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Original Research Paper

Outbreak of Chikungunya in Dehradun, Uttarakhand in 2022: Clinical Profile and Management Approach in Early Phase of the Disease.

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ABSTRACT:

Background: Chikungunya fever is a mosquito borne disease caused by Chikungunya virus. The acute phase is similar to dengue, which is transmitted by the same vector while some patients may develop severe polyarthralgia or a chronic inflammatory arthritis. Dehradun, the capital city of the north Indian state of Uttarakhand, witnessed a major outbreak of this disease in the post monsoon months of 2022. **Objective:** To describe clinical features and management approach of Chikungunya arthritis in early phase. **Methods**: The present study retrospectively analyzed records of confirmed or suspected cases of Chikungunya, presenting to a rheumatology clinic with predominant articular complaints. The data included demographic details, previous diagnosis or co-morbidities, joint involvement, inflammatory markers, diagnostic tests and treatment prescribed. **Results**: Records of 255 patients were available. 77.6% were females, mean age was 49.9 years, and mean follow up was 5.41 weeks. Seventy-seven patients (30.1%) had pre-existing autoimmune rheumatic diseases and were already on disease modifying agents. Fifty-six patients had positive IgM and 5 had positive PCR. Almost all patients received non-steroidal anti-inflammatory drugs (NSAIDs) and steroid. Methotrexate (87.5%) and Hydroxychloroquine (73.7%) were the two disease modifying agents used. Only 10 patients (3.9%) reported adverse effects. **Conclusion**: The present study provides valuable insights into the clinical profile of Chikungunya patients in acute and subacute phase presenting with predominantly articular symptoms. The importance of early diagnosis, standardization of diagnostic tests and future directions for treatment planning is discussed.

Keywords: Chikungunya, mosquito-borne diseases, viral arthritis, disease modifying anti-rheumatic drugs

INTRODUCTION:

Chikungunya fever (CHIK F) is a mosquito borne disease caused by Chikungunya virus (CHIK V) which belongs to family togaviridae [1]. Since its first appearance in India in 1963 [2], it has caused several outbreaks in different parts of the country. The disease is typically characterized by an acute phase of moderate to high fever, severe bodyache, and a combination of other features including skin rash, joint pains or swelling, myalgia, headache, vomiting and fatigue, a subacute or delayed phase of polyarthralgia (3 weeks to 3 months) and a chronic (>3 months) phase of inflammatory arthritis which can last for months or rarely years [3]. Two excellent reviews have been published recently with detailed description of the disease including etiopathogenesis, clinical features, management and preventive measures. [4, 5]. Being a hill state with relatively cold climate, Uttarakhand was free from mosquito- borne diseases like malaria. However, over the last 5 years, there have been two significant outbreaks of dengue in Dehradun, the state capital [6]. Following these outbreaks, there have been occasional cases of Chikungunya during the post-monsoon months. In 2022, there was a surprising and substantial increase in Chikungunya cases, far outnumbering dengue. The clustering of cases immediately after rains, self- limiting nature in many patients, involvement of whole families and neighborhoods and disabling pains going on for weeks made the diagnosis clear even in those patients who did not have serological evidence. According to National Center for Vector Borne Diseases Control (NCVBDC), 154 confirmed and 572 suspected cases were reported from Uttarakhand till 31st October, 2022 [7]. The author is a private practitioner catering to rheumatology patients. This provided an opportunity to see patients with persistent joint pains. Data collection was started in early October after seeing a sufficient number of cases with a typical presentation, although no set protocol was used.

OBJECTIVES:

1. To describe the clinical features of Chikungunya infection mainly pertaining to musculoskeletal system in acute and subacute phase.
2. To describe diagnostic approach in the setting of an epidemic and therapeutic options.

