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Review Article

A Review Article On The Chikungunya

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ABSTRACT

Chikungunya, caused by an alphavirus transmitted by Aedes mosquitoes, is an emerging public health challenge marked by acute and chronic musculoskeletal complications. Originating in 1952, chikungunya has evolved to re-emerge globally, with no approved antiviral treatment currently available. The acute phase is characterized by fever and severe polyarthritis, which may lead to persistent joint pain, significantly reducing quality of life and socioeconomic stability in endemic areas. Research efforts have targeted viral polymerase inhibitors like favipiravir, while plant-derived compounds such as berberine show promise in reducing viral load and inflammation. Transmission vectors Aedes aegypti and Aedes albopictus are linked to both urban and rural outbreaks, with the latter associated with a genetic mutation (E1-A226V) that enhances transmission efficiency. Chikungunya presents unique neonatal risks, especially during maternal viremia, and severe cases may lead to chronic rheumatic and cardiac conditions. The pathogenesis of chikungunya involves both hematopoietic and non-hematopoietic cells, with cytokine dysregulation playing a critical role. Promising research includes viral entry inhibitors, live-attenuated vaccines, and Wolbachia-infected vectors. Current challenges remain with comorbidities like diabetes and cardiovascular disease, which worsen disease severity. Early detection, particularly through molecular techniques, is essential for managing outbreaks effectively. This review synthesizes advancements in chikungunya research, covering viral biology, transmission dynamics, and potential therapeutic interventions.

INTRODUCTION

An alphavirus that causes chikungunya spreads to people through the Aedes species mosquito **[1].** In contrast to inflammatory rheumatic illnesses like psoriatic arthritis or rheumatoid arthritis (RA), people with Chikungunya may experience chronic joint pain following an acute infection. Large outbreaks of Chikungunya can have major

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socioeconomic repercussions in endemic nations because people with the disease may have a significantly lower quality of life due to persistent Chikungunya-R rheumatic diseases. The focus is on acute symptomatic care and preventative measures aimed at vector management and avoiding mosquito bites by using repellents, mosquito nets, and protective clothing. There is no specific treatment for Chikungunya.

Virus outbreak: Robinson and Lumsden initially reported the Chikungunya virus disease in 1955, after an outbreak occurred in 1952 on the Makonde Plateau, which is located along the boundary between Mozambique and Tanganyika (present-day Tanzania). There is currently no licensed antiviral treatment for CHIKV infections, despite their global re-emergence **[2].**

Viral polymerase inhibitors: These are among the most effective antivirals used to treat viral infections, including those brought on by HIV, the hepatitis B virus (HBV), the hepatitis C virus (HCV), and herpes viruses. It has been reported that the influenza virus polymerase inhibitor favipiravir (T-705), which is authorized in Japan, prevents the *in-vitro* replication of various CHIKV isolates and shields AG129 mice infected with CHIKV from serious neurological illness.

Berberine: A plant-derived alkaloid called Berberine has been shown to lower the viral load and joint inflammation in mice infected with Chikungunya as well as to prevent the *in-vitro* replication of various Chikungunya strains. It's interesting to note that in Chikungunya-infected cells, Berberine was demonstrated to decrease the activation of the primary mitogen-activated protein kinase (MAPK) signaling pathways. It was discovered that, these pathways were important for the production of infectious virus particles and that they were activated during Chikungunya infection. The entry of Chikungunya into the host cell (by, for instance, flavaglines, obatoclax, and others) may be another target that HTAs block. The only entry inhibitor assessed in a clinical investigation to date is chloroquine, which prevents Chikungunya virus entry *in-vitro* by blocking endosome acidification.

Aedes albopictus: Important viral illnesses spread by mosquitoes, dengue and chikungunya have high rates of death and morbidity **[3].** The primary vector, Aedes aegypti, is typically found in metropolitan areas. Although not as effective, Aedes albopictus has been linked to the spread of CHIKV in rural areas. It has been discovered that the novel E1 alanine to valine 226 mutant CHIKV strain has better Aedes albopictus transmission, since the Indian Ocean Chikungunya epidemic. The big rural and suburban populations are now at higher risk of contracting chikungunya as a result of this. Chikungunya has an extrinsic incubation period of 7–15 days and an intrinsic incubation period of 2–4 days, respectively. However, the novel E1 A226V CHIKV strain has a reduced extrinsic incubation period of only 2–4 days. There have been reports of transmission from mother to child and through blood products. In October 2013, CHIKV was discovered for the first time in the Americas on the Caribbean island of Saint-Martin **[4].** Debilitating joint and periarticular involvement that lasts longer than three months following the beginning of symptoms—months or even years—is classified as chronic. During this stage, joint discomfort may be caused by inflammatory symptoms such as synovitis and tenosynovitis or by mechanical musculoskeletal abnormalities. Enthesopathy may present with a migratory and variable course. A small percentage of patients may experience destructive arthropathies, such as rheumatoid arthritis or psoriatic arthritis. Additional symptoms may include alopecia, headache, pruritus, rash, bursitis, tenosynovitis, neuropathic pain, Raynaud's phenomenon, cerebellar changes, sleep disorders, memory disorders, attention deficits, mood swings, visual disturbances, depression, and

