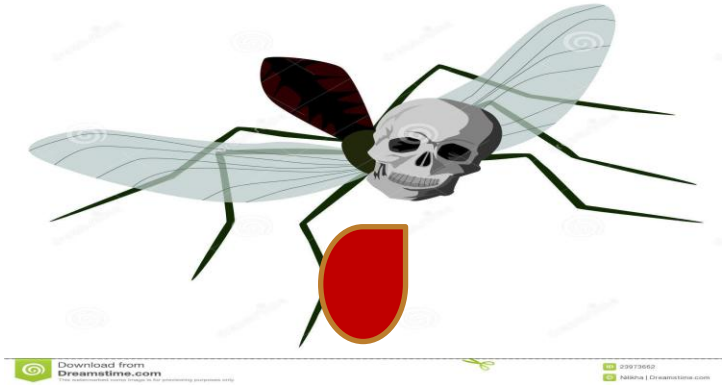
Chikungunya

Dengue

……Cont.



Malaria

I am extremely sorry to inform you all that your blood is too much dirty and I contacted all infection from you. I am not a killer of human being.

My intension is not to transmit Diseases , my intension is very clear to me that I just want one drop of your nutritious blood from you without causing any harm to survive and to maintain our kingdom.

Ashutosh Biswas

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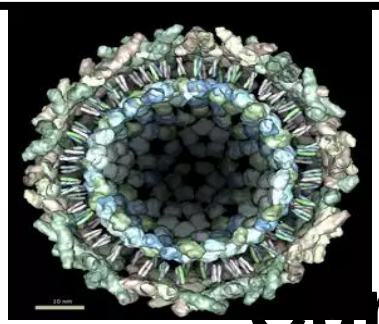
Professor of Medicine

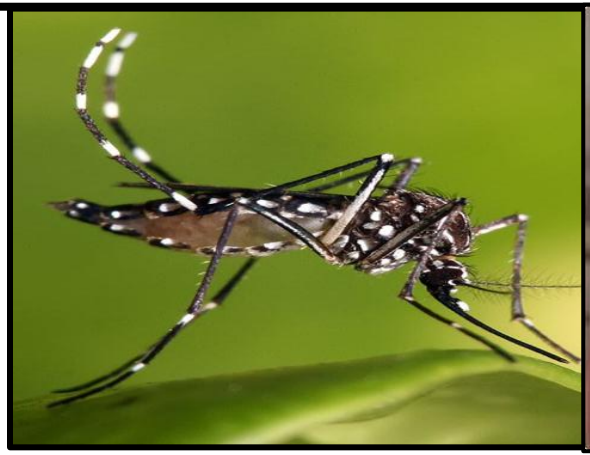
All India Institute of Medical Sciences (AIIMS),

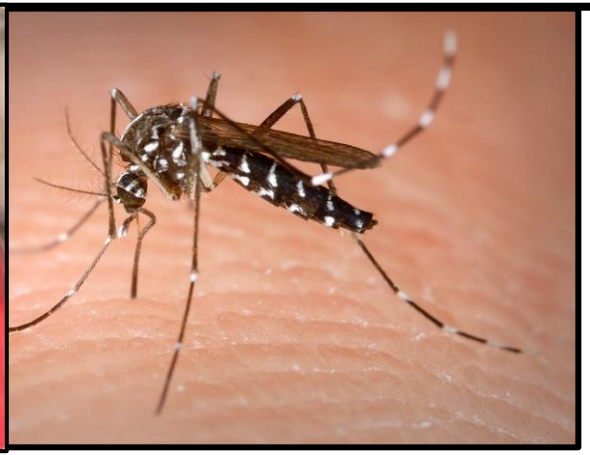
New Delhi, India

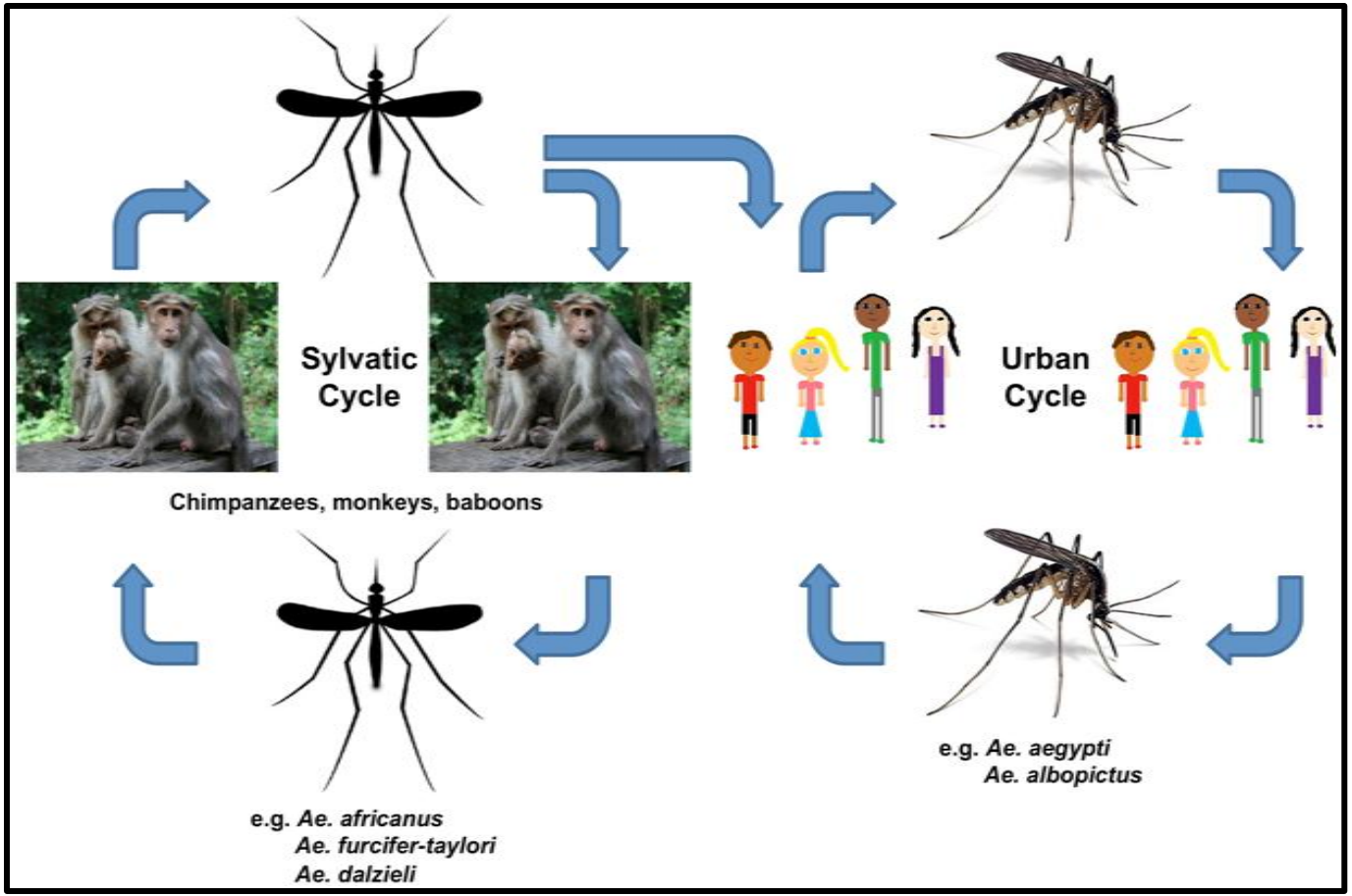


Chikungunya:

