HHS Public Access

Author manuscript

Microbiol Spectr. Author manuscript; available in PMC 2019 April 29.

Published in final edited form as:

Microbiol Spectr. 2016 June ; 4(3): . doi:10.1128/microbiolspec.EI10-0017-2016.

Chikungunya Virus: Current Perspectives on a Re-Emerging Virus

Clayton R. Morrison, **Kenneth S. Plante**, and **Mark T. Heise***

The Department of Genetics, The University of North Carolina, Chapel Hill, NC 27599, Phone: 919-843-1492

Introduction

Chikungunya virus (CHIKV) is a mosquito-borne alphavirus in the family *Togaviridae* that causes outbreaks of debilitating acute and chronic arthralgia in humans. Although historically associated with localized outbreaks in Africa and Asia, recent epidemics in the Indian Ocean region and the Americas have led to the recognition that CHIKV is capable of moving into previously unaffected areas and causing significant levels of human suffering. The severity of CHIKV rheumatic disease, which can severely impact life quality of infected individuals for weeks, months, or even years, combined with the explosive nature of CHIKV outbreaks and it demonstrated ability to quickly spread into new regions, has led to renewed interest in developing strategies for the prevention or treatment of CHIKV induced disease. Therefore, this chapter will briefly discuss the biology of CHIKV and the factors contributing to CHIKV dissemination, while also discussing the pathogenesis of CHIKV-induced disease and summarizing the status of efforts to develop safe and effective therapies and vaccines against CHIKV and related viruses.

Chikungunya Virus Emergence and Re-Emergence

CHIKV is believed to have originated in Africa and currently exists as three independent virus genotypes; West African, East/Central/South African (ECSA), and Asian. The first described incidence of human disease that was clearly attributable to CHIKV occurred on the Makonde Plateau of Tanzania (formerly Tanganyika) from October of 1952 until April of 1953 (1). The virus responsible for this first outbreak was isolated from the serum of a febrile patient and belonged to what was ultimately designated as the ECSA genotype. While this is the first documented incidence of CHIKV, phylogenetic and retrospective analyses of clinical data suggest that the virus may have been present and causing disease much earlier. Many researchers believe that Chikungunya fever (CHIK) may have been incorrectly identified as dengue fever, due to some overlapping symptomatology, in multiple areas throughout Southeast Asia as early as the start of the 18th century (2, 3).

During the initial outbreak in Tanzania, Lumsden and investigators noted appreciable numbers of *Aedes aegypti* mosquitoes in the huts of afflicted individuals, thereby providing initial evidence that the virus was vectored by mosquitoes. Subsequent studies suggested that

*Corresponding Author.

in Africa CHIKV is maintained through an enzootic (sylvatic cycle) involving non-human primates and arboreal *Aedes* mosquitoes (4, 5). Spill over events occur when these CHIKV infected, arboreal *Aedes* mosquitoes feed on naive humans and transmit the virus. If these infected individuals become viremic and are fed upon by urban *A. aegypti* mosquitoes, an urban transmission cycle involving human-to-mosquito-to-human transmission can be initiated, which can lead to significant disease outbreaks. Since the initial outbreak in Tanzania, sporadic outbreaks of CHIK disease have continued to occur throughout Africa, including in Uganda, Malawi, and Nigeria (4, 5).

In 1958, a CHIKV outbreak was recognized in Bangkok, Thailand (6). Phylogenetic analysis of that outbreak virus demonstrated that the virus was distinct from the virus identified in Tanzania, and was ultimately designated as a separate Asian genotype, which is now endemic in Southeast Asia. Sporadic outbreaks of Asian genotype CHIKV have continued to occur throughout the region including countries such as India, Vietnam, and Malaysia (7, 8). Unlike in Africa, evidence is lacking to support an enzootic cycle maintaining the Asian genotype virus in nature. Instead, Asian genotype CHIKV is believed to be maintained in an urban cycle between *Aedes* mosquitoes and naive human hosts(9).

While cases of CHIK have been reported in Africa throughout the 20th century, a new strain of virus classified as Indian Ocean Lineage (IOL) re-emerged in coastal Kenya in 2004 (10). The IOL strain of the virus quickly spread to Comoros and the Seychelles Islands before jumping to major population centers in the Indian Ocean region including the Indian sub-continent, where the virus was estimated to have caused over 1.5 million cases, and Sri Lanka (11–13).

Whole genome and partial E1 sequences of numerous clinical isolates suggests that the IOL strain most likely evolved from a closely related ECSA strain (14). An important distinction was a single amino acid substitution in the E1 protein, A226V, which was found in the IOL virus isolates compared to ECSA CHIKV. Subsequent in-vivo studies demonstrated that this change was necessary and sufficient for the virus to adapt to and efficiently utilize *Aedes albopictus* mosquitoes as a major vector of transmission (15). *Aedes aegypti* mosquitoes have historically been the primary vector for CHIKV transmission during other major outbreaks. However, the adaptation of IOL CHIKV to *A. albopictus* mosquitoes is viewed as a major factor, which allowed the virus to reach epidemic levels in the Indian Ocean region, especially in areas where *A. albopictus* mosquitos were the dominant mosquito species. Importantly, this expanded vector range also had implications for CHIKV's subsequent introduction and spread into temperate areas, such as Italy, where *A. albopictus* was the vector responsible for local transmission (16, 17).

Historically, CHIKV has been a public health threat contained to the Eastern hemisphere. However, the rapid spread of CHIKV throughout the Indian Ocean region, as well as its emergence in Italy and France, combined with the broad distribution of *Aedes* mosquitoes in both North and South America, raised concern that CHIKV might emerge in the Western hemisphere (16, 17). Despite frequent incidents of CHIKV infected individuals traveling into the Western hemisphere, including a number of viremic travelers entering the United States [Reviewed in (18)], there were no documented cases of localized CHIKV

transmission in the Americas during the height of the CHIKV outbreak in the Indian Ocean region (18). However, thoughts that CHIKV might not be capable of establishing infection in the Americas were disproved by an outbreak of CHIKV disease in late 2013, when the first reported cases of human-to-human transmission of CHIKV-induced disease appeared in the French region of the island of Saint Martin, Caribbean(19). These marked the first documented occurrence of non-traveler-associated CHIKV in the Western Hemisphere. Molecular and phylogenetic studies of viruses isolated from the outbreak have identified it as an Asian genotype virus, most closely related to those circulating in the Philippines, China, and Micronesia prior to the Caribbean outbreak (20, 21). The Caribbean strain of CHIKV quickly disseminated from St. Martin to other island nations of the Greater and Lesser Antilles, including the Virgin Islands, Aruba, and Barbados (22). By early 2014 cases of the virus were detected in mainland South America in French Guiana where local spread occurred there and into neighboring Guyana. Furthermore, limited localized transmission also occurred in Florida, with 12 reported cases of localized transmission (CDC ArboNet) (23). The Caribbean CHIKV outbreak virus has since caused local disease in Puerto Rico, the Dominican Republic, Columbia, and Mexico (Pan American Health Organization), with well over 1 million cases of CHIKV-induced disease occurring in the America's since CHIKV's introduction in 2013 (Pan American Health Organization). Importantly, CHIKV continues to cause disease in countries throughout South and Central America and therefore still has the ability to move into new areas, including the United States.

The recent CHIKV outbreaks in the Indian Ocean region, Southeast Asia, The South Pacific, and the Americas illustrate the importance of several factors in promoting CHIKV transmission. One of the major factors is the increased level of air travel, which almost certainly promotes the spread of CHIKV into new areas. During the height of the Indian Ocean outbreak, a number of CHIKV infected travelers, who were documented to be viremic, and thereby capable of transmitting the virus to permissive mosquitoes, entered the United States (18), and while no outbreak within the United States can be attributed to these individuals, it is likely that much if not all of the spread of CHIKV into other areas of the world was mediated by infected travelers (18). Furthermore, the localized transmission of the Caribbean strain of CHIKV observed in Florida in 2014 likely resulted from introduction of the virus by an infected traveler. A second major factor is the distribution of permissive mosquito vectors. Both *A. aegypti* and *A. albopictus* are capable of transmitting CHIKV, and the broad distribution of these mosquito vectors has certainly contributed to the expansion of CHIKV outbreaks in a manner similar to the global circulation of dengue virus, and the more recent introduction and spread of Zika virus (24, 25). Lastly, changes in the virus itself have also contributed to the virus's ability to cause widespread outbreaks. As noted above, a mutation in the IOL strain of CHIKV resulted in an expansion of the virus's host range to *A. albopictus* mosquitoes, an event which allowed the virus to be spread in more temperate areas where *A. aegypti* mosquitoes are not found (26). Importantly, unlike the ECSA CHIKV strains, viruses of the Asian CHIKV genotype, which is the type that was introduced into the Caribbean, are less able to adapt the enhanced transmission by *A. albopictus* mosquito vectors phenotype (24, 27). In vivo studies of *A. albopictus* mosquitoes infected with engineered mutants of Asian CHIKV indicated that two independent amino acid changes (T98A and E226V in E1), which have yet to be observed in Asian genotype

viruses found in nature, are required for the virus to efficiently adapt to use *A. albopictus* mosquitoes (27). Further findings from this study suggest that the ability of Asian genotype viruses to acquire these separate mutations are unlikely to occur due to intrinsic evolutionary constraints. This makes it less likely that the Caribbean strain of CHIKV will be capable of efficiently adapting to *A. albopictus* mosquitos, which might limit the virus's ability to be spread in temperate areas within the United States or other parts of the Americas. However, this might be complicated by the fact that in 2014 a strain of CHIKV belonging to the ECSA genotype re-emerged in Brazil and has caused significant disease in numerous regions of the country (28). This outbreak marks the first time an ECSA genotype strain of CHIKV has been found in the Western hemisphere associated with documented cases of local transmission. Abundant *A. aegypti* mosquitoes present in this environment have most likely fueled the outbreak, and currently, there is no evidence to suggest that this virus has mutated to adapt to *A. albopictus* mosquitoes, similar to what was observed with IOL CHIKV. Nevertheless, this virus still has the potential to gain a single adaptive mutation which could ultimately lead to vector expansion and movement of the virus into new regions of the world including the United States.