fatigue. In Africa and Asia, Aedes aegypti and Aedes albopictus are the infectious vectors **[5].**

Neonatal chikungunya: It is possible for pregnant women to become infected during their pregnancy. During the first trimester of pregnancy, miscarriage can stop the spread of infection. During childbirth, maternal viremia typically results in the transfer of viruses from the mother to her fetus. The initial reports of transplacental and perinatal infection transmission were related to the Reunion Island outbreak. Etiology was established by serologic testing or real-time polymerase chain reaction (RT-PCR) in 159 pregnant women with clinically evident illness. Thirty of the thirty-five pregnant mothers who were sick at the time of delivery came home with an infected kid. Neonatal chikungunya is a dangerous condition that shares clinical similarities with neonatal dengue virus infection. It has been suggested that CHIKV interacts with local dendritic cells (DCs), such as Langerhans cells, which aid in the virus's propagation to additional target organs such the brain, liver, kidney, heart, and muscles **[6].** It is now widely known that the innate immune system regulates CHIKV infection by utilizing both hematopoietic and non-hematopoietic cells. According to reports, non-hematopoietic fibroblast cells are the primary cell type infected in target tissues (skin, muscle, and joints) in both humans and mice, and they are also vulnerable to *in-vitro* CHIKV replication. CHIKV has also been shown to target monocytes and macrophages, which are implicated in the pathogenesis caused by the virus in both CHIKF humans and animal models.

Uveitis: It is among the most common eye symptoms linked to CHIKV infection. CHIKV has been demonstrated to target fibroblasts of eye tissues, such as the cornea, sclera, ciliary body, iris, and ocular motor muscles, in both mice models and individuals. Patients with poor prognoses can be identified and disease can be monitored because IL-1b, IL-6, and RANTES (Regulated on Activation, Normal T Expressed and Secreted) levels have been linked to the severity of the disease. The second-largest CHIKV transmitter is Aedes albopictus**.** Because of a mutation linked to an amino acid substitution in the encapsulated glycoprotein (E1–A226V), the virus was better able to adapt to the vector and spread more easily. **[7]** This discovery was made in the Indian Ocean lineage, a strain of CHIKV that was prevalent during an outbreak in the Indian Ocean islands. Other mosquito species from around the world, such as Eretmapodites chrysogaster, Culex annulirostris, Mansionia uniformis, Anopheles stephensi, and Opifex fuscus, can also spread CHIKV. The virus enters the bloodstream and skin following a mosquito bite. The virus spreads via the bloodstream to the liver, muscles, joints, spleen, lymph nodes, and brain after first replicating within dermal fibroblasts. 109 copies of the virus per milliliter of blood are found during the first week of infection. Two to ten days following infection may be the duration of the viraemic phase in the vertebrate host. The most typical manifestations include widespread erythema, with or without pruritus, facial oedema, and macular and maculopapular exanthemas. During this acute phase, additional cutaneous-mucosal lesions may also manifest as blisters, vesicles, exfoliative dermatitis, erythema nodosum, hyperpigmentation, photosensitivity, and worsening of pre-existing dermatoses, including psoriasis and oral mucosal ulcers.

Pregnant women: Paracetamol is the first-line treatment for managing chikungunya-related pain in pregnant women, with a maximum recommended daily dosage of 4 grams. Monkeys, rodents, and birds are the virus's reservoir hosts during the inter-epidemic phase **[8].** During epidemics, humans take their position as the hosts. Disease outbreaks in the community have been shown to occur periodically, which is most likely

caused by changes in the immunity of the monkey herd. Urban, nosocomial, vertical, and enzootic transmissions are the recognized routes of CHIKV transmission.