Current Concept in Diagnosis and Management





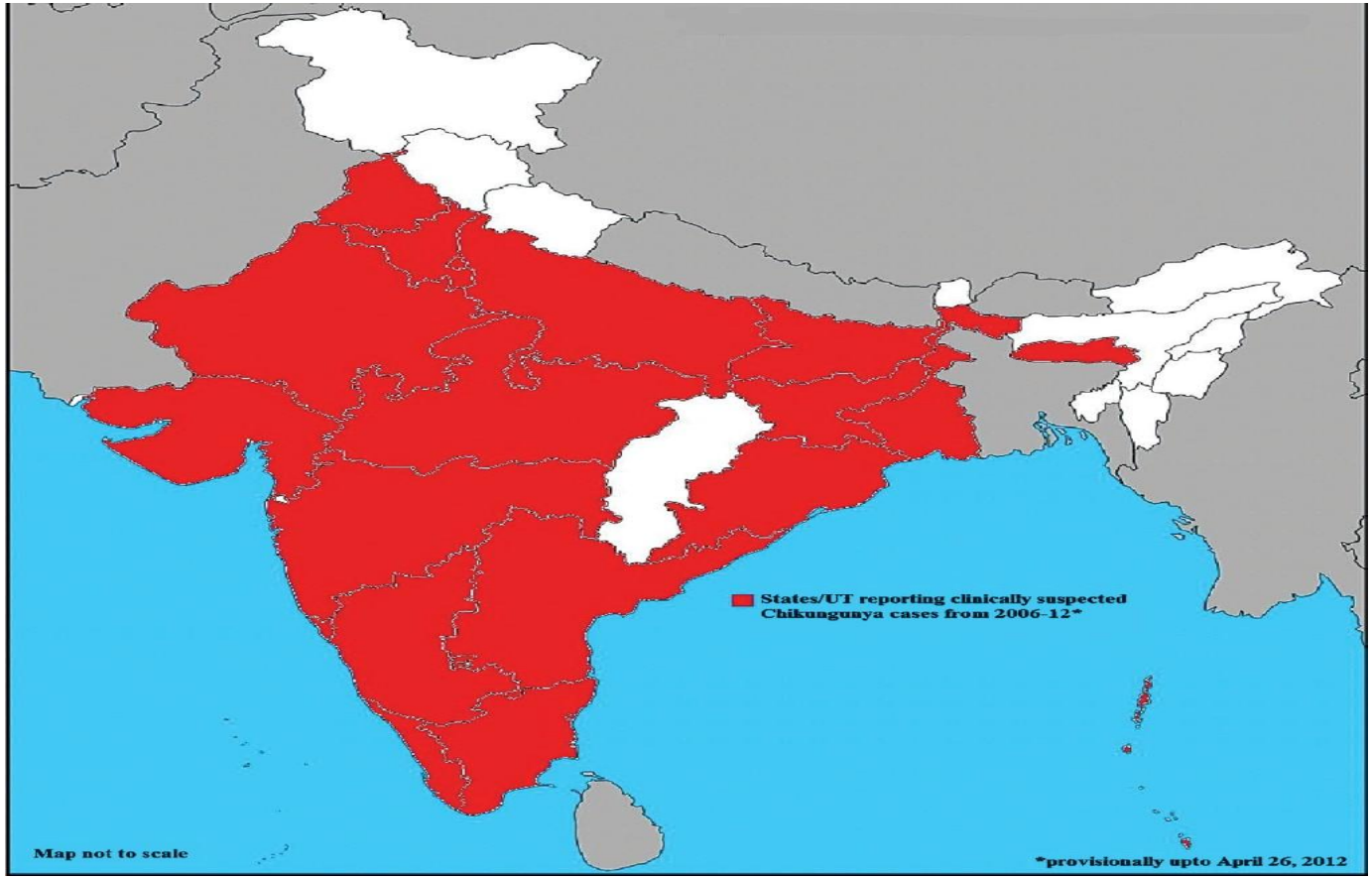


Thiboutot MM, Kannan S, Kawalekar OU, Shedlock DJ, Khan AS, Sarangan G, et al. (2010) Chikungunya: A Potentially Emerging Epidemic? PLoS Negl Trop Dis 4(4): e623. https://doi.org/10.1371/journal.pntd.0000623

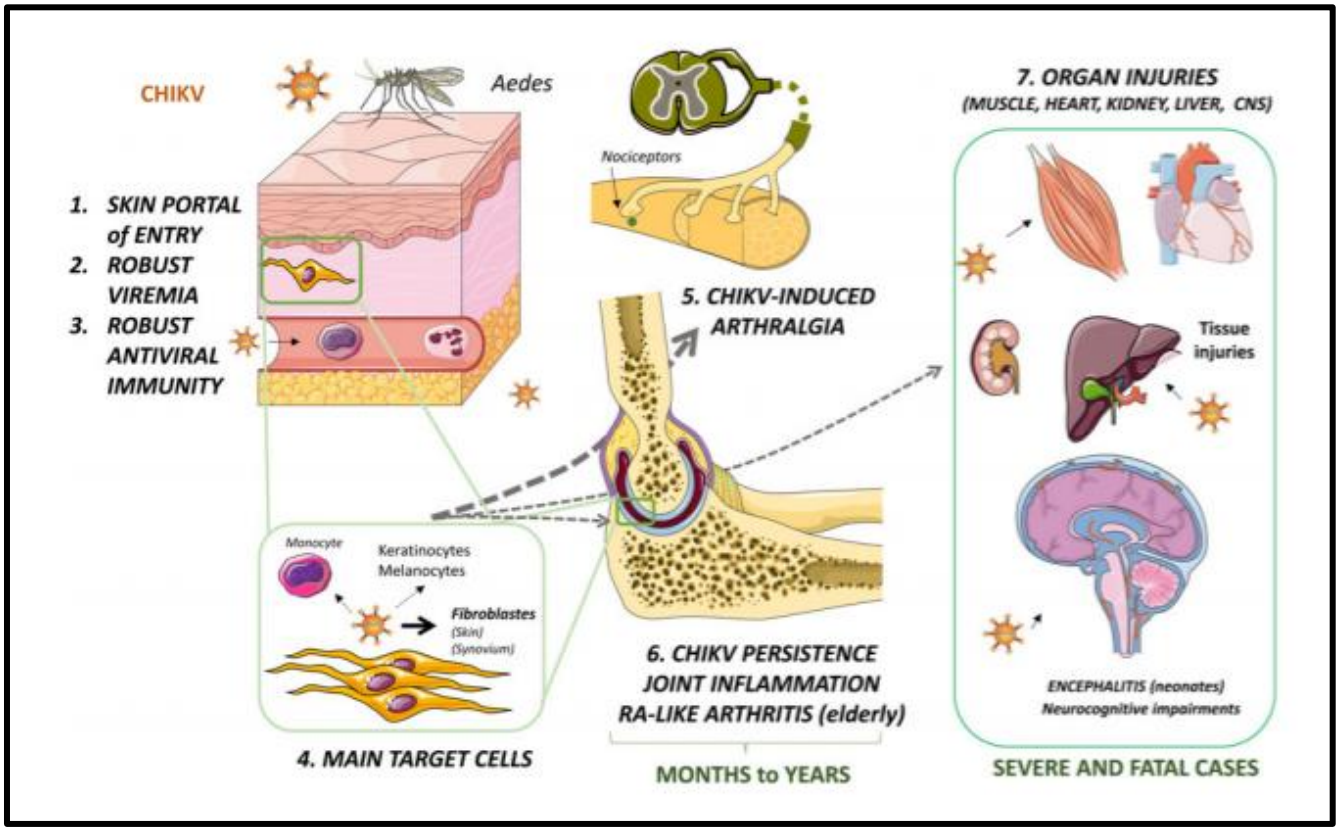
- Aedes breed in clean water collections.
- Transmission is related to rainfall and temperature.
- Increased virus transmission during monsoon and post monsoon season.
- Outbreak typically occurs in clusters, especially in congested localities, as the flight range of these vectors is less.
- Mosquitoes can transmit the disease to more than one person.

13,000 confirmed cases of Chikungunya reported in 2016 form 17ndistrics of Bangladesh