CHIKV Disease

Most patients suffering from acute CHIKV disease present with high fever and arthraligia, as illustrated by a study by Thiberville, et al, where 100% of outpatients suffering from acute CHIKV during the Reunion Island epidemic presented with high fever and arthralgia (29). CHIKV-induced arthridities are often debilitating and the name chikungunya, which is derived from the Makonde language, translates as "that which bends up", describing the posture taken by persons suffering from CHIKV-induced disease (1). Acute CHIKV-induced arthralgia resolves over a period of several days to weeks, however, arthralgia can persist in some individuals for months to years. In addition to fever and arthralgia, other common symptoms of acute CHIKV infection include asthenia, myalgia, and headache (Reviewed in (30)), while other symptoms, such as maculopapular rash and nausea are also frequently observed in CHIKV patients. Patients frequently present with lymphopenia, while elevated C-reactive protein, elevated liver enzymes, and signs of thrombocytopenia are also observed in a subset of acute CHIKV patients (30). Although the case fatality rate for CHIKV is extremely low, the recent outbreaks have seen a rise in atypical disease manifestations, including encephalitis in infants and multi-organ failure/mortality in elderly individuals or persons with underlying medical conditions [reviewed in (30)].

CHIKV-Induced Joint and Muscle Disease

Poly-arthralgia and myalgia are common attributes of many viral infections, however, severe incapacitating arthralgia is the most prominent feature of acute CHIKV infection [Reviewed in (30)]. Following CHIKV infection, patients often rapidly present with sudden onset of a severe fever, arthralgia and myalgia (29, 31). However, while other symptoms, such as fever, resolve within a few days, arthralgia resolves over a longer period of time, a disease attribute the distinguishes CHIKV-induced arthralgia from that induced by viruses such as dengue virus. This is illustrated by a study by Thiberville, et al, where CHIKV induced fever had resolved by day 7 after their first medical visit in 100% of patients (n = 54), while

approximately 65% of patients still reported joint pain 25 days after their initial doctors visit (29). Furthermore, as noted below, a significant fraction of individuals complain of persistent arthralgia for months to sometime years after onset (32). During the acute phase of the disease, arthralgia is usually symmetrical and affects multiple joints, with joints of the toes, fingers, ankle, wrist, knee, and elbow commonly affected (29, 31, 33). Although overt signs of inflammatory cell infiltration are evident in a small subset of affected individuals, acute CHIKV-induced joint disease is generally not erosive, and swelling around the joints is a common feature of acute CHIKV disease (34), however previously damaged joints may predispose individuals to increased risk of prolonged arthralgia (35).

As noted above, debilitating acute arthralgia is the defining symptom of CHIKV-induced disease, and although CHIKV-induced joint pain is generally most severe at early times post onset, resolution of acute arthralgia can often occur over a period of several weeks. In a subset of infected individuals symptoms fail to resolve for periods ranging from several months to years after the initial onset of disease, where this joint pain and stiffness can have a significant impact on quality of life(32, 35). The fraction of persons suffering from persistent CHIKV was historically considered to be low, as illustrated by a study by Brighton et al., that found that 12 percent of CHIKV patients had persistent symptoms up to three years post onset (36). However, during the recent outbreak on Reunion Island, chronic disease appeared to be more prevalent with 57% of subjects reported persistence or episodes of recurrence in one study (37), while a second study found 26% of patient reporting residual arthralgia in multiple joints at day 300 post disease onset (29). Furthermore, although recurrent joint stiffness and pain appear to be the major manifestations of chronic CHIKV arthralgia, there have been reports of more severe joint disease in persons suffering from persistent CHIKV-induced arthridities, including erosive arthritis (32, 36, 38). Although the factors that contribute to chronic CHIKV-induced arthralgia are poorly understood, it is clear that increased age, higher viral loads, and the severity of the acute phase of infection are major risk factor for developing persistent disease. Several studies have found that people over the age of 45 are more likely to develop long term joint pain and stiffness (29, 32, 37, 39), while results from Thiberville, et al., found that persons with ongoing joint pain at 300 days post infection presented with a higher number of affected joints during the acute stage of the disease (29).

The pathogenesis of acute and chronic CHIKV-induced arthralgia is not completely understood, however, there is strong evidence of CHIKV replication in affected tissues. Furthermore, a growing body of evidence suggests that viral replication within joint tissues elicits an overactive host inflammatory response, which then drives the development of joint pathology and arthralgia. Biopsy results from patients suffering from CHIKV-induced myositis provided evidence that CHIKV can replicate in muscle cells, and this was further confirmed in primary culture studies demonstrating that muscle satellite cells are capable of supporting CHIKV replication (40). Although there is little direct evidence for CHIKV replication within the joints of affected patients due to a lack of synovial biopsy samples from acute CHIVK patients, CHIKV has been shown to replicate efficiently in human synovial fibroblasts (41), and studies from mouse and non-human primate models have demonstrated that synovial joints are a major target of CHIKV replication in-vivo (42–45). There is also evidence suggesting that persistent viral replication may contribute to chronic

CHIKV disease. One study, by Hoarau, et al., found evidence for persistent CHIKV replication in a single patient suffering from chronic CHIKV arthralgia (46), however, considering the limited sample size in this study, additional studies are needed to confirm these results.

Given the difficulty in obtaining synovial biopsies that span the acute to chronic disease stages from CHIKV infected humans, a number of groups have turned to animal models to study chronic CHIVK disease. Studies in cynomolgus macaques found that replication was detectable in lymphoid tissues for up to three months postinfection (47). Likewise, experiments in mouse models have found detectable levels of CHIKV RNA in joint tissues for up to four months post infection (48), although infectious virus has not yet been detected in these systems. These results all suggest that CHIKV can persist in individuals for long periods of time, even in the face of a potent antiviral immune response. However, the nature of this persistence and whether persistent viral replication drives long term chronic joint disease in humans remains to be determined.

Although direct viral replication within joint tissues is thought to contribute to acute CHIKV-induced joint disease, and possibly chronic disease, there is also evidence suggesting that aspects of the host inflammatory response contribute to disease pathogenesis. While components of the innate and adaptive immune response, such as the type I IFN system and antiviral antibody, contribute to CHIKV control and clearance (Reviewed in (49)), a significant body of evidence suggests that overactive inflammatory responses clearly contribute to the pathogenesis of acute CHIKV-induced arthralgia and swelling. The severity of CHIKV induced arthralgia is associated with increased levels of a number of pro-inflammatory cytokines within the serum of infected humans (50, 51), and inflammatory cell infiltration into joint tissues is a prominent feature in CHIKV infected mice and non-human primates (42, 44, 45, 52), which suggests that aspects of the host inflammatory response contribute to CHIKV-induced joint disease. This is further supported by mouse studies, where depletion of monocytes reduced the severity of CHIKV-induced arthritis (44). Mouse studies also suggest that components of the adaptive immune response modulate the severity of CHIKV-induced arthritis, with CD4 T cells contributing to CHIKV-induced joint swelling (53). Therefore, careful targeting of specific immune components that promote disease may represent a therapeutic avenue in the treatment of CHIKV-induced disease

Neurologic involvement

Unlike encephalitic alphaviruses, such as Eastern and Venezuelan equine encephalitis viruses, neurologic disease is not usually associated with CHIKV. However, a small subset of adult patients requiring hospitalization exhibited signs of syndromes such as acute flaccid paralysis, Guillain-Barre syndrome, and encephalopathy (54–56). This is illustrated by a study during the Reunion Island CHIKV epidemic, where 25% of patients with atypical CHIKV infection reported neurological involvement, including malaise and meningo-encephalitis (57). Children are also at risk of developing neurologic complications, where vertical mother to child transmission puts newborns at significant risk of developing encephalopathy that can result in lifelong neurologic consequences (58–60).

Mortality associated with CHIKV infection

CHIKV-induced mortality, although rare, does occur, with an approximate case fatality rate of 1 in 1000 [Reviewed in (30)]. The very young (e.g. neonates) and elderly individuals, as well as people with underlying medical conditions comprise the majority of these cases, with causes of death ranging from encephalitis to hepatitis and multiple organ failure (30).

Other clinical manifestations

A transient maculopapular rash is a common on the thorax and the medial aspects of the limbs during CHIKV disease, however a small subset of individuals do develop more severe skin manifestations, including ulcers and vasculitis [Reviewed in (30)]. Although the pathogenesis of CHIKV-induced skin disease is poorly understood active viral replication within the skin might contribute to CHIKV-induced skin disease. Other rare, but potentially serious manifestations of CHIKV disease include ocular disease, including uveitis (61). Lastly, fatigue is a common complaint associated with CHIKV infection, and may persist for months to years in some individuals (62).

CHIKV Vaccines and Therapeutics

The re-emergence of CHIKV, with subsequent spread in the Indian Ocean region and its introduction into the South Pacific and the Americas has rekindled interest in the development of vaccines for the prevention of CHIKV-infection and therapeutics for treating acute and chronic CHIKV induced disease. Unfortunately, there are currently no approved CHIKV vaccines or therapies and despite the scope of the current CHIKV epidemic, treatment options for CHIKV-induced disease are generally limited to palliative care using non-steroidal anti-inflammatory drugs (NSAIDs) and hydration. Given the scope of the recent CHIKV outbreaks and the limited treatment/prevention options available, significant effort has been put into developing new vaccine and therapeutic pipelines for CHIKV, and we will briefly summarize current progress in both of these areas.