METHODS:

This was a retrospective study involving patients presenting to a private rheumatology clinic in Dehradun, Uttarakhand. The main inclusion criterion was acute onset joint pains with or without skin rash or fever presenting from September 2022 onwards. The possibility of alternate diagnosis like rheumatoid arthritis, reactive arthritis, spondyloarthritis, connective tissue disorder, fibromyalgia or mechanical pains was evaluated clinically and relevant investigations advised wherever considered necessary. Many patients with pre-existing autoimmune rheumatic disease (ARDs) were also included with typical history of sudden worsening of pains which was marked by fever in the majority of patients. The diagnosis was primarily clinical and patients with either negative or absent serological tests were not excluded. The principal presenting features were fever, skin rash, pruritus, oral ulcer, ankle swelling and polyarthralgia, the last one being the essential feature for inclusion. The medical records of patients who were diagnosed with provisional CHIK V arthritis from September 2022 to January 2023 were analyzed. As part of routine evaluation in a rheumatology clinic, examination included tender and swollen joint counts in all patients. The first patient was seen on 12th September 2022 with gradual increase in numbers through the next two months with peaking of the cases in the month of November and by mid-January the outbreak was near its end.

There was no predefined pro-forma for patient assessment and no set protocol for investigation and treatment and all patients were assessed as routine clinical care. CHIK V IgM was advised randomly in selected patients mainly considering the affordability and duration of symptoms. Pre-existing ARDs, other co-morbidities, duration of symptoms, duration of follow-up, joint tenderness, swelling, pattern of joint involvement, CHIK IgM or PCR , ESR and CRP (wherever available, two levels of CRP, at the onset of fever and at least 4 weeks later) were recorded. Some of the patients had only one visit without any follow-up, but they were also included for evaluation of clinical features and investigations. In many cases, patients had been seen elsewhere prior to their first visit to the clinic and had already undergone some testing. The repeat testing in such patients was guided by the need to monitor inflammatory markers and drug adverse effects.

RESULTS:

Demographics characteristics:

Records of 255 clinically suspected CHIK V cases were available. Of these, 77.6% were females and 22.4% were males. The mean (SD) age was 49.9 (±2.82) years with a range of 23-89 years. The mean duration of follow-up was 5.41 (±4.94) weeks with a range of 1-17 weeks. Thirty-two out of 255 patients (12.5%) did not have a follow-up visit. Seventy-seven patients (30.1%) had pre-existing ARDs and therefore already on disease modifying anti-rheumatic drugs (DMARDs) or steroid. Thirty-seven patients (14.5%) had diabetes and 64 (25.0%) had other chronic painful conditions like osteoarthritis, fibromyalgia or soft tissue rheumatism.

Clinical features:

The mean duration of fever was 3.40 (±1.49) days. Out of the 255 patients, 3 had no fever, 9 had a fever for 10 or more days, and the remaining 243 patients (95.3%) had a fever for 5 days or less. The mean duration of articular symptoms (from the onset of fever till first visit) was 4.67 (1.41) weeks. More than two-third of patients had symptom onset within the first month. Eight patients (3.0%) presented after 12 weeks of fever onset, and 3 patients were seen on the second day of their fever. However, not all patients were continuously symptomatic for this duration, as some patients had recovered fully from the initial phase of fever and bodyache and developed polyarthralgia a few weeks later. Figure 1 describes the salient features of patients.

