EPIDEMIOLOGY

- Outbreaks of chikungunya disease have occurred in Africa, Asia, Europe, islands in the Indian and Pacific Oceans, and subsequently in the Americas. Most outbreaks occur during the tropical rainy season and abate during the dry season. However, outbreaks in Africa have occurred after periods of drought, where open-water containers serve as vector-breeding sites.
- Chikungunya is transmitted by the mosquito vectors *Aedes aegypti* and *Aedes albopictus*. Infected travelers can import chikungunya into new area; in areas with *Ae. aegypti* and/or *Ae. albopictus* mosquitoes, local transmission can follow. This has been described in many Asian and European countries as well as in the Americas and Australia
- **Dengue** and **Zika** viruses are transmitted by the same mosquito vectors as chikungunya virus. The viruses can cocirculate in a geographic region, and confections have been documented

●*Mosquito bites*

- The major chikungunya virus mosquito vectors are Ae. aegypti and Ae. albopictus
- they **bite primarily during the day** but also at night.
- It prefers the human host and breeds readily in flowerpots and in trash. It often enters homes and will feed indoors and outdoors
- Chikungunya virus can spread geographically via travel of infected individuals between regions with appropriate season/climate where competent mosquitoes exist for perpetuation of local transmission .In addition, dissemination of mosquitoes can occur via transport of mosquito larvae and eggs by ships and air transport to new areas with suitable environmental and climatic conditions [

- ***Blood products and organ transplantation***
  - a nurse was infected by exposure to blood while caring for a patient infected in Réunion
  - transmission of chikungunya via solid organ transplantation has not been documented. Transmission via organ transplantation is ***theoretically possible***
- ***Maternal-fetal transmission***
  - Pregnant women infected with chikungunya virus **are not at increased risk** for atypical or severe disease. Maternal-fetal transmission of chikungunya virus has been described, and maternal chikungunya virus infection has been associated with miscarriage

  - ***intrapartum period*** (two days before delivery to two days after delivery). During this period, vertical transmission occurs in approximately half of cases; among 39 women in the Réunion outbreak with viremia at the time of delivery, the rate of vertical transmission was 49 percent.
  - ***Cesarean delivery was not protective*** against vertical transmission
- Chikungunya virus **has not been detected** in breast milk, and transmission of chikungunya virus via breastfeeding has not been reported. Women may be encouraged to breastfeed even in areas where chikungunya virus is circulating

PATHOGENESIS

- viremia may precede the onset of symptoms by several days.
- the level of viremia closely parallels the fever curve at early times. The fever curve may be “saddleback”; fever may abate 4 to 8 days after onset
- Acute disease correlated with a dramatic increase in IFN-γ and IL-12, and chronic arthritis correlated with prolonged elevated levels of IL-12 in Réunion patients. IL-12 returned to normal in association with recovery.
- A strong innate and adaptive immune response was associated with recovery among patients in Gabon as well, with elevated levels of IL-4, IL-10, and IFN-γ
- leukopenia with relative lymphocytosis
- IgM antibody titers rise during the acute phase and remain at a high plateau. As viremia fades and the first phase of the fever subsides, HI and neutralizing IgG antibody titers