CHIKV Vaccines

Although CHIKV is a threat to spread within developed countries, such as the United States and European Countries, developing countries have borne the brunt of CHIKV induced disease over the past 10 years, and are at greatest risk of continued CHIKV spread. Therefore, for a CHIKV vaccine to be useful in this areas, it would need to be relatively inexpensive to manufacture and administer, preferable be highly immunogenic after a single dose, while having no to minimal side effects. Furthermore, since older individuals are at increased risk of developing both chronic CHIKV-induced arthralgia and for severe CHIKV-induced disease (29, 32, 37, 39), a successful vaccine would ideally be safe and immunogenic in this population. While multiple vaccine strategies have been explored in preclinical studies (reviewed in depth (63)), to date, four vaccines have entered human trials and many vaccines are in differing stages of preclinical testing (Table 1). For the purposes of this review, we will focus on vaccines that have entered into clinical trials, while briefly discussing other vaccine strategies.

CFIIKV vaccine research dates back 40 years, with much of the early CFIIKV vaccine work focusing on traditional inactivated and or cell culture adapted live attenuated vaccines. Initial attempts at generating a CFIIKV vaccine focused on using formalin inactivated virus derived from the African 167 CFIIKV strain, which was produced from green monkey kidney (GMK) cells, chicken embryo cells or concentrated suspension cultures(64). This inactivated vaccine was initially tested by intraperitoneal inoculation into 3–4 week old Swiss Bragg mice with a prime-boost, 2 dose schedule, followed by intracerebral challenge. The vaccine exhibited good efficacy in the mouse model and was later tested for efficacy in humans, where is was found to elicit a neutralizing antibody response with no adverse events (65).

The second vaccine that was tested in humans was developed at the Walter Reed Institute of Research, where Levitt *et al.* set out to increase the efficacy of the GMK-based inactivated vaccine by generating a live-attenuated vaccine. A human CFIIKV isolate from a 1962 Thai outbreak, strain 15561, was plaque purified and passaged 18 times in human embryonic lung MRC-5 cells (66). On the 18^{th} passage, three plaque purified clones named 25-27, which exhibited a uniform plaque morphology, underwent safety testing by intracranial inoculation into neonatal (1-3 day old) mice. In contrast to the parental virus, which caused 61% mortality, none of the three passaged viral isolates caused mortality. In subsequent efficacy studies, clone 25 exhibited 100% protection against lethal CHIKV challenge in weanling mice, and this virus was thereby designated as 181/25. Following the successful testing in mice, the 181/25 vaccine was then taken forward for additional evaluation in non-human primates (66). In a dose escalation experiment where the vaccine was administered at doses ranging from 3.5 $\log_{10}$ to 5.5 $\log_{10}$ PFU, vaccinated animals exhibited complete protection from CFIIKV viremia following challenge (66).

Following the mouse and non-human primate studies, the 181/25 vaccine was tested for virulence in humans in a phase I clinical trial. In a small trial involving 15 people, there were no adverse events reported with no conclusive evidence of a difference between the naive group receiving either then 181/25 vaccine or a mock vaccination (67). Therefore, 181/25 was considered to be avirulent in humans and proceeded to phase II trials, where the 181/25 vaccine (now called TSI-GSD-218) was evaluated in a double-blind 73 person efficacy trial (68). Following intramuscular injection, with 0.5 logio PFU of vaccine (n=59) or a mock vaccine (n=14), subjects were interviewed to discuss symptoms on days 1-4, 10, 14, and 28 post-vaccination. The group that received the vaccine developed neutralizing antibodies in 98.3% of cases by 28 days post-vaccination, with 85% of the vaccinees remaining seropositive 1 year later(68). Some members of both the experimental and control groups experienced local symptoms at the site of inoculation and flu like symptoms, with no statistically significant difference between the groups. However, 5 of the 59 patients that received the vaccine developed transient unilateral arthralgia in 1 to 2 of their joints, compared to 0 cases in the control group, which lead the TSI-GSD-218 vaccine to be abandoned following the phase II trial (68).

Although development of the 181/25 vaccine was halted in phase II trials, with the re-emergence of CHIKV and subsequent large scale epidemics, there has been some interest in revisiting this vaccine (69). However, recent work has illustrated potential pitfalls associated with this vaccine, including spread into mosquito species and reversion to virulence. The

181/25 vaccine strain was evaluated for transmission competence in *Aedes albopictus* and *Aedes aegypti* mosquitoes by Turell *et at,* and while the 181/25 virus was found to infect and transmit less effectively than the parental 15561 virus, it was still able to be spread by mosquitoes (70). Additionally, Gorchakov *et at* found that the attenuation of the 181/25 vaccine was attributed to two point mutations in the E2 protein (71), with a mutation located at position 82 that is associated with heparin sulfate binding believed to be the major attenuating determinant within the virus (72, 73). The capacity for 181/25 to rapidly revert to virulence was further described by Plante *et al.,* who discovered that the 181/25 vaccine could revert to a virulent phenotype after 5 serial mouse brain passages in neonatal type I $IFN^{-/-}$ mice. This reversion to virulence was caused by both direct revertants of the previously identified residue 82 mutation and by other loss of positive charge, surface exposed mutations near residue 82 of the E2 protein(74). This work strongly suggested that more stable attenuation strategies were needed for developing safe live-attenuated CHIKV vaccines.

Another promising live-attenuated vaccine has been extensively studied in the preclinical stage is the CHIKV/IRES vaccine produced by Plante *et al (75).* By utilizing an encephalomyocarditis virus (EMCV) internal ribosomal entry site (IRES) that is incapable of translation in arthropod cells, they were able to produce an immunogenic and attenuated vaccine which was incapable of growing in the mosquito vector. This vaccine was found to be efficacious and safe in multiple mouse models and non-human primates (75, 76). The CHIKV/IRES vaccine was further tested for safety and stability by trying to mutate the virus in a worse-case scenario serial mouse brain passage experiment. The IRES-based vaccine remained attenuated, while the 181/25 vaccine that was run in parallel as a control, became neurovirulent, leading to fatal outcomes in $IFNA^{-/-}$ mice (74). The vaccine was also successfully tested for its ability to protect against a closely related virus in the Semliki Forest clade, o'nyoung-nyong (77). It was further shown that the neutralizing antibody response elicited by CHIKV/IRES in mice was significant and sufficient to elicit full protection against a lethal challenge (78).

After CHIKV's re-emergence, the first new vaccine strategy to go forward for testing in humans was a virus-like particle (VLP) vaccine produced and tested by Akahata *et al.* (79). The VLPs were produced in HEK293T cells using CHIKV glycoproteins derived from the 37997 CHIKV strain in a lentiviral vector along with the vesicular stomatitis virus G protein. A three dose vaccination regimen in non-human primates elicited neutralizing antibody which when passively transferred to mice were protective against lethal CHIKV challenge (79). The vaccine has been evaluated in a phase I dose escalation trial (80), where three different doses of 10 μg, 20 μg, and 40 μg were administered three time over a period of 20 weeks in cohorts of 5, 10, and 8 people. All three doses elicited a strong neutralizing antibody response, and were well tolerated by the subjects (80).

The most recent vaccine candidate to have been evaluated in human trials is a measles virus (MV)-vectored VLP produced by Brandler *et al.*(81). This vaccine uses a live-attenuated Schawrz measles virus as a vector for CHIKV structural proteins from the La Reunion (OPY2006) strain. This recombinant virus (MV-CHIKV) was tested in type I IFN receptor deficient (IFNAR) mice transgenic for the human CD46 measles receptor that are capable of

supporting measles virus replication. Three doses (3 $\log_{10}$ PFU, 4 $\log_{10}$ PFU, and 5 $\log_{10}$ PFU) were tested by inoculating mice twice over a month interval. All three doses elicited neutralizing anti-CHIKV antibody responses and the low dose was found to be 80% efficacious, and the higher two doses were 100% protective against a lethal challenge. This vaccine then proceeded in a randomized, double-blind, placebo-controlled, phase I clinical trial (82). Three doses of either 1.5×10^4 PFU 7.5×10^4 PFU, or 3.0×10^5 PFU were administered to 12 subjects of each cohort, and a negative control cohort of 6 people received a Priorix MMR vaccine, with each cohort received a total of three inoculations on days 0, 28 and 90. The vaccine did elicit neutralizing antibody in a dose dependent manner, and importantly, previous measles vaccination did not adversely affect the vaccine's ability to elicit CHIKV specific immune responses. The vaccine was also relatively well tolerated at the lower two doses, with most adverse events being classified as mild or moderate. However, 58% of the individuals in the 3.0×10^5 PFU cohort did exhibit adverse events including flu-like illness, site of injection pain, and dispersed but transient myalgia (82).

A multitude of other CHIKV vaccine candidates have been produced and are in different stages of preclinical testing. An inactivated vaccine was produced and tested by Tiwari *et al.,* utilizing a Vero cell adapted ECSA strain of CHIKV and proved capable of producing neutralizing antibodies (83). Several chimeric viruses were tested, utilizing the either alphavirus or adenovirus vectors with the structural genes of CHIKV. (84, 85). These vaccines were capable of eliciting a neutralizing antibody response and protecting mice from a virulent challenge. Two DNA based vaccines were also produced and were also found to protect mice, and in NHP, found to induce a robust immune response (86, 87). Other vaccine strategies were attempted such as a series of subunit vaccines (88, 89), and a VLP based vaccine produced from insect cells(90). These strategies also were found to have their strengths.

As previously stated, a vaccine for CHIKV should exhibit multiple traits for effective use. These traits would be slightly different for a travelers vaccine compared to one intended for implementation in the endemic regions for this virus. A traveler's vaccine could be a multi-dose, expensive, and only convey short-lived protection. However, since this virus disproportionately effects equatorial developing countries, cost and efficacy take on added weight when considering utility. For one, the vaccine would have to be manufactured quickly, and at low cost, to be implemented in the large and relatively poor populations most at risk. The vaccine should illicit a strong and long lived immune response and do so with a single dose. A multi-dose vaccine may prove ineffective if the patient either chooses not to return or is incapable of coming in for subsequent booster vaccinations. The vaccine would have to be safe and easy to administer due to the lack of advanced healthcare in some of the endemic regions. Another important trait of any live-attenuated vaccine is that it proves stable in its non-virulent phenotype and is not going to be accidently spread by the mosquito vectors. Though this is not an issue in other vaccine platforms, the live-attenuated vaccine strategy is thought to be the best option for a virus that so heavily impacts developing countries.