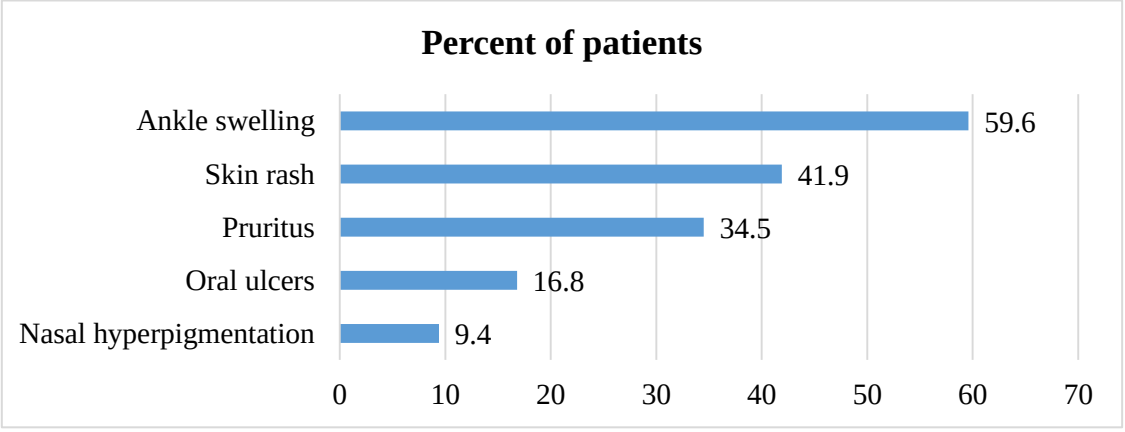
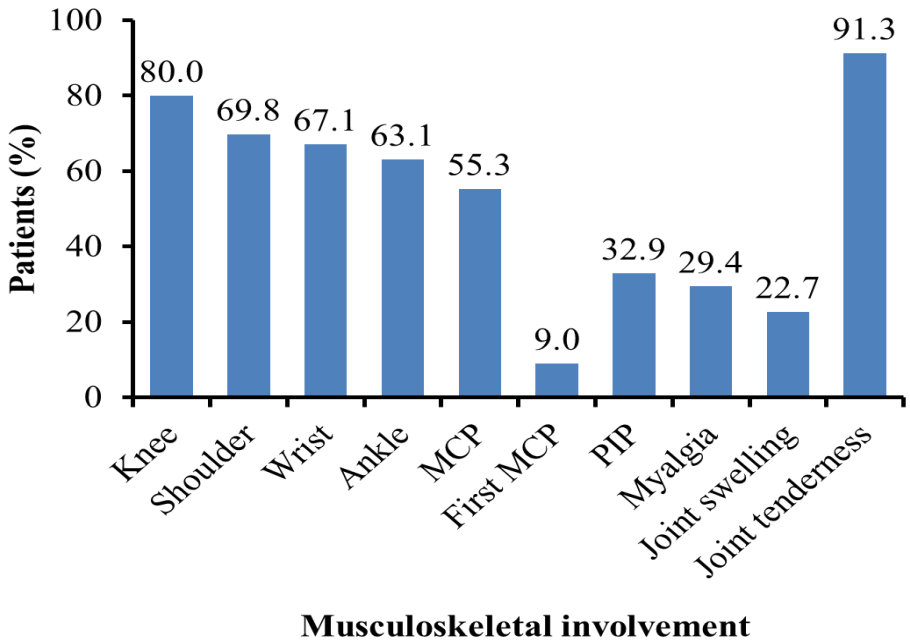


Figure 1: Main Clinical features with frequency

The most frequent extra-articular manifestation was swelling in the ankles or lower legs, which was present in 152 patients (59.6%). Eighty-eight patients (34.5%) had skin rash and only 24 (9.41%) had the characteristic nasal hyperpigmentation. Pruritus, mainly in face and extremities was present in 107 patients (41.9%) and oral ulceration in 43 patients (16.8%). Other less common symptoms including generalized swelling, primarily in the face and extremities, and skin exfoliation in the hands and feet, which were each reported by fewer than 5.0% of the patients. In 14 patients (5.4%), the skin rash developed after taking drugs, either Non-steroidal anti-inflammatory drugs (NSAID) or Hydroxychloroquine.

Articular Involvement*:*

Joint involvement showed no consistent pattern; both large and small joints were affected in the majority of patients. The only consistent observation was symmetry of joint involvement across patients. Figure 2 describes the pattern of musculoskeletal involvement.



MCP, metacarpophalangeal; PIP, proximal interphalangeal
Figure 2: Pattern of musculoskeletal involvement

Among the joints affected, knee was the most commonly involved, followed by shoulder, wrist, and ankle. Joint swelling was observed in 22.7% of patients while joint tenderness was seen in 91.3% of patients (Figure 2). Some typical features of CHIK V arthritis which were a helpful clue in differentiating it from Rheumatoid Arthritis (RA) were pain and limitation out of proportion to actual tenderness or swelling observed in examination, abrupt onset of symptoms rendering patients severely restricted within one or two days, very less joint swelling, and worsening of pain with sudden increase in activity. Involvement of 1st MCP joint (base of thumb) was also a peculiar feature, although present in a small number. In a small minority of patients (<5%), there was a second episode of fever, 2-4weeks later which heralded the onset of arthritis. Nine patients also complained of paresthesia in extremities, especially in hands typically suggestive of carpal tunnel syndrome (CTS).

