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Chikungunya fever

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Abstract

Chikungunya virus is widespread throughout the tropics, where it causes recurrent outbreaks of chikungunya fever. In recent years, outbreaks have afflicted populations in East and Central Africa, South America and Southeast Asia. The virus is transmitted by *Aedes aegypti* and *Aedes albopictus* mosquitoes. Chikungunya fever is characterized by severe arthralgia and myalgia that can persist for years and have considerable detrimental effects on health, quality of life and economic productivity. The effects of climate change as well as increased globalization of

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Author contributions

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Competing interests

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commerce and travel have led to growth of the habitat of *Aedes* mosquitoes. As a result, increasing numbers of people will be at risk of chikungunya fever in the coming years. In the absence of specific antiviral treatments and with vaccines still in development, surveillance and vector control are essential to suppress re-emergence and epidemics.

Introduction

Chikungunya virus (CHIKV) is an *Aedes* mosquito-borne alphavirus (family *Togaviridae*) presenting a global health threat. CHIKV infection presents as an acute febrile illness known as chikungunya fever. Infection is usually self-limiting and characterized by severe polyarthralgia and myalgia (pain in the joints and skeletal muscle, respectively) that can become chronic, with debilitating rheumatic disease in a substantial portion of infected individuals¹. Chikungunya fever-induced arthropathy (disease of the joints) has a considerable effect on the quality of life of individuals with chronic disease and results in economic losses, especially in developing countries.

CHIKV was first discovered in 1952 on the Makonde Plateau in East Africa. The word chikungunya is derived from the Kimakonde root verb *kungunyala* meaning “that which bends up”, “to become contorted” or “to walk bent over”¹. Between the 1960s and 1990s, CHIKV outbreaks were reported in Asia and Africa, and the virus was thought to be maintained in a sylvatic cycle (cyclical transmission between non-human animal host and insects) with occasional transmission into humans. Today, CHIKV has been reported in more than 60 countries in Africa, Asia, Europe and the Americas as a consequence of globalization of travel and trade as well as climate change that has led to the dispersal of *Aedes* mosquitoes to an increasing number of temperate regions. In addition, the *Aedes albopictus* mosquito has adapted to slightly colder environments, further increasing its global distribution^{1–3}. Sylvatic cycles still exist in Africa and likely also in parts of Asia; however, urban transmission between humans and mosquitoes is increasingly more important^{4–6} (Fig. 1).

The pandemic potential of CHIKV has long been recognized, and the virus is listed by the Coalition for Epidemic Preparedness Innovations (CEPI) as a priority pathogen for vaccine development⁷. In 2018, CHIKV was added to the WHO shortlist for priority research and development, which notably also included pandemic coronaviruses⁸. There is no specific antiviral treatment against CHIKV infection, but several preventive vaccines are close to market authorization and may, together with classical and new vector control strategies, contribute to reducing the burden of chikungunya fever.

In this Primer, we outline the current understanding of chikungunya fever based on research in patients and animal models, which have provided considerable insights into the complex spectrum of disease manifestations and the mediators of arthritic immunopathology. We review the epidemiology, basic virology and mechanisms underlying the immunopathophysiology of CHIKV infection as well as the clinical management of chikungunya fever. Finally, we discuss effects on the quality of life of patients and new strategies for the prevention of CHIKV infection.

Epidemiology

CHIKV is the most prevalent alphavirus transmitted to humans by the bite of a female *Aedes* mosquito^{4,9}. Although still unclear, it is thought that CHIKV is maintained in a sylvatic cycle in Africa and Asia involving non-human primates (and possibly other yet-undiscovered animal species) and forest-dwelling mosquitoes, with urban penetration and human-to-human transmission being driven by two anthropophilic (preferring human blood over that of other animals) mosquitoes of the genus *Aedes*^{5,6}. The most commonly reported CHIKV transmission is associated with periurban or urban *Aedes aegypti* populations but, over the past decades, *Ae. albopictus*, originally a zoophilic (preferring non-human, animal blood) forest-dwelling mosquito species from Asia has become increasingly important as a vector for CHIKV^{5,6,10–13}. With the increasing global distribution of the *Aedes* mosquitoes and their ability to adapt to urban settings, the urban transmission cycle is increasingly important. Here, during a blood meal on an infected person, the female mosquito ingests the virus, which infects various mosquito tissues, including the salivary glands. During a subsequent blood meal by the infected mosquito, the virus is deposited in the skin of an uninfected person along with mosquito saliva, infecting the person and perpetuating the viral replication cycle¹⁴.

Phylogenetic analysis identified three distinct lineages corresponding to their respective geographical origin: West African, East Central South African (ECSA) and Asian lineage^{15,16}. The ECSA lineage is further divided into two clades: ECSA1, which consists entirely of ancestral CHIKV sequences, and ECSA2, which contains sequences from the Central African Republic, Cameroon, Gabon and the Republic of Congo^{17,18}. Since its discovery in 1952, CHIKV has been reported to be circulating and causing sporadic outbreaks in sub-Saharan Africa. In 2004, an ECSA CHIKV strain emerged in Kenya and subsequently spread to the Indian Ocean Islands, where it caused outbreaks of an unprecedented magnitude, particularly in La Réunion^{19–24}. The extent of this outbreak has led to the emergence of a fourth phylogenetic lineage termed Indian Ocean lineage, which has subsequently dispersed to Asia and India²⁵ and caused autochthonous transmission (local disease spread) in Mediterranean Europe (Italy and France)^{26,27}.

In December 2013, another major outbreak occurred when a strain from the Asian lineage emerged for the first time on the Caribbean Saint Martin Island, from where the virus spread to more than 50 countries of the South American continent, causing a conservatively estimated 1 million infections^{28,29}. In 2014, the ECSA lineage was reported in Northeast Brazil, where it continues to circulate as the most prevalent strain today³⁰.

Most of the Indian Ocean lineage is characterized by an adaptive mutation in the E1 glycoprotein, which was first reported in the ECSA lineage in 2005 but is absent from other lineages. The E1-A226V mutation was found to be responsible for a 40-fold increase in transmission by *Ae. albopictus* mosquitoes without affecting viral fitness (replication efficiency) in the otherwise main vector *Ae. aegypti*. Additional adaptive mutations that facilitate transmission by *Ae. albopictus* have been identified in E1 (A98T, K211E) as well as in E2 (D60G, R198Q, L210Q, I211T, K233E, K252Q)^{31–33}, which forms a heterodimer with E1 on the surface of the viral particle and drives receptor interaction and entry.

Similar to E1-A226V, E2-L210Q is responsible for increased CHIKV dissemination in *Ae. albopictus* by increasing infectivity for epithelial cells lining the mosquito midgut³⁴. E2-I211T has a low prevalence in ECSA strains yet it occurs in all viruses that harbour E1-A226V. In vitro studies showed that E1-A98T and E2-I211T have epistatic effects by providing a prerequisite background for E1-A226V to exert its beneficial effect on infectivity³⁵.

Apart from repeated viral adaptation³⁶ to *Ae. albopictus*, climate change and the globalization of travel and trade are the main driving forces for the extending habitat of *Ae. albopictus* and, to a somewhat lesser extent, of *Ae. aegypti* in newly temperate regions. Unlike *Ae. aegypti*, *Ae. albopictus* is better adapted to surviving cold winters and can therefore inhabit regions that are less temperate than the historical distribution of the *Aedes* mosquito^{1–3}. Together, viral adaptation, climate change and globalization have led to geographical expansion of CHIKV beyond the tropics and neotropics. As >100 countries report circulation of CHIKV and there are >10 million cumulative cases of chikungunya fever today, an estimated 1.3 billion people are at risk of chikungunya fever globally³⁷. Climate change models predict that many more regions in the world might become more conducive from a climatological perspective for CHIKV transmission in the future, including parts of China, sub-Saharan Africa, Europe and the Americas^{38–40} (Fig. 1).

Risk factors

CHIKV infection is mostly self-limiting, but a considerably more complex spectrum of less common and severe atypical manifestations is now being recognized in specific subgroups of patients with comorbidities, co-infections or particular genetic backgrounds such as Toll-like receptor polymorphisms¹⁴. Hospitalization and mortality for CHIKV infection range from 0.6% to 13%^{41–43} and from 0.024% to 0.8%^{41,43–47}, respectively. Risk factors for developing severe forms of chikungunya fever and mortality have been poorly studied. In a study conducted on a population of Brazilian patients dating from the 2016–2017 epidemic, the risk factors for mortality were reported as pre-existing heart or kidney failure and the presence of fever, abdominal pain, dyspnoea, apathy or cytopenia at hospital admission. The contextual risk factors found in the literature are poorly described, but a few studies are nevertheless available in cohorts from major epidemics. In a study carried out in La Réunion on 2,101 participants aged >15 years, the contextual and lifestyle risk factors for developing chikungunya fever were: the declaration of a history of chikungunya fever in the neighbourhood and household, a maximum temperature of >28.5°C in the month preceding the infection, a socioeconomically disadvantaged district, the altitude of residence, a cumulative rainfall of >65 mm in the month preceding the infection, a sedentary occupation, lack of knowledge of CHIKV transmission and obesity⁴⁸. Severity also seems to be related to viral genotype, with an overall non-recovery rate of 50% (95% CI 40–60%) and 36% (95% CI 20–52%) associated with ECSA lineage and Asian lineage, respectively⁴⁹.

Mechanisms/pathophysiology

Chikungunya virus

CHIKV belongs to the genus alphavirus of the *Togaviridae* family⁵⁰. The enveloped viral particles are spherical and measure 65 nm in diameter^{51,52}. The positive-sense single-stranded RNA CHIKV genome is packaged by a viral capsid core and enveloped by a host cell-derived membrane that accommodates the viral envelope proteins, which make up the glycoprotein shell^{51–53} organized in an icosahedral symmetry (T = 4)^{51,52}. The ~12 kb genomic RNA (gRNA) contains two open-reading frames, respectively coding for the non-structural polyprotein and structural polyprotein⁵⁴. The virion-packaged gRNA resembles cellular mRNA as it carries a 5' Cap and is 3' polyadenylated, enabling immediate translation of the gRNA on release into the host cell cytoplasm⁵⁵ (Fig. 2).

Function of nsPs.

The four non-structural proteins (nsP1–4) are translated from the 5' ORF of the incoming viral gRNA and form the replicase complex that catalyses the production of new viral RNA^{56,57}. In the replicase complex, nsP4 provides RNA-dependent RNA polymerase and polyadenylation activities while a concerted action of nsP1 and nsP2 add a 5' Cap-0 to the newly formed positive-strand viral RNA^{58–61}. nsPs are produced as polyproteins (p123 and p1234) and their timed cleavage into separate nsPs by the nsP2 protease regulates the subsequent steps in viral RNA genesis. The replicase is localized to the plasma membrane through targeting of a dodecamer ring of nsP1 to form the neck of a replication spherule containing double-stranded RNA intermediates and from which 5' capped and 3' polyadenylated gRNA and subgenomic RNA (sgRNA) are released^{62–68}. sgRNA is translated to produce the structural proteins while the newly formed gRNA is packaged into new virions (Fig. 2).