Antivirals Against Chikunqunva Virus

As noted above, although there are multiple CHIKV vaccines in various stages of preclinical and clinical development, there are currently no vaccines approved for use in humans. The situation with antiviral therapies is similar, in that while a number of antiviral strategies are being pursued, currently approved treatments for acute CHIKV infection are limited to non-steroidal anti-inflammatory drugs (NSAIDs). However, given that CHIKV outbreaks can afflict hundreds of thousands or even millions of individuals with severe incapacitating arthralgia, which can have significant impact on an individual quality of life (30), and a major fraction of these individuals (> 1 million individuals (32) suffering from long term rheumatologic complaints, there is a significant need for new therapies treating for CHIKV disease. With this in mind a number of different therapeutic strategies are in development, and these efforts have identified promising pharmacologic and biological-based strategies that have the potential to limit the scope and severity of disease in humans infected with CHIKV. Therefore, this section will provide an overview of some of the major therapeutic approaches that are being evaluated as treatments for acute and chronic CHIKV-induced disease (Table 2).

Treatment of Acute CHIKV Disease

Therapeutic strategies for treating acute CHIKV disease can be roughly broken down in to antiviral therapies, which target the virus to reduce viral loads, or host targeted therapies which can either inhibit host processes that are required for viral infection, thereby reducing viral loads, or interfere with components of the host inflammatory response that promote CHIKV-induced disease.

Virus-targeted Antivirals

One of the earliest candidate antivirals for treating acute CHIKV disease was Ribavirin, a synthetic guanosine nucleoside analogue that exhibits broad-spectrum antiviral activity, and which received FDA approval for the treatment of respiratory syncytial virus and hepatitis C virus infections in 1985 (FDA Application No. (NDA) 018859). While the direct antiviral mechanism(s) of Ribavirin have yet to be completely elucidated, it has been suggested that the drug largely acts by depleting cellular pools of GTP through the inhibition of the cellular inosine monophosphate dehydrogenase enzyme (IMPDH) (91). The depletion of GTP is also postulated to indirectly result in the incorporation of deleterious mutations in various RNA and DNA virus genomes. Notably, Ribavirin has been shown to have antiviral activity against CHIKV both in vitro and in a small clinical study (92, 93), which suggests that ribavirin may have utility in treating CHIKV cases.

Several other promising antiviral compounds include mycophenolic acid, 6-Azauridine, and Harringtonine. Similar to Ribavirin, Mycophenolic acid (MPA) acts to inhibit IMPDH, reduces cellular GTP pools, and therefore exhibits broad-spectrum antiviral activity. In-vitro studies have shown that MPA protects cells against CHIKV-induced apoptosis and reduces viral yields from treated cells (94). The compound 6-Azauridine, is a uridine nucleoside analog which inhibits the enzyme orotidine monophosphate decarboxylase (ODCase) required for the synthesis of pyrimidines. Inhibition of pyrimidine synthesis leads to reduced UTP levels, and therefore 6-Azauridine has antiviral activity against a number of DNA and

RNA viruses, including CHIKV, where the drug shows strong inhibition of CHIKV replication in-vitro (93). Harringtonine and its derivative, Homoharringtonine, are natural plant alkaloids which inhibit protein synthesis in eukaryotic cells. Synthetic Homoharrigntonine, renamed Omacetaxine mepesuccinate, received FDA approval for the treatment of chronic myelogenous leukemia (CML) (FDA Application No. (NDA) 203585). It is believed to function by stalling host translation by competing with tRNAs at the ribosome and can also halt the cell cycle (95, 96). Recently, Harringtonine has been shown to effectively inhibit CHIKV protein synthesis in vitro at low EC50 (97), however it has not been tested for efficacy *in-vivo.*

Antibody Therapies

Anti-CHIKV antibody has long been known to be a correlate of CHIKV vaccine mediated protection, and a number of passive immunization studies have shown that CHIKV specific neutralizing antibodies can protect animals from CHIKV replication and disease (79, 98). Therefore, CHIKV antibodies have been evaluated as both prophylactic and post-exposure therapies for the treatment of acute CHIKV disease in patient populations, and a number of antibody formulations are at various stages of pre-clinical development. Couderc et al. were able to demonstrate protection against CHIKV disease in both neonatal and interferon receptor knockout mice (*Ifnar*$^{-/-}$) through passive transfer of human donor convalescent plasma (98). In this study protection from disease was achieved when antibodies were administered within the first 24h of infection. Akahata et al. have also found that non-human primate polyclonal antibodies directed against CHIKV VLPs protected *Ifnar*$^{-/-}$ mice against disease (79).

In addition to polyclonal antibody studies, both human and murine monoclonal antibodies (MAbs) directed at the E1 and E2 structural glycoproteins have also been identified that neutralize virus in vitro and are protective in mice (99, 100). Many of the E2 antibodies target diverse regions of the protein to neutralize virus. Generally, clinical improvements in mice are observed when MAb treatment is started within the first 24h following infection (101-103). In addition to single MAb therapies other investigators have developed combinatorial MAb therapies to help prevent against neutralization escape variants (43). Pal et al. recently demonstrated that genetically engineered escape mutants of CHIKV, with resistance to neutralization by two independent MAbs, were mildly attenuated in mice and fail to revert to wild-type in both mosquitoes and mice (104). The combination of studies on polyclonal and MAb therapies against CHIKV suggest that they have strong potential for use in humans at higher risk for disease, when treated early in infection. However, it remains unclear whether antibody therapy would be useful in general populations during CHIKV outbreaks due to costs and logistical concerns around antibody delivery. However, anti-CHIKV antibody therapies might be very useful in specific at risk populations, such as laboratory workers suffering from known virus exposures, immune suppressed individuals, or CHIKV infected women during the late stage of pregnancy (60, 105). Of particular note, given that maternal to child CHIKV transmission during child birth puts infants at increased risk of developing CHIKV-induced neurologic disease, which can result in sequelae with lifelong consequences, anti-CHIKV antibodies represent a promising approach for protecting this population. This could take the form of administering antibodies to women in

the latter stages of pregnancy who have active CHIKV infections or reside in an active outbreak locality, as a means of reducing CHIKV viremia and thereby limiting chances of transmission to the infant, or by direct administration of antibody to the neonate.

Host-targeted Antivirals

Clinical trials with host targeted antivirals have focused on chloroquine, a class of 4-aminoquinolone drug discovered in 1934, which was originally used as an antimalarial drug (FDA Application No. (NDA) 006002). Chloroquine has also been demonstrated to have potent antiviral activity against CHIKV in-vitro. Mechanistic studies suggest that the drug increases endosomal pH, thus preventing the low-pH fusion of the E1 protein during early entry of the virus (106). While Kahn et. al. were able to demonstrate efficacy of the drug when used pre-infection, during infection, and post-infection at micro-molar concentrations in-vitro, it was shown to be ineffective when used greater than 3 hours post-infection. An early report from Brighton found that chloroquine treatment improved chronic CHIKV-associated joint symptoms in 50% of a small cohort of patients (107). However, this was an open study with a small number of patients. Importantly, in follow-up studies, chloroquine was found to be ineffective during two separate human clinical trials conducted in India and La Reunion Island (108, 109). In a study conducted by De Lamballerie et al., patients who received Chloroquine complained of more frequent arthralgia than those that received placebo by day 200 of treatment. Taken together, the early mode of action of chloroquine coupled with its ineffectiveness in several clinical studies, suggest that it may have limited potential for treatment of acute human CHIK disease.

As noted above, there is a significant body of evidence which suggests that the host inflammatory response contributes to the pathogenesis of CHIKV-induced arthridities. Therefore, therapies that inhibit aspects of the host inflammatory response also hold promise in the treatment of CHIKV-induced disease. Bindarit, a small molecule inhibitor of monocyte chemotactic protein-1 (MCP-1) synthesis, has shown potent antiinflammatory actions against cancer-induced inflammation and autoimmune inflammation in several rodent models (110, 111). In mouse models of CHIKV pathogenesis, macrophage numbers and MCP-1 levels have been tightly associated with joint inflammation, arthritis, and myositis. Chen et. al. demonstrated that intraperitoneal administration of Bindarit, twice a day from the day of infection, resulted in significant reductions in symptoms and the duration of disease in mice, which was independent of viral loads in affected tissues (112). However, Poo et al. have recently shown that mice deficient for the cognate receptor of MCP-1, CCR2, have prolonged and more severe symptoms and inflammation than wild-type mice challenged with CHIKV(113). Notably, cellular inflammation in *CCR2*$^{-/-}$ mice is dominated by neutrophils and later, eosinophils, as opposed to the classical monocyte/macrophage response seen in wild-type mice. Based upon these conflicting results, the use of Bindarit in humans to treat CHIKV would require additional small animal model studies to clarify mode of action of the drug, while additional the safety and efficacy tests in other models, such as non-human primate models of CHIKV infection are likely warranted.

Therapies for Chronic CHIKV Disease

As noted above, a significant fraction of CHIKV infected individuals suffer from chronic joint pain and stiffness for months or even years post infection. Given the duration of these symptoms and the fact that they cause a significant decrease in quality of life (30), there is a clear need for effective therapies for treating chronic CHIKV-associated joint pain. Unfortunately, the development of effective therapies is hampered by the fact that the pathogenesis of chronic CHIKV-associated joint pain is poorly understood. For example, although there is limited data suggesting the CHIKV persistence within joints may contribute to chronic disease (46), it is unclear whether drugs that inhibit CHIKV replication will have any benefit if administered during the chronic stage of disease. Furthermore, there is evidence for ongoing inflammation in the joints of at least a subset of individuals suffering from the most severe aspects of chronic CHIKV-induced arthralgia, and evidence suggests that these individuals are likely to be helped by treatment with NSAIDs, as well as disease modifying anti-rheumatic drugs (DMARDs) such as methotrexate (32, 114). However, it is unknown whether broad application of stronger anti-inflammatory and immune suppressive therapies will be of benefit in treating chronic CHIKV disease, at which point in the disease process these strategies should be applied, or whether more specific anti-inflammatory drugs that target specific host pathways will be of benefit. Therefore, the development of more effective therapies, or even approaches for safely using existing treatments, such as methotrexate, for treating chronic CHIKV disease is likely to require a much better understanding of the viral and host factors that drive disease pathogenesis.

