Chikungunya Virus: Epidemiology, Clinical Manifestations, Virology, Immunology, Prevention, Control and Future Directions

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Abstract

Aedes mosquitoes carry the Chikungunya virus (CHIKV), an emerging arboviral disease that can cause a high fever, severe joint pain (arthralgia), rash, and myalgia, along with other common symptoms like nausea, vomiting, headache dizziness etc. Since its discovery in Tanzania in 1952, it has proliferated throughout the world, with current outbreaks documented in tropical and subtropical areas, such as Asia and Africa. CHIKV is predominately transmitted via mosquito bites, and in certain situations, its clinical signs can result in chronic arthritis, neurological problems, and mental health problems. Although there isn't an approved antiviral medication, *nonsteroidal anti-inflammatory drugs (*NSAID) are used to relieve symptoms. Although there is presently no commercial vaccination for the virus, immunity to it lasts for a long time. Particularly in the viremic phase, diagnostic techniques like RT-PCR and serology aid in early diagnosis. Vector management is still essential for stopping transmission, even though the creation of a vaccine similar to VLA1553 is encouraging. To reduce the worldwide burden of chikungunya, future efforts must concentrate on developing vaccines, researching antiviral medications, and developing sustainable vector control methods. Continuous surveillance and public health campaigns are crucial for efficient management.

Keywords: Chikungunya, *Aedes aegypti*, Arthralgia, Vector, RT-PCR

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Introduction

Since the 1940, zoonotic diseases have accounted for over 60% of the roughly 400 emerging infectious diseases identified (Rohr et al. 2019). Chikungunya is one of these emerging disease. It is currently spreading around the world and is expected to pose a serious concern in the near future. Aedes mosquito species, particularly *Aedes albopictus, Aedes aegypti*, and *Aedes polynesiensis*, are among the arboviral disease-carrying insects that transmit chikungunya (Powell & Tabachnick, 2010; Rougeron et al., 2015). The development of the electron microscope opened the door for the in-depth structural analysis of animal viruses, such as influenza and poliovirus, as well as plant viruses and bacteriophages. According to a study, roughly 2000 viruses were found in the middle of the 20th century, including the Chikungunya virus, which was first identified in Tanzania in 1952 (Ross, 1956). The Chikungunya virus, which has a diameter of roughly 60–70 nm, is a member of the genus Alphavirus and family Togoviridae. It is a single-stranded, tiny, spherical virus that is 11.8 kilobytes long. Its RNA is enclosed in a variety of protein coats, which can be classified as either structural or nonstructural. Genes encoding structural proteins and genes encoding nonstructural proteins are two categories of genes based on a CHIKV genomic and structural organization (Li et al., 2012). The start of viral genome replication is controlled by the viral protein's attachment to the host specific receptor site (Zhang et al., 2011).

Tropical and subtropical areas are where it primarily spreads. With the exception of arthralgia, which is a symptom unique to chikungunya only, dengue and chikungunya share the same vector, geographic distribution, and symptoms, making them near relatives (WHO, 2022). Patients who already have a medical condition like diabetes, liver, renal, or other medical conditions are more likely to experience arthralgia for longer periods of time than a typical Chikungunya patient. A high temperature and excruciating joint pain that can be named as polyarthralgia are symptoms of chikungunya. This harrowing joint status, limits body movement. Other significant symptoms include headache, nausea, dizziness, peripheral edema, myalgia, rash all over the body, and swellings primarily on the joints (Guzman et al., 2016). Mental disorders, confusion, memory issues have also been observed in many cases. Polyarthralgia may last for a few weeks to a few months, around 12 weeks to 2 years, or more than 10 years and may remain throughout life in certain individuals. Additionally, the patient's age and

immunity have a role. Vertical transmission from mother to child is another way that can spread chikungunya. According to certain researches conducted on animals, CHIKV mostly affects the fibroblast, causing peripheral edema, headaches, nausea, dizziness, and other symptoms (Gardner et al., 2010; Hoarau et al., 2010).

Epidemiology

Chikungunya was initially identified during an epidemic in Tanzania in 1952 and 1953, and it has since spread to regions of Asia and Pacific Africa. It has also occurred in nations like India, Sri Lanka, Pakistan, Cambodia and the Philippines, Thailand and Indonesia. In several of these countries multiple outbreaks have been reported over time. The disease is found in places like South Africa and West Africa. While there have been no local epidemics in Europe or America, there have been reports of migrants in places like Switzerland, Italy, the French West Indies, and Germany. It encourages tourists returning from catastrophe zones to be aware that this ailment is susceptible to spread, particularly in places where mosquitoes like *Aedes aegypti* are present.