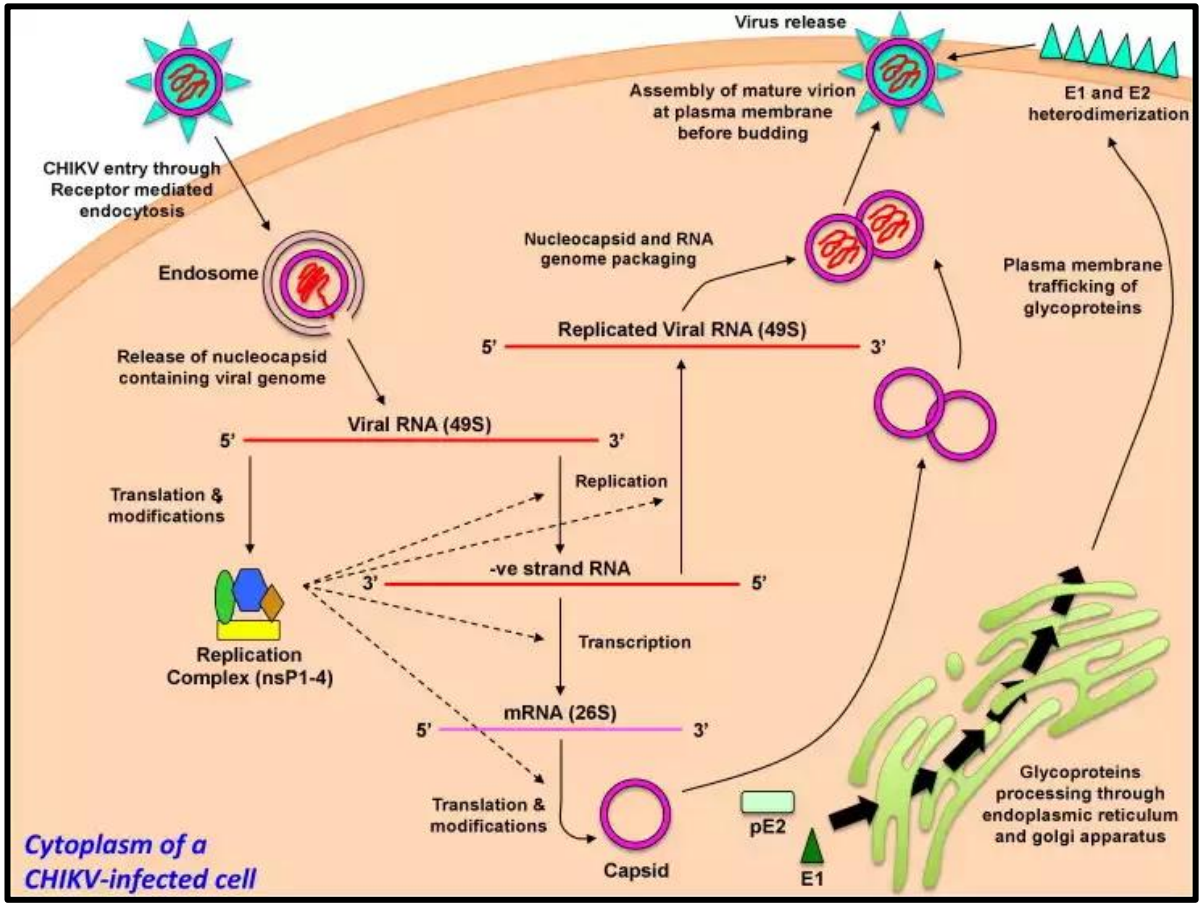
Chikungunya in India



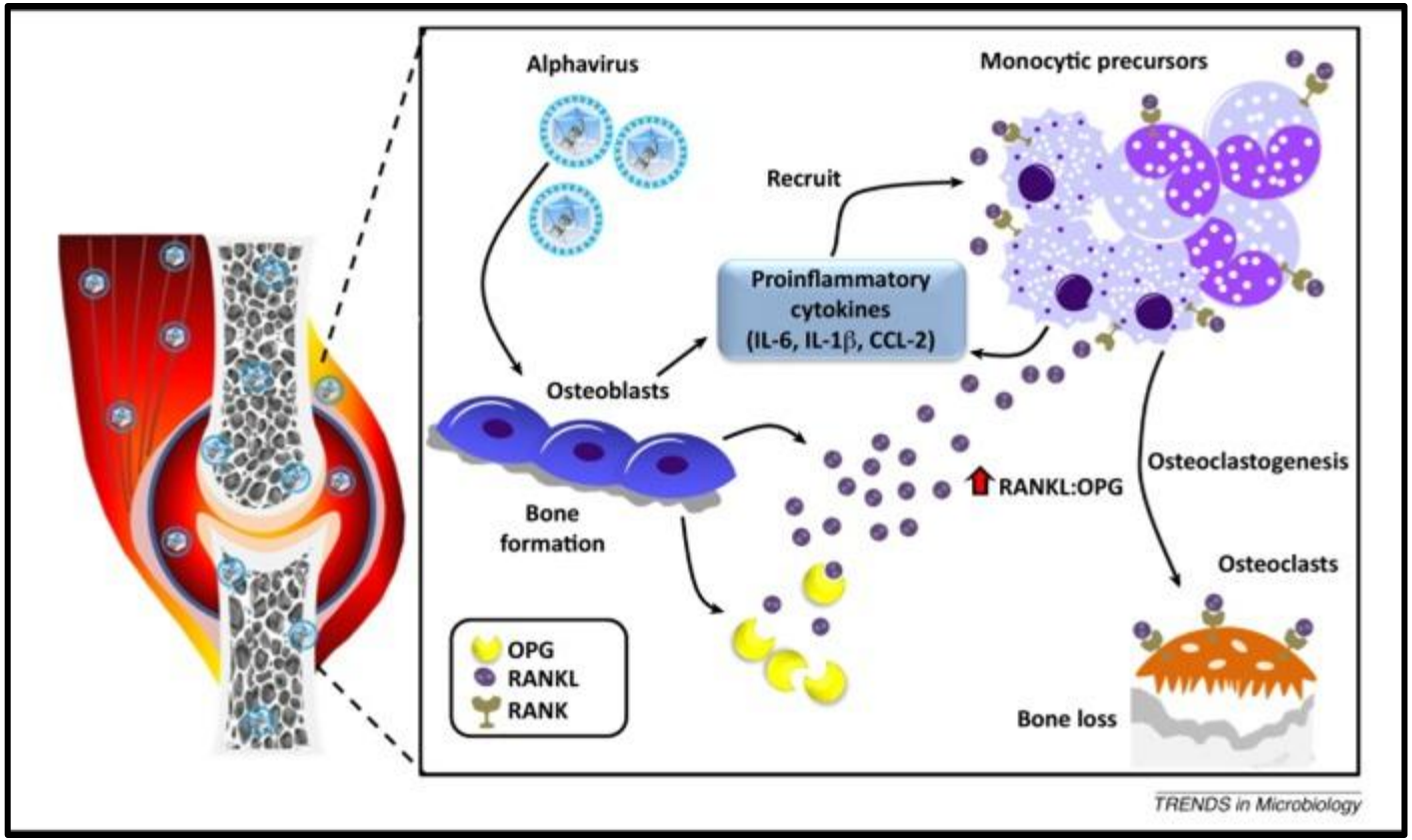
CHIKUNGUNYA PATHOGENESIS



Gasque P, Bandjee MC, Reyes MM et al. Chikungunya pathogenesis: From the clinics to the bench. J Infect Dis 2016 Dec 15;214 (suppl 5):S446-S448.



Lum FM, Ng LF. Cellular and molecular mechanisms of chikungunya pathogenesis. Antiviral Res 2015 Aug;120:165-74.



Chen W, Foo SS, Sims NA et al. Arthritogenic alphaviruses: new insights into arthritis and bone pathology. Trends Microbiol 2015 Jan;23(1):35-43.

The pathogenesis..

A high viral load, as high as 10^{10} virus particles per milliliter of blood may be found during first few days of infection.

Such a high viral load triggers activation of innate immune system, which produces numerous proinflammatory mediators

IFN alpha

IL4, IL10, IFN gamma

CD8+ T lymphocyte response in early stages

CD4+ T lymphocyte response in later stages

Severity of disease in acute phase is related to the viral load.

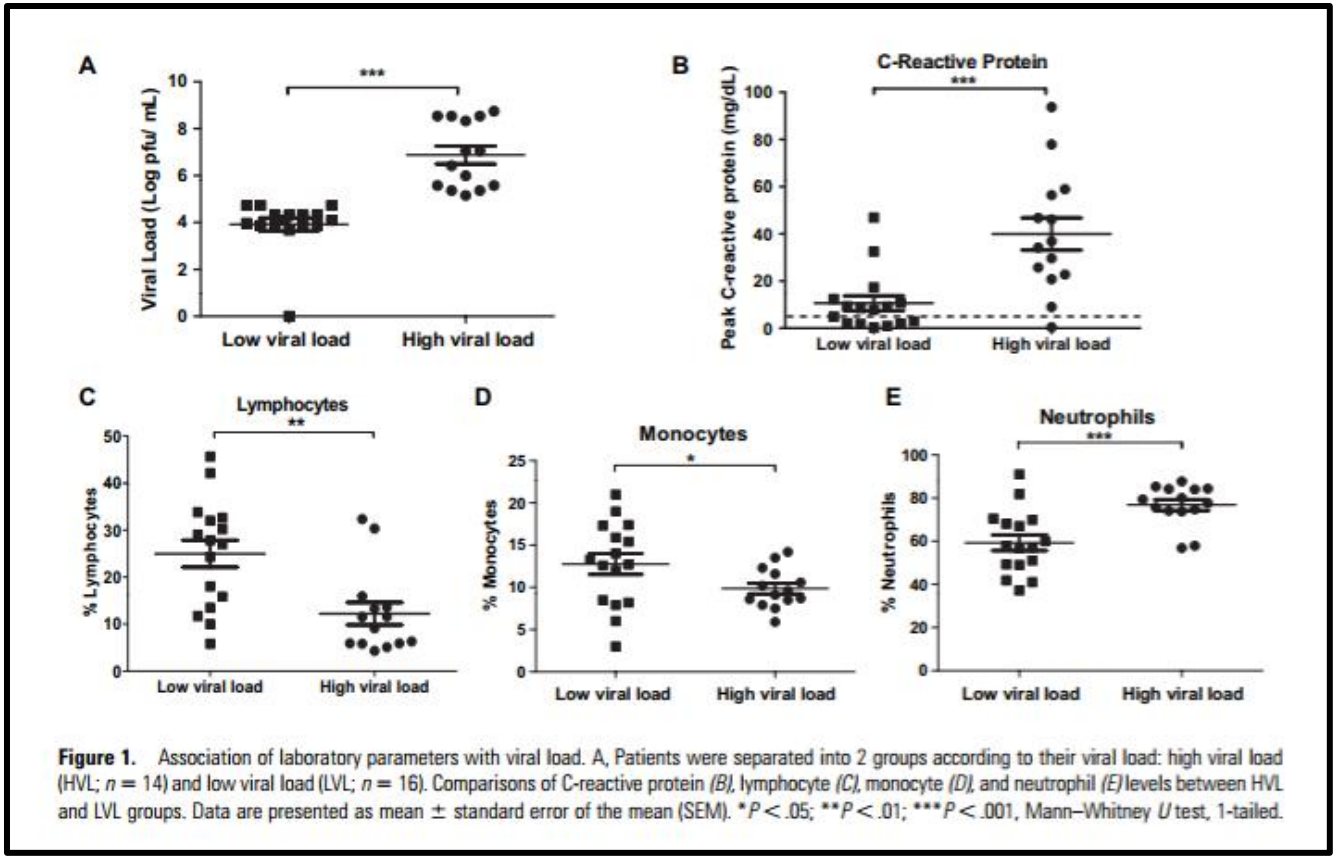


Figure 1. Association of laboratory parameters with viral load. A, Patients were separated into 2 groups according to their viral load: high viral load (HVL; $n = 14$) and low viral load (LVL; $n = 16$). Comparisons of C-reactive protein *(B)*, lymphocyte *(C)*, monocyte *(D)*, and neutrophil *(E)* levels between HVL and LVL groups. Data are presented as mean ± standard error of the mean (SEM). $^{*}P < .05$; $^{**}P < .01$; $^{***}P < .001$, Mann–Whitney *U* test, 1-tailed.

