

Review of chikungunya virus infection: molecular biology, clinical and epidemiological characteristics in Brazil

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Abstract

The present study aims to describe data reported in the literature on the epidemiological history, molecular biology, and clinical characteristics of Chikungunya virus (CHIKV) in Brazil. This knowledge is important to guide new approaches for the control and prevention of future CHIKV outbreaks. Methodology: We selected 80 relevant articles, published between 2010 and 2022, in the National Library of Medicine National Institutes of Health (PubMed) electronic databases via MEDLINE, CAPES Periodicals Portal, Latest Medical News, Clinical Trials, Guidelines - Medscape, Springer, Latin American and Caribbean Literature on Health Sciences (LILACS) and Scientific Electronic Library Online (SciELO), using the descriptors in English: Chikungunya virus; Epidemiology; diagnostic and Portuguese: Chikungunya fever; pathogenesis; streaming; Aedes. Results: CHIKV in the last decade has become a consistent health problem globally and specifically in Brazil due to its rapid spread; the difficulty in accessing rapid and accurate diagnoses has contributed to the spread of vectors and consequently of CHIKV and the lack of a licensed vaccine together with new research in disease prophylaxis are extremely important to prevent outbreaks and protect vulnerable populations.

Keywords: Chikungunya, virus, Alphavirus, epidemiology, diagnosis and molecular biology.

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INTRODUCTION

Chikungunya fever (CHIKF) is an arbovirus caused by the Chikungunya virus (CHIKV). The CHIKV arbovirus is included in the Alphavirus genus of the Togaviridae family. This virus was first isolated in 1952–53 from mosquitoes and human serum during an epidemic in Tanzania (ROBINSON, 1955). CHIKV is transmitted by the bite of a mosquito, a female hematophagous arthropod of the genus *Aedes*, mainly *Aedes aegypti*, *Aedes albopictus* and *Aedes polynesiensis* infected arthropods. Reports of transmission of the CHIKV virus by arthropods of the genus *Culex* spp., *Anopheles* spp. and *Mansonia* spp. (MATUSALI et al, 2019). The name "chikungunya" is derived from the Makonde word "kungunyala" which means "one who bends over", thus describing the hunched carriage of individuals afflicted with Chikungunya fever (ZANNOLI et al, 2017).

From the genomic sequencing and phylogenetic analysis of fragments of the gene that expresses the E1 envelope glycoprotein and of the complete genome of the CHIKV viruses, four distinct genotypes or lineages (strains) were described. (RODRIGUES et al, 2020), characterized according to the geographic area of occurrence. These are: Asian genotype (Asian) and Indian Ocean Lineage (IOL), West African West Africa (West African - WA) and East-Central-South African (East, Central and South African (ECSA)) (SY et al, 2016; MOIZEIS et al, 2018). Research on sequencing revealed that interestingly, an epidemic strain of the virus that was isolated after an outbreak in La Reunión in 2005 (SCHUFFENECKER, et al, 2006), in the French island, showed a substitution of the amino acid alanine by valine at position 226 of the E1 glycoprotein, which resulted in a point mutation, being a virus originated from a single exclusive common ancestor, termed as a clade belonging to the ECSA lineage, and was named as Indian Ocean Lineage (IOL) (OLIVEIRA et al, 2022; HUCKE et al, 2021; MINH et al, 2020). The mutation generated an adaptation process for the virus allowing greater efficiency in biological processes, including infectivity and replication, allowing it to be transmitted by *Ae. albopictus* without affecting transmission by *Ae. aegypti*. The possible explanation for implications for propagation in new areas where the main vector is not *Ae. aegypti* was the adaptation of this new viral genotype in non-endemic regions such as Europe (OLIVEIRA et al, 2022; BURT et al, 2017).

METHODOLOGY

A bibliographic review of scientific articles, manuals and epidemiological bulletins was carried out on the epidemiological history of CHIKV, molecular biology, clinical features, and diagnostic methods. The databases used for the search were: National Library of Medicine National Institutes of Health (PubMed) via MEDLINE, CAPES Periodicals Portal, Latest Medical News, Clinical Trials, Guidelines – Medscape, Springer, Latin American and Caribbean Literature in Science of Health (LILACS) and Scientific Electronic Library Online (SciELO). Using the descriptors in English: Chikungunya virus; Epidemiology; diagnostic and Portuguese: Chikungunya fever; pathogenesis; streaming; *Aedes*. Articles published between the years 2010 and 2022 in Portuguese, Spanish and English were used as inclusion criteria, which were directly related to the topics described above and epidemiological aspects of *Aedes albopictus*

and *Aedes aegypti* vectors, responsible for the arboviruses CHIKV found in Brazil. All articles published in French, quick communications, editorials, author letters and all publications that differed from the inclusion criteria were excluded.

A total of 158 articles were found, only 81 were compatible with the theme of the study, the rest were outside the theme, all were available in the databases used. Of these, 80 were used and 78 were excluded. Some articles, published before 2000, were also studied and added to the review because they present important data on the course of the emergence and identification of CHIKV.

Organization of the Chikungunya virus genome

Chikungunya has a positive-sense single-stranded RNA genome approximately 12kb in size. (HARAPAN et al, 2019). It is a spherical particle about 70nm (nanometers) in diameter with its icosahedral, enveloped nucleocapsid (ÁLVAREZ-ARGÜELLES et al, 2019). The genome has two open reading frames (ORFs) (GANESAN et al, 2017), separated by an interacting region. Two thirds of the 5'ORF code is responsible for encoding non-structural proteins directly from genomic RNA to produce the four non-structural proteins (nsP1, nsP2, nsP3 and nsP4) (STRAUSS; STRAUSS, 1994), these proteins interact with cellular factors to form the replication complexes (RCs) that synthesize the double-stranded replicative intermediates (ds) RNA. These dsRNAs are the templates for positive viral conformation (42S) genomic and (26S) subgenomic RNAs. The 3'ORF which is encoded by a subgenomic RNA is responsible for translating the structural proteins of the capsid (Cp) and envelope proteins (E1 and E2) and two peptides (E3 and 6K) (SILVA ;DERMODY, 2017; STRAUSS; STRAUSS, 1994).