Conclusions

The re-emergence of CHIKV and its subsequent global spread illustrates how a combination rapid global transit, broad mosquito vector distribution, and a lack strategies for treating or controlling emerging pathogens can significantly impact public health, a scenario that is now be repeated with the emergence and spread of Zika virus in the Americas. In the case of CHIKV, the response to outbreaks over the past 12 years has provided important new insights into the pathogenesis of CHIKV disease, as well as strategies for developing new vaccines and therapies for treating acute and chronic CHIKV. However, additional work is needed in all of these areas both to deal with the ongoing CHIKV epidemic in the Americas and to prepare for future CHIKV outbreaks.

Acknowledgments

Funding was provided by NIH Grant U19 A1 109680 to MTH and CRM, and by T32-AI007151 to KSP.

References

1. Lumsden WH. 1955 An epidemic of virus disease in Southern Province, Tanganyika Territory, in 1952–53. II. General description and epidemiology. Trans R Soc Trop Med Hyg 49:33–57. [PubMed: 14373835]
2. Kuno G. 2015 A Re-Examination of the History of Etiologic Confusion between Dengue and Chikungunya. PLoS Negl Trop Dis 9:e0004101. [PubMed: 26562299]
3. Carey DE. 1971 Chikungunya and dengue: a case of mistaken identity? J Hist Med Allied Sci 26:243–262. [PubMed: 4938938]

4. McIntosh BM, Harwin RM, Paterson HE, Westwater ML. 1963 An Epidemic of Chikungunya in South-Eastern Southern Rhodesia. Cent AfrJ Med 43:351–359.

5. Muyembe-Tamfum JJ, Peyrefitte CN, Yogolelo R, Mathina Basisya E, Koyange D, Pukuta E, Mashako M, Tolou H, Durand JP. 2003 [Epidemic of Chikungunya virus in 1999 and 200 in the Democratic Republic of the Congo], Med Trop (Mars) 63:637–638. [PubMed: 15077435]

6. Hammon WM, Rudnick A, Sather GE. 1960 Viruses associated with epidemic hemorrhagic fevers of the Philippines and Thailand. Science 131:1102–1103. [PubMed: 14399343]

7. Lam SK, Chua KB, Hooi PS, Rahimah MA, Kumari S, Tharmaratnam M, Chuah SK, Smith DW, Sampson IA. 2001 Chikungunya infection--an emerging disease in Malaysia. Southeast Asian J Trop Med Public Health 32:447–451. [PubMed: 11944696]

8. Deller JJ Jr., Russell PK. 1967 An analysis of fevers of unknown origin in American soldiers in Vietnam. Ann Intern Med 66:1129–1143. [PubMed: 5338939]

9. Thiboutot MM, Kannan S, Kawalekar OU, Shedlock DJ, Khan AS, Sarangan G, Srikanth P, Weiner DB, Muthumani K. 2010 **Chikungunya: a potentially emerging** epidemic? PLoS Negl Trop Dis 4:e623. [PubMed: 20436958]

10. Chretien JP, Anyamba A, Bedno SA, Breiman RF, Sang R, Sergon K, Powers AM, Onyango CO, Small J, Tucker CJ, Linthicum KJ. 2007 Drought-associated chikungunya emergence along coastal East Africa. Am J Trop Med Hyg 76:405–407. [PubMed: 17360859]

11. Kariuki Njenga M, Nderitu L, Ledermann JP, Ndirangu A, Logue CH, Kelly CH, Sang R, Sergon K, Breiman R, Powers AM. 2008 Tracking epidemic Chikungunya virus into the Indian Ocean from East Africa. J Gen Virol 89:2754–2760. [PubMed: 18931072]

12. Paquet C, Quatresous I, Solet JL, Sissoko D, Renault P, Pierre V, Cordel H, Lassalle C, Thiria J, Zeller H, Schuffnecker I. 2006 Chikungunya outbreak in Reunion: epidemiology and surveillance, 2005 to early January 2006. Euro Surveill 11:E060202–060203.

13. Mavalankar D, Shastri P, Raman P. 2007 Chikungunya epidemic in India: a major public-health disaster. Lancet Infect Dis 7:306–307. [PubMed: 17448932]

14. Schuffenecker I, Iteman I, Michault A, Murri S, Frangeul L, Vaney MC, Lavenir R, Pardigon N, Reynes JM, Pettinelli F, Biscornet L, Diancourt L, Michel S, Duquerroy S, Guigon G, Frenkiel MP, Brehin AC, Cubito N, Despres P, Kunst F, Rey FA, Zeller H, Brisse S. 2006 Genome microevolution of chikungunya viruses causing the Indian Ocean outbreak. PLoS Med 3:e263. [PubMed: 16700631]

15. Tsetsarkin KA, Vanlandingham DL, McGee CE, Higgs S. 2007 A single mutation in chikungunya virus affects vector specificity and epidemic potential. PLoS Pathog 3:e201. [PubMed: 18069894]

16. Rezza G, Nicoletti L, Angelini R, Romi R, Finarelli AC, Panning M, Cordioli P, Fortuna C, Boros S, Magurano F, Silvi G, Angelini P, Dottori M, Ciufolini MG, Majori GC, Cassone A, group Cs. 2007 Infection with chikungunya virus in Italy: an outbreak in a temperate region. Lancet 370:1840–1846. [PubMed: 18061059]

17. Grandadam M, Caro V, Plumet S, Thiberge JM, Souares Y, Failloux AB, Tolou HJ, Budelot M, Cosserat D, Leparc-Goffart I, Despres P. 2011 Chikungunya virus, southeastern France. Emerg Infect Dis 17:910–913. [PubMed: 21529410]

18. Gibney KB, Fischer M, Prince HE, Kramer LD, St George K, Kosoy OL, Laven JJ, Staples JE. 2011 Chikungunya fever in the United States: a fifteen year review of cases. Clin Infect Dis 52:e121–126. [PubMed: 21242326]

19. Khan K, Bogoch I, Brownstein JS, Miniota J, Nicolucci A, Hu W, Nsoesie EO, Cetron M, Creatore MI, German M, Wilder-Smith A. 2014 Assessing the origin of and potential for international spread of chikungunya virus from the Caribbean. PLoS Curr 6.

20. Nhan TX, Claverie A, Roche C, Teissier A, Colleuil M, Baudet JM, Cao-Lormeau VM, Musso D. 2014 Chikungunya virus imported into French Polynesia, 2014. Emerg Infect Dis 20:1773–1774. [PubMed: 25271852]

21. Tan KK, Sy AK, Tandoc AO, Khoo JJ, Sulaiman S, Chang LY, AbuBakar S. 2015. Independent Emergence of the Cosmopolitan Asian Chikungunya Virus, Philippines 2012 Sci Rep 5:12279.

22. Van Bortel W, Dorleans F, Rosine J, Blateau A, Rousset D, Matheus S, Leparc-Goffart I, Flusin O, Prat C, Cesaire R, Najioullah F, Ardillon V, Balleydier E, Carvalho L, Lemaitre A, Noel H, Servas V, Six C, Zurbaran M, Leon L, Guinard A, van den Kerkhof J, Henry M, Fanoy E, Braks M,

Reimerink J, Swaan C, Georges R, Brooks L, Freedman J, Sudre B, Zeller H. 2014 Chikungunya outbreak in the Caribbean region, December 2013 to March 2014, and the significance for Europe. Euro Surveill 19.