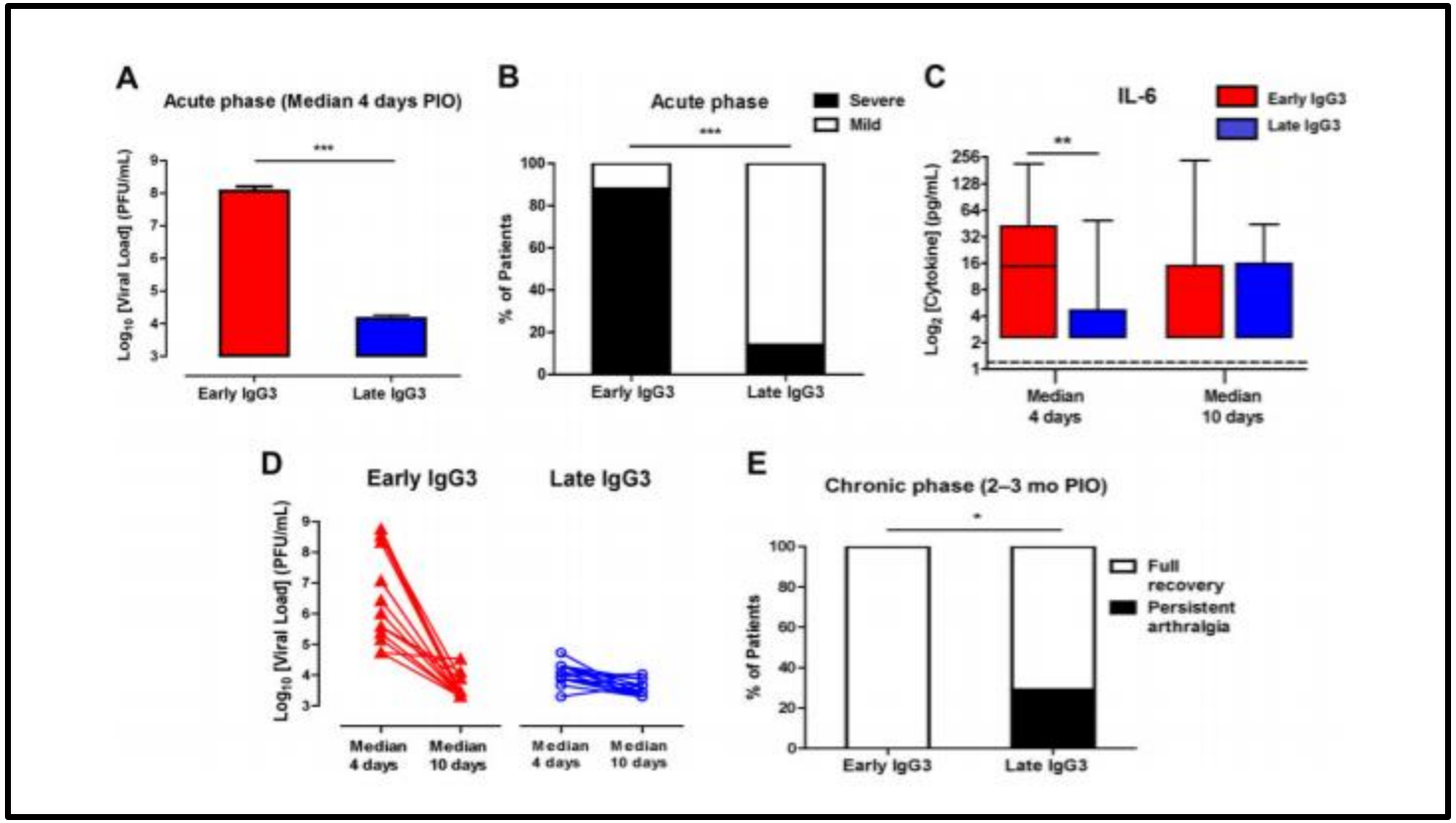
Chow A, Her Z, Ong EK et al. Persistent arthralgia induced by Chikungunya virus infection is associated with interleukin 6 and granulocyte macrophage colony stimulating factor. J Infect Dis 2011 Jan 15;201(2):149-57.

Four unique immune mediator profiles

1. Rapid short lasting production of mediators - early antiviral innate response.
2. Early convalescent phase - mediators involved in both innate immune response & establishment of antiviral T cell response.
3. Late convalescent phase - increased RANTES and EGF levels.
4. Chronic phase - high level of IL17.

DIFFERENT PHASES OF anti CHIKV IMMUNE RESPONSE

* Chow A, Her Z, Ong EK et al. Persistent arthralgia induced by Chikungunya virus infection is associated with interleukin 6 and granulocyte macrophage colony stimulating factor. J Infect Dis 2011 Jan 15;201(2):149-57.



Kam YW, Simarmata D, Chow A et al. Early appearance of neutralizing Immunoglobulin G3 antibodies is associated with Chikungunya virus clearance and long term clinical protection. J Infect Dis 2012 Apr 1;205(7):1147-54.

Pathology of severe & fatal chikungunya fever

In severe cases mortality can occur within first few days after hospital admission despite aggressive therapy.

These fatal cases show neurological and respiratory deterioration with progression to multiorgan failure.

Renal failure and elevated transaminase levels are frequently seen in these patients.

Acute hepatitis, acute myopericarditis, severe encephalitis have been documented.

Pathology of severe & fatal chikungunya fever

Histopathological studies are difficult to perform.

Lungs - generalized alveolar edema without inflammatory infiltrates.

Kidneys - glomerular edema, tubular interstitial nephritis, tubular necrosis.

Heart - acute pericarditis with inflammatory mononuclear infiltrates.

Liver - coagulative non confluent hepatocellular necrosis.

Spleen - congestion with reactive plasmacytosis.

CLINICAL FEATURES

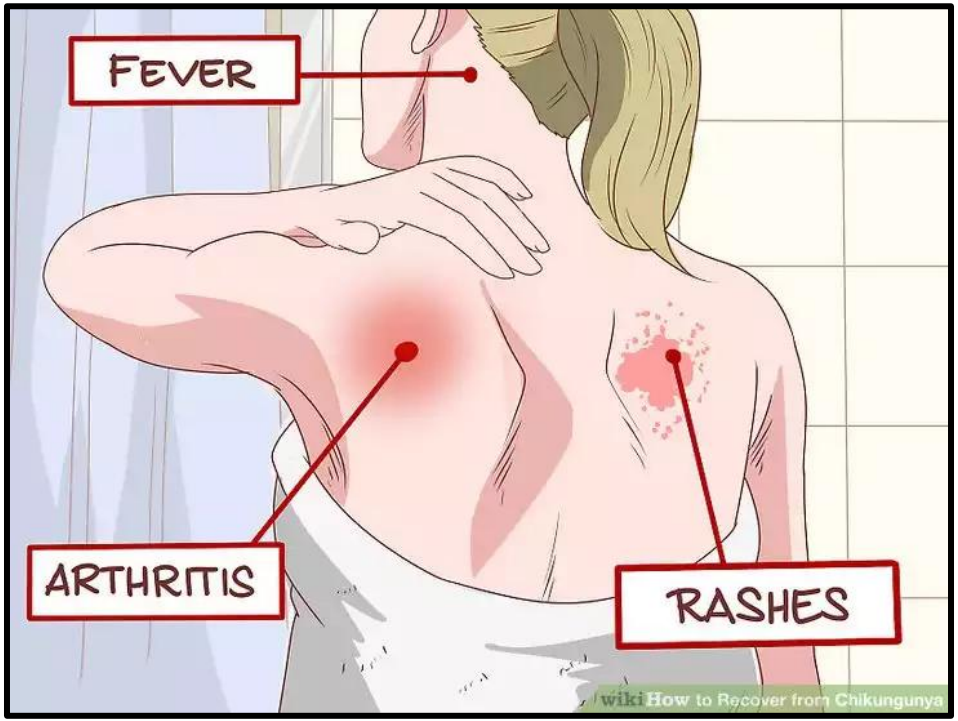
CLINICAL FEATURES

CHIK virus causes an acute febrile illness with an incubation period of 3-7 days (can be 2- 12 days).

Viremia may persist for 5 days after onset of symptoms.

Serosurveys indicate that 3%-25% of persons with anti-CHIKV antibodies have asymptomatic infections.

In Chikungunya mostly symptoms have an "**abrupt onset**" with high grade fever (usually > 38.9°C), single or multiple joint pains, skin rashes, headache and myalgia.



Fever and arthralgia are the hallmark of Chikungunya fever.

CLINICAL FEATURES

Clinical presentation of Chikungunya usually follows **3 phases** which are as follows:

a. **Acute phase** : Less than 3 weeks

b. **Subacute phase** : > 3 weeks to 3 months

c. **Chronic phase** : > 3 months

Clinical presentation may be **mild**, **moderate** or **severe**; most of the symptoms subside within 3 weeks from the onset of symptoms.