CHIKV nsPs also counteract various cell-intrinsic antiviral responses⁶⁹, including the function of the antiviral innate immune mediator tetherin and the unfolded protein response⁷⁰. Furthermore, activation of *IFNB* and other antiviral genes in the infected cells is prevented by suppression of genome-wide transcription and interferon-induced JAK–STAT signalling^{71,72}. Finally, the formation of stress granules that suppress translation of the viral genome is also prevented⁷³.

Despite these and other mitigating strategies by CHIKV to escape recognition by innate immune sensing, such as sequestration of double-stranded RNA into replication spherules and addition of a cap to its 5' end gRNA and sgRNA, virus replication is a potent stimulator of cell-intrinsic innate immune responses^{74–79}. These responses include the activation of interferon genes after detection of non-self RNA species by RIG-I-like or Toll-like receptors^{74–77}, the unfolded protein response to suppress translation of viral genes⁷⁸, and activation of the inflammasome⁷⁹. Potent activation of the NLRP3 inflammasome and release of IL-1 β and IL-18 contribute to the inflammatory joint pathology of CHIKV infection⁸⁰.

Function of structural proteins.

Structural proteins are translated from sgRNA as a single polyprotein (C–E3–E2–6K/TF–E1), from which capsid is autoproteolytically cleaved to remain cytoplasmic, and the envelope proteins are processed during their passage through the endoplasmic reticulum and trans-Golgi network to be presented as trimers of E2–E1 heterodimers on the plasma membrane^{51,66,81–86} (Fig. 2). Packaging of viral gRNA into virions follows capsid binding to gRNA-specific sequences⁸⁷, and interactions between capsid and the cytoplasmic tail of E2 coordinate enveloping of the nucleocapsid in budding virions. The E2 envelope subunit is the main determinant for receptor binding^{51,82,83}, while the E1 subunit contains a fusion loop allowing fusion of the viral and endosomal membrane in the newly infected cell to release the viral RNA in the cytoplasm⁸⁸. The E3 envelope subunit prevents premature release of the E1 fusion loop⁷⁷ and the 6K/TF protein functions as an ion channel in the endoplasmic reticulum to stimulate efficient budding⁸⁹.

Host receptors of CHIKV.

Entry of CHIKV into host cells is thought to be facilitated mainly by clathrin-mediated endocytosis after binding of a membrane receptor^{90,91}. This assumption is supported by the identification and in vivo validation of MXRA8 as a bona fide receptor in human cells for CHIKV and related arthritogenic alphaviruses⁹². MXRA8 is broadly expressed and supports infection of synovial fibroblasts, osteoblasts, chondrocytes and skeletal muscle cells in vitro⁸⁶, supporting its role in viral pathogenesis^{92,93}. However, incomplete suppression of viral replication in vivo on inhibition of the MXRA8 receptor binding by CHIKV in mice^{92,93} suggests the presence of additional receptors or attachment factors. Attachment factors support viral infection by increasing the residence time of the viral particle on the cell surface. The broadly expressed prohibitin⁹⁴, T cell immunoglobulin and mucin domain-containing protein 1 (TIM1), dendritic cell-specific intercellular adhesion molecule 3-grabbing non-integrin (DC-SIGN)⁸⁵ and basigin (CD147)⁹⁵ have also been suggested as entry or attachment factors for CHIKV as have glycosaminoglycans such as heparin and heparan sulfate⁹⁶ (Fig. 2). Further underscoring apparent plasticity in the usage of cell entry factors by CHIKV, no orthologue of MXRA8 was identified in mosquitoes⁸⁸. The same is true for ApoR2/VLDR and LDLR3, described as receptors in humans for related alphaviruses^{97,98}. No bona fide receptor for CHIKV in mosquito cells has yet been identified, but the ATP synthase β -subunit and HSC70 have been proposed as attachment factors^{99,100}.

CHIKV infection in vivo

Overview of infection.—Like other mosquito-borne arboviruses, CHIKV is inoculated in the skin during the blood meal of an infected female mosquito as virus-containing saliva is deposited in the dermis and potentially directly into the bloodstream. Initial replication in dermis-resident cells produces virus that can enter the bloodstream or spread to draining lymph nodes by infected migrating cells, or possibly as free virus through the lymphatic fluid¹⁰¹. While the same route of infection and a broad cellular tropism is shared by most arboviruses, the consistently short incubation period (3 days) of CHIKV infection¹⁰² and its remarkably high viraemia¹⁰³ are suggestive of particularities in its spread and replication

in patients compared with other arboviruses such as flaviviruses or phleboviruses. As most available data are derived from in vitro experiments, the general view is that, in the skin, the first cells to be productively infected are dermal fibroblasts, keratinocytes, melanocytes, and endothelial cells and that local infection of Langerhans cells and dendritic cells enables the virus to spread to draining lymph nodes as the cells migrate to initiate the adaptive immune response¹⁰⁴. Comparing the infectivity of alphaviruses in presence and absence of mosquito saliva showed an important proviral role for mosquito saliva components by modulating the local immune response, promoting influx of susceptible myeloid cells and retention of virus and permissive cells following local oedema^{105,106}. The propensity to infect skin-resident cells is thought to contribute to the maculopapular rash accompanying CHIKV infection. Mouse and non-human primate models established that subsequent systemic spread of the virus to various organs and tissues underpins the symptoms characterizing chikungunya fever^{107–110}. Viral replication in liver and spleen and infection of endothelial cells and monocytes in the peripheral blood is thought to contribute to the typical high viraemia^{107,108,111,112}. Infection of skeletal muscle-associated satellite cells and myoblasts^{113,114} as well as potentially of myofibres themselves causes muscle tissue necrosis and directly underlies myalgia during the acute phase of infection^{109,115}. During the acute phase, CHIKV infects macrophages and fibroblasts in the synovial joints, causing tissue destruction, driving production of pro-inflammatory cytokines and stimulating the influx of immune cells, including macrophages, T cells, B cells and natural killer cells, creating an inflammatory environment that drives the characterizing arthritic joint pains^{116,117} (Fig. 3).

Although the virus is invariably systemically cleared within days to undetectable levels in peripheral blood following potent interferon-mediated and humoral immune responses, long-term infection of the synovial macrophages, in which the sustained presence of virus-derived RNA and proteins has been detected¹¹⁶, is thought to be an important driver of sustained immune reactivity in joint tissue. The presence of long-term residual viral RNA and antigens in macrophages, fibroblasts and myofibres has also been noted in various mouse models and in a non-human primate model of CHIKV pathology^{110,117}. Viral persistence has been proposed as a contributor to the chronic arthritic joint pains that many patients experience¹¹⁸. In addition, infection of osteoblasts and chondrocytes explains the connective tissue damage and bone loss observed in patients most affected by CHIKV infection^{119,120}. However, the use of immunosuppressive therapies in chronic CHIKV treatment without increased disease¹²¹ and the absence of detectable viral proteins or RNA in the synovial fluids of patients with chronic joint pain over extended periods¹²² suggests involvement of other disease mechanisms.

Pathophysiology and immunology

Acute disease.—Rash, fever and joint pain encompass the clinical triad of CHIKV infection. However, like for other arboviruses, disease severity varies widely, ranging from a mild self-limited illness, to severe neurological manifestations, and to long-term debilitating arthralgias (Figs. 3 and 4). Initial infection is notable for high-level viraemia accompanied by a robust innate immune response^{123,124}, driving an abrupt onset of fever¹²⁵ after a 4–7 day incubation period. The fever is often high grade (> 39 °C), with defervescence occurring

after 4–5 days¹²⁶. Viraemia typically resolves by 8 days from symptom onset but longer durations of up to 10–12 days have been reported^{127–132}.

Debilitating joint pain is a prominent symptom during acute infection, with onset 2–5 days after fever. Arthralgias are usually symmetrical and tend to affect distal more than proximal joints. While typically self-limiting, with >50% of patients reporting resolution after 1 month, chronic arthritis can develop, making the pathogenesis of arthralgia and arthritis an important area of study¹²⁵.

In vitro and animal models suggest that CHIKV directly infects macrophages, leading to the release of inflammatory cytokines within the joint space^{108,133}. Additionally, CHIKV can directly infect human osteoblasts, which leads to an increase in the expression of IL-6, thereby activating RANKL and inhibiting osteoprotegerin (OPG)^{134,135} (Figs. 3 and 4), leading to the breakdown of bone. Impaired osteoblast function further decreases levels of alkaline phosphatase production, which affects bone mineralization¹³⁶.

About two-thirds of patients develop a transient rash during acute infection that is macular or papular. Desquamation of the rash and involvement of mucus membranes has also been reported¹²⁵. Additionally, a cross-sectional study found that 21% of patients were noted to develop a central facial rash, similar in appearance to the malar rash associated with systemic lupus erythematosus¹²⁵.

Apart from the triad of fever, arthralgias and rash, various additional symptoms can occur in acute CHIKV infection. Although rare, neurological manifestations are the most worrisome acute clinical manifestation given their increased association with intensive care unit (ICU) admissions and death^{137,138}. CHIKV is known to affect the central nervous system, causing a wide range of symptoms, from encephalopathy to acute disseminated encephalomyelitis^{139–142}. Patients on either end of the age spectrum are most likely to develop neurological symptoms of infection¹⁴³ (Fig. 3).

The neuroinvasive character of CHIKV has been confirmed by the detection of CHIKV RNA or anti-CHIKV IgM in the cerebral spinal fluid of persons suspected of having neurological involvement^{138,143}. Inferred production of inflammatory mediators by astrocytes^{77,144} agrees with evidence of inflammatory cytokines isolated in the cerebral spinal fluid of affected persons¹⁴⁵.

A systematic review found ocular involvement of CHIKV infection in about a quarter of patients, with inflammation, visual defects and pain being the most common symptoms, and conjunctivitis and optic neuritis the most common signs¹⁴⁶. Rare but serious syndromes have been reported, including uveitis, corneal involvement, episcleritis, retinitis and exudative retinal detachments^{147,148}. Isolation of viral RNA in the anterior chamber of the eye suggests direct infection, whereas cases of delayed retinitis also suggest an immune-mediated component¹⁴⁹.

Compared with dengue virus, laboratory abnormalities in CHIKV infection are usually less severe. Mild thrombocytopenia can be observed, but platelet levels typically remain >100,000/ μ l, with a very low incidence of haemorrhagic complications^{150–152}. Lymphopenia

(lymphocyte count $<1,000$ cells/mm³) has been reported as the most common laboratory abnormality but was found to be severe (<500 cells/mm³) in only about one-third of patients¹⁵⁰. Transaminitis is rarely observed and is usually mild. Finally, hypocalcaemia is commonly reported, although the mechanism is not well understood^{150,152}.

Chronic disease.—After the acute phase of infection, some patients develop chronic joint pain. The post-acute phase extends from 21 days to 3 months after the onset of symptoms¹⁵³. Chikungunya fever is considered to pass to the chronic form when the clinical manifestations, among which arthralgias predominate, persist for >3 months^{116,153}. The proportion of patients progressing to this form is difficult to estimate and seems to depend on patient age and CHIKV genotype, but 40–80% of patients are considered to experience chronic disease^{116,121,154–156}. Increased viral loads as well as arthralgias, body aches and weakness during acute infection are associated with an increased risk of developing chronic arthralgias but replicative virus has not been detected^{116,155,156}. Additionally, those with underlying osteoarthritis are more likely to be affected¹⁵⁶. The reported prevalence of joint pain outbreaks varies and may depend on the length of follow-up, but most estimates suggest that one-quarter of patients are affected at 1 year^{155–158}.