  start to increase,

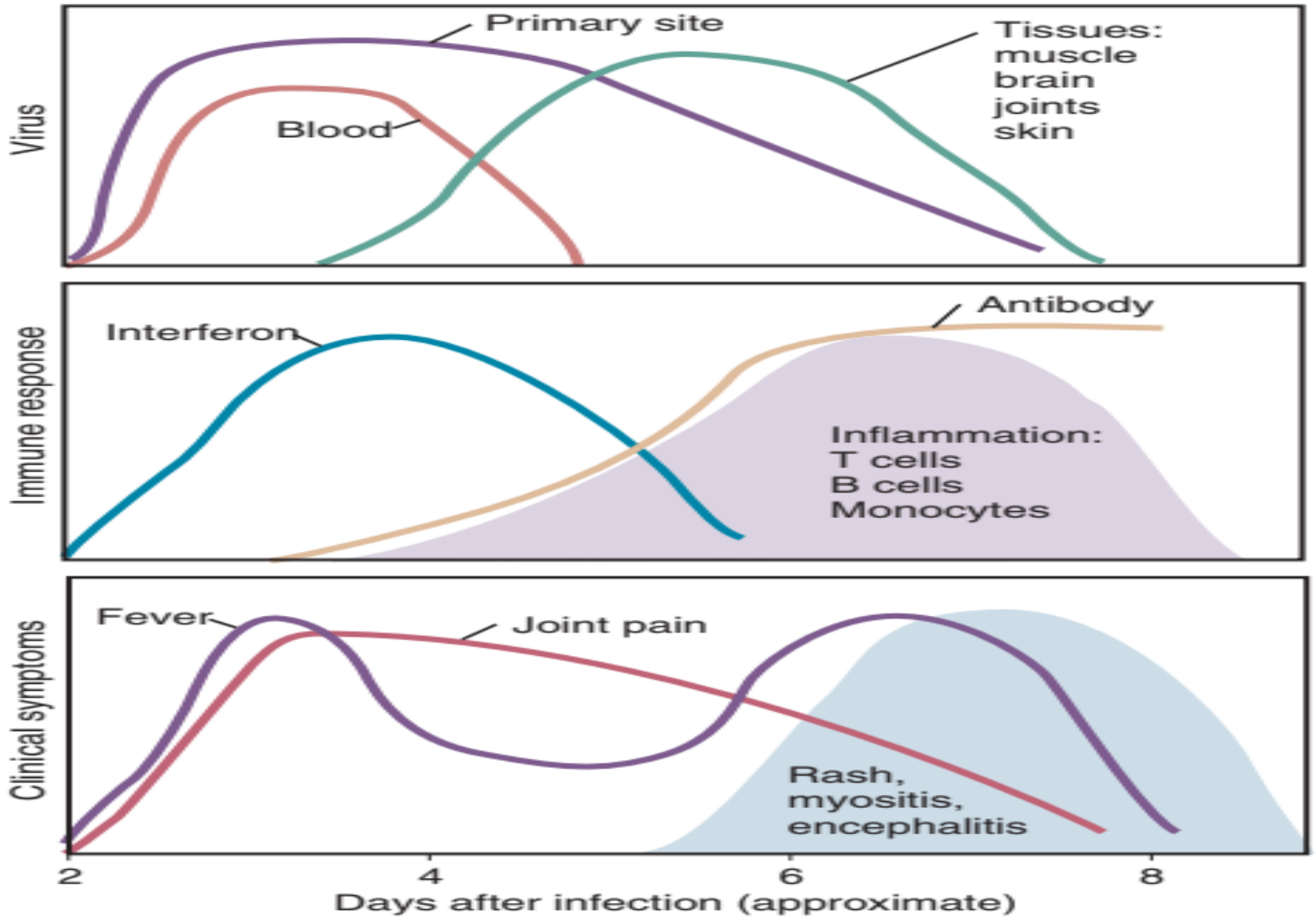


FIG. 151.2 Schematic diagram of the pathogenesis of alphavirus-induced disease. Viremia may be accompanied by production of interferon, other proinflammatory cytokines, and fever. Virus then spreads through the blood to other target tissues. As the immune response is induced, the viremia is terminated, but fever is renewed with the appearance of a mononuclear inflammatory response in the infected tissues. In infections that lead to rash and arthritis, joint pain usually appears early after infection and before the appearance of the rash. *(From Griffin D. The alphaviruses. In: Knipe DM, Howley PM, eds.* Fields Virology. *5th ed. Philadelphia: Lippincott Williams & Wilkins; 2007:1031.)*

CLINICAL MANIFESTATIONS

- ***Acute infection***:
- Following an incubation period of 3 to 7 days (range 1 to 14 days),
- Joint pain may precede fever
- abruptly with fever and malaise
- Fever may be high grade (>39ºC); the usual duration of fever is 3 to 5 days (range 1 to 10 days).
- Other manifestations include joint symptoms and dermatologic involvement. The duration of acute illness is usually 7 to 10 days.
- The musculoskeletal manifestations of chikungunya infection can persist for weeks, months, or years

CLINICAL MANIFESTATIONS

- **Arthralgia and arthritis**
  - ***Arthralgia is a prominent feature (***about 70 percent of patients) Polyarthralgia is present in 70 to 100 percent of patients; joint swelling has
  - Most frequently affected joints include hands (50 to 76 percent), wrists (29 to 81 percent), and ankles (41 to 68 percent)
  - Involvement of the axial skeleton was noted in 34 to 52 percent

  - Arthralgia is usually bilateral and symmetric, involves distal joints more than proximal joints, and is associated with morning stiffness

