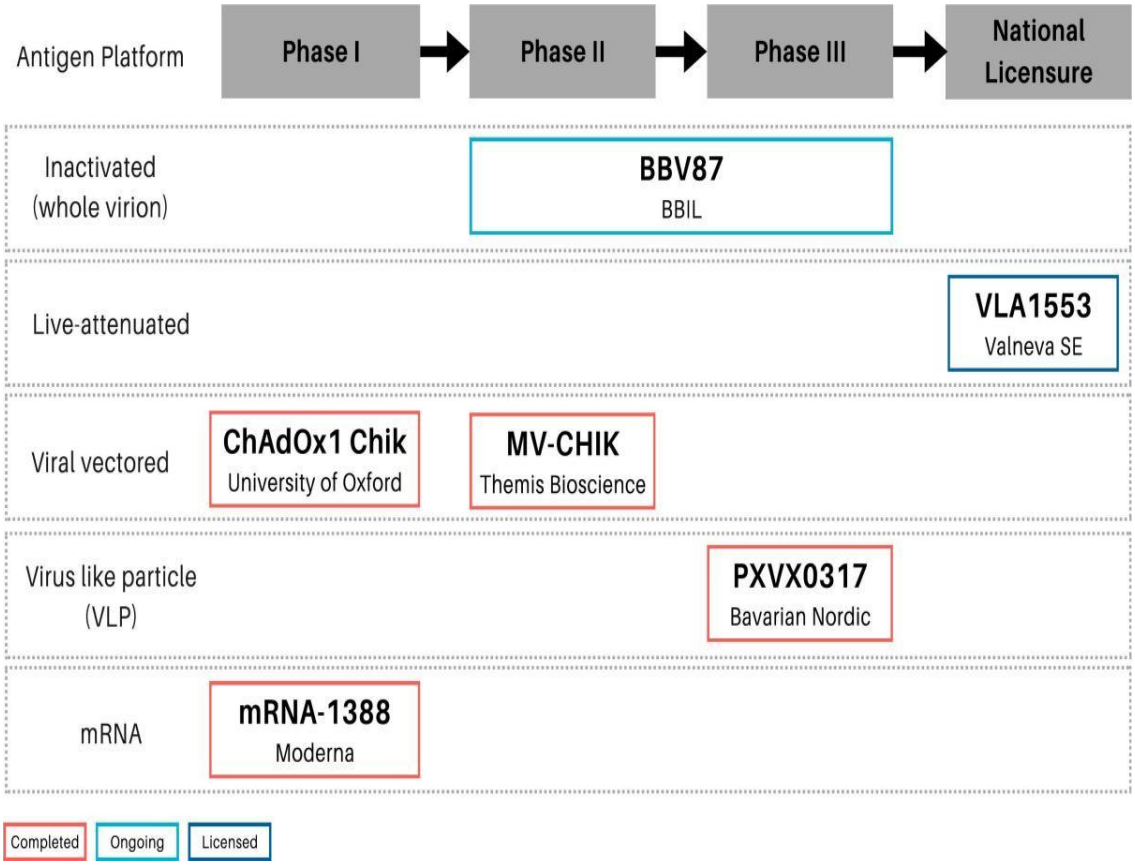

Figure 4: Chikungunya Vaccine Development Progress Chart (Partial, Incomplete) for different technology routes[3]

We cannot overlook the limitations of current prevention and control strategies. The management of Chikungunya fever primarily depends on controlling mosquito vectors, and the sustainability of this approach is influenced by various factors. Research indicates that the lack of effective mosquito control measures, especially in rapidly urbanizing areas, increases the risk of virus transmission[53]. Additionally, the accessibility of existing treatment drugs remains a critical issue, particularly in resource-limited countries and regions, where difficulties in obtaining vaccines and medications may undermine control efforts. Therefore, further exploration of more effective prevention and control strategies and technologies is essential to ensure lasting protection against the threat posed by the Chikungunya virus.

Furthermore, establishing a more open and efficient system for international cooperation will be crucial for the successful development of Chikungunya virus vaccines in the future. Enhancing international data sharing and conducting multi-center clinical trials will help accelerate vaccine development and approval. Vaccine development should not be confined to a single country or region; global collaboration can effectively integrate resources and technologies, thereby optimizing the vaccine development process. For vaccine clinical trials, regulatory agencies across different countries should coordinate the standardization and mutual recognition of neutralizing antibody measurement methods and licensing guidelines. This coordination will expedite the approval processes for Chikungunya vaccines, as well as vaccines for general epidemics and pandemics, ensuring that vaccines can rapidly address global public health needs [54–56].

In conclusion, research on the Chikungunya virus will encounter numerous challenges but also presents significant opportunities. By continuously optimizing vaccine design, strengthening multi--disciplinary collaboration, and enhancing public health response measures, we can achieve more effective disease control and elimination. It is important to recognize that only through comprehensive and systematic research and collaboration can we maintain scientific response capabilities to effectively prevent and control Chikungunya fever amid complex epidemics.

Competing interests

The authors declare all financial and non-financial competing interests.

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