The mechanism of chronic CHIKV infection is an area of ongoing research, with immune responses implicated more often than ongoing direct infection. Synovial fluid analysis of nearly 40 Colombian patients with persistent arthritis after a median of 22 months from initial CHIKV infection was unable to detect virus on culture or PCR¹²². Moreover, studies consistently demonstrate aberrant immune responses in affected individuals. Persons with chronic arthralgias were found to have higher levels of IL-6 than those who had recovered from initial infection, which suggests an ongoing distorted ratio of RANKL to OPG^{134,135}, leading to persistent bony erosions. Levels of IL-17, another cytokine associated with bone breakdown and resorption, were also higher among those with persistent arthralgias¹³⁴.

Chronic arthralgias due to CHIKV infection are also often compared with rheumatoid arthritis, both in terms of inflammatory pathogenesis (IL-17 and IL-6 are both implicated cytokines in rheumatoid arthritis) and clinical features, with one study finding that one-third of >200 patients with CHIKV-associated chronic arthralgias met American College of Rheumatology criteria for rheumatoid arthritis¹⁵⁷. Rheumatoid factor assessment is rarely positive¹⁵⁸, but one study showed a high proportion of patients with positive anti-CCP antibodies, which are a marker for rheumatoid arthritis^{122,158}. Imaging findings are similar between the two disease entities and include chronic erosive changes, joint effusions, marrow oedema, synovial thickening and tendonitis¹⁵⁷. Disease-modifying antirheumatic drugs (DMARDs) are often utilized for the treatment of chronic CHIKV arthralgias owing to these similarities¹⁵⁹.

Congenital infection.—Mother-to-child CHIKV transmission does occur. A systematic review found a pooled mother-to-child transmission risk of 15%, with an increased risk of ~50% estimated when infection occurred during the intrapartum period (that is, viraemic at time of delivery)¹⁶⁰, which is hypothesized to result from placental openings from contractions during labour¹⁶¹. One study found an association between intrapartum maternal infection and an increased risk of pregnancy complications, including the need for urgent

caesarean section due to fetal distress¹⁶¹, but others have found no difference in rates of pregnancy complications between women with CHIKV infection and those without at the time of delivery^{162,163}.

The rate of symptomatic disease among neonates with CHIKV infection has been estimated at ~50%, with neonates presenting within the first week of life with fever, irritability, hyperalgesia, limb oedema and rash; severe presentations included sepsis and meningoencephalitis¹⁶⁰. CHIKV-confirmed antepartum fetal death has been reported at a rate of 0.3%¹⁶⁰, with viral detection reported in amniotic fluid, placenta and fetal brain tissues¹⁶⁴.

During the 2005–2006 outbreak in La Reunion, vertical transmission occurred in ~50% of peripartum maternal infection, with half of these neonates developing encephalopathy shortly after birth¹⁶¹. The CHIMERE study subsequently followed these infants and found that those with initial neurological involvement had worse cognitive outcomes at 2 years compared with unaffected peers, although the sample size was small¹⁶⁵.

Diagnosis, screening and prevention

In patients presenting with febrile illness and polyarthralgia, especially in travellers returning from CHIKV-endemic areas, diagnostics can be used to confirm a clinical diagnosis of CHIKV infection to guide appropriate patient management. Confirmation of CHIKV diagnosis in sentinel populations (a population that is sampled regularly for surveillance purposes) provides data and early alerts of outbreaks to inform disease control strategies. Monitoring disease trends and transmission patterns has become increasingly important as climate change and global travel have led to the expansion of mosquito vectors into new habitats and geographical regions. Local epidemiological data can also be entered into clinical support applications to help clinicians improve their differential diagnosis of acute febrile illness and to identify sites for clinical trials of vaccines and therapeutics.

Diagnostic approaches

As the clinical presentation of chikungunya fever is often non-discernible from that of other arboviruses, a definitive diagnosis requires the use of diagnostic tests (Table 1). During the acute phase of infection, it is possible to detect the presence of viral RNA in serum samples. After the period of viraemia peaks, chikungunya fever is more optimally diagnosed indirectly using serological methods¹⁶⁶. The US CDC recommends that, during the first 8 days of CHIKV infection, detecting viral RNA in serum using nucleic acid amplification techniques should be the preferred diagnostic method¹⁶⁷. A negative nucleic acid amplification technique result should be followed with IgM antibody testing if the sample was taken 4 days after symptom onset. The US CDC also recommends confirmation of positive IgM test results with a test for neutralizing antibodies; however, neutralization assays are not widely available in most CHIKV-endemic areas. WHO recommends that both serological and virological testing methods should be used for patient specimens collected during the first week after the onset of symptoms¹⁶⁸.

Detection of viral nucleic acid.—CHIKV RNA can be detected with high specificity and sensitivity in serum or plasma samples collected from patients during the first 8 days of illness using various reverse transcription–PCR approaches^{169–171}. These assays can be performed outside of laboratory settings and are field deployable using small equipment that can be run on mains or battery power and have data transmission capability^{172,173}.

Detection of antibodies in response to infection.—CHIKV-specific IgM antibodies normally develop towards the end of the first week of illness (at 4–5 days post onset of symptoms) and reach their highest levels around 3–5 weeks after the onset of illness, persisting for ~2 months. Thus, to definitively rule out the diagnosis, convalescent-phase samples should be obtained from patients whose acute-phase samples test negative. A positive CHIKV IgM test is suggestive of current CHIKV infection or infection in the past 2 months, especially in patients with long-lasting arthralgia. In addition to laboratory-based quantitative assays, antibody tests are also available as single-use, disposable rapid diagnostic tests (RDTs) for point-of-care use.

The detection of neutralizing antibodies using the plaque reduction neutralization test (PRNT) provides the most specific evidence of infection but PRNT is technically demanding and not widely available. A retrospective diagnosis of chikungunya fever can also be made by demonstrating a fourfold rise in IgG antibody titres between serum samples collected during the acute and convalescent phases of infection.

Cross-reactivity with other viruses

A scoping review of the landscape of chikungunya fever RDTs found 43 products that are either commercially available or in development¹⁷⁴. Evaluation results from 11 studies showed that the sensitivity of the RDT IgM component was 20–100% and specificity was 73–100%. In regions where CHIKV is co-endemic with other arboviruses, high diagnostic specificity is important to avoid false positive test results. Extensive comparison of commercially available RDTs and ELISAs to validated laboratory assays remains crucial to verify their sensitivity and specificity^{175,176} as cross-reactivity towards related alphaviruses, such as Mayaro virus¹⁷⁷, and even flaviviruses (dengue virus)¹⁷⁸ was shown to severely impair confident diagnosis. Although Mayaro virus is only found in the Americas, other closely related alphaviruses with potential cross-reactivity are found nearly throughout Africa, Asia and Europe. Distinguishing CHIKV from O'nyong'nyong virus (ONNV) infections using serology, even a PRNT, can also be inconclusive. This is an important problem because both are widespread in Africa even though they have completely different vectors and control strategies.

Overall, commercially available nucleic acid tests for chikungunya fever have high sensitivity and specificity but are not widely used because of costs, requirement for equipment and technical expertise, and the need for hours, if not days, for the result to be provided to the clinician. Serological assays are available in both high throughput laboratory immunoassays and as single-use disposable RDTs that can be used in community settings with a rapid time to result of 15–20 min. However, the performance of these serological assays has been shown to be highly variable, with potential for false positive results due

to cross-reactivity. The development of RDTs to detect specific CHIKV antigens should improve the diagnosis of chikungunya fever¹⁷⁴.

Vaccine-based prevention of chikungunya fever

After >60 years of CHIKV vaccine research and development, the first CHIKV vaccine might be approved by the FDA in under a year^{179–182}. This breakthrough will be the result of decades of studying an array of vaccine platforms and an international effort by the Global Chikungunya Vaccine Clinical Development Program to push chikungunya fever to the forefront for funding and regulatory review¹⁸³.

Ideally, a CHIKV vaccine would elicit rapid (for example, 14 days) and durable (for example, lasting >2 years) immune responses (Box 1) as chikungunya fever outbreaks are unpredictable in terms of timing and geography, with a short time lag between identified cases and the peak of the epidemic. In addition, an optimal CHIKV vaccine would provide protection against all potential CHIKV variants as the virus strain in an outbreak is similarly unpredictable (although less genetically diverse than comparable arboviruses such as dengue)^{184,185}. As CHIKV is rarely a lethal disease, the primary goal of vaccination is to decrease morbidity; therefore, the safety and tolerability thresholds are set very high. Finally, because chikungunya fever typically affects low-income and middle-income countries, a vaccine must be affordable to the most vulnerable populations and easy to store and ship in tropical environments. The explosive nature of chikungunya fever outbreaks further complicates the implementation of large-scale phase III efficacy trials, with the need for surrogate markers of vaccine-induced immunity that enable evaluation by regulatory bodies.

Encouragingly, seroepidemiological studies following natural CHIKV infections indicate that neutralizing antibody levels, which may persist for decades, likely predict how well a vaccinated person will be protected from infection^{186–194}. Taken together, in 2019, the FDA Vaccines and Related Biological Products Advisory Committee agreed on a regulatory pathway for current CHIKV vaccines in development supported by seroepidemiological studies, animal challenge studies following passive transfer of pooled IgG from immunized humans and measurement of CHIKV viraemia in animals as a relevant end point for non-human primate studies.

Lead CHIKV vaccine candidates.—Currently, the most advanced CHIKV vaccine in development is VLA1553, a live-attenuated, singledose vaccine (Table 2). A full licensure application to the FDA was begun in August 2022, following FDA Fast Track and Breakthrough Therapy designations in 2018 and 2021, respectively^{182,195}. VLA1553 was also granted PRiority MEDicine (PRIME) designation by the European Medicines Agency (EMA) in 2020, and regulatory submissions are planned in Europe in 2023 (refs. 182,195,196).

Following decades of clinical development efforts of these live-attenuated vaccines^{179,180,197–199}, the VLA1553 vaccine was developed using a CHIKV ECSA strain (LR 2006-OPY1) isolated during the outbreak in La Réunion in 2006 (refs. 132,200). A three-dose phase I trial of VLA1553 found that low and medium vaccine doses were

well tolerated and immunogenic; encouragingly, there was no discernible immune response following the third dose, suggesting that vaccinated participants were protected against, essentially, a repeat viral challenge (for example, had sterilizing immunity)^{201,202}. Follow-up studies in mice and non-human primates demonstrated that passive transfer of serum samples from the VLA1553 phase I study led to protection against CHIKV challenge²⁰⁰.

In 2022, the results of a USA-based randomized controlled trial of VLA1553 showed that nearly 100% of participants, including persons aged 65 or older, had met the proposed threshold for seroprotection after a single dose, and the vaccine was deemed safe and well tolerated²⁰². Follow-up on a subgroup of participants will continue for 5 years and an additional trial in adolescents is under way in Brazil, with the hope that it may be one of the first countries in an endemic area to provide approval.