  - Pain may be ***intense and disabling***, leading to ***immobilization***
  - ***synovitis or periarticular swelling*** has been observed in 32 to 95 percent of cases

CLINICAL MANIFESTATIONS

- **Dermatologic involvement**
  - Skin manifestations 40 to 75 percent of patients.
  - ***macular or maculopapular rash*** (three days or later after onset of illness and lasting three to seven days)
  - The rash often starts on the limbs and trunk, can involve the face, and may be patchy or diffuse. Pruritus has been reported in 25 to 50 percent of patients in some series.
  - ***Hemorrhagic manifestations are uncommon***

- **Additional manifestations** gastrointestinal symptoms; these are usually self-limited and resolve within one to three weeks. Peripheral lymphadenopathy (most often cervical)
- Oral lesions, often painful ulcers, were found in approximately 20 percent of patients in one series



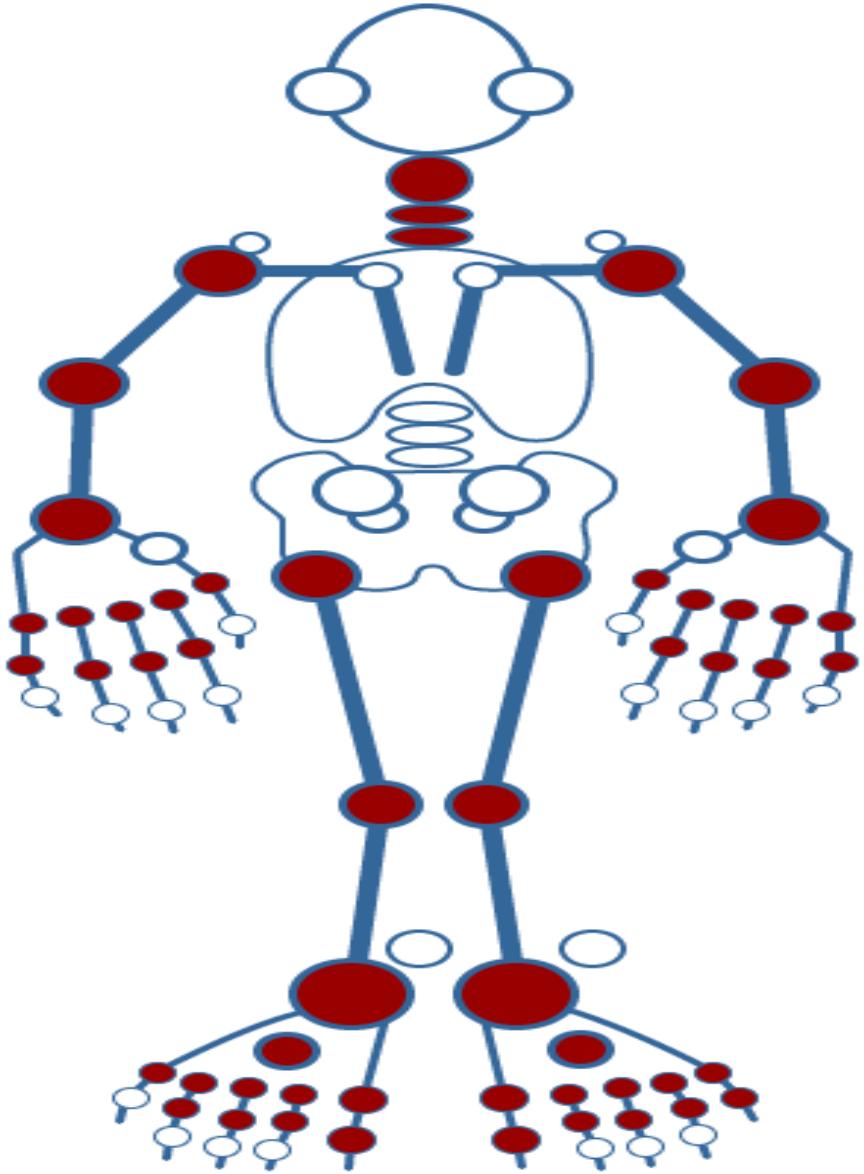
Severe complications

- ***Severe complications include***
  - respiratory failure,
  - cardiovascular decompensation, myocarditis,
  - acute hepatitis,
  - renal failure,, and
  - neurologic involvement Meningoencephalitis is the most common neurologic complication; other neurologic manifestations include acute flaccid paralysis, Guillain-Barre syndrome, myelitis, seizures (primarily in children), and cranial nerve palsies