CHIKV broadcast

The chikungunya virus is transmitted mainly to people through the bite of infected *Aedes* mosquitoes, being common in Africa, India, Pakistan, Nepal, Guam, Southeast Asia, New Guinea, China, Mexico, South and Central America, islands in the Caribbean, Indian and Pacific Oceans and in certain regions of Europe (<https://www.cdc.gov/chikungunya/transmission/>).

The Asian strain, the IOL sub-strain and some ECSA strains, have shown a direct relationship with health problems caused by CHIKV. CHIKV outbreaks that have occurred in the last 15 years are related to these three classes (LANGSJOEN et al, 2018). *A. albopictus* is distributed worldwide, can be found at an altitude of up to 1,800 meters and is resistant to low temperatures. (NGOAGOUNI et al, 2017). *A. albopictus* is distributed worldwide, can be found at an altitude of up to 1,800 meters and is resistant to low temperatures. (RÜCKERT et al, 2017). Because it has a diversity of natural and artificial deposits where the eggs are postulated, greater tolerance to cold and quantity of eggs deposited, it is considered a vector of difficult control. Initially it was seen in Asia and today it is present in several regions of the globe, including in urban centers. (COFFEY et al, 2014).

It is noteworthy, however, that not all classes of arthropods (non-mosquito-arthropods) are related in vector transmission of CHIKV, but it has already been isolated from arachnids (ticks) collected in Senegal and the Republic of Guinea in a very low percentage. (BRÈS et al, 1969; KONSTANTINOV et al, 1990; MATUSALI et al, 2019).

CHIKV is naturally transmitted to humans by the bite of infected mosquitoes after a viremic blood meal, with viral titers ranging from 10³–10⁵ plaque forming units per ml (PFU/mL). After the virus is ingested by the mosquito (arthropod vector), it reaches the midgut, penetrating the epithelium, possibly through endocytosis probably mediated by the enzyme clathrin for further viral replication (MATUSALI et al, 2019). Subsequently, the viral particles reach the salivary glands of the mosquitoes. The incubation period in the mosquito until the phase of transmission to susceptible humans can vary from seven to ten days (SILVA et al, 2018; LIM et al, 2018), while in humans, the intrinsic incubation period varies from one to twelve days, and in ten days the infected individuals may present viremia (SILVA et al, 2018).

There are two suggested mechanisms for the spread of CHIKV, one that occurs in the midgut of the mosquito spreading to secondary organs. In this case, newly formed chikungunya virions that accumulate at the level of the basal lamina of the midgut of the mosquito (BL) pass to secondary organs thanks to BL remodeling mediated by collagenase enzymes (KANTOR et al, 2018). In the second, *virions* enter the tracheal cell system around the midgut and migrate to secondary organs (MATUSALI et al, 2019).

Humans are therefore the main host of the Chikungunya virus, in which CHIKV can infect several types of cells, including macrophages, dendritic cells, synovial fibroblasts (they seem to be the main site of viral replication and amplification), myocytes and endothelial cells. When the infection occurs in osteoblasts, the infected human being can acquire joint pathologies and erosive diseases observed in patients who contracted the virus and developed chronic arthritis, causing cartilage degradation and bone loss in joints (DE LIMA CAVALCANTI et al, 2022; NORET et al, 2012).

Cases of maternal-fetal transmission in humans have been reported, even though the majority of CHIKV transmissions occur by mosquitoes, and the greatest risk for this transmission can happen during childbirth (perinatal) and can cause serious central nervous system (CNS) diseases. which can be fatal (CONTOPOULOS-IOANNIDIS et al, 2018).

Still in relation to the transmission of the Chikungunya virus, an important finding was documented by Junior and collaborators demonstrating that CHIKV can also be transmitted by blood transfusion, since in their research carried out during an epidemic that occurred in southern Thailand, they showed the potential risk of a blood donor viremic asymptomatic have transmitted the virus for 2,429 donations (JÚNIOR et al, 2022).

CHIKV has also been detected in human breast milk, but there is no evidence of transmission through breast-feeding (CAMPOS et al, 2017). Therefore, according to CDC recommendations, mothers should be encouraged to breastfeed even if they are infected with the chikungunya virus or live in an endemic area for the virus.

Similarly, CHIKV RNA has been evidenced in human semen 30 days after the onset of symptoms, indicating a possible sexual transmission, but horizontal transmission between humans has not yet been reported (BANDEIRA et al, 2016; SILVA et al, 2018).

The blood transmission of CHIKV by occupational accidents has also been documented, both during the handling of blood from infected people and during the collection of blood from patients infected with CHIKV.

In summary, the risk of a person transmitting CHIKV to a mosquito or through blood is higher when the patient is viremic, that is, during the first week of illness.

Clinical manifestations

Individuals with CHIKV develop disease symptoms after a silent incubation period ranging from 2 to 7 days after viral infection (can last for up to 12 days), then abrupt symptoms appear: high fever and severe arthralgia. 2019; GANESAN et al, 2017). The most common clinical symptoms associated with CHIKV infection are characterized by 2 clinical conditions: acute and chronic phase (RAGHAVENDHAR et al, 2019).

The acute phase lasts up to 21 days and is characterized by a high fever (above 38.9°C) with sudden onset accompanied by debilitating polyarthralgia, bilateral, but not always symmetrical, involving feet, ankles, wrists, and hands, may occur. still fatigue, tenosynovitis, accompanied by headache, severe back pain, chills, myalgia, arthrosis and arthritis in multiple joints, maculopapular rash, nausea and vomiting, these symptoms may persist for several days. At this early stage, most patients are symptomatic. At this stage, asymptomatic individuals can occur, which can be a major contributing factor to the spread of the disease when the vector is present (GODAERT et al, 2017).