Although VLA1553 is the most advanced CHIKV vaccine in development, downsides to live-attenuated vaccines exist that open the door for competing platforms. For example, live-attenuated vaccines require growing large quantities of live virus in highly contained and secure facilities. Moreover, live-attenuated vaccines, in general, often cause more systemic reactogenicity such as the high fevers and transient arthralgia and arthritis reported in some studies of VLA1553 (refs. 199,202). Live vaccines cannot be used in certain vulnerable populations, for example, during pregnancy or among immunocompromised hosts. One alternative to a live-attenuated vaccine is a product based on virus-like particles (VLPs). VLPs are composed of key viral proteins that self-assemble into structures that resemble the real virus but do not replicate. They are much simpler to manufacture than live-attenuated vaccines, are easy to store and ship, and have a proven safety profile²⁰³.

In 2014, results were released from the first clinical trial of a CHIKV VLP vaccine, developed by the US National Institutes of Health Vaccine Research Center, called VRC-CHKVLP059-00-VP, which consists of CHIKV E1, E2 and capsid proteins of a West African strain²⁰⁴. In this and other studies performed in endemic and non-endemic regions, VRC-CHKVLP059-00-VP was shown to be safe and immunogenic up to 72 weeks after administration^{199,205}. Baseline CHIKV antibody titres correlated with a higher neutralization titre following immunization, suggesting that pre-existing immunity can be successfully boosted. Although these data are promising, VRC-CHKVLP059-00-VP required two doses, 1 month apart, to elicit peak immunogenicity at 8 weeks^{199,205}. Given the explosive nature of chikungunya fever outbreaks, this response is likely too slow to be effective, particularly at the population level. As a result, the next step of VLP development was to add an adjuvant at the time of administration as a dose-sparing strategy.

In 2022, a phase II trial of PXVX0317, a VLP in combination with aluminium hydroxide was conducted²⁰⁶. This study found that the adjuvant substantially enhanced the neutralization response after the first injection, with seropositivity rates rising within only 7 days and reaching 100% by day 57. Importantly, a single high dose showed a rapid ~10-fold increase of neutralizing antibodies within a week and ~100-fold at 28 days, with a durable increase up to ~2 years. In addition, a booster dose at 18 months after the first active injection elicited a strong memory response. Joint pain was reported in 6% of participants after the first vaccination compared with joint pain in 12% of volunteers who received

VLA1533 (ref. 201). The single high dose regimen is currently being tested in a phase III clinical trial, and PXVX0317 is under an FDA Fast Track designation^{207,208}.

In addition to live-attenuated viruses and VLP vaccines, viral vectors have been explored to deliver CHIKV antigens. The leading example is a live-attenuated recombinant, measles-vectored CHIKV vaccine, V184 (also known as MV-CHIK), based on the Schwarz measles vaccine strain^{209–211} modified to include CHIKV structural genes derived from the 2006 La Réunion Island strain²¹². A phase I trial demonstrated that the vaccine was safe and immunogenic at all dose levels, with better responses at the higher doses; pre-existing measles immunity did not impair immunogenicity²¹⁰. In the 2016–2017 follow-up phase II trial, the high dose of V184 induced considerably higher concentrations of neutralizing antibodies than the lower dose but required a second dose to achieve 95.7% seroconversion by day 56 (ref. 209), and neutralizing antibody titres remained lower than those in a cohort of patients with infection¹⁹¹. Nevertheless, passive transfer of neutralizing antibodies induced in clinical trial participants vaccinated with V184 protected against chikungunya fever²¹³. The vaccine was generally safe and well tolerated, and the safety profile was very similar to the licensed control vaccine Priorix. Based on these promising phase II results, the vaccine received FDA Fast Track designation²¹⁴ and PRIME designation by EMA²¹⁵ as well as funding support to launch a phase III trial from CEPI²¹⁶ but a phase III trial is not yet registered in [ClinicalTrials.gov](https://clinicaltrials.gov). Additional ancillary studies are under way looking at V184 in endemic areas and among those with pre-existing chikungunya fever immunity^{217,218}.

BBV87 is an inactivated CHIKV vaccine currently under development based on an Indian strain of CHIKV (DRDE-06) from an ECSA lineage outbreak in 2006 (refs. 183,219) (Table 2). One of the advantages of inactivated virus vaccines is that they are thermostable, making shipping and storage feasible in low-income and middle-income countries. They are also less reactogenic and are safe to use in all populations, including during pregnancy and in immunocompromised individuals. However, inactivated virus vaccines require secure facilities to culture live virus (before inactivation) and are also less immunogenic than live-virus vaccines.

A phase I trial of BBV87 (with aluminium hydroxide adjuvant) was completed in 2020 in India. According to a press release by CEPI, an “optimum immune response was elicited” in this phase I trial, but further details are not available and the results are not published²²⁰. Owing to support from major international agencies and the initiation of a phase II/III trial in Costa Rica in 2021, BBV87 can be considered a lead vaccine in development.

Other CHIKV vaccines in development.—Efforts to develop a CHIKV mRNA vaccine predate the COVID-19 pandemic and, in 2019, results of a phase I study to evaluate mRNA-1388 were reported²²¹. mRNA-1388 consists of a single mRNA encoding the full native structural polyprotein (C–E3–E2–6K–E1) of CHIKV, which assembles into VLPs that are released from cells²²². In the 60-participant phase I study, neutralizing seroresponse reached 100% only after the second vaccination at day 56 and observed neutralizing antibody titres are not yet published. Arthralgia was reported in 21.4% of participants but all events were grade <2 and resolved by day 4 (ref. 222).

In 2021, the results of a trial of a single dose of a replication-deficient simian adenovirus-vectored CHIKV vaccine, ChAdOx1, were reported²²³. ChAdOx1 expresses the CHIKV structural cassette polyprotein, leading to the formation and release of CHIKV VLPs in transduced cells. In 24 participants, all doses tested were effective at rapidly inducing broadly neutralizing antibodies against CHIKV E2 surface protein, with 100% seroconversion by day 14 and neutralization of four distinct CHIKV genotypes.

Additional CHIKV vaccines are in the preclinical development phase such as chimeric alphaviruses (Venezuelan equine encephalitis virus, eastern equine encephalitis virus or Eilat virus) encoding CHIKV-specific proteins^{224,225} and heterologous viral vector vaccines based on vesicular stomatitis and modified vaccinia Ankara viruses^{226–228}.

New strategies for chikungunya fever prevention

One of the major challenges in a chikungunya fever outbreak is how to elicit immunity rapidly, before the peak of an outbreak. A new solution to this problem is based on the use of a lipid nanoparticle-encapsulated mRNA (mRNA-1944) encoding a particularly potent anti-CHIKV monoclonal antibody (CHKV-24)²²⁹. A phase I trial testing mRNA-1944 administered as an infusion reported that, overall, 50% of participants had generally mild to moderate treatment-related adverse events, nearly all of which were attributed to infusion-related reactions²³⁰. The administration of mRNA-1944 resulted in dose-related increases in CHKV-24 IgG serum levels after a single administration and in a 1.8-fold linear accumulation of CHKV-24 IgG concentrations after a second dose. The mean half-life was ~69 days. This study demonstrated the ability to produce functional proteins from separate mRNAs encoding different proteins and the feasibility of using a repeat dose regimen with this mRNA platform.

Vector control

CHIKV is primarily spread via the mosquito vectors *Ae. aegypti* and *Ae. albopictus*; thus, traditional methods of mosquito control can be harnessed to control chikungunya fever outbreaks. In theory, these would include mass spraying of either chemical adulticides and larvicides or mechanical methods to eliminate standing water. In reality, CHIKV is now fully adapted to urban transmission cycles, and outbreaks have increasingly occurred in dense populous settings where widespread use of toxic chemical spraying is not possible²³¹. In addition, outdoor insecticide spraying is ineffective at reaching indoor resting *Ae. aegypti* mosquitoes²³². Use of chemical insecticides is also limited by the rapid selection for resistance. A more environmentally sound approach is to use trapping systems that result in the capture, death or sterilization of vectors²³³. For mosquito vectors, these methods include mass-trapping with sticky gravid traps placed in 60–80% of homes, dry attractive toxic sugar bait, electromechanical traps, and traps coupled with ultra-low-volume spraying^{234–236}. A novel approach is the use of inactivated yeast interfering RNA formulations that are specific for killing mosquito larvae²³⁷. Tablets of interfering RNA that silence essential mosquito genes can be placed in water inside trap containers. Early warning systems are also being developed using thousands of mosquito traps in targeted areas, where surveillance for CHIKV and other arboviruses can be performed on captured mosquitoes²³⁸.

Finally, genetic control technologies are being developed to suppress or modify mosquito populations to reduce the transmission of viral pathogens. These technologies include the introduction of male mosquitoes infected with the intracellular parasite *Wolbachia* and transgenic mosquitoes that produce sterile females or inhibit viral replication of target pathogens²³⁹. It is unlikely that any of the above mosquito control methods will be completely effective in controlling CHIKV if used alone but, if used in an integrated control programme with other synergistic mosquito control tools and vaccines, effective control might be achievable.

Management

Management of acute chikungunya fever

Treatment and severity assessment of chikungunya fever.—The treatment of uncomplicated, acute forms of chikungunya fever only requires resting, oral hydration and simple, well-conducted analgesia^{153,240}. Outpatient care at home is also possible and recommended by WHO²⁴¹. It is also important to distinguish those patients presenting with simple forms of chikungunya fever from those presenting with severe forms that require hospitalization and monitoring in a specialized environment. Severity criteria requiring hospitalization are the presence of haemodynamic failure, pain not controlled by level 1 (paracetamol) and level 2 (tramadol or codeine) analgesics, signs of bleeding, comorbidities associated with decompensation or atypical chikungunya fever symptoms (respiratory, cardiac, neurological, hepatic, haematological or renal manifestations)²⁴¹. The management of patients requiring hospitalization in an ICU consists almost exclusively of multimodal support treatment (that is, extra-renal purification, mechanical ventilation, haemodynamic support) for multiple organ failure. Only adjuvant treatment with intravenous immunoglobulins in the event of associated polyneuropathy seems to provide benefit in certain patients^{242,243} (Fig. 5).

Pain management.—Acute pain is one of the most disabling symptoms occurring in the acute phase of chikungunya fever. Assessment of pain traditionally uses validated pain rating scales such as the visual analogue scale (VAS), which ranges from 0 to 10 (refs. 153,240,244). The use of multimodal analgesia by creating synergistic combinations relating to the level of pain is recommended¹⁵³. The standard therapeutic approach during chikungunya fever should use, as first line, a combination of level 1 and level 2 analgesics and NSAIDs. When the pain persists or when it is immediately very severe in the initial phase (VAS >7), level 3 analgesics (opioids or equivalent) can be used. These therapies must be used with caution and soliciting the opinion of a doctor specializing in pain management is recommended²⁴⁵.

If neuropathic pain is suspected during clinical examination, which may reveal allodynia (pain from a stimulus that does not usually provoke pain), neuralgia (sharp, shocking pain), paraesthesia (burning, prickling sensation) or hypoaesthesia (reduced sensation), optimization of analgesia requires evaluation using the validated DN4 questionnaire consisting of both sensory descriptors and signs related to bedside sensory examination (four questions aimed at looking for signs such as paraesthesia, hypoaesthesia or allodynia)²⁴⁶.