Virus penetration into organs: When CHIKV is present, the virus spreads to several important organs, including the liver, spleen, lymph nodes, skin, muscles, bones, and central nervous system. Innate immune cells, including monocytes, macrophages, neutrophils, natural killer cells, and adaptive immune cells of the CD4 and CD8 T cell lineage, infiltrate these tissues when a virus enters them. Even when the viral load in the blood is low, the virus can persist and multiply for longer in these targeted organs as well as in the macrophages of infected animals. During an acute CHIKV infection, immune cell infiltration causes pathological musculoskeletal symptoms such myositis, persistent active tenosynovitis, and inflammatory arthritis. In CHIKV, it has been demonstrated that infiltrating myeloid cells produce more pro-inflammatory cytokines. The main cytokines and chemokines released by macrophages were tumor necrosis factor (TNF), IFN-α, IL-6, IFN-γ, and monocyte chemoattractant protein-1 (MCP-1). The function of cytokines and chemokines such as IL-1β, IL-6, IL18, MIF, RANTES, CXCL9, CCL2, and CXCL10 has not been well studied. These tests have not been employed in routine clinical practice due to the heterogeneity of these biomarkers in various populations and the absence of validation. Wang et al. used a high-throughput screening system based on the CHIKV 26S-mediated insect cell fusion inhibition experiment to examine the potential of anti-CHIKV medications *in-vitro*. Niclosamide and nitazoxanide were identified as the two chemicals that inhibited the entry and transmission of the CHIK virus among the four tested. This could end up becoming a therapeutic target in the future. There is evidence that suramin, a competitive inhibitor of heparin and glycosaminoglycans, possesses anti-CHIKV properties. Ae. albopictus eggs can survive dry seasons and are more resilient to drying out **[9].** Three separate CHIKV phylogroups (strains), known as the West African (WA), East-Central-South African (ECSA), and Asian genotypes, were identified prior to the La Réunion outbreak by phylogenetic analyses based on both partial (E1 glycoprotein) and whole genome analysis. Analysis of the genomes of CHIKV strains obtained during the 2005 and 2006 La Réunion epidemic showed that a mutant strain derived from the ECSA isolates was the cause of the outbreak.

Bacterial strain: Aliota demonstrated a significant reduction in the multiplication and transmission capability of CHIKV by introducing the wMel strain of Wolbachia pipientis into Ae. aegypti mosquitoes. Comparable findings have been reported for other arboviruses, including as DENV, the Zika virus, and the Yellow Fever virus, which all have Ae. aegypty as a common vector. It appears that the bacterial strain can affect the degree of pathogen reduction. The benefits of live-attenuated vaccines are inexpensive production costs, long-lasting and effective protection, and the need for infrequent administration. TSI-GSD-218, the first live-attenuated CHIKV vaccine to reach clinical trials, was created by cultivating CHIKV 181/clone 25 in cell culture one after the other. It seems to offer a long-lasting and effective immunity. Nevertheless, 8% of the vaccinated individuals experienced minor arthralgia throughout the phase 2 study. After research revealed attenuation instability, raising safety concerns, the candidate was dropped. Comorbid conditions such heart disease, diabetes type I and type II, and hypertension might increase the severity of chikungunya and the need for intensive care unit hospitalizations **[10].**

Diabetes : It can lengthen the duration and severity of chikungunya, and in people with hyperglycemia and diabetes, chikungunya

infection is linked to increasing diabetic symptoms (such as acute complications and poor glycaemic control). Increased morbidity is also linked to the presence of comorbidities. For instance, 1% of patients with chikungunya in a cross-sectional study of an outbreak in northeastern Brazil had chronic kidney disease (among other comorbidities that included diabetes, hematological disorders, liver disease, hypertension, and autoimmune diseases); these patients also had higher mortality rates and higher frequencies of the primary acute manifestations of chikungunya than patients without chronic kidney disease. The activation marker CD69112 is expressed by synovial NK cells (identified by their CD56+ CD3− expression) in patients with chronic chikungunya, and evidence from mouse models indicates that NK cells play a pathogenic role in acute arthropathy. A primary target of CHIKV infection, fibroblasts in connective tissues generate a variety of IFNα subtypes and IFNβ119, cytokines having well-established arthritogenic characteristics 36. Supernatants from CHICKV-infected human synovial fibroblast cells can promote osteoclastogenesis *in-vitro* by secreting RNKL, IL-6, IL-8, and CCL2.