In the chronic phase, the initial inflammatory symptoms persist, including arthralgia and arthritis in most patients after 12 months post-infection and last for years respectively (JÚNIOR et al, 2022). The patient may also exhibit persistent bursitis, tenosynovitis accompanied by morning stiffness. These symptoms can then progress to a continuous or irregular form (SIMON et al, 2015). There are cases in which arthralgia persists for months or years, becoming chronic. The virus can also cause a variety of atypical manifestations, usually related to preexisting pathological processes exacerbated by the infection (CUNHA et al, 2020) causing morbidity to the patient. Less commonly at this stage, meningoencephalitis, meningeal irritation syndrome, seizures and Guillain-Barré syndrome are also observed (MEHTA et al, 2018).

Other symptoms are also reported for CHIKV infection, more frequently in the elderly and have complications in their health status (BALAVOINE et al, 2017). There are also descriptions of complications associated with the virus, from the most common to the least common, including respiratory failure, cardiovascular decompensation, meningoencephalitis, severe acute hepatitis, severe cutaneous effects, other central nervous system problems and renal failure (JÚNIOR et al, 2022). In the eye region it can cause inflammation in the optics, iris or retina. In the heart can have heart failure, arrhythmia, and pericarditis. On the skin, darkening of certain areas, appearance of blisters or aphthous ulcers. In the renal system, inflammation, and renal failure (BOUQUILLARD et al, 2017).

Diagnosis of CHIKV

Differentiating the clinical signs of CHIKV infection from other pathologies is challenging work, especially when it comes to regions where arboviruses are co-circulating (SILVA et al, 2018). Individuals infected with arboviruses may present with a broad spectrum of similar clinical symptoms (KHONGWICHIT et al, 2021), diagnosis based on clinical symptoms alone does not reliably differentiate CHIKV infections from other etiologies. Thus, it is extremely necessary to carry out laboratory diagnosis to

differentiate CHIKV from arboviruses such as Malaria, Dengue (DENV) or Zika virus (ZIKV), as they present the same initial symptoms (HUCKE et al, 2021).

Laboratory diagnosis

Laboratory tests to specifically diagnose CHIKV infection are performed by examining the plasma or serum of suspected patients. (SILVA et al, 2018; JOHNSON et al, 2016). Several methods are used to identify CHIKV, including viral isolation using cell culture and viral nucleic acid detection by reverse transcription polymerase chain reaction (RT-PCR) and detection of CHIKV-specific IgM antibodies using a serological assay.

Molecular tests remain central to confirming chikungunya. In acute manifestations, the viral load can exceed 11,010 copies/ml of serum, and the sensitivity to detect RNA remains high during the first 5 days of illness in most cases (CHUA et al, 2017). Several molecular tests for CHIKV are described and commercially available. The most described include conventional RT-PCR, real-time RT-PCR (rRT-PCR), isothermal methods (PATEL et al, 2016) and multiplex assays (SANTIAGO et al, 2018). Currently, real-time molecular diagnosis for CHIKV has offered a high sensitivity and specificity providing faster results when compared to viral isolation, however the cost is higher (WU et al, 2018). Multiplex tests contribute to the ease of diagnosis when dealing with a set of pathogens in patients, and the usefulness of this approach is demonstrated in places where there is transmission of multiple arboviruses (NATRAJAN et al, 2019). Molecular tests for CHIKV need to be analyzed in comparison with other Alphaviruses more similar to CHIKV as it may cross-react (WAGGONER et al, 2016).

Serological tests provide valuable diagnostic information about immune responses to CHIKV infection (COSTA et al, 2021). Detection of Anti-CHIKV IgM and IgG antibodies are alternative diagnostic methods that can be used in both the acute and chronic phases of the infection. ELISA has been shown to be a sensitive test with good performance, but it also presents possible cross-reactions with other Alphaviruses, such as ONNV and MAYV (ADAM; JASSOY, 2021). Plaque Reduction Neutralization Tests (PRNTs) are important accurate to confirm ELISA results but require the need for more skilled labor and facilities in BSL-3 laboratories. Although little performed in clinical laboratories, PRNT remains in use for diagnosis when available due to its high specificity and sensitivity (CLEMENTS et al, 2019).

Techniques for diagnosing CHIKV have their limitations. Molecular techniques and material collection need to be performed during the acute phase of the disease, until the fifth day after the onset of symptoms, at the time of greatest viremia. On the other hand, immunological tests do not need this limitation in relation to the time of collection of material for examination. However, they do not have the same sensitivity and specificity as molecular methods and may have the highest number of cross-reactions with other arboviruses, which are part of the Semliki Forest Virus (SFV) antigenic complex.

Treatment

Current treatment for CHIKV focuses on lessening the severity of viral symptoms rather than curing the disease. Treatment mainly involves the use of antipyretics and NSAIDs, steroids have been used to treat patients in the acute phase of infection, mixed success has been tentatively used due to the possibility of worsening of post-treatment

symptoms). The use of chloroquine, an antimalarial as well, has been frequently prescribed to manage symptoms of CHIKV, however its effectiveness in relieving symptoms during the acute phase of the infection is questioned (MASCARENHAS et al, 2018). For severe chronic arthralgia, disease-modifying antirheumatic drugs (DMARDs) including methotrexate, hydroxychloroquine, or sulfasalazine have been proposed (GANESAN et al, 2017), but their effectiveness as an effective treatment option has not been evaluated in any studies. Several therapeutic strategies to combat CHIKV have been investigated (ABDELNABI et al, 2015). To date, ribavirin is the only FDA-licensed drug tested in humans that has tested positive in CHIKV-infected patients.

Although many studies have shown attempts to develop a vaccine against CHIKV since the 1960s, as the virus is now endemic in many regions, there are currently no vaccines available. Importantly, a vaccine produced to combat the virus needs to be cost-effective, easy to handle and easy to transport, thus allowing developing regions to afford a mass vaccination campaign. Currently, no vaccine has been approved so far, but several candidates are being investigated in preclinical and clinical trials worldwide (HUCKE et al, 2021; REZZA; WEAVER, 2019).

The best strategy to treat CHIKV is prevention, as there is no medication or vaccine to fight the virus specifically and effectively.