10 – 15 % of patients with severe Chikungunya progress to sub-acute or chronic phase.

HIGH RISK GROUP

Co-morbid conditions:

- Hypertension
- Diabetes
- CAD/CVD
- Geriatric age
- Pregnancy
- COPD
- Hypothyroid

Coinfections:

- Tuberculosis
- Enteric fever
- Pneumonia
- HIV
- Malaria
- Dengue

Based on clinical presentation severity of Chikungunya is classified into three categories

MILD	MODERATE
Low grade Fever	Low to high grade persistent fever
Mild Arthralgia	Moderate joint pain
Mild focal Myalgia	Generalized myalgia
General weakness	Hypotension
Skin rash/itching	Mild bleeding
	Retro-orbital pain
	Oliguria

Based on clinical presentation severity of Chikungunya is classified into three categories

SEVERE

Persistent high grade fever

Severe Joint pain

Persistent vomiting / Diarrhoea

Altered sensorium

Bleeding (GI bleeding due to use of Analgesics)

Shock due to persistent vomiting and diarrhoea

COMMON

1. Arthralgia/arthritis
2. Fever
3. Rash + itching
4. Bodyache
5. Headache

RARE

1. Photophobia
2. Retro-orbital pain
3. Hypotension
4. Vomiting
5. Diarrhea
6. Meningeal syndrome
7. Acute encephalopathy

Arthralgia/Arthritis

Soon after onset of fever, majority of the patients develop severe debilitating polyarthralgias.

Usually polyarticular, symmetrical, usually peripheral joints, involving predominantly small joints of hands & feet (wrists, elbows, fingers, knees, ankles).

Proximal, larger joints (knees, shoulders) may also get involved.

Joint pains worse in morning, tends to get better with activity.

Arthralgia/Arthritis

Pain may remit in 2-3 days, then reappear in saddle back pattern in some patients.

Joints with previous trauma/degeneration may get involved early.

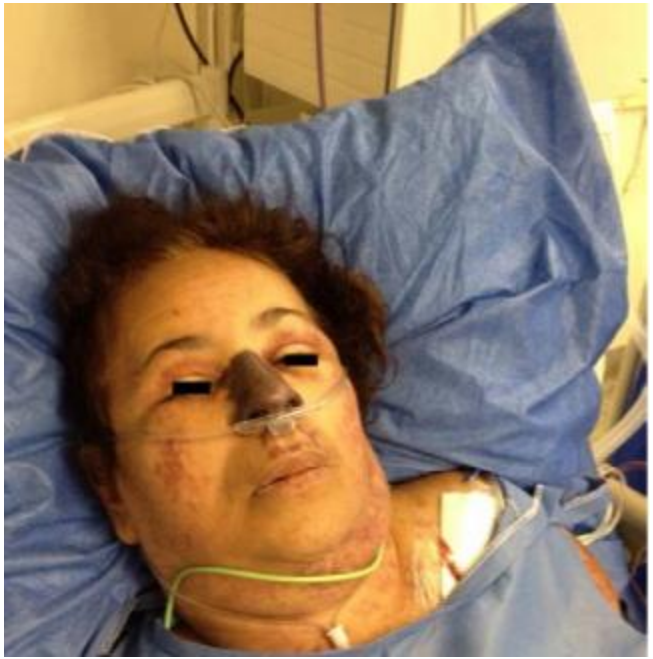
Arthralgia/arthritis affects 73-80% of patients & can persist in

33% of patients for 4 months

15% for 20 months

10% for 3-5 years

Lower extremity arthralgias can be severely disabling, which results in slow, broad based, halting gait which can persists for months.



Nasal skin necrosis: An unexpected new finding in severe chikungunya fever
Torres JR, Cordova LG, Saravia V et al. Clinical infectious diseases 2016;62(1):78-81.

CUTANEOUS MANIFESTATIONS OF CHIKUNGUNYA

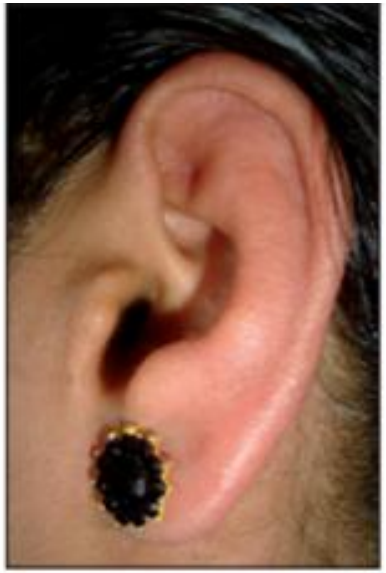


Figure 1: Erythema and swelling of pinna mimicking Milian's sign

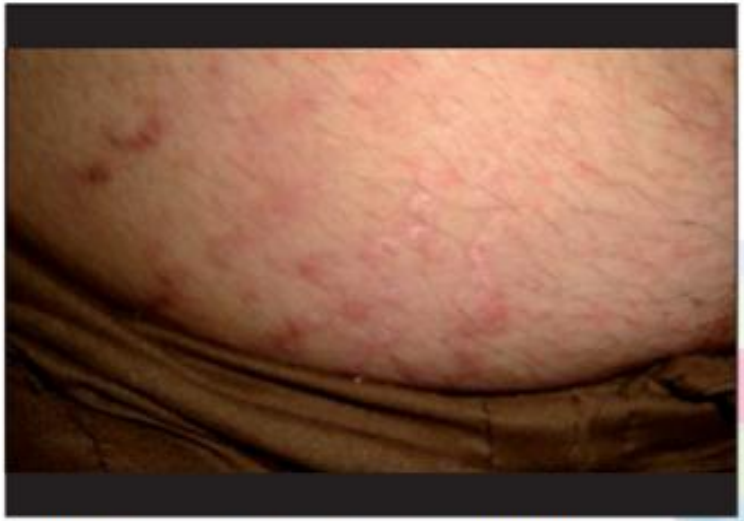
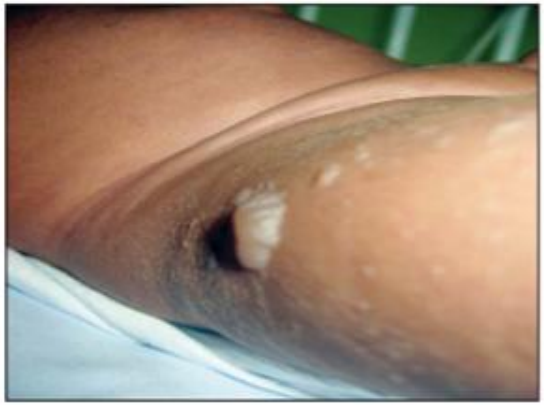


Figure 2: Erythema and swelling of abdominal striae-mimicking "scar phenomenon"

How to cite this article: Riyaz N, Riyaz A, Rahima, Abdul Latheef EN, Anitha PM, Aravindan KP, *et al.* Cutaneous manifestations of chikungunya during a recent epidemic in Calicut, north Kerala, south India. Indian J Dermatol Venereol Leprol 2010;76:671-6.

Received: February, 2010. **Accepted:** July, 2010. **Source of Support:** Nil. **Conflict of Interest:** None declared.



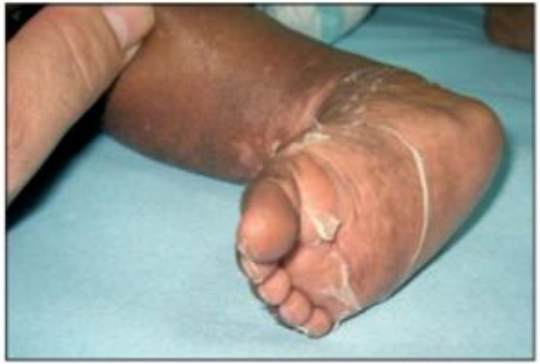


Figure 5: Chikungunya virus can be detected by PCR in blister fluid

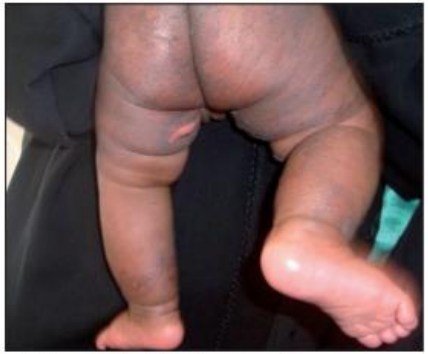


Figure 3: Charring, flaccid bullae and peeling

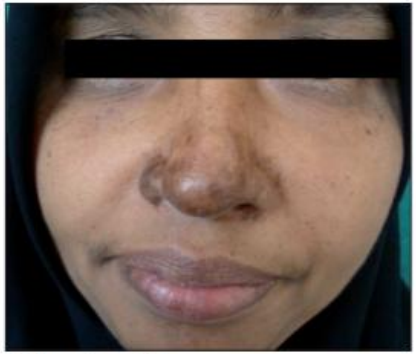


Figure 4: Nose pigmentation

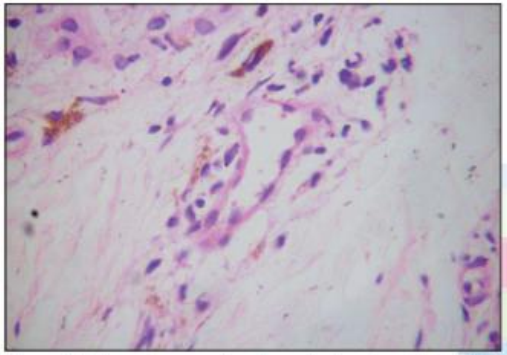


Figure 5: Melanophages and perivascular lymphocytic infiltrate in erythematous macules (H and E, ×40)