Cardiomyopathy: CHIKV penetrates myocytes and causes direct damage to muscle fibers, increasing the inflammatory response and leading to secondary damage from hypersensitivity and necrosis. These changes can persist for a long time and increase the susceptibility of heart tissue to repeated harm from other microorganisms, which promotes the development of dilated cardiomyopathy rather than myocarditis. The extent of cardiac injury is one of the elements that determines full recovery. Despite the description of pericardial involvement, rhythm irregularities, and other modest consequences, CHIKV-related myocarditis continues to be the most common CV complication. Since the acute presenting phase has a high mortality rate and might lead to persistent dilated cardiomyopathy, early detection is crucial. The diagnosis of chikungunya is determined by the epidemiological setting and clinical presentation. High CHIKV titers are typically present in the blood within the first three to five days after symptom onset, resulting in a viremia that is highly sensitive and specific to RT-PCR detection. For diagnosis beyond this early phase, IgM titration using ELISA-like techniques is commonly employed and recommended; however, cross-reactive antibodies may cause up to 6% of dengue-infected patients to exhibit anti-CHIKV IgM. Treatment for cardiovascular involvement remains controversial, and there is currently no specific vaccine or treatment for chikungunya. Nonetheless, it is widely accepted that treatment should be initiated early in the illness to prevent cardiogenic shock and heart failure. Supportive interventions, including oxygenation, rigorous cardiac monitoring, and inotropic medication as needed, are strongly encouraged. Some of the major emerging infectious illnesses and major health issues facing the globe today are caused by arthropod-borne viruses, or arboviruses **[12].**

Acetaminophen: It is used to treat pain and fever. If additional analgesics are needed, they should be used sparingly. Due to the risk of platelet dysfunction and clinically significant bleeding, some experts caution against the indiscriminate use of corticosteroids and nonsteroidal anti-inflammatory drugs (NSAIDs), particularly aspirin. Furthermore, because dengue infections share symptoms with chikungunya, the CDC advises against the use of NSAIDs due to the increased risk of bleeding. Furthermore, because dengue infections share symptoms with chikungunya, the CDC advises against using NSAIDs due to the risk of bleeding. Malvy et al. examined the cytokine profile of a patient who developed progressive erosive arthritis two years after the commencement of CHIKV infection, both before and four months after receiving MTX

(17.5 mg/week) **[13].** After four months of MTX treatment, the patient's symptoms and radiological results significantly improved. IL-1β, IL-6, IL-8, IL-10, TNF-α, and IFN-γ cytokine levels were higher in lymphocyte supernatants before MTX administration. With MTX treatment, these proinflammatory mediators were significantly decreased. Elevated levels of IL-6 and GM-CSF were shown in a study of the cytokine profiles of 30 patients with chronic CHIK arthritis. Higher levels of proinflammatory cytokines including IL-1, IL-6, IL17, and TNF-α, which are linked to osteoclastogenesis and erosive illness in RA, have also been linked in a number of additional studies to higher severity in CHIK arthritis. There are thirty species of arthropod-carried alphaviruses, often known as arboviruses since they are derived from arthropod-borne viruses, and they all share seven distinct antigenic complexes **[14].** The most common laboratory result is lymphopenia, which is defined as having <1000 lymphocytes/mL3. Leukopenia, raised liver enzymes, anemia, elevated creatinine, elevated creatinine kinase, and hypocalcemia are occasionally observed in addition to lymphopenia. With an average of 107 pfu/mL, the acute stage of CHIKV is known to have a high viremic burden.

CHIKV Cycles: There are two distinct cycles of CHIKV transmission: Sylvatic and Urban. Human-to-mosquito transmission is known as the "Urban cycle," whereas animal-to-mosquito-to-human transmission is known as "Sylvatic transmission". In Africa, the principle method of maintenance is the sylvatic cycle. In more densely populated places, CHIKV is mostly maintained through an urban cycle, where humans serve as the primary hosts and Aedes mosquitoes serve as the vectors. Peripheral tissue infection was shown to reduce in rhesus macaques treated with two monoclonal antibodies, CHK-152 and CHK-166. A DNA vaccine that expressed structural proteins E1–3 had comparable immunogenic effects to those observed in humans following CHIKV infection when tested on rhesus macaques. In environments with limited resources, being aware of this cutaneous characteristic (chik sign) is crucial for making a retroactive diagnosis of cystic fibrosis **[15].** Numerous mucocutaneous abnormalities may be seen, including diffuse hyperpigmentation of the face and extremities, flagellate pigmentation, mucosal hypermelanosis of the tongue and palate, maculopapular rash, aphthous-like ulcers, transient nasal erythema, ecchymosis, vasculitic lesions, and centrofacial freckle-like macules. A few weeks following the febrile episode, the noticeable pigmentation across the nose, known as the "chik sign," appears and lasts for a long time. Chikungunya fever is a major public health concern because of its high rate of morbidity, which can occasionally worsen and develop into a chronic condition **[16].**