23. Kendrick K, Stanek D, Blackmore C, Centers for Disease C, Prevention. 2014 Notes from the field: Transmission of chikungunya virus in the continental United States--Florida, 2014. MMWR Morb Mortal Wkly Rep 63:1137. [PubMed: 25474035]
24. Vega-Rua A, Zouache K, Girod R, Failloux AB, Lourenco-de-Oliveira R. 2014 High level of vector competence of Aedes aegypti and Aedes albopictus from ten American countries as a crucial factor in the spread of Chikungunya virus. J Virol 88:6294–6306. [PubMed: 24672026]
25. Marcondes CB, Ximenes MF. 2015 Zika virus in Brazil and the danger of infestation by Aedes (Stegomyia) mosquitoes. Rev Soc Bras Med Trop doi:10.1590/0037-8682-0220-2015.
26. Vega-Rua A, Zouache K, Caro V, Diancourt L, Delaunay P, Grandadam M, Failloux AB. 2013 High efficiency of temperate Aedes albopictus to transmit chikungunya and dengue viruses in the Southeast of France. PLoS One 8:e59716. [PubMed: 23527259]
27. Tsetsarkin KA, Chen R, Leal G, Forrester N, Higgs S, Huang J, Weaver SC. 2011 Chikungunya virus emergence is constrained in Asia by lineage-specific adaptive landscapes. Proc Natl Acad Sci U S A 108:7872–7877. [PubMed: 21518887]
28. Teixeira MG, Andrade AM, Costa Mda C, Castro JN, Oliveira FL, Goes CS, Maia M, Santana EB, Nunes BT, Vasconcelos PF. 2015 East/Central/South African genotype chikungunya virus, Brazil, 2014. Emerg Infect Dis 21:906–907. [PubMed: 25898939]
29. Thiberville SD, Boisson V, Gaudart J, Simon F, Flahault A, de Lamballerie X. 2013 Chikungunya fever: a clinical and virological investigation of outpatients on Reunion Island, South-West Indian Ocean. PLoS Negl Trop Dis 7:e2004. [PubMed: 23350006]
30. Thiberville SD, Moyen N, Dupuis-Maguiraga L, Nougairede A, Gould EA, Roques P, de Lamballerie X. 2013 Chikungunya fever: epidemiology, clinical syndrome, pathogenesis and therapy. Antiviral Res 99:345–370. [PubMed: 23811281]
31. Sissoko D, Ezzedine K, Moendandze A, Giry C, Renault P, Malvy D. 2010 Field evaluation of clinical features during chikungunya outbreak in Mayotte, 2005–2006. Trop Med Int Health 15:600–607. [PubMed: 20214759]
32. Javelle E, Ribera A, Degasne I, Gauzere BA, Marimoutou C, Simon F. 2015 Specific management of post-chikungunya rheumatic disorders: a retrospective study of 159 cases in Reunion Island from 2006–2012. PLoS Negl Trop Dis 9:e0003603. [PubMed: 25760632]
33. Simon F, Parola P, Grandadam M, Fourcade S, Oliver M, Brouqui P, Hance P, Kraemer P, Ali Mohamed A, de Lamballerie X, Charrel R, Tolou H. 2007 Chikungunya infection: an emerging rheumatism among travelers returned from Indian Ocean islands. Report of 47 cases. Medicine (Baltimore) 86:123–137. [PubMed: 17505252]
34. Borgherini G, Poubeau P, Staikowsky F, Lory M, Le Moullec N, Becquart JP, Wengling C, Michault A, Paganin F. 2007 Outbreak of chikungunya on Reunion Island: early clinical and laboratory features in 157 adult patients. Clin Infect Dis 44:1401–1407. [PubMed: 17479933]
35. Borgherini G, Poubeau P, Jossaume A, Gouix A, Cotte L, Michault A, Arvin-Berod C, Paganin F. 2008 Persistent arthralgia associated with chikungunya virus: a study of 88 adult patients on reunion island. Clin Infect Dis 47:469–475. [PubMed: 18611153]
36. Brighton SW, Simson IW. 1984 A destructive arthropathy following Chikungunya virus arthritis—a possible association. Clin Rheumatol 3:253–258. [PubMed: 6088159]
37. Sissoko D, Malvy D, Ezzedine K, Renault P, Moscetti F, Ledrans M, Pierre V. 2009 Postepidemic Chikungunya disease on Reunion Island: course of rheumatic manifestations and associated factors over a 15-month period. PLoS Negl Trop Dis 3:e389. [PubMed: 19274071]
38. Chaaithanya IK, Muruganandam N, Raghuraj U, Sugunan AP, Rajesh R, Anwesh M, Rai SK, Vijayachari P. 2014 Chronic inflammatory arthritis with persisting bony erosions in patients following chikungunya infection. Indian J Med Res 140:142–145. [PubMed: 25222790]
39. Manimunda SP, Vijayachari P, Uppoor R, Sugunan AP, Singh SS, Rai SK, Sudeep AB, Muruganandam N, Chaitanya IK, Guruprasad DR. 2010 Clinical progression of chikungunya fever during acute and chronic arthritic stages and the changes in joint morphology as revealed by imaging. Trans R Soc Trop Med Hyg 104:392–399. [PubMed: 20171708]

40. Ozden S, Huerre M, Riviere JP, Coffey LL, Afonso PV, Mouly V, de Monredon J, Roger JC, El Amrani M, Yvin JL, Jaffar MC, Frenkiel MP, Sourisseau M, Schwartz O, Butler-Browne G, Despres P, Gessain A, Ceccaldi PE. 2007 Human muscle satellite cells as targets of Chikungunya virus infection. PLoS One 2:e527. [PubMed: 17565380]
41. Phuklia W, Kasisith J, Modhiran N, Rodpai E, Thannagith M, Thongsakulprasert T, Smith DR, Ubol S. 2013 Osteoclastogenesis induced by CHIKV-infected fibroblast-like synoviocytes: a possible interplay between synoviocytes and monocytes/macrophages in CHIKV-induced arthralgia/arthritis. Virus Res 177:179–188. [PubMed: 24012515]
42. Morrison TE, Oko L, Montgomery SA, Whitmore AC, Lotstein AR, Gunn BM, Elmore SA, Heise MT. 2011 A mouse model of chikungunya virus-induced musculoskeletal inflammatory disease: evidence of arthritis, tenosynovitis, myositis, and persistence. Am J Pathol 178:32–40. [PubMed: 21224040]
43. Pal P, Dowd KA, Brien JD, Edeling MA, Gorlatov S, Johnson S, Lee I, Akahata W, Nabel GJ, Richter MK, Smit JM, Fremont DH, Pierson TC, Heise MT, Diamond MS. 2013 Development of a highly protective combination monoclonal antibody therapy against Chikungunya virus. PLoS Pathog 9:e1003312. [PubMed: 23637602]
44. Gardner J, Anraku I, Le TT, Larcher T, Major L, Roques P, Schroder WA, Higgs S, Suhrbier A. 2010 Chikungunya virus arthritis in adult wild-type mice. J Virol 84:8021–8032. [PubMed: 20519386]
45. Messaoudi I, Vomaske J, Totonchy T, Kreklywich CN, Haberthur K, Springgay L, Brien JD, Diamond MS, Defilippis VR, Streblow DN. 2013 Chikungunya virus infection results in higher and persistent viral replication in aged rhesus macaques due to defects in anti-viral immunity. PLoS Negl Trop Dis 7:e2343. [PubMed: 23936572]
46. Hoarau JJ, Jaffar Bandj'ee MC, Krej'bich Trotot P, Das T, Li-Pat-Yuen G, Dassa B, Denizot M, Guichard E, Ribera A, Henni T, Tallet F, Moiton MP, Gauzere BA, Bruniquet S, Jaffar Bandjee Z, Morbidelli P, Martigny G, Jolivet M, Gay F, Grandadam M, Tolou H, Vieillard V, Debre P, Autran B, Gasque P. 2010 Persistent chronic inflammation and infection by Chikungunya arthritogenic alphavirus in spite of a robust host immune response. J Immunol 184:5914–5927. [PubMed: 20404278]
47. Labadie K, Larcher T, Joubert C, Mannioui A, Delache B, Brochard P, Guigand L, Dubreil L, Lebon P, Verrier B, de Lamballerie X, Suhrbier A, Cherel Y, Le Grand R, Roques P. 2010 Chikungunya disease in nonhuman primates involves long-term viral persistence in macrophages. J Clin Invest 120:894–906. [PubMed: 20179353]
48. Hawman DW, Stoermer KA, Montgomery SA, Pal P, Oko L, Diamond MS, Morrison TE. 2013 Chronic joint disease caused by persistent Chikungunya virus infection is controlled by the adaptive immune response. J Virol 87:13878–13888. [PubMed: 24131709]
49. Long KM, Heise MT. 2015 Protective and Pathogenic Responses to Chikungunya Virus Infection. Curr Trop Med Rep 2:13–21. [PubMed: 26366337]
50. Chow A, Her Z, Ong EK, Chen JM, Dimatatac F, Kwek DJ, Barkham T, Yang H, Renia L, Leo YS, Ng LF. 2011 Persistent arthralgia induced by Chikungunya virus infection is associated with interleukin-6 and granulocyte macrophage colony-stimulating factor. J Infect Dis 203:149–157. [PubMed: 21288813]
51. Ng LF, Chow A, Sun YJ, Kwek DJ, Lim PL, Dimatatac F, Ng LC, Ooi EE, Choo KH, Her Z, Kourilsky P, Leo YS. 2009 IL-1beta, IL-6, and RANTES as biomarkers of Chikungunya severity. PLoS One 4:e4261. [PubMed: 19156204]
52. Long KM, Ferris MT, Whitmore AC, Montgomery SA, Thurlow LR, McGee CE, Rodriguez CA, Lim JK, Heise MT. 2015 gammadelta T Cells Play a Protective Role in Chikungunya Virus-Induced Disease. J Virol 90:433–443. [PubMed: 26491151]
53. Teo TH, Lum FM, Claser C, Lulla V, Lulla A, Merits A, Renia L, Ng LF. 2013 A pathogenic role for CD4+ T cells during Chikungunya virus infection in mice. J Immunol 190:259–269. [PubMed: 23209328]
54. Rampal, Sharda M, Meena H. 2007 Neurological complications in Chikungunya fever. J Assoc Physicians India 55:765–769. [PubMed: 18290551]
55. Wielanek AC, Monredon JD, Amrani ME, Roger JC, Serveaux JP. 2007 Guillain-Barre syndrome complicating a Chikungunya virus infection. Neurology 69:2105–2107. [PubMed: 18040016]