Initially preventing bites and vector control are the two brands to avoid infections. When traveling to endemic areas, general personal protection measures should be taken, such as wearing long-sleeved clothing or using insect repellent and mosquito nets are important to avoid being bitten by a CHIKV positive mosquito. Increase environmental care, do not leave standing water in easily accessible containers for transmitting agents to proliferate, such as bottles, tires, potted plants (SRIDHAR et al, 2018).

Epidemiology of the Chikungunya virus in Brazil

The description of the first well-characterized CHIKV outbreak was reported in the southern province, in the Tanganyika territory of Tanzania in 1952, settling in an urban transmission cycle that continues to this day, with *Ae. aegypti* the main vector (LUMSDEN, 1955). Subsequently, new sporadic outbreaks were identified in other regions of Africa and Asia during the 1950s and 1960s, followed by a resurgence in the 2000s with the epidemic in Kinshasa, capital of the Democratic Republic of Congo (WEAVER; LECUIT 2015; VOLK et al, 2010). Since 2005, the Southwest Indian Ocean and Southeast Asia have reported high numbers of cases of the virus (HARAPAN et al, 2019).

Until 2004, CHIKV cases were restricted to African and Asian countries only. However, in April 2005, an epidemic of the ECSA lineage of CHIKV re-emerged being detected in the southwestern Indian Ocean (Comoros Islands) (HIGGS, 2006) probably introduced by viremic travelers, affecting 1.4 million people, raising concern regarding to the virus (SERGON et al, 2008; AZEVEDO et al, 2015). In La Reunion, the outbreak affected about a third of the population (THIBERVILLE et al, 2013) in India, the viruses infected more than 1.3 million people during 2005-2006 (STAPLES et al, 2009). In Sri Lanka, the viruses infected more than 100,000 people, and CHIKV later spread to Southeast Asia, including Indonesia. Cases of CHIKV (IOL lineage) (BURT et al, 2017; AUBRY et al, 2015) have been described in Europe since 2007, when an outbreak was reported in northeastern Italy, with a total of 217 cases (REZZA et al,

2007). Since then, autochthonous cases of CHIKV fever have occurred in France, Croatia, Spain, and Italy (WAHID et al, 2017; DELISLE et al, 2015).

In the years 2009-2010, cases of CHIKV were imported from travelers from Indonesia and India to the United States, France, and Brazil. In this period, the first case of CHIKV in Brazil was reported in the city of Rio de Janeiro, but there was no record of virus isolation by molecular techniques. As of 2011, the Democratic Republic of Congo had an outbreak of CHIKV with more than 11,000 cases, which alerted to the probable introduction of the virus in Latin America (AZEVEDO; OLIVEIRA; VASCONCELOS, 2015).

In 2014, as countries neighboring Brazil were reporting several cases of chikungunya fever, there was a high risk of introduction of the virus into the country, due to the large displacement of competent travelers and vectors (BURT et al, 2017). The first autochthonous transmission was detected in September 2014, in the city of Oiapoque, in the state of Amapá (North) and Feira de Santana, in the state of Bahia (Northeast), with 1,688 cases confirmed by laboratory criteria and 1,683 by epidemiological criteria (NUNES et al, 2015), then the first suspected cases were also recorded in Amazonas. Genetic analysis of the viruses identified two lineages: the Asian lineage, found in Oiapoque and the lineage - Eastern, Central and Southern Africa (ECSA), detected in Feira de Santana (RODRIGUES et al, 2016; MADARIAGA et al, 2016; SILVA et al, 2018).

In 2015, the Ministry of Health reported a total of 20,661 suspected cases of CHIKV - 7,823 (38%), (35%) of which were confirmed clinically and (3%) were laboratory confirmed, distributed in 84 cities in Brazil - of which Feira de Santana reported a high number of cases (4,088 in 2015 alone) (BRASIL, 2015). Across the country in 2016, according to the Ministry of Health, 271,824 suspected cases of CHIKV were registered, with distribution in 2,829 municipalities. deaths, with an average age of 62 years. Of the total number of suspected cases, 804 were registered in the state of Rondônia (BRASIL, 2016; SOUZA; SANTOS, 2016). There were 47,791 probable cases of CHIKV in 2017 registered in Brazilian states, of which 30,251 were confirmed by clinical tests and another 11,503 suspected cases were discarded. In the same year, the Southeast region presented the highest number for CHIKV (24,307) in relation to the total of the country (BRASIL, 2017). In the following year (2018) of the 23 laboratory confirmed cases, 8 of these were deaths (BRASIL, 2018).

In 2019 for CHIKV, 132,205 probable cases were reported, with an incidence rate of 62.9 cases/100,000 inhabitants in Brazil. The Northeast and Southeast, as in previous years, showed high incidence rates, with 59.4 cases/100,000 inhabitants and 104.6 cases/100,000 inhabitants, respectively. Rio Grande do Norte and Rio de Janeiro were the states that concentrate 75.6% of probable cases (MINISTÉRIO DA SAÚDE, 2019; NAVECA et al, 2019).

For 2020, 78,808 cases of probable CHIKV were reported, with an incidence rate of 37.5 cases/100,000 inhabitants. This year there was a decrease in the number of reported cases, compared to the previous year, as well as in the incidence rates. However, the regions with high incidence rates (Southeast and Northeast) are maintained, compared to 2019, but the number of probable cases had a reversal, as in 2019 the Southeast reported more cases than in 2020, with 22.7 cases/100 thousand inhabitants, with a drop in the incidence rate. The Northeast, which in 2019, was higher when compared to 2020, with 99.4 cases/100,000 inhabitants, showing 40 more

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cases were reported in 2019 to 2020 (MINISTÉRIO DA SAÚDE, 2020; REZENDE, 2021).

Regarding the CHIKV data for the year 2021, there were 93,043 probable cases with an incidence rate of 43.6 cases per 100,000 inhabitants in the country. These numbers correspond to a 33.2% increase in cases compared to the previous year. The Northeast Region had the highest incidence with 111.1 cases/100,000 inhabitants, followed by the Southeast (29.1 cases/100,000 inhab.) and Midwest (6.8 cases/100,000 inhab.) regions. The North region, when compared to those mentioned, presented only 39 cases of the disease under investigation and 4 of these confirmed, even though it is a very endemic region for arbovirus. In the same year, 13 deaths were confirmed by laboratory criteria, which occurred in the state of São Paulo (6), Pernambuco (2), Espírito Santo (2), Sergipe (1), Bahia (1), Minas Gerais (1). It is noteworthy that 25 deaths remain under investigation (MINISTRY OF HEALTH, 2021).