Patients with a DN4 score of 4 (where 10 is the highest pain) may require an associated treatment such as pregabalin, gabapentin, amitriptyline or clomipramine tricyclic antidepressants, and an anticonvulsant²⁴⁷.

Anti-inflammatory treatment.—NSAIDs are an integral part of the management of inflammation following chikungunya fever. Although there remains controversy regarding the use of NSAIDs in acute phase treatment, most international guidelines favour the use of NSAIDs for the treatment of chikungunya fever in its acute phase^{153,240,241,248}. No NSAID has demonstrated superiority over another. The most used NSAIDs are naproxen, ibuprofen, diclofenac or aceclofenac²⁴⁹. NSAIDs can only be taken in combination with co-analgesia comprising, at least, a level 1 analgesic.

Other therapeutics.—Some scientific societies, particularly in Brazil, refer to the daily use of hydroxychloroquine in the event of persistent symptoms^{240,244}. WHO also recommends daily hydroxychloroquine or chloroquine for 4 weeks in the event of musculoskeletal symptoms resistant to conventional symptomatic treatment²⁵⁰. However, the effectiveness of hydroxychloroquine and chloroquine has not been proven and most of the recommendations from other expert societies are not in favour of their use^{153,241,251}.

There is currently no place for joint infiltration (that is, NSAIDs or even corticosteroids by intra-articular injection) in the management of chikungunya fever in the acute disease phase. However, it is possible to consider repeated icing of painful joints and temporary immobilization of the affected joints to reduce pain, for example, by wearing an orthotic during sleep²⁴¹.

Management of chronic chikungunya fever

Pain management and anti-inflammatory treatments.—Systemically administered corticosteroids are not recommended by experts for the treatment of the acute phase of chikungunya fever (<3 weeks) but may be offered in the post-acute phase at low doses in case of resistance or contraindication to NSAIDs or opioids^{153,241,244}. Their administration is beneficial only in the post-acute and chronic phase (>3 months after infection)^{121,252–254}, especially in patients presenting with inflammatory manifestations in the joints (tenosynovitis, synovitis, tunnel syndrome), neurological manifestations or inflammation in other prominent localizations^{140,255,256}. They can also be combined with other analgesics (level 1 and level 2) in the event of resistance or ineffectiveness of NSAID treatment.

Disease-modifying antirheumatic drugs.—DMARDs act on rheumatological symptoms. This drug class has pleiotropic effects and acts both as an immunomodulator and as an anti-inflammatory drug^{252,257,258}. DMARDs are used in the treatment of chronic chikungunya fever with beneficial effects in the control of joint symptoms related to the chronic pro-inflammatory process^{153,255,259}. The French guidelines advise the use of DMARDs only after the eighth week of infection (post-acute phase) in patients with persistent joint symptoms from manifestations such as arthritis, synovitis or tenosynovitis, or tunnel syndrome¹⁵³. The Brazilian guidelines recommend a more systematic use of

methotrexate in combination with hydroxychloroquine and low doses of corticosteroids for a period of 6–8 weeks after the acute phase (that is, after a minimum of 15 days for post-acute or chronic phases)²⁴⁹. In any event, differential diagnoses, particularly chronic inflammatory arthritis, should be eliminated during a specialist consultation with a rheumatologist before considering this type of treatment^{121,260}.

Methotrexate is the treatment of choice, particularly for chronic inflammatory rheumatism, which includes possibly clinically severe rheumatic arthritis^{252,255}. Treating chronic inflammatory rheumatism occurring in the chronic phase with methotrexate improved joint symptoms in 75% of patients with partial remission in 8% of patients²⁶¹. However, 9% of patients were non-responders and a considerable number of patients experienced adverse effects²⁶¹. Other studies have evaluated methotrexate in combination (usually dual therapies) with other DMARDs. An evaluation of the efficacy of methotrexate combined with hydroxychloroquine in a cohort of patients in India with a 6-month follow-up showed clinical efficacy in 49% of treated patients²⁶². Another study evaluated the effectiveness of the addition of methotrexate in patients that stopped a combination of hydroxychloroquine and sulfasalazine after 3 months of well-conducted treatment^{262,263}, showing clinical improvement in >90% of patients at 24 months and increased efficacy of methotrexate in patients positive for rheumatoid factor or anti-CCP. One study investigated the response to treatment combining methotrexate, sulfasalazine and hydroxychloroquine compared with treatment using hydroxychloroquine plus low-dose corticosteroids for 6 weeks. Both groups received corticosteroid therapy for 6 weeks. This study demonstrated the efficacy of the therapeutic combination of several DMARDs with corticosteroid therapy, with efficacy at 24 months on disease activity, functional prognosis and pain scores (VAS)²⁶⁴.

Finally, other therapeutics, such as tumour necrosis factor inhibitors, have been proposed as an alternative to DMARDs in cases of chikungunya fever resistant to other treatments^{153,240}.

Adjuvant physical and rehabilitation medicine.—Physical measures (kinesiotherapy and physical rehabilitation manoeuvres) and physiotherapy complete the care and aim to limit the general effects of joint and musculoskeletal disorders by improving joint mobility and helping to reduce chronic pain^{121,252,255}. The evidence for passive and active mobilization, proprioception, and muscle strengthening (exercise training) is favourable^{257,265}. Other therapeutic approaches, such as neuromodulation, also seem to be of interest by reducing pain scores (VAS) in the short and medium term^{266,267}. Analgesics and relaxation physiotherapy techniques have a lower level of evidence, but benefits in relation to pain are sometimes observed when using analgesics and DMARDs in combination with other therapies (ultrasound, cryotherapy, electrotherapy and transcutaneous electrical nerve stimulation techniques) by acting on the patient's psychic component^{244,255}.

Quality of life

Chikungunya fever and further complications

The quality of life of patients with chikungunya fever can deteriorate not only during the acute phase of the infection (first 21 days following the first clinical signs) but also during

the chronic phase of the disease, characterized by joint and neurological damage, or even damage to other organs.

During the acute phase, fatigue and low thymic activity with depressive symptoms seemed to be the most debilitating symptoms. In a study conducted in La Réunion in 2006, evaluating the effect of chikungunya fever on military personnel aged 19–55 years, clinically significant to very significant fatigue was found in 47% of 662 patients, making normal activities impossible in 37% of patients²⁶⁸. Depressive symptoms were also noted, with a drop in morale and major depression in 35% and ~5% of patients, respectively²⁶⁸.

In addition to the consequences on morbidity and mortality observed to be directly attributable to the chronic form of chikungunya fever, the infection aggravates pre-existing pathologies in many patients, leading to particularly severe clinical problems. During the 2005–2006 epidemic in La Réunion, 237 deaths were the direct or indirect consequence of chikungunya fever owing to decompensation of pre-existing pathologies²⁶⁹. In a study from 2016 of 65 patients admitted to the ICU for chikungunya fever during American and Caribbean epidemics, 54 (83%) patients presented with a pre-existing chronic condition and 27 of these were admitted for decompensation of this pathology due to CHIKV infection^{16,270}.

Complications and effects on quality of life are, by far, most likely to occur in the chronic disease phase. A study set in South India found a considerable reduction in quality of life according to validated SF-36 questionnaires in 403 patients who presented clinical manifestations of chikungunya fever compared with a control group²⁷¹. Compared with the control group, the quality of life of patients who still had active clinical manifestations of chikungunya fever after 3 months and that of patients who had recovered had a 20-fold and 5-fold reduction, respectively. Young age, male sex, absence of rash, less than five affected joints and joint manifestations lasting <2 weeks were associated with patient recovery. Of note, the Asian CHIKV lineage seems to be less virulent than most ECSA lineages, including the Indian Ocean lineage^{272,273}. These lineages indeed seem to be associated with a more severe evolution and a more impacted quality of life in the long term⁴⁹. Few studies have focused on the long-term follow-up of these patients, but it seems that those with chronic forms suffer from disabling clinical manifestations for several months or even years after the initial infection^{153,245}. The signs and symptoms most frequently observed at >6 months of follow-up are joint pain, tendinitis and tenosynovitis with thickening of the synovial tissues as well as bone lesions, fatigue and paraesthesias suggestive of chronic neuritis^{121,157}. In the cohort of military personnel from La Réunion, chronic pain was noted as continuous in 41% of patients and as discontinuous with clinical remission and relapses in 59% of patients²⁶⁸. Self-rated fatigue was disabling in 5% and very severe or severe in 43% of patients; mood alteration was described as totally depressed in 2%, demoralized in 38% and debilitated in 44%²⁶⁸.

Psychosocial support and adjuvant physical measures

The psychosocial effects of CHIKV infection can be considerable in the acute phase and affect the daily life of patients; however, most psychosocial problems are reported in the chronic phase of the disease. This may require the use of social support, particularly in

the form of assistance at home or close visits by nursing staff. A psychological opinion may also be required in the event of substantial functional loss and presence of pain refractory to simple analgesics such that a psychological component of the pain is not overlooked^{240,252,257,274}. The levels of evidence concerning physical and rehabilitation medicine are the same in the chronic phase as in the acute phase²⁵⁷. WHO and many international scientific societies recommend physical rehabilitation interventions at all stages of the disease. These interventions include daily physical exercise, manual therapies and physiotherapy^{274,275}. There is good evidence that physical exercise reduces pain during the chronic phase²⁶⁵. The psychosocial impact is greater in the chronic phase due to joint damage and an impact is found in nearly 71% of patients with joint pain²⁷⁶ — given that chronic pain has a major effect on quality of life, this may explain why psychosocial support is so important²⁵⁰. Thus, considering the significant decline in quality of life criteria in these patients, a multidisciplinary approach combining psychosocial support and physical rehabilitation is necessary in the chronic phase^{277,278}.

Outlook

CHIKV infection causes an acute febrile illness that can result in persisting polyarthralgia in a substantial proportion of patients^{4,9,14,116,118,121,154,156}. The mechanisms of chikungunya fever pathogenesis are influenced by a complex interplay of human and viral factors. Considerable progress has been made in the past decade to identify key host molecules involved in CHIKV infection and immunopathogenesis^{69–80}, but further studies are still required to validate these findings in relevant cellular systems, animal models and patients.

Interdisciplinary research with the integration of clinical, epidemiological and basic biomedical research of the interactions between the virus, mosquito vector and human host is required for a better understanding of transmission dynamics, to develop better diagnostic tools and to disentangle chronic pathogenesis, including chronic forms. Various studies on CHIKV immunobiology have outlined several mechanisms that the virus uses to subvert or counteract human innate immune responses^{69–73}. Advancing the molecular understanding of immune evasion pathways would help refine knowledge of CHIKV pathogenesis and the development of chronic disease, and may offer a starting point to develop new virus-specific therapeutics that may be useful not only for the treatment of chikungunya fever but possibly also for related arthritogenic alphaviruses. Indeed, although CHIKV is currently, by far, the most important mosquito-transmitted alphavirus, several other alphaviruses that are still geographically confined to the Americas (Mayaro virus, Venezuelan equine encephalitis virus, eastern equine encephalitis virus and western equine encephalitis virus), Africa (ONNV, Middelburg virus, Semliki Forest virus and Ndumu virus), Oceania (Ross River virus and Barmah Forest virus) and Europe (Sindbis virus) have the potential for emergence at the global scale as many of the insect vectors implicated in transmission have a broader geographical presence or are expanding their presence from the regions where these viruses are presently circulating^{6,279–281}. Unfortunately, no medical countermeasures are currently available for these emerging alphaviruses and containment of these viruses from becoming epidemic relies on virus surveillance and vector control^{5,6}.