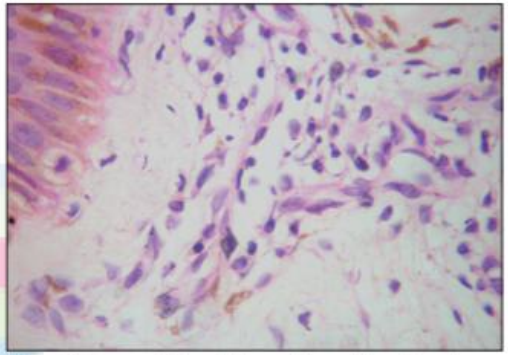


Figure 6: Increased basal pigmentation with melanophages and perivascular lymphocytic infiltrate in pigmented macules (H and E, ×40)

How to cite this article: Riyaz N, Riyaz A, Rahima, Abdul Latheef EN, Anitha PM, Aravindan KP, *et al.* Cutaneous manifestations of chikungunya during a recent epidemic in Calicut, north Kerala, south India. Indian J Dermatol Venereol Leprol 2010;76:671-6.

Received: February, 2010. **Accepted:** July, 2010. **Source of Support:** Nil. **Conflict of Interest:** None declared.

Neurological manifestations

These are considered to be the severe manifestations of the disease and fortunately are not common.

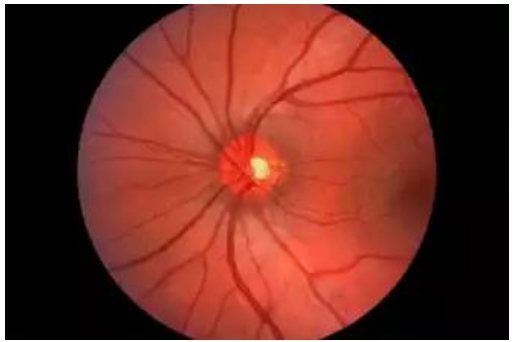
Various neurological complications described in the recent epidemic include: meningoencephalitis, myeloradiculitis, myelitis, myeloneuropathy, GBS, external ophthalmoplegia, facial palsy, sensorineural deafness, ADEM and optic neuritis.

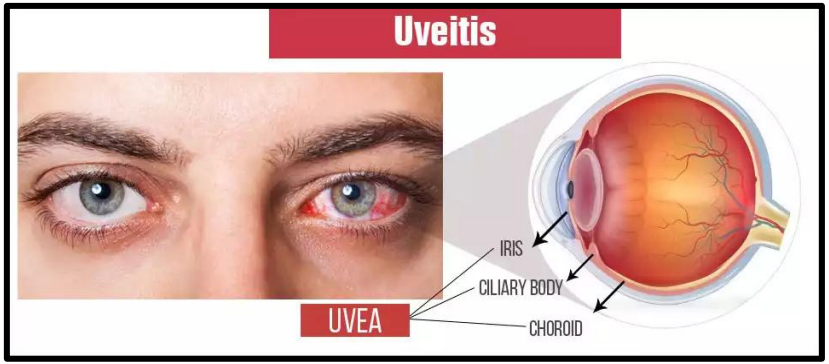
Encephalitis is the most common clinical manifestation.

Chikungunya virus: The neurology J. M. K. Murthy Neurology India | Mar-Apr 2009 | Vol 57 | Issue 2

Clinical features - ocular involvement

Conjunctivitis, episcleritis, anterior uveitis, keratitis, retinitis with vitritis, B/L neuroretinitis, multifocal choroiditis, optic neuritis, retrobulbar neuritis, exudative retinal detachment, panuveitis, central retinal artery occlusion - have been documented.





Clinical diagnosis of Chikungunya Fever

CLINICAL CRITERIA - Acute onset of fever & severe arthralgia/arthritis ± skin rash & residing or having left an epidemic area 15 days prior to onset of symptoms.

LABORATORY CRITERIA - At least one of following tests done in acute phase of illness -

Direct evidence (Virus isolation/Presence of viral RNA by RT-PCR)

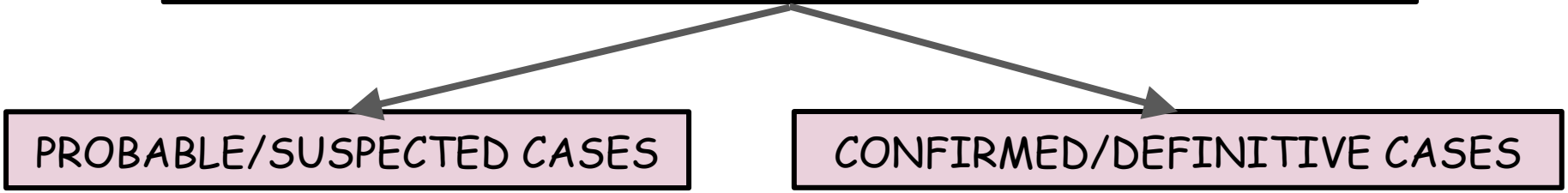
Indirect evidence -

Presence of virus specific IgM antibodies in single serum sample collected in acute or convalescent stage.

Four-fold increase in IgG values in samples collected at least three weeks apart.

Chikungunya should be suspected when epidemic occurs with the characteristic of abrupt onset of fever, arthralgia and myalgia, with or without rash.

Cases are categorized for the purpose of epidemiological reporting.



- Probable/suspected cases: A patient meeting the clinical criteria only.
- Confirmed/definitive cases: A patient meeting both the clinical and laboratory criteria.

Laboratory diagnosis

The confirmation of CHIK fever is through any of the following Tests

- Virus culture : First 3 days of illness
- RT-PCR: Day 1 -8

- IgM antibody assay. ; Day 4 - 2 months
- IgG or neutralizing antibody :: assay showing rising titers ,Two samples separated by 14 days, where first sample is collected after day 7

No significant hematological finding is seen. Leucopenia with lymphocyte predominance is the usual observation. Thrombocytopenia is rare. Erythrocyte sedimentation rate is usually elevated. C-Reactive Protein is increased during the acute phase and may remain elevated for a few weeks.

Some of the signs & symptoms progress to Subacute or chronic phase.

Arthralgia

Myalgia

Arthritis

Persistent Joint stiffness

Restricted joint movement

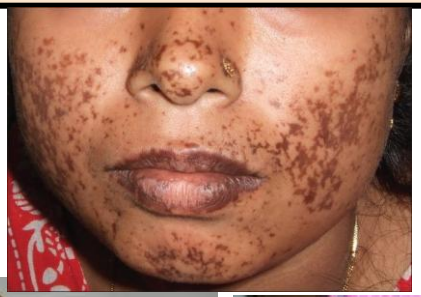
Painful joint movement

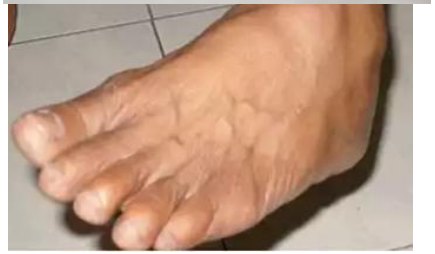
Enthesopathy

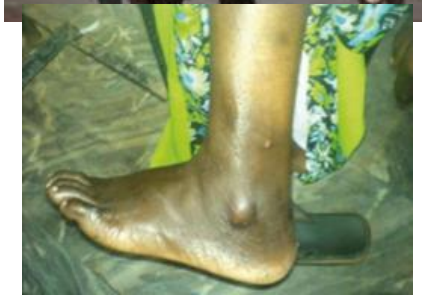
Tendinitis

Skin pigmentation

Skin rash







The sequelae..

CHIK is a self limiting disease, however rheumatological sequelae seen in severe form of disease.

The relative frequency of post chikungunya musculoskeletal involvement is highly variable ranging from 14.4% to 87.2% depending upon the follow up period.

Fortunately, this is regressive and most of the patients improve with time.

Joint involvement may be continuous or intermittent with symptoms interspersed with asymptomatic periods.

The sequelae...

Presence of osteoarthritis increase the sequelae of CHIKF.

Clinical evaluation in the acute stage is sufficient to assess the chronic impact of musculoskeletal lesions by identifying the site and intensity of arthralgia, arthritis and tenosynovitis.

The musculoskeletal manifestations are widely heterogeneous and may include synovium, cartilage, bone, tendon and/or enthesis.

This heterogeneous involvement may be due to high tropism of chikungunya virus to fibroblasts.

The sequelae

Certain local manifestations - reactionary edema, entrapment syndromes, joint stiffness or neuropathic pain.

Severe asthenia & neuropsychological disorders - if significant pain persists beyond the acute phase.

The dermatological sequelae - skin pigmentation.

The sequelae...

Spectra of persistent rheumatic/systemic manifestations in subacute phase -

- Inflammatory joint involvement
- Inflammatory periarticular involvement
- Other types of locoregional involvement
- Systemic manifestations

The sequelae...