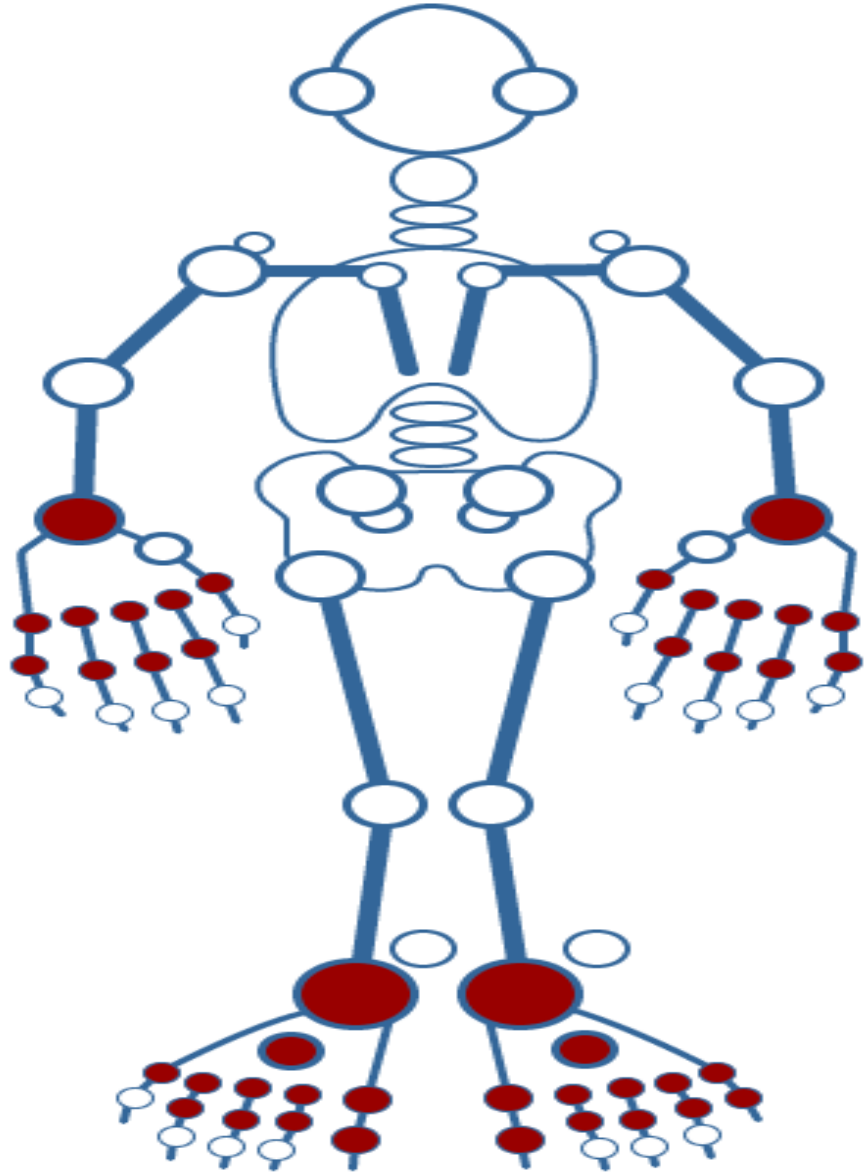
- These occur more often among patients >65 years and patients with underlying chronic medical problems (eg, most commonly diabetes and cardiovascular disease)

Chronic arthritis and arthralgia

- ***chronic musculoskeletal disease*** occurs in 25 to 75 percent of patients .***The range*** may be due to variability in geography, virus strain, and individual comorbidities.
- The joint disease can be relapsing or unremitting and incapacitating. Patients may develop a new chronic inflammatory polyarthritis or may have flares of pre-existing arthritis during and following infection
- Persistent and sometimes severe polyarthralgia is the most prominent feature, often **without objective signs of inflammation on examination**. These patients typically have prolonged morning stiffness and may respond clinically to conventional disease-modifying anti-inflammatory drugs, suggesting that inflammatory arthritis is likely to be the underlying cause of symptoms