According to data from the Ministry of Health's epidemiological bulletin, Brazil recorded a 32.7% increase in CHIKV cases between the beginning of 2021 and the beginning of 2022 compared to the same period of the previous year. (MINISTRY OF HEALTH, 2022).

Although the origins of the virus remain less understood, in Brazil, the growth of CHIKV cases is notorious in many regions, including cases of autochthonous transmission in the states of Brazil (RODRIGUES et al, 2016).

CONCLUSIONS

It is concluded that in the last decade, there has been an increase in the spread of CHIKV infections; There is difficulty in accessing quick and accurate diagnoses, including bedside diagnoses; the population most affected are those from low-income countries; rapid diagnosis, RT-PCR or ELISA, are the most used, but they have some negative points, high value and low sensitivity; there has been a number of CHIKV cases in the last two years, probably due to the lack of investigation or availability of diagnostic tests; Therefore, the present review highlights important considerations about epidemiological aspects, specific diagnosis and the need for studies on viral infection in endemic areas for arboviruses, and finally, in the absence of a licensed vaccine, new research in the area of CHIKV disease prophylaxis is needed. extremely important to prevent outbreaks and protect vulnerable populations.

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REFERENCES

1. ABDELNABI R, NEYTS J, DELANG L T. antivirals against chikungunya virus. *Antiviral Res.*121:59–68. 2015.
2. ADAM A, JASSOY C. Epidemiology and Laboratory Diagnostics of Dengue, Yellow Fever, Zika, and Chikungunya Virus Infections in Africa. *Pathogens.*10(10):1324. 14 Oct 2021.
3. ÁLVAREZ-ARGÜELLES M E, ALBA S R, PÉREZ M R, RIVEIRO J A B, GARCÍA S M. Diagnosis and Molecular Characterization of Chikungunya Virus Infections. *Current Topics in Neglected Tropical Diseases.* DOI: 10.5772/intechopen.86957. 2019.

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4. AUBRY M, TEISSIER A, ROCHE C, RICHARD V, YAN A S, ZISOU K, ROUAULT E, MARIA V, LASTÈRE S, CAO-LORMEAU V M, et al. Chikungunya Outbreak, French Polynesia, 2014. *Emerg. Infect. Dis.* 21:724–726, 2015.
5. AZEVEDO R S S, OLIVEIRA C S, VASCONCELOS P F C. Chikungunya risk for Brazil. *Rev Saude Publica.* 49: 58. doi: 10.1590/S0034-8910.2015049006219, Sep 29, 2015.
6. BALAVOINE S, PIRCHER M, HOEN B, HERRMANN-STORCK C, NAJJOULLAH F, MADEUX B, SIGNATE A, VALENTINO R, LANNUZEL A, LOUIS MS, SYLVIE CASSADOU, CABIÉ A, SCHEPERS K. Guillain-Barré Syndrome and Chikungunya: Description of All Cases Diagnosed during the 2014 Outbreak in the French West Indies. *The American Journal of Tropical Medicine and Hygiene.* 97(2): 356–360, 2017.
7. BANDEIRA A C, CAMPOS G S, SARDI S I, ROCHA V F, ROCHA G C. Neonatal encephalitis due to Chikungunya vertical transmission: first report in Brazil. 5:57–59; IDCases. 2016.
8. BOUQUILLARD E, PIANU A, BANGIL M, CHARLETTE N, RIBÉRA A, MICHAULT A, FAVIER F, SIMON F, FLIPO R M. Rheumatic manifestations associated with Chikungunya virus infection: A study of 307 patients with 32-month. *American Journal.* 01.014, 2017.
9. BRASIL. Ministério da Saúde. Secretaria de Vigilância em Saúde. Monitoramento dos casos de dengue, febre de chikungunya e febre pelo vírus Zika até a Semana Epidemiológica 50. Brasília: Ministério da Saúde, 2017b. Disponível em: <http://portalarquivos2.saude.gov.br/images/pdf/2018/janeiro/10/2017-046-Publicacao.pdf>. Acesso em: 02 maio.2022.
10. BRÈS P, CAMICAS J L, CORNET M, ROBIN Y, TAUFFLIEB R. Epidemiology of arbovirus diseases in Senegal. *Bull. Soc. Pathol. Exot. Filiales.* 62:253–259; 1969.