56. Singh SS, Manimunda SP, Sugunan AP, Sahina, Vijayachari P. 2008 Four cases of acute flaccid paralysis associated with chikungunya virus infection. Epidemiol Infect 136:1277–1280. [PubMed: 18634716]
57. Economopoulou A, Dominguez M, Helynck B, Sissoko D, Wichmann O, Quenel P, Germonneau P, Quatresous I. 2009 Atypical Chikungunya virus infections: clinical manifestations, mortality and risk factors for severe disease during the 2005–2006 outbreak on Reunion. Epidemiol Infect 137:534–541. [PubMed: 18694529]
58. Gerardin P, Couderc T, Bintner M, Tournebize P, Renouil M, Lemant J, Boisson V, Borgherini G, Staikowsky F, Schramm F, Lecuit M, Michault A, Encephalchik Study G. 2016 Chikungunya virus-associated encephalitis: A cohort study on La Reunion Island, 2005–2009. Neurology 86:94–102. [PubMed: 26609145]
59. Fritel X, Rollot O, Gerardin P, Gauzere BA, Bideault J, Lagarde L, Dhuime B, Orvain E, Cuillier F, Ramful D, Samperiz S, Jaffar-Bandjee MC, Michault A, Cotte L, Kaminski M, Fourmaintraux A, Chikungunya-Mere-Enfant T. 2010 Chikungunya virus infection during pregnancy, Reunion, France, 2006. Emerg Infect Dis 16:418–425. [PubMed: 20202416]
60. Gerardin P, Barau G, Michault A, Bintner M, Randrianaivo H, Choker G, Lenglet Y, Touret Y, Bouveret A, Grivard P, Le Roux K, Blanc S, Schuffenecker I, Couderc T, Arenzana-Seisdedos F, Lecuit M, Robillard PY. 2008 Multidisciplinary prospective study of mother-to-child chikungunya virus infections on the island of La Reunion. PLoS Med 5:e60. [PubMed: 18351797]
61. Mahendradas P, Ranganna SK, Shetty R, Balu R, Narayana KM, Babu RB, Shetty BK. 2008 Ocular manifestations associated with chikungunya. Ophthalmology 115:287–291. [PubMed: 17631967]
62. Soumahoro MK, Gerardin P, Boelle PY, Perrau J, Fianu A, Pouchot J, Malvy D, Flahault A, Favier F, Hanslik T. 2009 Impact of Chikungunya virus infection on health status and quality of life: a retrospective cohort study. PLoS One 4:e7800. [PubMed: 19911058]
63. Weaver SC, Osorio JE, Livengood JA, Chen R, Stinchcomb DT. 2012 Chikungunya virus and prospects for a vaccine. Expert Rev Vaccines 11:1087–1101. [PubMed: 23151166]
64. White A, Berman S, Lowenthal JP. 1972 Comparative immunogenicities of Chikungunya vaccines propagated in monkey kidney monolayers and chick embryo suspension cultures. Appl Microbiol 23:951–952. [PubMed: 4624213]
65. Harrison VR, Eckels KH, Bartelloni PJ, Hampton C. 1971 Production and evaluation of a formalin-killed Chikungunya vaccine. J Immunol 107:643–647. [PubMed: 4999088]
66. Levitt NH, Ramsburg HH, Hasty SE, Repik PM, Cole FE, Lupton HW. 1986 Development of an attenuated strain of chikungunya virus for use in vaccine production. Vaccine 4:157–162. [PubMed: 3020820]
67. McClain DJ, Pittman PR, Ramsburg HH, Nelson GO, Rossi CA, Mangiafico JA, Schmaljohn AL, Malinoski FJ. 1998 Immunologic interference from sequential administration of live attenuated alphavirus vaccines. J Infect Dis 177:634–641. [PubMed: 9498442]
68. Edelman R, Tacket CO, Wasserman SS, Bodison SA, Perry JG, Mangiafico JA. 2000 Phase II safety and immunogenicity study of live chikungunya virus vaccine TSI-GSD-218. Am J Trop Med Hyg 62:681–685. [PubMed: 11304054]
69. Enserink M. 2006 Infectious diseases. Massive outbreak draws fresh attention to little-known virus. Science 311:1085. [PubMed: 16497896]
70. Turell MJ, Malinoski FJ. 1992 Limited potential for mosquito transmission of a live, attenuated chikungunya virus vaccine. Am J Trop Med Hyg 47:98–103. [PubMed: 1322072]
71. Gorchakov R, Wang E, Leal G, Forrester NL, Plante K, Rossi SL, Partidos CD, Adams AP, Seymour RL, Weger J, Borland EM, Sherman MB, Powers AM, Osorio JE, Weaver SC. 2012 Attenuation of Chikungunya virus vaccine strain 181/clone 25 is determined by two amino acid substitutions in the E2 envelope glycoprotein. J Virol 86:6084–6096. [PubMed: 22457519]
72. Silva LA, Khomandiak S, Ashbrook AW, Weller R, Heise MT, Morrison TE, Dermody TS. 2014 A single-amino-acid polymorphism in Chikungunya virus E2 glycoprotein influences glycosaminoglycan utilization. J Virol 88:2385–2397. [PubMed: 24371059]

73. Ashbrook AW, Burrack KS, Silva LA, Montgomery SA, Heise MT, Morrison TE, Dermody TS. 2014 Residue 82 of the Chikungunya virus E2 attachment protein modulates viral dissemination and arthritis in mice. J Virol88:12180–12192. [PubMed: 25142598]
74. Plante KS, Rossi SL, Bergren NA, Seymour RL, Weaver SC. 2015 Extended Preclinical Safety, Efficacy and Stability Testing of a Live-attenuated Chikungunya Vaccine Candidate. PLoS Negl Trop Dis 9:e0004007. [PubMed: 26340754]
75. Plante K, Wang E, Partidos CD, Weger J, Gorchakov R, Tsetsarkin K, Borland EM, Powers AM, Seymour R, Stinchcomb DT, Osorio JE, Frolov I, Weaver SC. 2011 Novel chikungunya vaccine candidate with an IRES-based attenuation and host range alteration mechanism. PLoS Pathog 7:e1002142. [PubMed: 21829348]
76. Roy CJ, Adams AP, Wang E, Plante K, Gorchakov R, Seymour RL, Vinet-Oliphant H, Weaver SC. 2014 Chikungunya Vaccine Candidate Is Highly Attenuated and Protects Nonhuman Primates Against Telemetrically Monitored Disease Following a Single Dose. J Infect Dis **doi:**10.1093/infdis/jiu014.**doi:**
77. Partidos CD, Paykel J, Weger J, Borland EM, Powers AM, Seymour R, Weaver SC, Stinchcomb DT, Osorio JE. 2012 Cross-protective immunity against o'nyong-nyong virus afforded by a novel recombinant chikungunya vaccine. Vaccine 30:4638–4643. [PubMed: 22583812]
78. Partidos CD, Weger J, Brewoo J, Seymour R, Borland EM, Ledermann JP, Powers AM, Weaver SC, Stinchcomb DT, Osorio JE. 2011 Probing the attenuation and protective efficacy of a candidate chikungunya virus vaccine in mice with compromised interferon (IFN) signaling. Vaccine 29:3067–3073. [PubMed: 21300099]
79. Akahata W, Yang ZY, Andersen H, Sun S, Holdaway HA, Kong WP, Lewis MG, Higgs S, Rossmann MG, Rao S, Nabel GJ. 2010 A virus-like particle vaccine for epidemic Chikungunya virus protects nonhuman primates against infection. Nat Med 16:334–338. [PubMed: 20111039]
80. Chang LJ, Dowd KA, Mendoza FH, Saunders JG, Sitar S, Plummer SH, Yamshchikov G, Sarwar UN, Hu Z, Enama ME, Bailer RT, Koup RA, Schwartz RM, Akahata W, Nabel GJ, Mascola JR, Pierson TC, Graham BS, Ledgerwood JE, Team VS. 2014 Safety and tolerability of chikungunya virus-like particle vaccine in healthy adults: a phase 1 dose-escalation trial. Lancet 384:2046–2052. [PubMed: 25132507]
81. Brandler S, Ruffie C, Combredet C, Brault JB, Najburg V, Prevost MC, Habel A, Tauber E, Despres P, Tangy F. 2013 A recombinant measles vaccine expressing chikungunya virus-like particles is strongly immunogenic and protects mice from lethal challenge with chikungunya virus. Vaccine 31:3718–3725. [PubMed: 23742993]
82. Ramsauer K, Schwameis M, Firbas C, Mullner M, Putnak RJ, Thomas SJ, Despres P, Tauber E, Jilma B, Tangy F. 2015 Immunogenicity, safety, and tolerability of a recombinant measles-virus-based chikungunya vaccine: a randomised, double-blind, placebo-controlled, active-comparator, first-in-man trial. Lancet Infect Dis 15:519–527. [PubMed: 25739878]
83. Tiwari M, Parida M, Santhosh SR, Khan M, Dash PK, Rao PV. 2009 Assessment of immunogenic potential of Vero adapted formalin inactivated vaccine derived from novel ECSA genotype of Chikungunya virus. Vaccine 27:2513–2522. [PubMed: 19368794]
84. Wang E, Kim DY, Weaver SC, Frolov I. 2011 Chimeric Chikungunya viruses are nonpathogenic in highly sensitive mouse models but efficiently induce a protective immune response. J Virol 85:9249–9252. [PubMed: 21697494]
85. Wang D, Suhrbier A, Penn-Nicholson A, Woraratanadharm J, Gardner J, Luo M, Le TT, Anraku I, Sakalian M, Einfeld D, Dong JY. 2011 A complex adenovirus vaccine against chikungunya virus provides complete protection against viraemia and arthritis. Vaccine 29:2803–2809. [PubMed: 21320541]
86. Muthumani K, Lankaraman KM, Laddy DJ, Sundaram SG, Chung CW, Sako E, Wu L, Khan A, Sardesai N, Kim JJ, Vijayachari P, Weiner DB. 2008 Immunogenicity of novel consensus-based DNA vaccines against Chikungunya virus. Vaccine 26:5128. [PubMed: 18471943]
87. Mallilankaraman K, Shedlock DJ, Bao H, Kawalekar OU, Fagone P, Ramanathan AA, Ferraro B, Stabenow J, Vijayachari P, Sundaram SG, Muruganandam N, Sarangan G, Srikanth P, Khan AS, Lewis MG, Kim JJ, Sardesai NY, Muthumani K, Weiner DB. 2011 A DNA vaccine against chikungunya virus is protective in mice and induces neutralizing antibodies in mice and nonhuman primates. PLoS Negl Trop Dis 5:e928. [PubMed: 21264351]

88. Kumar M, Sudeep AB, Arankalle VA. 2012 Evaluation of recombinant E2 protein-based and whole-virus inactivated candidate vaccines against chikungunya virus. Vaccine 30:6142–6149. [PubMed: 22884660]

89. Metz SW, Geertsema C, Martina BE, Andrade P, Heldens JG, van Oers MM, Goldbach RW, Vlak JM, Pijlman GP. 2011 Functional processing and secretion of Chikungunya virus E1 and E2 glycoproteins in insect cells. Virol J 8:353. [PubMed: 21762510]

90. Metz SW, Gardner J, Geertsema C, Le TT, Goh L, Vlak JM, Suhrbier A, Pijlman GP. 2013 Effective chikungunya virus-like particle vaccine produced in insect cells. PLoS Negl Trop Dis 7:e2124. [PubMed: 23516657]