In Pakistan and India, where other infections, like dengue, have been widely reported for the past three decades, the Chikungunya virus, whose primary vector is *Aedes aegypti* (Yergolkar et al. 2006), is an arboviral, mosquito-borne pathogenic disease that has emerged as a new public health concern and for the past 15 to 20 years, Chikungunya patients have been neglected. It was first recorded in India in 1973. Following that, an estimated 1.4 million cases were reported in 2006 (Ravi, 2006). The Chikungunya anti-virus was discovered in some humans and animals in the 1980s (Mishra et al., 2021), and it was reinforced by a widespread outbreak in Pakistan in 2016. The absence of surveillance systems, control measures, and other hygienic circumstances that facilitate mosquito development and transmission, such as food and drug administration, are some of the variables that render Pakistan susceptible to this type of outbreak (Roghani et al., 2024).

In Asia and some areas of the Indian Ocean, *Aedes aegypti* and *A. albopictus* have emerged as the main vectors of transmission, whereas in African regions, the environment of other mosquito species has been implicated in the spread of these species. It didn't end there; it proceeded to Asia, Australia, Europe, India, and the Americas before emerging as a major worldwide vector. Understanding the biology of the virus is challenging due to patterns observed in the Chikungunya outbreak (Enserink, 2006). It can also cproduce strains and have ability to change (Bonn, 2006). The disparity in diameters has caused alarm on a global scale, particularly during Europe's summer months. Controlling its spread is extremely challenging due to its numerous reservoirs, primarily because humans are the virus's major host and other animals, such rats and monkeys, also sustain it. There were two different forms of damage that this battle showed: the epidemic form and the inamic form.

Clinical Manifestations

In a typical chikungunya virus infection, individuals experience acute symptoms, like headache, nausea, vomiting, high fever, dizziness, and swelling mainly in the joints and face which are common in nearly all cases. Even though the virus's incubation period is silent and typically lasts two to four days, once it enters the body (Lam et al., 2001). Following the incubation period, the patient has a number of sudden symptoms, including a high temperature, joint, back pain, rash, myalgia, and arthralgia. However, Chikungunya is not typically regarded as fetal (Paixão et al 2018). Pain begins in the foot and moves to the knees and ankles. The discomfort progressively worsens and spreads to the wrist, phalanges, and all other joints, including short and long joints (Hochedez et al., 2006; Saxena, 2006; Quatresous, 2006). Bullous rash in youngsters and a full-body skin rash that primarily affects the thorax have been reported in approximately 50% of chikungunya patients (Robin et al., 2010). In Thailand, haemorrhagic fever has been recorded in patients with pediatric infections (Sirivichayakul et al., 2012). Some individuals also experience psychological symptoms, such as extreme annoyance and irritation, in certain instances neurological issues may develop. Chikungunya has also been linked to encephalitis and meningitis. Additionally, neonatal Chikungunya (Cordel, 2006) has been linked to pregnant women who are more likely to spread the Chikungunya virus to their newborn children.

An individual with CHIKV can also have full-body rash as one of the symptoms. It manifests as little red dots or spots. Since the patient does not experience the impulse to scratch, it is not an itchy condition. Moreover, these red stains can be seen solely and cannot be felt upon contact.

Arthralgia and Arthritis

Erratic, regressive, and incapacitating Chikungunya is characterized by arthritis causing excruciating joint pain, a disorder that seldom affects children but the basic underlying process behind this is unknown (Robin et al., 2010). A form of arthritis known as polyarthralgia causes pain in all of the body's joints even the smallest joint (Hossain et al., 2022). Patients in this disease feel incapacitated because they are unable to stand or sit without assistance, which makes it difficult to do daily tasks. The length of time these arthralgic symptoms last might range from two years to many years, depending on the patient's age, immunity, and physical health. It is the most severe illness in older people, but the symptoms usually go away in 18 months for the younger ones (Silva et al., 2021).

Diagnosis

In rare instances, especially for unusual or severe manifestations, serology is beneficial for confirming chikungunya virus infection. Quantitative real-time RT-PCR has exhibited significant sensitivity, with research indicating viral loads reaching 10^9 copies/mL, a magnitude rarely observed in other arthropod-borne illnesses (Weaver & Lecuit, 2015). Moreover, antigen detection, viral culture, and PCR are utilized in epidemiological research to identify the virus in mosquitoes and evaluate their vector competence. Notwithstanding the existence of these sophisticated diagnostic instruments, restricted access in resource-limited endemic areas continues to pose a substantial obstacle to precise and prompt diagnosis by diverse biological techniques, such as viral isolation, RT-PCR, and serological assays (Morrison, 2014).