11. BURT F J, CHEN W, MINER J J, LENSCHOW D J, MERITS A, SCHNETTLER E, KOHL A, RUDD P A, TAYLOR A, HERRERO L J, et al. Chikungunya virus: An update on the biology and pathogenesis of this emerging pathogen. *Lancet Infect. Dis.* 17:e107–e117. doi: 10.1016/S1473-3099(16)30385-1. 2017.
12. CHUA C L, SAM I C, CHIAM C W, CHAN Y F. The neutralizing role of IgM during early chikungunya virus infection. *PLoS One* 12:e0171989. 2017.
13. CLEMENTS T L, ROSSI C A, IRISH A K, KIBUUKA H, ELLER L A, ROBB ML, KATAAHA P, MICHAEL N L, HENSLEY L E, SCHOEPP R J. Chikungunya and O'nyong-nyong Viruses in Uganda: Implications for Diagnostics. *Jan* 3;6(3). *Open Forum Infect Dis.* 2019.
14. COFFEY L L, FAILLOUX A-B, WEAVER S C. Chikungunya virus-vector interactions. *Viruses*, 6, n. 11, p. 4628-4663, 2014.
15. CONTOPOULOS-IOANNIDIS, D. et al., Mother-to-child transmission of Chikungunya virus: A systematic review and meta-analysis. *PLOS Neglected Tropical Diseases*, 12, n. 6, p. e0006510, Jun 2018.
16. COSTA J, FERREIRA E C, SANTOS C. COVID-19, Chikungunya, Dengue and Zika Diseases: An Analytical Platform Based on MALDI-TOF MS, IR Spectroscopy and RT-qPCR for Accurate Diagnosis and Accelerate Epidemics Control. *Microorganisms.* 9(4):708; 30 Mar 2021.
17. CUNHA M S. et al. Chikungunya Virus: An Emergent Arbovirus to the South American Continent and a Continuous Threat to the World. *Frontiers in Microbiology*, v. 11, n. June, 2020.
18. DE LIMA CAVALCANTI T Y V, PEREIRA M R, DE PAULA S O, FRANCA R F O. A Review on Chikungunya Virus Epidemiology, Pathogenesis and Current Vaccine Development. *Viruses.*14(5):969; May 5 2022.
19. DELISLE E. et al. Chikungunya outbreak in montpellier, France,September to October 2014. *CrossRefView Record in Scopus Euro Surveill*, 20 (17), p. 21108, 2015.
20. DONASILIO M R, FREITAS A R R, Chikungunya in Brasil: an emerging challenge, *Revista Brasileira De Epidemiologia*, v. 18, p. 283-285, 2015.
21. GANESAN V K, DUAN B, REID S P. Chikungunya Virus: Pathophysiology, Mechanism, and Modeling. *Viruses*, 9, n. 12, 12 2017.
22. GODAERT LIDVINE. Screening for Chikungunya virus infection in aged people: Development and internal validation of a new score. *Plos One.* [s.l.], v. 12, n. 8, p.1- 9, 2017.
23. GOUPIL B A, MORES C N. Review of Chikungunya Virus-induced Arthralgia: Clinical Manifestations, Therapeutics, and Pathogenesis. *The Open Rheumatology Journal*, v. 10, n. 1, p. 129–140, 2019.
24. HARAPAN H, MICHIE A, MUDATSIR M, NUSA R, YOHAN B, WAGNER A L, SASMONO R T, IMRIE A. Chikungunya virus infection in Indonesia: a systematic review and evolutionary analysis. *BMC Infectious Diseases.* 19:243, 2019.
25. HIGGS S. The Chikungunya epidemic in the Indian Ocean. *Vector Borne Zoonotic Dis.* 6:115–116, 2006.
26. HUCKE F I L, BESTEHORN-WILLMANN M & BUGERT J J. Prophylactic strategies to control chikungunya virus infection. *Virus Genes* 57, 133–150. <https://doi.org/10.1007/s11262-020-01820-x>. 2021.
27. JOHNSON B W, RUSSELL B J, GOODMAN C H. Laboratory diagnosis of chikungunya virus infections and commercial sources for diagnostic assays. 214(suppl 5):S471–S474. *J. Infect. Dis.* 2016.
28. JÚNIOR AF P, AZEVEDO E A N, NETO R D L, VIANA I F T. Chikungunya: da epidemiologia ao desenvolvimento de vacinas. *Fatores de virulência microbianos e terapias emergentes. Latin American; Vol. 03 – Vírus.* p. 215-232; 2022
29. KANTOR A M, GRANT D G, BALARAMAN V, WHITE T A, FRANZ A W E. Ultrastructural analysis of chikungunya virus dissemination from the midgut of the yellow fever mosquito, *aedes aegypti*. 10:571; *Viruses.* 2018.