91. Graci JD, Cameron CE. 2006 Mechanisms of action of ribavirin against distinct viruses. Rev Med Virol 16:37–48. [PubMed: 16287208]

92. Ravichandran R, Manian M. 2008 Ribavirin therapy for Chikungunya arthritis. J Infect Dev Ctries 2:140–142. [PubMed: 19738340]

93. Briolant S, Garin D, Scaramozzino N, Jouan A, Crance JM. 2004 In vitro inhibition of Chikungunya and Semliki Forest viruses replication by antiviral compounds: synergistic effect of interferon-alpha and ribavirin combination. Antiviral Res 61:111–117. [PubMed: 14670584]

94. Khan M, Dhanwani R, Patro IK, Rao PV, Parida MM. 2011 Cellular IMPDH enzyme activity is a potential target for the inhibition of Chikungunya virus replication and virus induced apoptosis in cultured mammalian cells. Antiviral Res 89:1–8. [PubMed: 21070810]

95. Fresno M, Jimenez A, Vazquez D. 1977 Inhibition of translation in eukaryotic systems by harringtonine. Eur J Biochem 72:323–330. [PubMed: 319998]

96. Fan IJ, Han R. 1979 [The effect of harringtonine on the cell cycle of L-1210 cells and the bone marrow stem cells in mice (author's transl)]. Yao Xue Xue Bao 14:467–473. [PubMed: 532646]

97. Kaur P, Thiruchelvan M, Lee RC, Chen H, Chen KC, Ng ML, Chu JJ. 2013 Inhibition of chikungunya virus replication by harringtonine, a novel antiviral that suppresses viral protein expression. Antimicrob Agents Chemother 57:155–167. [PubMed: 23275491]

98. Couderc T, Khandoudi N, Grandadam M, Visse C, Gangneux N, Bagot S, Prost JF, Lecuit M. 2009 Prophylaxis and therapy for Chikungunya virus infection. J Infect Dis 200:516–523. [PubMed: 19572805]

99. Warter L, Lee CY, Thiagarajan R, Grandadam M, Lebecque S, Lin RT, Bertin-Maghit S, Ng LF, Abastado JP, Despres P, Wang CI, Nardin A. 2011 Chikungunya virus envelope-specific human monoclonal antibodies with broad neutralization potency. J Immunol 186:3258–3264. [PubMed: 21278338]

100. Goh LY, Hobson-Peters J, Prow NA, Gardner J, Bielefeldt-Ohmann H, Pyke AT, Suhrbier A, Hall RA. 2013 Neutralizing monoclonal antibodies to the E2 protein of chikungunya virus protects against disease in a mouse model. Clin Immunol 149:487–497. [PubMed: 24239837]

101. Selvarajah S, Sexton NR, Kahle KM, Fong RH, Mattia KA, Gardner J, Lu K, Liss NM, Salvador B, Tucker DF, Barnes T, Mabila M, Zhou X, Rossini G, Rucker JB, Sanders DA, Suhrbier A, Sambri V, Michault A, Muench MO, Doranz BJ, Simmons G. 2013 A neutralizing monoclonal antibody targeting the acid-sensitive region in chikungunya virus E2 protects from disease. PLoS Negl Trop Dis 7:e2423. [PubMed: 24069479]

102. Jin J, Liss NM, Chen DH, Liao M, Fox JM, Shimak RM, Fong RH, Chafets D, Bakkour S, Keating S, Fomin ME, Muench MO, Sherman MB, Doranz BJ, Diamond MS, Simmons G. 2015 Neutralizing Monoclonal Antibodies Block Chikungunya Virus Entry and Release by Targeting an Epitope Critical to Viral Pathogenesis. Cell Rep 13:2553–2564. [PubMed: 26686638]

103. Smith SA, Silva LA, Fox JM, Flyak AI, Kose N, Sapparapu G, Khomandiak S, Ashbrook AW, Kahle KM, Fong RH, Swayne S, Doranz BJ, McGee CE, Heise MT, Pal P, Brien JD, Austin SK, Diamond MS, Dermody TS, Crowe JE Jr. 2015 Isolation and Characterization of Broad and Ultrapotent Human Monoclonal Antibodies with Therapeutic Activity against Chikungunya Virus. Cell Host Microbe 18:86–95. [PubMed: 26159721]

104. Pal P, Fox JM, Hawman DW, Huang YJ, Messaoudi I, Kreklywich C, Denton M, Legasse AW, Smith PP, Johnson S, Axthelm MK, Vanlandingham DL, Streblow DN, Higgs S, Morrison TE, Diamond MS. 2014 Chikungunya viruses that escape monoclonal antibody therapy are clinically attenuated, stable, and not purified in mosquitoes. J Virol 88:8213–8226. [PubMed: 24829346]

105. Ramful D, Carbonnier M, Pasquet M, Bouhmani B, Ghazouani J, Noormahomed T, Beullier G, Attali T, Samperiz S, Fourmaintraux A, Alessandri JL. 2007 Mother-to-child transmission of Chikungunya virus infection. Pediatr Infect Dis J 26:811–815. [PubMed: 17721376]

106. Khan M, Santhosh SR, Tiwari M, Lakshmana Rao PV, Parida M. 2010 Assessment of in vitro prophylactic and therapeutic efficacy of chloroquine against Chikungunya virus in vero cells. J Med Virol 82:817–824. [PubMed: 20336760]

107. Brighton SW. 1984 Chloroquine phosphate treatment of chronic Chikungunya arthritis. An open pilot study. S Afr Med J 66:217–218. [PubMed: 6087474]

108. Chopra A, Saluja M, Venugopalan A. 2014 Effectiveness of chloroquine and inflammatory cytokine response in patients with early persistent musculoskeletal pain and arthritis following chikungunya virus infection. Arthritis Rheumatol 66:319–326. [PubMed: 24504804]

109. de Lamballerie X, Ninove L, Charrel RN. 2009 Antiviral treatment of chikungunya virus infection. Infect Disord Drug Targets 9:101–104. [PubMed: 19275698]

110. Mirolo M, Fabbri M, Sironi M, Vecchi A, Guglielmotti A, Mangano G, Biondi G, Locati M, Mantovani A. 2008 Impact of the anti-inflammatory agent bindarit on the chemokinome: selective inhibition of the monocyte chemotactic proteins. Eur Cytokine Netw 19:119–122. [PubMed: 18775807]

111. Zoja C, Corna D, Benedetti G, Morigi M, Donadelli R, Guglielmotti A, Pinza M, Bertani T, Remuzzi G. 1998 Bindarit retards renal disease and prolongs survival in murine lupus autoimmune disease. Kidney Int 53:726–734. [PubMed: 9507220]

112. Chen W, Foo SS, Taylor A, Lulla A, Merits A, Hueston L, Forwood MR, Walsh NC, Sims NA, Herrero U, Mahalingam S. 2015 Bindarit, an inhibitor of monocyte chemotactic protein synthesis, protects against bone loss induced by chikungunya virus infection. J Virol 89:581–593. [PubMed: 25339772]

113. Poo YS, Nakaya H, Gardner J, Larcher T, Schroder WA, Le TT, Major LD, Suhrbier A. 2014 CCR2 deficiency promotes exacerbated chronic erosive neutrophil-dominated chikungunya virus arthritis. J Virol 88:6862–6872. [PubMed: 24696480]

114. Ganu MA, Ganu AS. 2011 Post-chikungunya chronic arthritis--our experience with DMARDs over two year follow up. J Assoc Physicians India 59:83–86. [PubMed: 21751641]

Table 1.

CHIKV Vaccine Strategies

Vaccine	Platform	Dosing Scheme	Stage of Development	Year of Original Description	References
167 Inactivated	Inactivated	Multi-Dose	Phase I	1971	Harrison 1971 White 1972
181/25	Live Attenuated	Single Dose	Phase II	1986	Levitt 1986 Turell 1992 McClain 1998 Edelman 2000 Gorchakov 2012
Consensus Capsid DNA	DNA	Multi-Dose	Pre-Clinical	2008	Muthumani 2008
ECSA Based Inactivated	Inactivated	Multi-Dose	Pre-Clinical	2009	Tiwari 2009
VSV/CHIKV VLP	VLP	Multi-Dose	Phase I	2010	Akahata 2010 Chang 2014
Structural Gene DNA	DNA	Multi-Dose	Pre-Clinical	2011	Mallilankaraman 2011
Adenovirus Chimera	Chimeric	Single Dose	Pre-Clinical	2011	Wang 2011
Insect Cell VLP	VLP	Single Dose	Pre-Clinical	2011	Metz 2011 Metz 2013
CHIKV/IRES	Live Attenuated	Single Dose	Pre-Clinical	2011	Plante 2011 Partidos 2011 Partidos 2012 Roy 2014 Plante 2015
Alphavirus Chimera	Chimeric	Single Dose	Pre-Clinical	2011	Wang 2011
E2 Protein	Subunit	Multi-Dose	Pre-Clinical	2012	Kumar 2012
MV/CHIKV VLP	VLP	Multi-Dose	Phase I	2013	Brandler 2013 Ramsauer 2015

Table 2.

Chikungunya Antivirals

Antiviral	Target	FDA Approval [a]	References
Ribavirin	Virus	(NDA) 018859	Briolant 2004 Ravichandran 2008
Mycophenolic acid	Virus	(NDA) 050791	Khan 2011
6-Azauridine	Virus		Briolant 2004
Homoharringtonine (Omacetaxine mepesuccinate)	Virus	(NDA) 203585	Kaur 2013
Polyclonal Antibodies	Virus		Couderc 2009 Akahata 2010
Monoclonal Antibodies	Virus		Warter 2011 Goh 2013 Pal 2013 Pal 2014
Chloroquine	Host	(NDA) 006002	Brighton 1984 De Lamballerie 2008 Khan 2010 Chopra 2014
Bindarit	Host		Rulli 2011 Chen 2015

[a]Reflects Approval for Applications Other Than CHIKV