New molecular diagnostic and antigen detection tests and a better understanding of pathogenic mechanisms will enable surveillance, earlier diagnosis and more effective clinical management of alphavirus infections. Little is known about whether previous alphavirus infection leads to cross-protection or, more importantly, to more severe disease manifestations in secondary infections with a related alphavirus as has been documented for dengue virus^{282–284}.

Moving forward, the discovery of more specific biomarkers of CHIKV infection should be a high priority. For example, preliminary work showed that an E2 region is a dominant B cell epitope throughout the course of CHIKV disease in patients and that its amino acid sequence is highly conserved across most CHIKV lineages²⁸⁵. The antibody responses to the E2 region showed 58% cross-reactivity with sera from patients infected with non-CHIKV alphaviruses (samples positive for antibodies against Ross River virus, Barmah Forest virus, Sindbis virus and combined Barmah Forest and Ross River viruses) but only 6–7% cross-reactivity with dengue and other flaviviruses. These findings show the potential of using specific markers to enable early detection of CHIKV infection and, in areas where CHIKV is co-endemic with dengue virus, to guide appropriate clinical management. Further studies are needed to find unique CHIKV serology markers that are not cross-reactive with non-CHIKV alphaviruses and with flaviviruses that may be co-circulating.

The different vaccine platforms used in the development of candidate CHIKV vaccines are also amenable to vaccines for related alphaviruses^{181,286,287} (Table 2). However, uncertainties remain as current vaccine strategies rely primarily on the induction of neutralizing antibodies as a protective mechanism²⁸⁶ but other immune correlates, including T cell and innate immune responses, should be considered and studied in depth. Furthermore, vaccine trial site selection (sites with realistic sample sizes to allow studies to reach valid conclusions on the efficacy of a vaccine) is complicated by the uncertainty of anticipating where chikungunya fever outbreaks will occur. With herd immunity starting to develop in affected populations in the past few years, serological studies are needed to identify potential trial sites where herd immunity is lacking and where sufficient transmission is likely to occur for a vaccine trial to be feasible²⁸⁸.

In the past few years, considerable advances have been made in selecting monoclonal antibodies for possible therapeutic use as well as in the production processes and modifications to extend antibody half-life. Passive transfer of purified polyclonal or monoclonal antibodies with neutralizing or non-neutralizing activity (that is, Fc-mediated effector functions) can protect from alphavirus infection in animal models. Interestingly, all protective antibodies target the E1, E2 or E3 proteins on the alphavirus heterodimeric E-protein^{289–291}. To date, no anti-alphavirus monoclonal antibody has been licenced for therapeutic or preventive use in humans and, although animal studies have shown feasibility^{291–293}, limitations exist with regard to the high cost of treatment and the complexity of delivering monoclonal antibodies to patients.

In the absence of an effective vaccine, viral suppressive therapies for CHIKV fever could be instrumental in lowering viraemia during the acute phase of the infection and, consequently, in limiting the progression to chronic disease. However, as for other arboviral

infections, the onset of symptoms can be sudden and the viraemic period short, leaving only limited opportunity for therapeutic intervention following confident diagnosis. Thus, it is expected that the development of exceedingly safe antivirals will also enable their use as prophylactic treatment, for example, to be taken by travellers to endemic regions or household members of patients²⁹⁴. Several promising candidate drugs targeting the viral enzymatic functions have been reported, including new or nature-derived chemical compounds inhibiting the capping, macrodomain and capsid protease functions of nsPs^{294–296}. However, none of these compounds has yet been tested in vivo or entered preclinical evaluation. By contrast, in a drug repurposing screen, the FDA-approved drugs novobiocin and telmisartan were identified as CHIKV protease inhibitors but their antiviral potential in vivo remains to be established²⁹⁷. Notably, the broad-spectrum nucleobase analogues favipiravir and sofosbuvir, targeting CHIKV RNA-dependent RNA polymerase activity, have shown some in vivo antiviral potential against CHIKV, and sofosbuvir, which is successfully used in hepatitis C virus infections, shows particular promise to become clinically relevant^{298,299}. Targeting the viral entry pathway, and specifically targeting the viral envelope–MXRA8 receptor interaction using recombinant Fc-MXRA8 fragments or combinations of neutralizing monoclonal antibodies³⁰⁰, has shown promise in animal models, and these approaches have a low risk of off-target effects. Other therapeutic strategies being investigated involve targeting host cell pathways that support or suppress viral replication, including fatty acid synthesis and cholesterol trafficking pathways, dysregulation of endosome acidification to suppress virus entry, inhibition of nucleobase biosynthesis, or immunomodulatory therapies to stimulate an interferon response^{294–296}. For promising broad-spectrum candidate compounds that show antiviral activity against several viruses, off-target toxic effects due to disruption of cellular pathways are to be expected; nevertheless, preclinical and clinical evaluations are still lacking^{132,157,199–296}.

CHIKV is regarded as a priority pathogen by the international community of virologists and health-care experts^{7,301,302} but this status is insufficiently reflected in commitments, investments and available research funding by governments and international organizations. If we want to be prepared for future pandemics and, ideally, prevent these pandemics from emerging, research into CHIKV and other arthropod-borne viruses in general needs to urgently be escalated in priority.

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Box 1**Desired features of a chikungunya virus vaccine**

- Rapid onset of immunity (7–14 days)
- Durable immunity (>2 years)
- Single dose
- Protection against multiple viral strains
- Very few adverse effects and no arthritis
- Easy to store and ship
- Affordable in low-income and middle-income countries
- An established immune correlate of protection

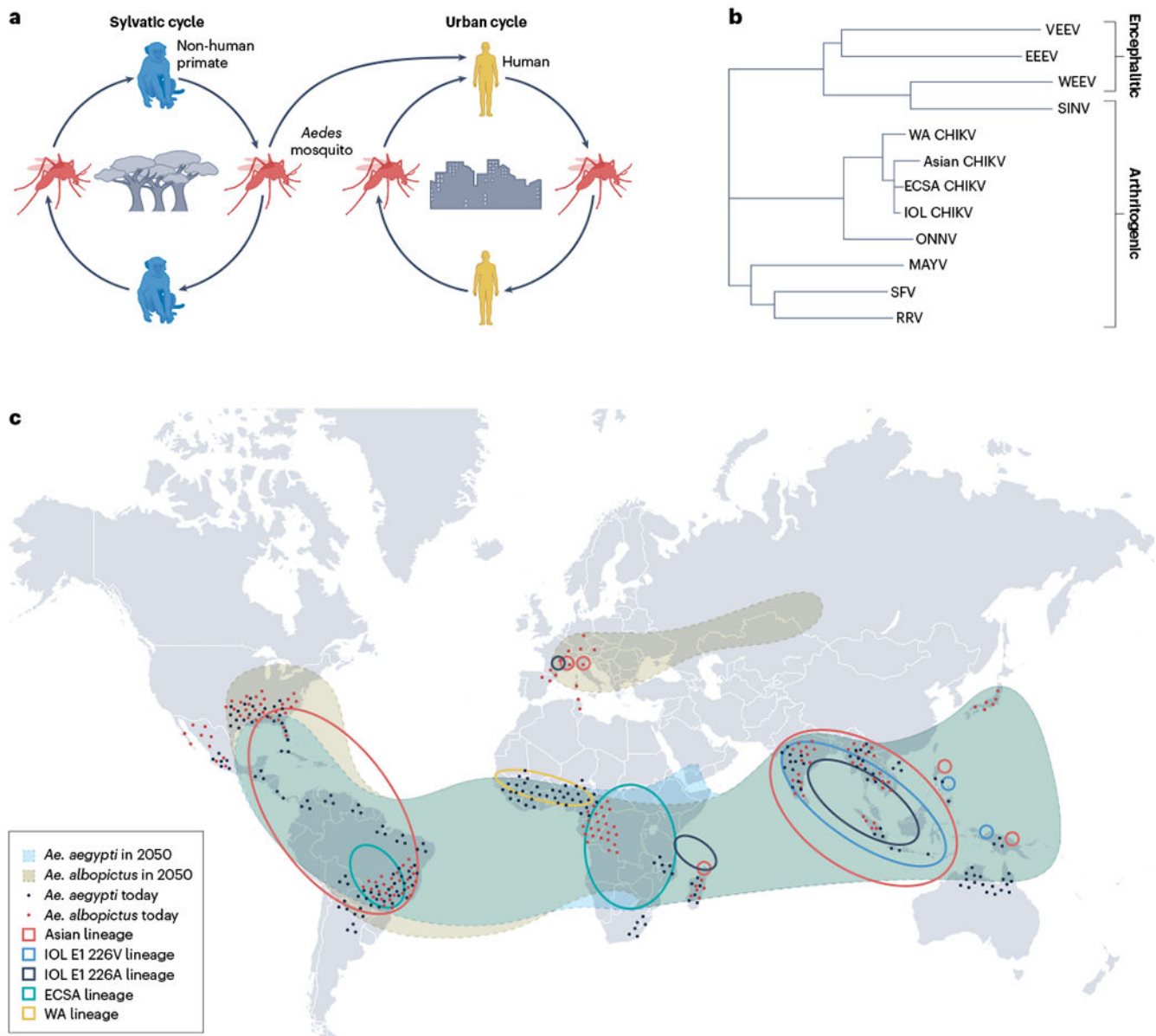


Fig. 1 | Phylogenetic tree of alphaviruses and spread of CHIKV lineages.

a, The sylvatic and urban cycle of chikungunya virus (CHIKV) transmission. **b**, Phylogenetic tree of human pathogenic alphaviruses that are transmitted by mosquitoes, including CHIKV lineages, based on structural protein sequences. The mosquito-transmitted alphaviruses can be broadly classified according to their main pathogenic characteristics, with CHIKV and related viruses causing arthritic symptoms as compared to the more distantly related alphaviruses causing encephalitis in affected persons. **c**, World map showing the spread of CHIKV lineages²⁴⁹ and the dominant *Aedes* mosquito vectors. Dotted patterns indicate contemporary presence of *Aedes* mosquitoes³⁰³ and projected spread by 2050 is indicated by coloured area shading³⁰⁴. Predictions of future spread of the *Aedes* mosquitoes account for their potential for invading expanding urban areas and increased environmental suitability following climate change³⁰⁴. In the coming 5–15 years, expansion

is expected to be mainly due to invasion of anthropogenic niches (environmental changes caused by humans) after long-distance introductions driven by global air transport or along well-travelled ground routes of people and goods³⁰⁵. *Aedes aegypti* is expected to spread largely within its tropical range and sufficiently temperate regions in the USA and China while largely avoiding Europe apart from southern Italy and Turkey. *Aedes albopictus*, of which dormant eggs allow survival in colder winters, are projected to become established throughout Europe, the northern USA, highland regions of South America and eastern Africa^{304,306,307}. Only after this period of 5–15 years are climate change factors, mainly increased temperatures, expected to drive further *Aedes* mosquito habitat expansions³⁰⁴. ECSA, East Central South African lineage; EEEV, eastern equine encephalitis virus; IOL, Indian Ocean lineage; MAYV, Mayaro virus; ONNV, O’nyong’nyong virus; RRV, Ross River virus; SFV, Semliki Forest virus; SINV, Sindbis virus; VEEV, Venezuelan equine encephalitis virus; WA, West African lineage; WEEV, western equine encephalitis virus.