Molecular structure: The single-stranded positive-RNA genome of CHIKV is shielded by an icosahedral symmetric capsid, which is encased in a lipid envelope made up of glycoproteins and forms a spherical particle with a diameter of roughly 70 nm. The genome appears as a typical messenger RNA, about 11.8 kb in size, with a poly A-tail at the 3' end and a cap at the 5' end. Two untranslated sections are included in it : a brief one at the 5' end and a lengthy one at the 3' end with direct repetitions. These are believed to be related to the virus's adaptation to the mosquitoes that act as its vectors of transmission to vertebrates. The primary point mutation in the gene encoding the E1 glycoprotein caused the CHIKV to undergo genetic changes during its history, which enhanced the vectors' virulence and transmissibility. It has been demonstrated that Ae. albopictus is more effective at spreading the mutant strain (E1-226 V), which is of genotype IOL and was isolated in 2006 in the French Republic in the Indian Ocean. This strain is descended from the wild genotype ECSA, which is a common ancestor of

E1-226A and E1-98A. This strain possesses a point mutation that results in the replacement of ala-nine for valine at position 226 of the viral E1 gene. This mutation is linked to a reduction in the arthropod vector's reliance on cholesterol for infection. For hundreds of years, alphaviruses and several flaviviruses spread by mosquitoes have been present throughout Africa **[17].** Over the past few decades, these viruses have rapidly resurfaced and spread around the world. The resurgence of these viruses could be caused by a number of factors, including host and viral genomes, vector competence, increasing international travel, fast urbanization, and global climate change.

Recombinant Ross River virus (RRV): In order to investigate the physiopathological causes of alphaviral arthritis, Belarbi et al. created a recombinant Ross River virus (RRV) that expresses a NanoLuc reporter (RRV-NLuc). The near-native replication kinetics and great stability of this reporter virus enable real-time tracking of tissue tropism and viral dissemination *in-vivo*. For the right medical care, a viral infection must be accurately diagnosed. Developing new preventatives and treatments requires a thorough grasp of the fundamental mechanisms underlying disease and host immunological responses. This is especially the case for arthritogenic alphaviral illnesses, which are basically virally-induced self-perpetuating inflammatory processes. Adults with chronic arthritis appear to have a longer type I interferon response **[18].** Less is known about adaptive immunity against CHIKV, which only appears after the first week when innate immunity has stopped viral reproduction. While CHIKV-specific immunoglobulins guard against infection, B and T lymphocytes may also play a role in pathogenesis and chronic joint illness.

Skin pigmentation: Maculopapular rash, intertriginous aphthous-like ulcers, and pigmentary alterations in the centrofacial area are the skin lesions that are most commonly observed. Usually lasting five days, the rash might occasionally be followed by hyperpigmentation. Babies under six months old may have blistering and large bullous skin lesions that cover up to 35% of their body surface area. 9 About 10% of pediatric cases also exhibit hemorrhagic symptoms, such as purpura, gingival hemorrhage, and epistaxis. According to reports, CHIKF is a dengue-like infection that causes fever, rash, arthralgia, myalgia, and occasionally hemorrhagic symptoms in Thailand **[19].** The Madras, India, CHIKV outbreak in 1964, Jadhav et al. provide a thorough description of pediatric CHIKV infection. Eleven of the 33 infants who had a dengue-like disease were hospitalized. Five of the 11 babies had fevers that were higher than 104 °F. Of the eleven babies, ten experienced a macular erythematous rash. Four babies had diarrhea, and one baby had excruciating arthralgia. Two babies suffered from febrile seizures. Subsequent research clarified that CHIKV of the Asian lineage was responsible for the outbreaks in Vietnam and Thailand.

CHIKV-WH : Invading Mexico from 2014 to 2015, CHIKV-WH sparked an outbreak in the Yucatan region in July 2015. A one-month-old baby with a CHIKV-WH infection was brought to the hospital in this instance. He was diagnosed with septic shock secondary to CHIKF after presenting with fever, lethargy, and an erythematous maculopapular rash. Soon after, the baby's perfusion deteriorated, and a ventilator was attached . He experienced deadly septic shock and tonic-clonic seizures a few hours later. In 2013, an Aedes aegypti-vectored strain of the ancient Asian CHIKV virus was brought to the French portion of the Caribbean island of St. Martin and proceeded to spread throughout Florida and South America **[20].** Monoclonal antibodies (mAbs) as a post-exposure treatment for infections caused by the alpha virus. Two recombinant IgG1 human mAbs, 5F10 and 8B10, that target the CHIKV E1/E2 trimer, gave mice a 100% protection rate against a

lethal CHIKV challenge and markedly delayed CHIKV-related motrtality.