Alana Fernandes, Cintia Oliveira, Pricilla Oliveira, Edson Junior– **Review of chikungunya virus infection: molecular biology, clinical and epidemiological characteristics in Brazil**

30. KHONGWICHIT S, CHANSAENROJ J, CHIRATHAWORN C, POOVORAWAN Y. Chikungunya virus infection: molecular biology, clinical characteristics, and epidemiology in Asian countries. *J Biomed Sci.* Dec 2;28(1):84. 2021.
31. KONSTANTINOV O, K. Ticks of the Ixodidae family as reservoir of arboviruses in the Republic of Guinea. II. Arboviruses. *Rev. Elev. Med. Vet. Pays Trop.* 43:15–22:1990.
32. LANGSJOEN R M, et al. Chikungunya virus strains show lineage-specific variations in virulence and cross-protective ability in murine and nonhuman primate models. 9(2):02449-17; *mBio.* 2018.
33. LIM E X Y, LEE W S, MADZOKERE E T, HERRERO L J. Mosquitoes as suitable vectors for alphaviruses. *Viruses.* 10(2):2018.
34. LUMSDEN WH. An epidemic of virus disease in Southern Province, Tanganyika territory, in 1952-53. II. General description and epidemiology. *Trans R Soc Trop Med Hyg.*49(1):33–57. 1955.
35. MADARIAGA M, TICONA E, RESURRECCION C. Chikungunya: bending over the Americas and the rest of the world. *Braz J Infect Dis.*; 20 (01), p. 91-8, Jan-Feb. 2016.
36. MASCARENHAS M, GARASIA S, BERTHIAUME P, CORRIN T, GREIG J N G V, YOUNG I, WADDELL L. A scoping review of published literature on chikungunya virus. *Nov 29;13(11):e0207554.* doi: 10.1371/journal.pone.0207554. *PLoS One.* 2018.
37. MATUSALI G, COLAVITA F, BORDI L, LALLE E, IPPOLITO G, CAPOBIANCHI M R, Castilletti, C. Tropism of the chikungunya virus. *Viruses* 11(2):175, 2019.
38. MEHTA R, et al. The neurological complications of chikungunya virus: A systematic review. *Reviews in Medical Virology*, v. 28, n. 3, p. e1978, maio 2018.
39. MINH B Q, et al. IQ-TREE 2: new models and efficient methods for phylogenetic inference in the genomic era. 37(5):1530–1534. *Mol Biol Evol.* 2020.
40. Ministério da saúde. (2019). Monitoramento dos casos de arboviroses urbanas transmitidas pelo Aedes (dengue, chikungunya e Zika), Semanas Epidemiológicas 01 a 52. *Boletim Epidemiológico*, 51 (02), 1-5. 2019
41. Ministério da saúde. (2020). Monitoramento dos casos de arboviroses urbanas transmitidas pelo Aedes Aegypti (dengue, chikungunya e zika), semanas epidemiológicas 1 a 46. *Boletim Epidemiológico*, 51 (48), 1-7. https://www.gov.br/saude/pt-br/media/pdf/2020/dezembro/11/boletim_epidemiologico_svs_48.pdf. 2020.
42. Ministério da saúde. (2021). Monitoramento dos casos de arboviroses urbanas causados por vírus transmitidos pelo mosquito Aedes (dengue, chikungunya e zika), semanas epidemiológicas 1 a 47, 2021. *Boletim Epidemiológico*. [boletim_epidemiologico_svs_44-2.pdf](https://www.gov.br/saude/pt-br/media/pdf/2021/maio/11/boletim_epidemiologico_svs_44-2.pdf) (www.gov.br). 2021.
43. Ministério da saúde. (2022). Monitoramento dos casos de arboviroses urbanas causados por vírus transmitidos pelo mosquito Aedes (dengue, chikungunya e zika), semanas epidemiológicas 1 a 7, 2022. *Boletim Epidemiológico*. [boletim-epidemiologico-SVS-07-2022.pdf](https://www.gov.br/saude/pt-br/media/pdf/2022/maio/11/boletim_epidemiologico_svs_07-2022.pdf) (saude.gov.br). 2022.
44. Ministério da Saúde. Secretaria de Vigilância em Saúde. *Boletim Epidemiológico*, v.47, n. 38. Brasil, 2015.
45. Ministério da Saúde. Secretaria de Vigilância em Saúde. *Boletim Epidemiológico*, v. 48, n. 3. Brasil, 2016.
46. Ministério da Saúde. Secretaria de Vigilância em Saúde. *Vigilância de chikungunya no Brasil: desafios no contexto da Saúde Pública, Epidemiol. Serv. Saude, Brasília*, 27(3):e2017127, Brasil, 2018.
47. MOIZÉS R N C, FERNANDES T A A M, GUEDES P M M, PEREIRA H W B, LANZA D C F, AZEVEDO J W V, GALVÃO J M A, FERNANDES J V. Chikungunya fever: a threat to global public health. *Pathogens and global health*, v. 112, n. 4, p. 182-194, 2018.
48. NATRAJAN M S, ROJAS A, WAGGONER J J. Beyond fever and pain: Diagnostic methods for chikungunya virus. *Journal of Clinical Microbiology*, v. 57, n. 6, p. 1–14, 2019.
49. NAVECA F G, et al. Genomic, epidemiological and digital surveillance of chikungunya virus in the Brazilian Amazon. *PLOS Neglected Tropical Diseases*, <https://doi.org/10.1371/journal.pntd.0007065>, March 7 2019.
50. NGOAGOUNI C, KAMGANG B, KAZANJI M, PAUPY C, NAKOUNÉ E. Potential of Aedes aegypti and Aedes albopictus populations in the Central African Republic to transmit enzootic chikungunya virus strains. 10(1):164; *Parasit Vectors.* 2017.
51. NORET M, HERRERO L, RULLI N, ROLPH M, SMITH P N, LI R W, ROQUES, GRAS G, MAHALINGAM S, RANKL I. and osteoprotegerin expression by chikungunya virus-infected human osteoblasts. 206:455–459; *J. Infect. Dis.* 2012.
52. NUNES M R T, FARIA N R, DE VASCONCELOS J M, GOLDING N, KRAEMER M U, DE OLIVEIRA L F, AZEVEDO R, DA SILVA AZEVEDO R D S, DA SILVA D E A, DA SILVA E V P, et al. Emergence and potential for spread of Chikungunya virus in Brazil. *BMC Med.* 13:102. 2015.
53. OLIVEIRA M E S P, LIMA M V S A, ASSUNÇÃO M A S, LIMA V K A. Arboviroses: Aspectos Virais, Ecológicos, Clínicos e Epidemiológicos. *Fatores de virulência microbianos e terapias emergentes Vírus. Latin American Publicações.* 03, 154- 182. 2022.
54. PATEL P, ABD E L WAHED A, FAYE O, PRUGER P, KAISER M, THALOENGSOOK S, UBOL S, SAKUNTABHAI A, LEPARC-GOFFART I, HUFERT F T, SALL A A, WEIDMANN M, NIEDRIG M. A field-deployable reverse transcription recombinase polymerase amplification assay for rapid detection of the chikungunya virus. *PLoS Negl Trop Dis* 10:e0004953. 2016.
55. RAGHAVENDHAR B S, PATEL A, KABRA S K, LODHA R, RATAGERI V H, RAY P. Virus load and clinical features during the acute phase of Chikungunya infection in children. *PLoS ONE.* 14:e0211036. 2019.

Alana Fernandes, Cintia Oliveira, Pricilla Oliveira, Edson Junior– **Review of chikungunya virus infection: molecular biology, clinical and epidemiological characteristics in Brazil**