RT-PCR is most efficacious during the early viremic phase (days 0–7), facilitating the identification of viral RNA in blood, urine, or semen, with recent innovations employing safer fluorescent dyes for real-time assessment. This technique also helps distinguish chikungunya fever from other mosquito-borne illnesses like dengue and Zika, which frequently result in misdiagnosis due to similar symptoms like fever, rash, and arthralgia (Soumahoro et al., 2009). IgM antibodies, which manifest within 1–12 days and last for up to 3 months, or IgG antibodies, which

arise after convalescence and are detectable for years, can be found using serological techniques such as ELISA (Sanderson et al., 2023). However, serological data may be complicated by cross-reactivity with arboviruses such as the O'nyong'nyong virus or dengue (Schwartz & Albert, 2010).

Virology

Untranslated sections (UTRs) at the 5′ and 3′ ends border around the 11.8kb single-stranded positive RNA genome of the tiny, spherical, enveloped chikungunya virus (CHIKV). These UTRs, which have a poly [A] tail at the 3′ end and a protective cap at the 5′ end, control transcription, viral replication, and packing. The non-translated junction region divides the genome's two open reading frames (ORF1 and ORF2) (Zhang et al., 2011).

Viral capping enzyme NsP1, ATPase, RNA helicase, and protease NsP2, RNA-binding and ADP-ribose-1-phosphate phosphatase NsP3, and RNA-dependent RNA polymerase NsP4 are the four non-structural proteins (NsP1–NsP4) that are essential for viral replication and are encoded by ORF1. Five structural proteins are encoded by ORF2: accessory proteins (E3 and 6K), envelope glycoproteins (E1 and E2), and capsid protein (C). The E1-E2 heterodimer helps the virus bind and enter host cells by creating glycosylated spikes on the viral envelope. The three-dimensional structure of CHIKV has been made visible by sophisticated imaging methods like cryo-electron microscopy, which also highlights the complex arrangement of the spike proteins' receptor-binding domains and envelope (Ahola & Ahola, 2016).

Immunology

Long-lasting immunity can be induced by CHIKV, which means that if a person is suspected of having a virus, they will never get it again. Animal studies have shown that chikungunya and other alphaviruses can cross-protect each other (Fumagalli et al., 2021; Raju et al., 2023). That was being said, there isn't a commercial vaccination against the chikungunya virus (Costa et al., 2023) but in November, 2023 America has successfully launched a vaccine named IXCHIQ (VLA1553) that is commercially available in USA (Valneva, 2023). A number of candidate vaccines have been tested, including the live-attenuated TSI-GSD-218 vaccine, which is based on a strain of the Thai virus. With 98% seroconversion by day 28 and antibody persistence in 85% of subjects after one year, the US Army Medical Research Institute's initial investigations demonstrated encouraging outcomes. However, when research goals changed in 2003, experiments were halted. With increased cooperation between the French and US health institutes, a phase III trial is being prepared Since there are currently no approved treatments for chikungunya virus infections, nonsteroidal anti-inflammatory medications such as ibuprofen and paracetamol are the only option for managing symptoms (Soumahoro et al., 2009). Certain chemicals, such as suramin and chloroquine, have demonstrated promise in vitro by preventing viral entry into host cells; however, their clinical effectiveness has not yet been established, and the disadvantages of suramin outweigh its advantages (Schwartz & Albert, 2010). Preliminary research has showed potential for modified suramin derivatives and other inhibitors that target viral proteins such as NsP1, NsP2, and NsP4. Furthermore, plant extracts from the Euphorbiaceae family that have substantial anti-CHIKV potential and protein kinase C inhibitory action suggest directions for further study (Cavalcanti et al., 2022).

Inoculating mosquito, mammalian, or mouse cell cultures is the basis for virus isolation. RT-PCR and serology IGM or IgG are available diagnostic techniques. RT-PCR transcription of RT-PCR Rivers for the identification and detection of the virus during the first mixing phase, PCR is a very successful technique. In epidemiological research, it is a helpful instrument. It not only makes it possible to identify the virus in mosquitoes but also to assess the vector's proficiency (Khan et al., 2012). Individual serological testing is primarily performed on patients returning from endemic areas.

Vaccination and Specific Immunity

Because chikungunya antibodies confer lifelong immunity, a person who contracts the Chikungunya virus is more likely to remain immune to the virus for the remainder of his life. This is known as long-term immunity. Patients have access to the most recent Chikungunya virus vaccinations. Certain vaccines have been tested on humans by certain scientists. In order to effectively treat the Chikungunya virus, the live attenuated vaccine of the virus isbeing utilized (Schneider et al., 2023).

Prevention

The main methods of preventing chikungunya are vector management and personal protection from mosquito bites, until a vaccine is developed. Like dengue, control techniques include removing mosquito breeding grounds, using pesticides, and using protective measures like bed nets (Morrison, 2014), especially in hospitals and childcare centers. DDT has been successful in large-scale campaigns against Aedes aegypti, but not Aedes albopictus. However, despite obstacles like insecticide resistance and mosquito migration into treated regions, vector management is still time-consuming, expensive, and dependent on community collaboration (Kaur & Chu, 2013). Novel strategies have showed potential, such as the sterile insect technique.