Reduced tourism: Due to rising medical expenses and a drop in tourism, which is a vital source of economic growth in many impacted nations, viral epidemics can have a serious long-term effect on a nation's economy. About 300,000 persons were afflicted by the CHIKV outbreak in La Réunion in 2006, which reduced tourism by 60% and resulted in an estimated 44 million euros in associated economic costs. According to estimates, the financial burden of such an outbreak is more than 300 times more than the expenses of taking action. Three traditional symptoms define the acute phase that follows the incubation period: abruptly elevated temperature, rash, and joint discomfort **[21].** Leukopenia, marked lymphopenia, neutropenia, thrombocytopenia, hepatic cytolysis, and increased creatinine kinase and creatinine levels are among the frequent biological abnormalities. Nevertheless, dengue fever is more likely than CHIKV infection to cause thrombocytopenia. Viralemia appears to be linked to a drop in the lymphocyte count. About three quarters of infected individuals tend to have higher levels of acute-phase reactants of inflammation (erythrocyte sedimentation rate, C-reactive protein).

Rheumatic symptoms: The following characteristics are linked to persistent rheumatic manifestations with CHIKV infection: female gender, age over 45, first joint pain severity, underlying rheumatic condition or previously injured joints, and IgG levels. There have been reports of RA, spondyloarthritis, gout, and primarily osteoarthritis as rheumatic conditions that may lead to chronic rheumatic symptoms. Age over 45 years and the severity of CHICKV-induced chronic rheumatism were found to be strongly correlated in the TELECHIK research, a cohort study carried out in La Réunion.

Kenya: A massive CHIKV outbreak in 2004 spread from Kenya's coast to the Indian Ocean islands of Comoros, Mayotte, Seychelles, Reunion, Madagascar, Sri Lanka, and the Maldives, as well as to India, Southeast Asia (Malaysia, Singapore, Thailand), and China **[22].** *In-vitro*, CHIKV has been shown to infect a range of cell lines, including Vero cells (derived from the kidney of a green monkey), BHK21 baby hamster kidney cells, and several insect cell lines. More recently, human cellular tropism was described. In humans, fibroblasts in the muscle, joint capsule, and dermis appear to be the main targets of CHIKV infection. It has also been noted that CHIKV infects human epithelial and endothelial cells as well as muscle progenitors, or satellite cells. The CHIKV virus appears to be resistant to macrophages but vulnerable to lymphocytes and monocytes. Only the major commercial and government reference laboratories should think about routine diagnostic testing for CHIKV until trustworthy kits for molecular detection of the virus and CHIKV antibodies are available, as approved by the Food and Drug Administration. To prove CHIKV transmission in the US, the Centers for Disease Control and Prevention provides facilities for sample testing. This ability is also present in certain state and local health departments as well as other government organizations.

Antiviral medication:

The CHIKV is a commonly used target for many antiviral drugs because its entry and fusion are influenced by a wide range of parameters and, consequently, potential targets **[23].** In several cell lines, the broad-spectrum antiviral medication arbidol also referred to as umifenovir, and its metabolites have been demonstrated to be early-stage inhibitors of CHIKV propagation. By choosing an arbidol-resistant version with an arginine (G407R) mutation found in the viral E2 glycoprotein, a type I transmembrane protein

implicated in the virus's attachment to the host membrane, the method of action was verified. Sulfoxides and tert-butyl esters in indole-based arbidol analogs have shown improved potency and selectivity index.

Suramin: An FDA-approved medication for trypanosomiasis, suramin, is a symmetrical sulfonated naphthylurea chemical that has also been shown in several independent studies to suppress the early stage of the CHIKV replication cycle using both time of addition assays and in silico techniques.

Micafungin: It is a medication licensed by the FDA to treat candidiasis, demonstrated a wide range of inhibitory effects against many alphaviruses, such as SFV, CHIKV, and SINV. The strong antiviral medication amantadine is demonstrated by the 6K protein's potential as a target for antiviral medication development. This FDA-approved anti-influenza medication targets the influenza virus's M2 viroporin, which forms ion channels. Additionally, electrophoresiology studies showed that amantadine changes the shape of CHIKV virus-like particles and inhibits the ion channel function of CHIKV 6K.