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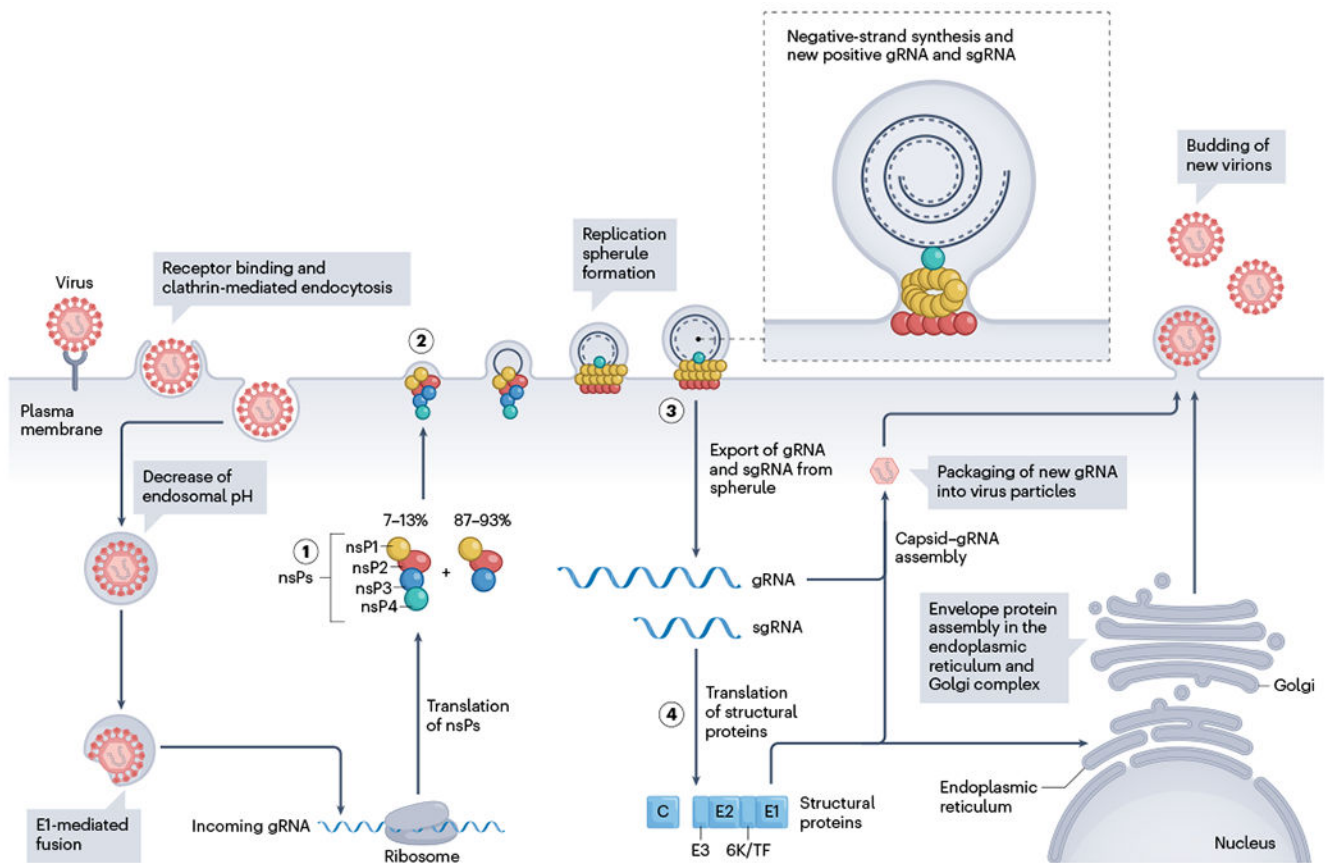


Fig. 2 | CHIKV replication.

Chikungunya virus (CHIKV) replication cycle with indication of genomic replication steps (1–4). Infection starts with cellular entry after receptor binding and clathrin-mediated endocytosis^{83–85}. Direct fusion at the plasma membrane, clathrin-independent endocytosis and macropinocytosis have also been implicated but their contribution to in vivo infection remains unclear. Viral genomic RNA (gRNA) is released into the cytoplasm following E1-mediated fusion of virion and endosomal membrane, and is translated to produce the non-structural proteins (nsPs) that form the replicase complex (step 1)^{56,57}. nsPs are produced as polyproteins nsP1–3 and nsP1–4 after ribosomal readthrough. The four nsPs are sequentially separated by the protease activity of nsP2 to coordinate the timed maturation of the replicase complex (extensively reviewed in refs. 308,309). The replicase complex is then translocated to the plasma membrane (step 2) to form replication spherules, the neck of which is formed by a 12-mer nsP1 ring and in which nsP4 RNA-dependent, RNA polymerase activity-mediated, negative-strand and new positive-strand viral gRNA and subgenomic RNA (sgRNA) production takes place (step 3)^{61–65}. The newly formed positive-strand RNAs are 5′ m⁷GMP Cap-0 capped by concerted action of nsP1 and nsP2 and 3′ polyadenylated by nsP4 (refs. 58–61). After expulsion from the replication spherule, sgRNA is translated to produce the structural polyprotein C–E3–E2–6K/TF–E1 (step 4), from which capsid is autoproteolytically cleaved through its own protease activity to remain cytoplasmic while the envelope proteins are produced at the endoplasmic reticulum membrane and mature after cleavage by trans-Golgi network-localized furin proteases and glycosylation^{85,86}. Packaging

of viral gRNA into virions is induced by capsid binding to gRNA-specific sequences, avoiding packaging of sgRNA. E2 and E1 are type I transmembrane proteins and form heterodimers, three of which form a trimeric spike; 80 of these trimeric spikes are presented on the viral particle. E1 is a pH-dependent type II fusion protein and its association with the E3–E2 precursor (p62) during maturation prevents premature activation of its fusion loop^{84–86}. Following presentation of the envelope proteins on the plasma membrane, interactions between the cytoplasmic C-terminal region of E2 and capsid coordinate enveloping of the nucleocapsid in budding virions. The 6K/TF structural protein, with TF being produced after a frameshift of the *6K* gene, has not been identified in CHIKV virions but functional studies in related alphaviruses indicate their function as ion channels in the endoplasmic reticulum to stimulate efficient budding⁸⁹.

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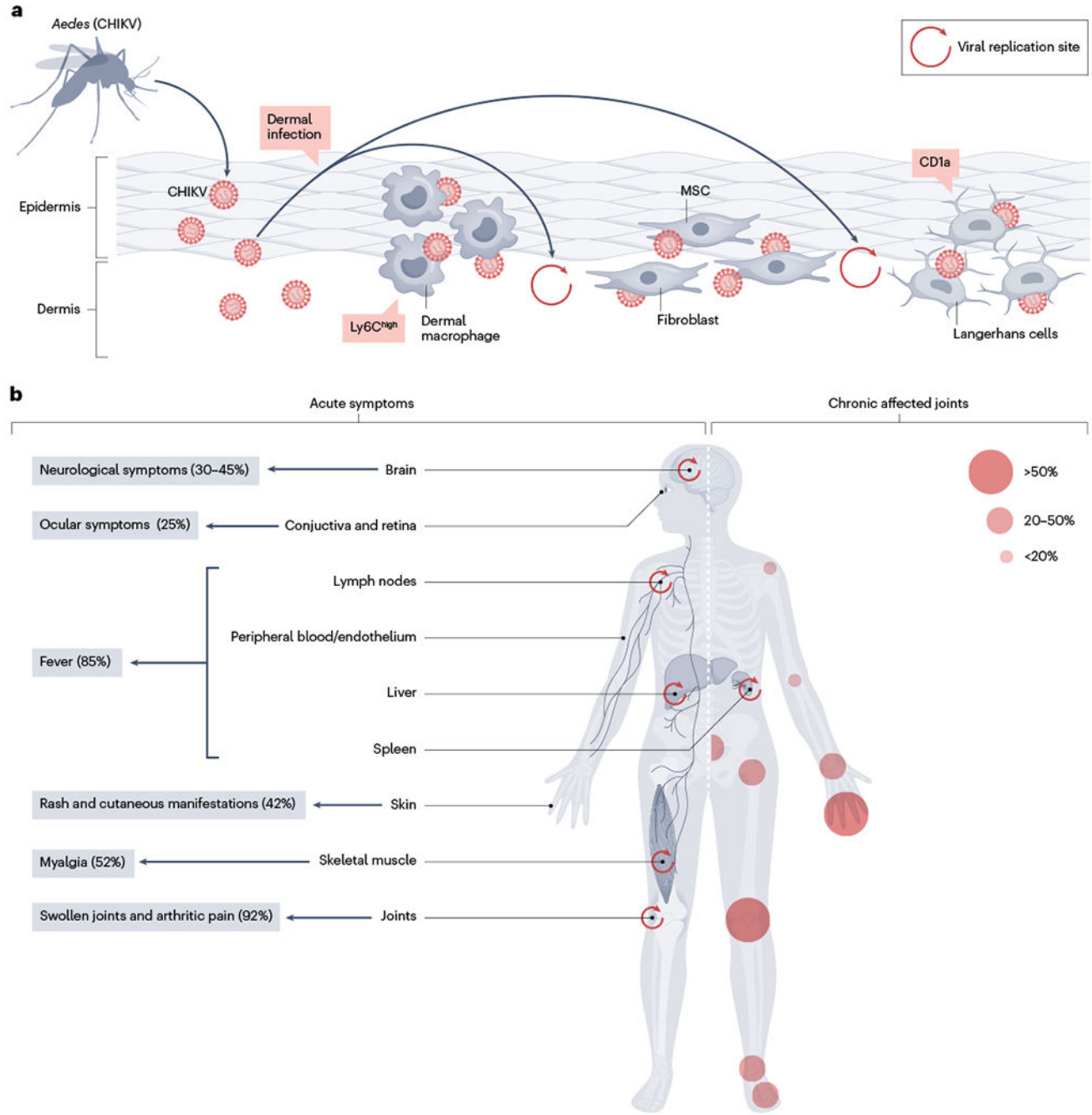


Fig. 3 | CHIKV infection and symptoms.

a. Chikungunya virus (CHIKV) infection occurs through bites of infected mosquitoes, resulting in a dermal infection phase. Initial rounds of CHIKV replication occur after infection of skin-resident cells such as dermal macrophages expressing high levels of Ly6C on their surface, fibroblasts, mesenchymal stromal cells (MSCs) and Langerhans cells expressing CD1a. **b.** Further CHIKV replication occurs in peripheral organs, including the lymph nodes, spleen and, in severe cases, the liver, brain and other organs. Acute symptoms are diverse and can occur in various organs and tissues with differing prevalence³¹⁰. In

the chronic phase, joints tend to be affected in a symmetrical manner, with the highest prevalence in peripheral joints¹¹⁸.