56. REZENDE R B. Epidemiological analysis of emerging and re-emerging arbovirus infections in Brazil between the years 2019 and 2020. *Research, Society and Development*, v. 10, n. 2, e33010212611, 2021.
57. REZZA G, WEAVER S C. Chikungunya as a paradigm for emerging viral diseases: evaluating disease impact and hurdles to vaccine development. *PLOS Negl Trop Dis*. 2019.
58. REZZA G, NICOLETTI L, ANGELINI R, ROMI R, FINARELLI A, PANNING M, CORDIOLI P, FORTUNA C, BOROS S, MAGURANO F, et al. Infection with chikungunya virus in Italy: An outbreak in a temperate region. *Lancet*. 370:1840–1846. doi: 10.1016/S0140-6736(07)61779-6. 2007.
59. ROBINSON M C. An epidemic of virus disease in Southern Province, Tanganyika Territory, in 1952–53. I. Clinical features. *Trans. R. Soc. Trop. Med. Hyg.* 49, 28–32. 1955.
60. FARIA N R, LOURENÇO J, MARQUES DE CERQUEIRA E, MAIA DE LIMA M, PYBUS O, CARLOS JUNIOR ALCANTARA L. Epidemiology of Chikungunya Virus in Bahia, Brazil, 2014–2015. *PLoS Curr*. Feb 1;8: 2016.
61. RODRIGUES A M, FONSECA L M S, SOUZA R R M, ROLO C A, CARVALHO R H. Genomic surveillance of the Chikungunya Virus (CHIKV) in Northeast Brazil after the first outbreak in 2014. *Rev. Soc. Bras. Med. Trop.* vol.53, Uberaba. 2020.
62. RÜCKERT C, WEGER-LUCARELLI J, GARCIA-LUNA S M, YOUNG M C, BYAS A D, MURRIETA R A. Impact of simultaneous exposure to arboviruses on infection and transmission by *Aedes aegypti* mosquitoes. 8:15412. *Nat. Commun*. 2017.
63. SANTIAGO G A, VAZQUEZ J, COURTNEY S, MATIAS K Y, ANDERSEN L E, COLON C, BUTLER A E, ROULO R, BOWZARD J, VILLANUEVA J M, MUNOZ-JORDAN J L. Performance of the Trioplex real-time RT-PCR assay for detection of Zika, dengue, and chikungunya viruses. *Nat Commun* 9:1391. 2018.
64. SCHUFFENECKER, et al, Genome microevolution of chikungunya viruses causing the Indian Ocean outbreak. 3(7):e263. *PLoS Med*. 2006.
65. SERGON K. Soroprevalência da infecção pelo vírus Chikungunya (CHIKV) na ilha de Lamu, Quênia, em outubro de 2004. *Am J Trop Med Hyg.* 78 (2), p. 333-7, Fev 2008.
66. SILVA J V J JR, LUDWIG-BEGALL L F, OLIVEIRA-FILHO E F, OLIVEIRA R A S, DURÃES-CARVALHO R, LOPES T R R, SILVA D E A, GIL L H V G. A scoping review of Chikungunya virus infection: epidemiology, clinical characteristics, viral co-circulation complications, and control.188:213-224; *Acta Trop*. 2018.
67. SILVA L A, DERMODY T S. Virus chikungunya: epidemiologia, replicação, mecanismos de doença e estratégias de intervenção prospectiva. *J Clin Invest.* 127(3):737-749. 2017.
68. SILVA N M. Vigilância de chikungunya no Brasil: desafios no contexto da Saúde Pública. *Epidemiol. Serv. Saúde.* 03 Set 2018.
69. SOUZA A C, SANTOS C A C. Infecção pelo vírus chikungunya: uma revisão bibliográfica. *Saber Científico, Porto Velho, V., n., p. – , mês./mês.* 2017.
70. SRIDHAR S, et al. Efeito do sorostatus da dengue sobre a segurança e eficácia da vacina contra a dengue. 379(4):327-340. *N Engl J Med*. 2018.
71. STAPLES J E, BREIMAN R F, POWERS A M. Chikungunya fever: an epidemiological review of a re-emerging infectious disease. *Clin Infect Dis.* 49(6):942–948. 2009.
72. STRAUSS J H, STRAUSS E G. The alphaviruses: gene expression, replication, and evolution. *Microbiol Rev* 58(3):491–562. DOI: 10.1128 / mmb.58.3.491-562. 1994.
73. SY A K, SAITO-OBATA M, MEDADO I A, TOHMA K, DAPAT C, SEGUBRE-MERCADO E, TANDOC A, LUPISAN S, OSHITANI H. Molecular characterization of chikungunya virus, Philippines, 2011–2013. *Emerging infectious diseases.* 22 (5): 887, 2016.
74. THIBERVILLE SD, et al. Chikungunya fever: epidemiology, clinical syndrome, pathogenesis and therapy. *Antiviral Res.* 99(3):345–370. doi: 10.1016/j.antiviral.2013.06.009. 2013.
75. VOLK S M, CHEN R, TSETSAKIN K A, ADAMS A P, GARCIA T I, SALL A A, NASAR F, SCHUH A J, HOLMES E C, HIGGS S, et al. Genome-Scale Phylogenetic Analyses of Chikungunya Virus Reveal Independent Emergences of Recent Epidemics and Various Evolutionary Rates. *J.84:6497–6504. Virol.* 2010
76. WAGGONER J J, BALLESTEROS G, GRESH L, MOHAMED-HADLEY A, TELLEZ Y, SAHOO M K, ABEYNAYAKE J, BALMASEDA A, HARRIS E, PINSKY B A. Clinical evaluation of a single-reaction real-time RT-PCR for pan-dengue and chikungunya virus detection. *J Clin Virol* 78:57–61. 2016.
77. WAHID B, ALIA A, RAFIQUEA S, IDRES M. Global expansion of chikungunya virus: mapping the 64-year history. *International Journal of Infectious Diseases* 58, p. 69–76. March 2017.
78. WEAVER S C, LECUIT M. Chikungunya virus and the global spread of a mosquito-borne disease. *N Engl J Med*372(13):1231–1239. 2015.
79. WICHIT S., HAMEL R., BERNARD E., TALIGNANI L., DIOP F., FERRARIS P, LIEGEOIS F, EKCHARIYAWAT P, LUPLERTLOP N, SURASOMBATPATTANA P, et al. Imipramine Inhibits Chikungunya Virus Replication in Human Skin Fibroblasts through Interference with Intracellular Cholesterol Trafficking. 7:3145. *Sci. Rep.* 2017.
80. WU W, WANG J, YU N, YAN J, ZHUO Z, CHEN M, SU X, FANG M, HE S, ZHANG S, ZHANG Y, GE S, XIA N. Desenvolvimento de multiplex em tempo real ensaio de reação em cadeia de polimerase reversa para

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detecção simultânea dos vírus Zika, dengue, febre amarela e chikungunya em um único tubo. *J Med Virol* 90:1681-1686. 2018.

81. ZANNOLI S, MOROTTI M, DENICOLÒ A, TASSINARI M, CHIESA C, PIERRO A, SAMBRI V. Global epidemiology of Zika and Chikungunya virus human infections. *Microbiol Med* 32:82-96. 2017.