Acute



Chronic

- tenosynovitis, frozen shoulder, and plantar fasciitis. New-onset Raynaud phenomena Carpal tunnel syndrome may result from hypertrophic tenosynovitis has been observed in up to 20 percent of cases . Occasionally, sternoclavicular or temporomandibular joints are involved
- Synovial fluid analysis has been reported in very few patients Reverse-transcription polymerase chain reaction testing was negative for chikungunya virus genomes in 10 of 10 samples tested by this method, even in two viremic patients

- No increase in the frequency of positive rheumatoid factor or anti-citrullinated peptide antibodies has been observed
- Long-term joint involvement has been reported in association with human leukocyte antigen B27

DIAGNOSIS

- leukopenia with relative lymphocytosis.
- The erythrocyte sedimentation rate is usually markedly elevated, and the C-reactive protein is positive.
- The diagnosis of chikungunya virus infection should be suspected in patients with acute onset of fever and polyarthralgia and relevant epidemiologic exposure
- The diagnosis of chikungunya is established by detection of chikungunya viral RNA via **real-time reverse-transcription polymerase chain reaction** (RT-PCR) or chikungunya virus serology
- For individuals presenting ***one to seven days*** following onset of symptoms, RT-PCR with excellent sensitivity and specificity (**100 and 98 percent, respectively**)
- For individuals presenting ≥8 days following onset of symptoms, chikungunya virus serologic testing via ELISA or IFA should be performed.

DIAGNOSIS

- Immunoglobulin IgM anti-chikungunya virus antibodies persist for several weeks to three months.

- IgG antibodies begin to appear about two weeks following onset of symptoms and persist for years

- Testing for dengue virus infection and Zika virus infection should also be pursued. A single PCR test to evaluate for the presence of all three infections is available through the United States Centers for Disease Control and Prevention and other qualified laboratories

DIFFERENTIAL DIAGNOSIS

- ***Mimics of acute infection***
- **Dengue fever** –
- Chikungunya virus infection is more likely to cause high fever, severe arthralgia, arthritis, rash
- whereas dengue virus infection is more likely to cause neutropenia, thrombocytopenia, hemorrhage, shock, and death. The diagnosis of dengue fever is established via polymerase chain reaction (PCR) or serology
- **Zika virus**
- Zika virus infection include fever, rash, headache, arthralgia, myalgia, and conjunctivitis.

DIFFERENTIAL DIAGNOSIS

- **Mimics of chronic arthritis:**
- **Seronegative rheumatoid arthritis**
  - inflammatory arthritis involving three or more joints for >6 weeks, with negative rheumatoid factor and anti-cyclic citrullinated peptide antibody tests. It is a diagnosis of exclusion

- **Reactive arthritis**
  - Clinical manifestations include at least one of the following: asymmetric oligoarthritis (often affecting the lower extremities), enthesitis (inflammation at the insertion site of ligaments and tendons to bone), dactylitis (inflammation of an entire digit), and inflammatory back pain.

TREATMENT

- Treatment is influenced by the phase and duration of the illness and the response to therapy.
- Inflammatory arthritis evident on physical examination and chronic arthralgia without physical findings are treated similarly
- Persistent and sometimes severe polyarthralgia is the most prominent feature, often without objective signs of inflammation on examination, such as swelling and erythema. These patients typically have prolonged morning stiffness and may respond to conventional DMARDs
- Acute disease —
  - we suggest acetaminophen (paracetamol; up to 500 to 1000 mg three times daily)
  - once dengue is excluded and if acetaminophen is inadequate for symptom relief, NSAIDs (eg, naproxen 375 to 500 mg twice daily, ibuprofen 400 to 800 mg three times daily, or another NSAID)

TREATMENT

- Typically, an NSAID should be tried for two weeks, and if it is ineffective, patients should be switched to a different NSAID. Both acetaminophen and NSAIDs should be used in the lowest dose and for the shortest duration necessary and avoided in patients with contraindications including known liver disease or elevated aminotransferases.
- In patients with acute disease and severe pain who are unable to take acetaminophen and NSAIDs, or who do not respond adequately to these agents, we selectively use opioid analgesics (eg, tramadol or oxycodone) in the lowest dose for the shortest duration necessary.
- In general, systemic glucocorticoids and other immunosuppressive medications should be avoided during acute infection. The safety of immunosuppression during acute infection is not well established(lasts approximately nine days)