Inflammatory joint involvement

1. Arthritis
2. Inflammatory arthralgia

Inflammatory periarticular involvement

1. Tenosynovitis
2. Tendinitis - risk of tendon rupture
3. Enthesitis
4. Bursitis
5. Capsulitis
6. Periostitis

The sequelae...

Locoregional Involvement

1. Mechanical arthralgia
2. Stiffness
3. Relapse of pain in previously injured/sick areas
4. Soft tissue edema (extremities)
5. Tunnel syndromes
6. Small fiber neuropathy
7. Peripheral vascular disorders - Raynaud's phenomenon

Systemic Manifestation

1. Chronic fatigue
2. Skin dyschromia, hair loss
3. Decompensation of metabolic/endocrine diseases
4. Decompensation of other pre-existing chronic diseases
5. Anxiety, depressive disorders
6. Memory problems
7. Ideational slowdown

Differentiate between inflammatory & noninflammatory

Assessment of inflammatory activity is made by the following clinical observations -

- Number of nighttime awakening.
- Duration of early morning stiffness.
- Number of painful joints involved.
- Number of swollen joints involved.
- CRP/ESR values.

Predictors of Chronic Chik Arthritis (CCA)

1. Increasing age (>45yrs).
2. Females.
3. Previous history of rheumatological diseases.
4. Presence of arthralgia 4 months after onset of the infection.
5. Severity of initial rheumatic manifestations.

BEYOND 3 MONTHS...

Chronic Phase….

The chronic phase

The chronic phase can last a few months to several years.

Chronic phase may culminate in one of the following outcomes

a. Disease progresses to cure (spontaneous or with treatment) without sequelae.

b. Prolonged persistence of joint and/or general symptoms.

c. Aggravation of symptoms because of inflammatory or degenerative processes.

A COPCORD project investigated the prevalence of rheumatic MSD in rural community of Trivandrum, Kerala about 15 months after a CHIKV epidemic (n=5277).

The study found that 26.5% of the patients had rheumatic musculoskeletal disorders attributable to CHIKV.

Significantly, 8.37% of the total patients evaluated did not have any complaints of pain prior to CHIKV epidemic.

- Knee was the commonest (83.3%) self reported pain site
- Majority of the patients (57%) had post viral non specific arthralgias.
- Soft tissue rheumatism was observed in 27.7% of patients
- However, RA and SpA were observed in just 6 and 11 patients respectively.

The rheumatic involvement in the chronic phase of illness may be either in the form of

Non inflammatory musculoskeletal disorders (MSD) or

Chronic inflammatory rheumatisms (CIR).

pCHIK-MSD is more common and has a better prognosis.

Development of post chikungunya psoriatic arthritis has also been reported by various case series.

pCHIK-CIR (RA, SpA or undifferentiated polyarthritis) is considered in patients presenting with at least 1 ch synovitis resistant to appropriate treatment at post acute stage (> 6 weeks) according to clinical, biological, and imaging data.

Patients with chronic rheumatic complaints are assessed clinically for the following parameters -

- Presence or absence of inflammatory symptoms – arthritis, enthesitis, tenosynovitis, inflammatory arthralgia
- Number of joints involved
- Level of clinical inflammatory activity – number of nighttime awakening due to pain, number of painful and swollen joints, duration of early morning stiffness
- Activity and functional impact of rheumatic manifestations – RAPID 3 assessment

A possibility of pCHIK-CIR is considered if

- There are absence of rheumatic signs before infection
- The symptoms of acute infection continue (intermittently/persistently) till the diagnosis of CIR.
- CHIK seropositivity is confirmed
- Other differential diagnoses are ruled out

RA and SpA can be recognized on the basis of their respective classification criteria

Non destructive arthritis not meeting the criteria of RA, SpA is considered undifferentiated polyarthritis after ruling out other causes of polyarthritis (microcrystalline, autoimmune, granulomatous secondary to chronic viral hepatitis).

Rheumatoid arthritis ACR/EULAR 2010 classification criteria -

Joint involvement

1 large joint - 0

2-10 large joints – 1

1-3 small joints (± involvement of large joints) - 2

4-10 small joints (± involvement of large joints) - 3

> 10 joints (including at least one small joint) - 5

Rheumatoid serology

Negative RF and negative ACPA – 0

Slightly positive RF or slightly positive ACPA – 2

Strongly positive RF or strongly positive ACPA – 3

ESR/CRP

Normal ESR & normal CRP – 0

Elevated ESR or CRP – 1

Duration of symptoms - < 6 weeks – 0; ≥ 6 weeks – 1

≥ 1 unexplained joint synovitis & score > 6/10

Spondyloarthritis ASAS 2011 criteria, peripheral spondyloarthritis

Adults < 45 years & synovitis/enthesis/dactylitis & ≥ 1 other sign among -

1. Psoriasis, inflammatory bowel disease, recent infection
2. HLA B 27 positive
3. Uveitis
4. Sacroiliitis (X ray or MRI)

OR ≥ 2 other signs among

1. Arthritis
2. Dactylitis
3. Enthesis
4. Inflammatory back pain
5. Family history of spondyloarthropathy

Chronic symptoms (pCHIK-MSD)

DIFFUSE

1. Distal polyarthralgia with edema (lack of synovitis helps to differentiate from remitting symmetrical seronegative synovitis with pedal edema-RS3PE
2. Polyalgia
3. Effort fatigue on exertion

LOCOREGIONAL

1. Exacerbation of arthrosis
2. Mono arthritis
3. Capsulitis
4. Tendinopathy
5. Periostitis
6. Bursitis
7. Osteonecrosis
8. Tunnel syndromes
9. Previously injured areas - exacerbation

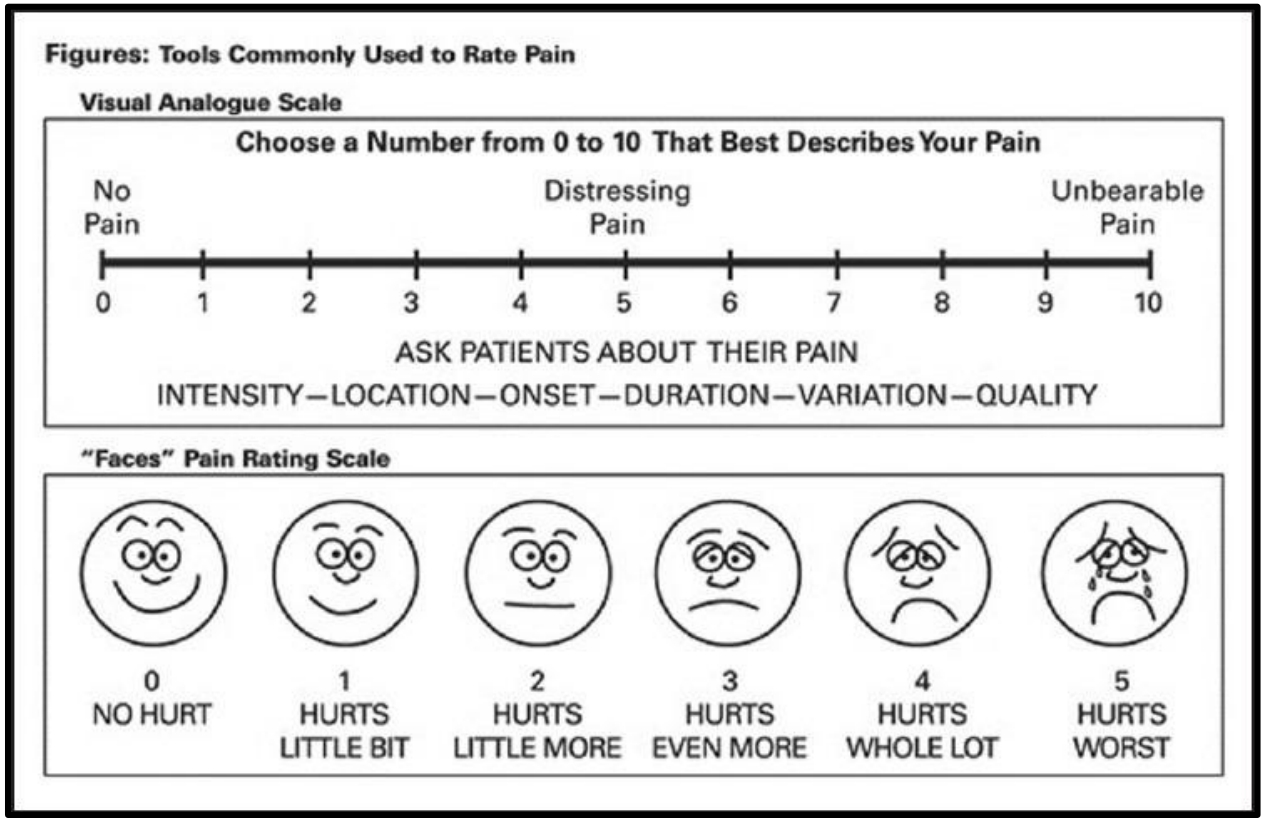
The chronic phase

One of the prospective rural community based from South Maharashtra during the 2006 epidemic found that 5.8% of the cases tested positive for rheumatoid factor.

This quanta of seropositivity was almost similar to the seropositivity reported in healthy Indians from Pune.