NSP4 protease: The most highly conserved protein in the alphavirus family is the nsP4 protease, which acts as an RNA-dependent polymerase (RdRp). As a result, numerous substances that target this protease have been shown to prevent the replication cycles of CHIKV and other alphaviruses. For instance, it has been shown that favipiravir (T-705, Figure 2) and its defluorinated counterpart T-1105 prevent the *in-vitro* reproduction of certain CHIKV strains and other (arthritogenic) alphaviruses.

Fatty acid synthase inhibition: The host cell membrane's sphingolipid and cholesterol are necessary for alphavirus fusion. Therefore, CHIKV and MAYV genome replication was reduced when the fatty acid synthase was inhibited by the anti-obesity medication orlistat, the antibiotic FASN inhibitor cerulenin, and the SCD1 inhibitor CAY10566.

Neuro-Chikhungunya development and other parts of body effected:

Even though CHIKV isn't usually thought of as a neurotropic virus, reports of occasional nervous system involvement date back to the 1960s **[24].** In patients with CHIK, nervous system involvement occurs 7–33% of the time. Guillain-Barré syndrome, acute disseminated encephalomyelitis, myelitis, encephalomyelitis, optic neuropathy, and neuroretinitis are the most common complications. Seizures, sensorineural hearing loss, stroke, cerebellitis, meningism, cranial nerve palsy, carpal tunnel syndrome, ophthalmoplegia, and disorientation are among the less common side effects.Up to 50% of infected neonates experience neurological symptoms and neurodevelopmental delay as a result of maternal-fetal transfer, which is a significant risk factor for the development of neuro-Chikhungunya. Pericarditis, cardiac tamponade, hypotension, shock, Raynaud's phenomenon, arrhythmias, cardiac murmurs, myocarditis, dilated cardiomyopathy, congestive insufficiency, and heart failure are among the several cardiovascular signs of CHIK. The most frequent renal findings were tubular damage and acute interstitial nephritis. Less often documented conditions include epithelioid granulomas, membranoproliferative glomerulonephritis, and nephrosclerosis. Elevated blood creatinine levels in patients with acute interstitial nephritis indicate compromised renal function. It is possible to develop post-inflammatory hypermelanosis, which is more prevalent in people with darker skin. This skin condition in the nose has been noted in case reports; some call this finding a "CHIK sign." It's also possible that the limbs and outer ear were impacted. Flagellated, freckle-simile, or distinct macules are some of the symptoms of hypermelanosis. Antipsychotics like olanzapine are used to treat manic episodes.

Depression is treated similarly to how it is in other contexts. Given the correlation between pain and psychiatric symptoms, analgesics may be useful in the treatment of persistent CHIK infections. Since few pharmaceutical interventions effectively lessen the burden of chronic CHIK, multifactorial and holistic methods are important components of optimal management.

Vaccine research: Biomarkers known as surrogate indicators are used to forecast how a vaccine may affect clinical outcomes **[25].** An essential surrogate indicator for assessing the effectiveness of the vaccine was the quantity of CHIKV-specific neutralizing antibodies against viral structural proteins, particularly the E2. Examples of immunoassays include the microneutralization test (μNT) and the plaque reduction neutralization test (PRNT), whose outcomes are assessed by the inhibition of 50–90% cytopathic effect (CPE) and 50–90% plaque titration (PRNT50, or PRNT90), respectively. The appearance of viral-specific antibodies that were previously negative before infection is known as seroconversion. Therefore, if the neutralizing activities of the viral-specific antibodies were demonstrated, seroconversion might be associated with protection. Mice and non-human primates are two instances of animal models of CHIKV infection. CHIKV-induced arthritis in adult immunocompetent mice to test CHIKV vaccines and therapies; mice lacking type I IFN that are also susceptible to a lethal challenge for pathogenesis study and vaccine safety and efficacy tests; and a lethal neonatal challenge that develops lethal encephalitis, representing severe neonatal encephalitis, were the acute phase models used in mice. Although the chronic mouse model was not yet fully developed, as was previously mentioned, persistent CHIKV infection was linked to inadequate T and B cell responses. Additionally, rhesus macaques and cynomolgus showed clinical signs of acute infection in humans; as a result, they are frequently employed in vaccination and immunotherapeutic research.