Although it is advised to combine this method with more conventional approaches, such as the use of insecticides and water management, to address the immigration of mated females, in field experiments, gamma-irradiated sterile male A. albopictus released at high rates significantly reduced egg density and achieved sterility levels sufficient to suppress local mosquito populations. There is hope for future prevention thanks to recent developments in vaccine development. By eliminating a portion of the gene encoding the non-structural protein NsP3, a French company called Valneva SE has created a single-shot live-attenuated vaccine candidate called VLA1553. In a key phase 3 clinical trial involving 4,115 individuals at 44 U.S. sites, the vaccine showed 98.5% protection after 28 days, with 3,082 participants reporting good safety and tolerability (Zhang et al., 2020)

Treatment and Control

VLA1553 vaccine has the potential to prevent outbreaks in the near future because it is made to defend against different CHIKV phylogroups

and strains. In the meanwhile, protective measures should be taken to control the vector, and the best way to manage the Chikungunya virus is to stop mosquitoes from spreading. This eliminates reading spots, and insecticides ought to be applied to them. Controlling birthday vectors is an expensive and time-consuming process, and most people do not cooperate with the government or follow its directives (Dambach et al., 2024).

Since there is currently no approved antiviral medication for CHIKV infection, symptomatic alleviation is the main focus of treatments. To reduce fever and pain, nonsteroidal anti-inflammatory medications (NSAIDs) such ibuprofen, acetaminophen (Schwartz & Albert, 2010), and paracetamol are frequently used; salicylates should be avoided. Despite research into a number of possible chemotherapeutic drugs, none have shown clinical efficacy (Kumar & Sharma, 2022). Chloroquine, for example, exhibited no discernible advantage in clinical studies but showed inhibitory effect against CHIKV entrance into host cells in vitro. In a similar vein, the FDA-approved medication suramin, which treats trypanosomiasis, has demonstrated anti-CHIKV action in vitro but is not appropriate for clinical usage since its side effects outweigh its advantages in moderate instances of chikungunya (Bahl et al., 2017).

Future Directions

Other possible treatments block the replication of the viral genome or target viral proteins such NsP1, NsP2 and NsP4. Furthermore, early research has indicated that plant extracts from the Euphorbiaceae family which have protein kinase C inhibitory action may be effective against CHIKV. Although interferon-α and ribavirin have been shown to work synergistically in vitro, further clinical data is needed to validate this claim. Effective antiviral therapies are still elusive despite research improvements, underscoring the need for more study into chikungunya therapy options (Goh, et al., 2021 & Kumar et al., 2023).

Research and control of the chikungunya virus should concentrate on a few important areas in the future. With continuous attempts to improve promising candidates like VLA1553 and guarantee their worldwide accessibility, especially in endemic regions, vaccine development continues to be a key priority (Hassett et al., 2019). Research on antiviral drugs must also be advanced, with a focus on finding substances that block viral replication or target viral proteins, as well as investigating combination treatments. Advances in vector control, like expanding the use of sterile insect methods and investigating genetically modifying mosquito populations, may offer long-term ways to lower transmission.

Improved epidemic identification and response can be achieved by enhanced epidemiological surveillance backed by global networks and predictive modeling. Long-term effects can be better understood and managed by looking at host-pathogen interactions, including immune response modulation and chronic disease mechanisms. Advances in diagnostics are essential for accurately and promptly distinguishing chikungunya from other arboviruses, especially through quick and inexpensive point-of-care testing. Last but not least, enhancing international cooperation, public health campaigns, and community involvement can provide a comprehensive strategy to fight chikungunya.

Conclusion

The chikungunya virus (CHIKV) continues to pose serious health risks to people around the world because of its quick geographic spread, lack of targeted antiviral therapies, and lack of a commercially viable vaccine. The illness, which is mostly spread by Aedes mosquitoes, has demonstrated an amazing capacity for adaptation and persistence, leading to frequent outbreaks with severe and frequently incapacitating symptoms, especially arthralgia. Effective control still depends on vector management and symptomatic treatment, even with improvements in diagnostic techniques and potential vaccine candidates like VLA1553.

Although there have been significant advancements in vaccine development, therapeutic research, and community-based prevention strategies, more work is needed to lessen the impact of this arboviral disease on public health. The long-term consequences of CHIKV infections, such as chronic arthritis and mental health implications, underscore the need for improved research into host-pathogen interactions and long-term disease management. Innovative vector control strategies, improved epidemiological surveillance, and international cooperation are essential to reducing the burden of chikungunya.

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