In fact, many studies have found low seropositivity for RF and ACPA in chikungunya related chronic arthritis.

Assessment of Pain - Visual analogue scale



DN4 QUESTIONNARE

1. **Does the pain have one or more of the following characteristics**
    a. Burning (Yes/No)
    b. Painful cold (Yes/No)
    c. Electric shocks (Yes/No)
2. **Is the pain associated with one or more of the following symptoms in the same area**
    a. Tingling (Yes/No)
    b. Pins and needles (Yes/No)
    c. Numbness (Yes/No)
    d. Itching (Yes/No)

DN4 QUESTIONNARE

1. **Is the pain located in an area where the physical examination may reveal one or more of the following characteristics**

    a. Hypoesthesia to touch (Yes/No)

    b. Hypoesthesia to prick (Yes/No)

2. **In the painful area, can the pain be caused or increased by**

    a. Brushing (Yes/No)

The total score is calculated as the sum of the 10 items and the cut off value for the diagnosis of neuropathic pain is a total score of 4/10

Bouhassira D, Attal N, Alchaar H, et al. "Comparison of pain syndromes associated with nervous or somatic lesions and development of a new neuropathic pain diagnostic questionnaire (DN4)." Pain 114.1-2 (2005): 29-36.

RAPID 3 QUESTIONNARE

1. Please circle the ONE best answer for your abilities over the past week:

OVER THE PAST WEEK, were you able to:	Without **ANY** Difficulty	With **SOME** Difficulty	With **MUCH** Difficulty	**UNABLE** to do it
Dress yourself, including tying shoelaces and doing buttons?	**0**	**1**	**2**	**3**
Get in and out of bed?	**0**	**1**	**2**	**3**
Lift a full cup or glass to your mouth?	**0**	**1**	**2**	**3**
Walk outdoors on flat ground?	**0**	**1**	**2**	**3**
Wash and dry your entire body?	**0**	**1**	**2**	**3**
Bend down to pick up clothing from the floor?	**0**	**1**	**2**	**3**
Turn regular faucets on and off?	**0**	**1**	**2**	**3**
Get in and out of a car, bus, train, or airplane?	**0**	**1**	**2**	**3**
Walk two miles?	**0**	**1**	**2**	**3**
Participate in sports and games as you would like?	**0**	**1**	**2**	**3**
Get a good night's sleep?	**0**	**1**	**2**	**3**
Deal with feelings of anzietyor being nervous?	**0**	**1**	**2**	**3**
Deal with feelings of depression or feeling blue?	**0**	**1**	**2**	**3**

RAPID 3 QUESTIONNARE

2. How much pain have you had because of you condition OVER THE PAST WEEK? Please indicate below how severe your pain has been with a check or X:

NO PAIN																					HORRIBLE PAIN
	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o
	0	0.5	1	1.5	2	2.5	3	3.5	4	4.5	5	5.5	6	6.5	7	7.5	8	8.5	9	9.5	10

3. Considering all the ways in which illness and health conditions may affect you at this time, please indicate below how you are doing with a check or X:

VERY WELL																					VERY POORLY
	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o	o
	0	0.5	1	1.5	2	2.5	3	3.5	4	4.5	5	5.5	6	6.5	7	7.5	8	8.5	9	9.5	10

RAPID 3 QUESTIONNARE

The RAPID3 score is computed as follows:

1. Results of 13 questions are reduced to a score between 0 and 10.
2. Then, we add the pain and health scores.

RAPID 3 Categories

≤ 3.0	=	Near remission
3.01-6.0	=	Low severity
6.01-12.0	=	Moderate severity
> 12.0	=	High severity

Recommendations for the treatment of chikungunya fever.

1. In the **acute phase** of chikungunya fever, common analgesics and/or weak opioids should be used (in cases of severe or refractory pain and NSAIDs and salicylates should be avoided. Corticosteroids (CSs) are not recommended for musculoskeletal manifestations in this phase.

Agreement: 9.31 (SD ± 0.8906). GRADE: very low quality of evidence.

Treatment Cont.

2 . In the **subacute phase** of chikungunya fever, NSAIDs and/or adjuvant drugs may be used for pain management (anticonvulsants or antidepressants) in cases refractory to analgesics/opioids.

In patients with moderate to severe musculoskeletal pain or in those with contraindications to the use of these drugs, the use of **prednisone or prednisolone** at a dose of up to 20 mg/day is recommended, and withdrawal should be performed slowly and gradually, according to patient response.

Agreement: 9.24 (SD ± 1.057). GRADE: low to very low quality of evidence.

Treatment Cont.

3. In the **chronic phase** of chikungunya fever, the use of analgesics is recommended for symptom relief. Weak opioids (codeine and tramadol) may be used for refractory or severe pain symptoms (VAS ≥7).

Agreement: 9.57 (SD ± 0.741). GRADE: low to very low quality of evidence.

Treatment Cont.

4. In the **chronic phase** of chikungunya fever, NSAIDs are recommended, taking into consideration the clinical context, contraindications and therapeutic response. *Agreement: 8.97 (SD ± 1.679). GRADE: low to very low quality of evidence.*

5. In the **chronic phase** of chikungunya fever, oral corticosteroids may be used for musculoskeletal and neuropathic complaints, and low doses are recommended (5–20 **mg/day prednisone or prednisolone**). The time of use may range from six to eight weeks, and withdrawal should be slow and gradual due to the risk of recurrence of joint symptoms.

Agreement: 9.24 (SD ± 1.154). GRADE: low to very low quality of evidence.

Treatment Cont.

6. In the **chronic phase** of chikungunya fever, antimalarials, preferably **hydroxychloroquine**, may be used for the treatment of joint symptoms, alone or in combination with **MTX or SSZ.**

Agreement: 9.21 (SD ± 1.166). GRADE: low quality of evidence.

7. In patients with chikungunya fever progressing to the chronic phase and with inflammatory joint disease, with difficulties in CS withdrawal, we preferentially suggest MTX at doses of 10–25 mg/week.

Agreement: 9.43 (SD ± 0.858). GRADE: low to very low quality of evidence.

Treatment Cont.

8. In the **chronic phase of chikungunya fever, sulfasalazine may be used** at a dose of 2 to 3 g/day, alone or in combination, especially in patients with contraindication to or **failure with MTX**. *Agreement: 8.77 (SD ± 1.794). GRADE: low to very low quality of evidence.*

9. **Biological therapy may be prescribed after rheumatologist evaluation of patients with chronic inflammatory joint disease** after infection with CHIKV, refractory to the use of CS and DMARDs, following the recommendations used to treat RA or SpA. *Agreement: 8.97 (SD ± 1.267). GRADE: low to very low quality of evidence.*

Treatment Cont.

10. During the **acute phase, in patients undergoing biological therapy** for their underlying disease, drug therapy discontinuation is recommended. However, treatment **can be maintained in the subacute and chronic phases**. *Agreement: 8.97 (SD ± 1.884). GRADE: low to very low quality of evidence.*

Treatment Cont.

11. Rehabilitation interventions in all phases of chikungunya fever are recommended as a complementary non-pharmacological measure. In the acute phase, analgesic and anti-inflammatory therapies are indicated, and the use of heat should be avoided; furthermore, patient education, posture guidelines and manual therapy should be recommended, in addition to light-intensity exercise. In the subacute and chronic phases, the previous recommendations should be followed, which may also include heat, in addition to free, resisted, proprioceptive and active aerobic exercises, stretching, manual therapy and aquatic physical therapy. *Agreement: 9.43 (SD ± 0.935). GRADE: very low quality of evidence.*

Anti-TNFs

Infliximab, Etanercept, Adalimumab, Golimumab, Certolizumab

Future Challenges

Despite dramatic progress in our understanding of CHIKV infection, research must be continued into –

The pathogenesis of the long-lasting osteoarticular involvement.

If any drug could help the immune system to eliminate CHIKV.

Specific immunoprophylaxis or immunotherapy could provide a rapid antiviral action for persons at risk of severe acute CHIKV disease, notably neonates born from viremic mothers.

Future Challenges

Management of CHIKV-Infected Patients

The most important challenge is to reduce chronic pain and handicap during the chronic stage of the disease.

Future antiviral therapy for the chronic stage.

An urgent need exists to study the efficacy and safety of corticotherapy and DMARDs, especially methotrexate, to establish a strategy for the early treatment of destructive arthritis.

Future Challenges

Globalization and Prevention

The size and speed of international population movements and the progressive worldwide dissemination of the mosquito increase the risk of new epidemic emergence of CHIKV.

International collaboration in preparedness and response to CHIKV introduction in susceptible regions should limit this threat.

Controls in epidemic countries can be improved by prompt vector control and the isolation of infective patients.

Conclusions

Within less than a decade, CHIKV has become a new giant among arboviral diseases, next to dengue fever. This emergence is mostly the result of viral evolutionary convergence with Ae. albopictus. This epidemiological change has led to its global expansion, supported by the faster transport of CHIKV-viremic travelers to susceptible areas with Aedes spp activity. In epidemic countries, CHIKV is responsible for brutal outbreaks of febrile episodes, and, unlike dengue fever, for endemic chronic rheumatic disorders, the treatment and outcome of which remain uncertain. CHIKV raises modern challenges in science, patient care, and public health that should be promptly taken up to limit its current rapid spread and major consequences.

Thank you