The ECSA strain (CHK/03/06) was used in an attempt at standard formalin inactivation following the re-emerging CHIKV outbreak in India and the Indian Ocean Islands. Three subcutaneous doses of the hydrogel gel formulation were given, and six to eight weeks following vaccination, strong neutralizing antibodies were seen in the ELISA (1:51,200) and plaque reduction neutralizing antibodies (1:6,400). Moreover, elevated levels of pro- and anti-inflammatory cytokines suggested the TH1 and TH2 responses. However, no subsequent developments were noted. In 1985, the U.S. military created the first live attenuated CHIKV vaccine candidate, known as 181/clone 25 (181/25 or TSI-GSD-218). The field isolate AF15561 (Thailand, 1962) was repeatedly subpassaged in human embryonic lung cells (MRC-5) and primary grivet kidney cells until it lost all of its lethality in rhesus monkeys and neonatal mice.The foundation of a VSVΔG-CHIKV is a vesicular stomatitis virus (VSV) that substitutes the structural CHICKV envelope (E3-E2--6K-E1) of the S27 West African strain for its glycoprotein (G). volunteers participated in Phase I/II clinical studies of the Ebola vaccine (rVSV-ZEBOV), which evaluated the safety and immunogenicity of the VSVΔG backbone.

Chloroquine: Chloroquine, which is frequently used as an antimalarial medication, was utilized to treat the illness clinically during the La Reunion epidemics **[26].** Chloroquine showed little effect on patients, despite having potent anti-chikungunya properties in cell culture. While mycophenolic acid was found to be more efficient than ribavirin in regulating chikungunya virus replication in a number of cellular investigations, broad-spectrum antivirals such as ribavirin and interferon were also effective against the virus. It has been demonstrated that the polymerase

inhibitor favipiravir inhibits the chikungunya virus in both a lethal mice model and cell culture. Modified nucleosides like 6-azauridine and 3-deaza-adenosine are also effective against the replication of the chikungunya virus, albeit their exact mechanism of action is still unknown. Attempts have been made to find known protease inhibitors that may be able to inhibit the chikungunya virus nsP2, which functions as both a helicase and a protease. It is estimated that between 70 and 150 years ago, an ECSA strain first appeared outside of Africa in Asia **[27].** One of the biggest CHIKV outbreaks ever recorded began in late 2004 when an ECSA strain resurfaced during an outbreak in Kenya, spreading to regions far outside the virus's usual range. The virus expanded to several islands in the Indian Ocean, India, and portions of Southeast Asia during this catastrophic outbreak, resulting in an estimated 6 million infections.

The symptoms of chikungunya fever, which usually manifest quickly, include severe asthenia, arthralgia, myalgia, headache, and rash **[28]**. Only conventional antipyretic and analgesic therapies are available for the treatment of symptoms, and there is no approved medication to prevent the reproduction of the Chikungunya virus and enhance clinical outcomes. Clinical trials have failed to demonstrate the safety and effectiveness of ribavirin plus interferon, as well as favipiravir, despite their demonstrated antiviral activity *in-vitro.* The chikungunya virus also spreads to the central nervous system (CNS) in animal models, where it infects the meningeal and epithelial cells that surround the CNS, choroid plexuses, and cerebrospinal fluid. The signs and symptoms of severe chikungunya fever may be caused by underlying neuronal cells being affected by infection of the meninges and ependymal cells, as well as the cytopathic consequences and host responses they cause. Research on human placentas from viremic mothers and experimental infection of pregnant animals have demonstrated that, unlike other alphaviruses, the chikungunya virus does not directly infect trophoblastic cells but is most likely transferred to newborns through maternal-fetal blood exchange during delivery.

CONCLUSION

Chikungunya represents a complex and multifaceted infectious disease with both acute and chronic health implications. Its re-emergence underscores a pressing need for novel treatments and comprehensive prevention strategies. Current efforts, while promising, are yet to yield a specific antiviral or vaccine, necessitating a continued emphasis on vector control and symptomatic care. The potential of viral polymerase inhibitors, such as favipiravir, and plant-derived compounds like berberine, indicates a pathway toward effective therapeutics. Furthermore, the mutation-prone nature of the chikungunya virus, particularly the E1-A226V variant, has expanded its transmission potential in diverse ecological settings. These insights highlight the importance of integrating molecular and genetic approaches into public health frameworks to monitor and respond to chikungunya's evolving transmission patterns. While live-attenuated vaccines offer promise, safety concerns have thus far limited their development, prompting ongoing research into stable, effective candidates. The complexity of chikungunya's immune interaction, especially with cytokines and innate immune responses, suggests that targeted immunomodulatory therapies may mitigate chronic complications. Comorbidities like diabetes and cardiovascular disease underscore the need for personalized care in affected populations. As such, chikungunya research should prioritize not only therapeutic innovation but also improved diagnostic capabilities and public health policies aimed at long-term disease management and outbreak prevention. This review calls for a concerted effort to transform chikungunya control from reactive to

proactive, ultimately reducing its global health impact.

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