TREATMENT

- Treatment with daily NSAIDs and glucocorticoids (beginning in the second week of acute illness) has been associated with some symptomatic benefit during the first six weeks of illness
- Greater pain relief was observed among the patients who received prednisolone compared with the patients who did not receive prednisolone (an approximate reduction in pain scores from baseline of 75 versus 30 to 40 percent).
- ***Post-acute and chronic arthritis***
  - ***In patients with joint symptoms persisting into the post-acute phase (between one month and up to the end of the third month after onset of infection), we suggest continued analgesia (eg, acetaminophen) and, if needed, NSAIDs.***
  - ***Periodically, an effort should be made to reduce and discontinue medications. Joint symptoms may gradually resolve over several months, and ongoing treatment may no longer be required***

TREATMENT

- whose symptoms are refractory to two to three two-week courses of different NSAIDs and,
- tendinitis, or
- bursitis,
- especially those with evidence of severe synovitis and joint swelling
- persistent elevation of inflammatory markers,
- we suggest systemic glucocorticoids (prednisone 10 to 20 mg daily for five days, depending upon severity, tapered over 10 days)

Chronic arthritis

- the use of DMARD therapy in chronic arthritis (duration >3 months after infection) is similar to treatment for other chronic inflammatory arthritides. MTX has been the most commonly used DMARD, typically using the same approach as in RA
- In patients with chronic arthritis not controlled by NSAIDs or prednisone 5 to 7.5 mg daily (or equivalent), we suggest a conventional DMARD, usually MTX; SSZ or an alternative DMARD are other options,
- **Chronic peripheral arthritis**
  - who require ongoing therapy for symptomatic control, we suggest MTX,
  - The dosing and absorption of MTX should be optimized, as in RA, by use of parenteral therapy or split oral doses
  - **Alternatives** to MTX in patients unable to take the drug include **SSZ**,

Chronic arthritis

- **Chronic axial spondyloarthritis pattern**
- in whom MTX may not be effective, we suggest a TNF inhibitor,
- SpA either chloroquine or HCQ, for post-acute or chronic arthritis have not shown benefit and have limitations in study or trial design

Duration of therapy:

- complete response for at least six months, we attempt to discontinue DMARD therapy.
- recommended that DMARDs may be discontinued in most patients following symptom resolution
- We also prioritize discontinuation of glucocorticoids, but resume treatment if active disease recurs.

PROGNOSIS

- Nearly all patients with chikungunya arthritis eventually recover,

- The predictors of chronicity were age >40, severity of acute disease, and underlying osteoarthritis. Some studies have reported progressive joint injury

- 17 out of 30 patients who had been diagnosed with chikungunya virus-induced arthritis continued to have persistent inflammatory joint symptoms 13 years late
- there was no evidence of seroconversion to anti-cyclic citrullinated peptide (CCP) or rheumatoid factor (RF) positivity

PREVENTION

- Mosquito protection:
  - *Aedes* mosquitoes bite primarily during the daytime; they breed in standing water (particularly containers) .Measures to avoid mosquito bites include personal protection and environmental control measures
- Vaccine development:
  - a live-attenuated, measles-vectored vaccine expressing chikungunya virus structural proteins (MV-CHIK), or a measles vaccine prime and MV-CHIK, induced neutralizing antibodies against chikungunya virus after one or two immunizations
  - Seroconversion rates in those who received MV-CHIK ranged from 50 to 93 percent after one dose and 86 to 100 percent after a two doses.
  - Immune responses were durable up to six months after one or two doses and the vaccine was safe and well-tolerated.

PREVENTION

- The live VEE and CHIK vaccine candidates mentioned previously were derived in the early 1990s by serial passage of virulent human isolates in tissue culture, and neither one is licensed by any regulatory authority.
- f EEEV or CHIKV, in the context of a Sindbis infectious DNA. In another, a live-attenuated CHIKV was derived by insertion of the internal ribosome entry site from the encephalomyocarditis virus genome at the 5′ terminus of the CHIK genome to control translation
- Two groups are developing CHIK vaccines based on virus-like particles
- Virus-like particles resemble native virus particles by structural and antigenic criteria,

PREVENTION

- In a randomized phase 2 trial of a CHIK virus-like particle (VLP) vaccine,
  - received two intramuscular injections.
  - 88 percent had at least a fourfold increase from baseline neutralization titers,
  - The immune response was durable up to 72 weeks after vaccination
- A messenger RNA (mRNA)-based vaccine (VLA-181388) is in phase 1 clinical trials