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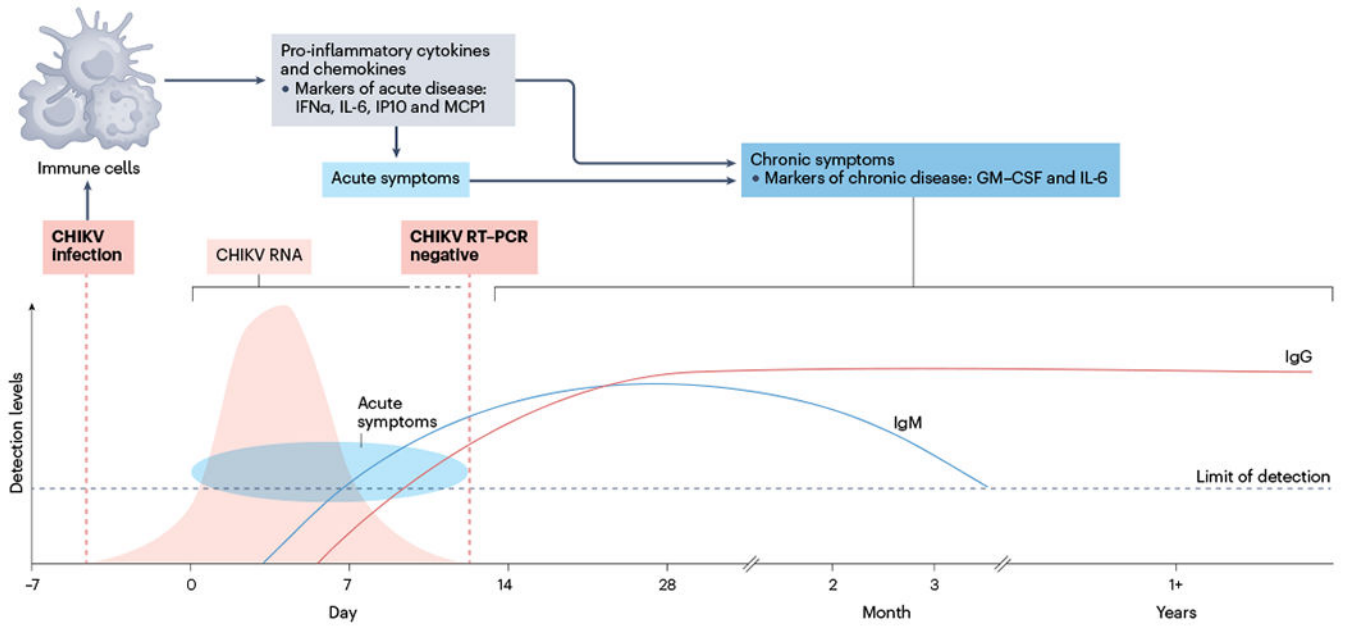


Fig. 4 | CHIKV-associated immunopathology.

Chikungunya virus (CHIKV) infection results in inflammation. Following dissemination into the bloodstream, viraemia occurs, which triggers the production of pro-inflammatory immune mediators, resulting in acute disease. Markers of acute disease include interferon- α (IFN α), IL-6, IP10 and MCP1 (ref. 311). Viraemia (CHIKV RNA) typically clears by 14 days post-infection. However, chronic disease develops in some patients, indicated by increased levels of chronic disease markers such as granulocyte-macrophage colony-stimulating factor (GM-CSF) and IL-6 (refs. 134,135). RT-PCR, reverse transcription-PCR.

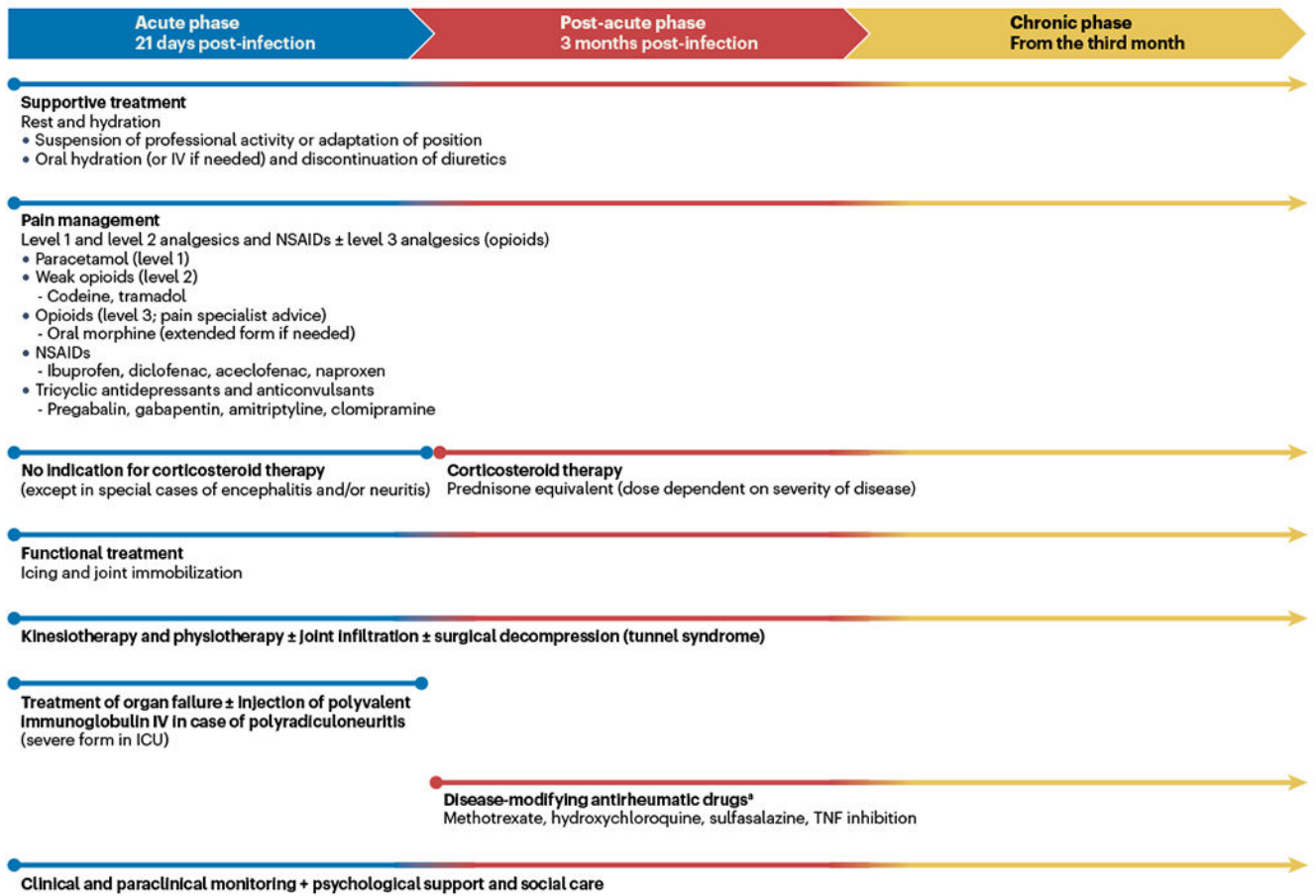


Fig. 5 |. Management of chikungunya fever.

The management and treatment of patients with chikungunya fever differs according to the stage of disease. The treatment of uncomplicated acute chikungunya fever requires resting, oral hydration and simple, well-conducted analgesia. Multimodal analgesia is recommended for acute pain management and NSAIDs are an integral part of the management of inflammation following chikungunya fever. Corticosteroids are not recommended during the acute phase but do have a place in the management of the post-acute and chronic phase of infection and can be combined with other analgesics (level 1 and level 2) in the event of ineffectiveness of NSAID treatment. Disease-modifying antirheumatic drugs act on the rheumatological symptoms often observed during the chronic phase. Adjuvant physical and rehabilitation medicine complete patient care and aim to limit the general effects of joint and musculoskeletal disorders. ^aIn case of proven inflammatory polyarthritis and after specialist advice from a rheumatologist. ICU, intensive care unit; IV, intravenous; TNF, tumour necrosis factor.

Table 1 |

Diagnostic tests for detection and control of chikungunya virus infection

Test	Detection target	Interpretation	Advantages	Limitations
Confirm clinical diagnosis				
Culture	Viable virus	Acute infection	Highly specific; can be quantitative; isolate can be further characterized	Requires specialized containment facility; can take days for a result
Molecular assays, for example, reverse transcription-PCR	Viral RNA		Highly sensitive and specific; multiplex, point-of-care testing available; time to result: 1–3 h	Expensive; requires equipment
Serological methods or immunoassay	IgM antibodies	High level of IgM antibodies is suggestive of recent infection (~ months)	Available as high throughput laboratory assays or lateral flow rapid tests that can be used outside of laboratory settings	IgM antibodies tend to persist for months; antibodies may be cross-reactive with those of other alphaviruses, giving a false positive result
	A fourfold rise in IgG antibody titre; IgM/IgG seroconversion	Definitive evidence of infection	Retrospective diagnosis of chikungunya virus infection	Requires collection of a second blood sample 7–14 days after the first sample
Surveillance and outbreak alert				
Molecular testing at sentinel sites	Viral RNA	Outbreak alert if a cluster of cases is detected	Multiplex arbovirus panels available to distinguish between different arboviruses	Expensive; requires technical expertise and equipment
Serological methods for communities	IgM antibodies	More IgM-positive cases or increased titres	Multiplex IgM rapid test panels are available for clinics	Needs confirmation of outbreak using nucleic acid amplification tests

Table 2 |

Chikungunya virus vaccine candidates

Vaccine	Type	Chikungunya virus lineage	Chikungunya virus strain	Advantages	Limitations	Status	Refs.
VLA1553	Live-attenuated virus	East Central South African	La Réunion Island, 2006	Rapid immune response (<14 days); single dose	Transient arthralgia and fever; cannot use in pregnancy or immunocompromised; durability >1 year unknown	Phase III study, complete; FDA license application started August 2022	Wressnigg et al. ²⁰¹ , Roques et al. ²⁰²
PXVX0317	Virus-like particle plus adjuvant	West African	Senegal, 1983	Rapid immune response (<14 days); durable immune response (2 years); thermostable; single dose; platform safe in pregnancy and immunocompromised	Requires an adjuvant	Phase III study, ongoing	Chang et al. ²⁰⁴ , Goo et al. ²⁰⁵ , Bennett et al. ²⁰⁶
V184	Measles vector	East Central South African	La Réunion Island, 2006	Platform based on the highly safe, effective and durable measles vaccine; also boosts measles immunity	May require 2 doses; durability >224 days unknown; cannot use in pregnancy or immunocompromised	Phase III study, not started	Reisinger et al. ²⁰⁹ , Ramsauer et al. ²¹⁰
BBY87	Inactivated virus plus adjuvant	East Central South African	India, 2006	Thermostable; platform safe in pregnancy and immunocompromised	Phase I data not published yet; requires 2 doses; requires an adjuvant	Phase II/III study, ongoing	CEPI press release ²²⁰