Investigations*:*

Among 97 patients with data of CHIK V IgM, 56 tested positive, while 41 tested negative. In almost half of patients in whom the test was negative, it was done within the first week. PCR testing was performed on five patients and all were positive, four of which were done before visiting the clinic and one was done after. Leukopenia (TLC < 4000) was recorded in only 24 patients (9.4%). ESR value was available in 165 patients, with a mean value of 33.17 mm, 92 having a value more than 25, and 32 having a value more than 50. As ESR is generally believed to be a marker with slow rise and slow decline, only one value of ESR was advised/noted, whereas wherever feasible, two values of CRP, at least 4 weeks apart were advised/noted to see the association of chronic pains with CRP. Initial CRP was available in 34 patients only, almost all done before their first visit with a mean value of 41.18 mg/dL. Repeat CRP was available in 133 patients, with

a mean value of 8.44 mg/dL with 68 having a negative CRP. This suggests that unlike RA and COVID 19, where CRP levels are usually associated with acute flare of disease or persistence of inflammation or immune activation, and thus provide a useful tool in monitoring, serial CRP assessment in early CHIK V arthritis is not helpful in the same way.

Treatment*:*

Almost all patients (excluding 2 patients with pre-existing chronic kidney disease and 2 with deranged liver and kidney functions due to infection) were initially prescribed NSAIDs which were gradually reduced and replaced with DMARDs. All patients had been previously taken Paracetamol (PCM) for fever, but none got relief in joint pains from it. Thirty patients (11.7%) were prescribed daily low dose steroid, 211 patients (82.8%) were prescribed weekly or biweekly steroid while the rest 14 (5.5%) were not prescribed any steroid at all. 188 patients (73.7%) were prescribed Hydroxychloroquine (HCQ), while 223 patients (87.5%) were prescribed methotrexate (MTX). The median dose was 15 mg/week. In those patients with ARDs who were already on these medications, the doses of these drugs were increased to control the arthritis. In four patients with RA, new drugs had to be added for disease control but in all others short duration addition/ increase in steroid was able to control the symptoms. As part of the routine assessment for CHIK V arthritis, 40 patients were labeled as having high disease activity based on joint counts, functional limitation and the need for NSAIDs and steroids. The rest were labeled as having low disease activity. This assessment was similar to the disease activity assessment used for other autoimmune rheumatic disease. Out of the total patients, only 35 (13.7%) had complete recovery with no need for further treatment at the last follow-up. The rest had partial recovery and continued to require treatment.

Adverse Effects*:*

Ten patients (3.9%) reported adverse effects. Three patients developed facial swelling and weight gain with steroid and one patient with diabetes experienced elevated blood sugar levels. Six patients had adverse effects from MTX, including dyspepsia in three, anorexia in two and hair loss in one. To address these adverse effects, the dose of the offending drug was either reduced, or in case of steroid, stopped completely for two patients. All the relevant data have been provided separately [8].

DISCUSSION:

There have been previous reports of a few cases of CHIK V in Uttarakhand, but this is the first time an outbreak of this magnitude has occurred. This may have been caused by a change in climate, deforestation, urbanization and poor sanitation and drainage, particularly during and after rains. The medical fraternity must be prepared to face such challenges including proper diagnosis and management as well as surveillance and prevention. The purpose of this study was to present the available data and provide key points on differential diagnosis and management.

When diagnosing acute febrile illnesses, particularly during the post-monsoon period, it is important to consider CHIK F in the differential diagnosis. The main differential diagnosis for CHIK F is dengue fever, and rarely Zika virus infection in some countries. As both CHIK F and Dengue can present with high fever associated with severe bodyache and debilitating joint pain along with other systemic symptoms, they can be difficult to distinguish, particularly in the early stages of the illness. As described in literature [9, 10], some clinical clues can be helpful, like presence of severe headache/ retro-orbital pain, petechial rash or generalized erythema, hypotension, and vomiting in dengue and presence of severe joint pains without much systemic features in CHIK F, but they cannot be uniformly and reliably used for management. The main reason for excluding dengue is in prescribing NSAID and/or steroid in early CHIK F, which can be harmful in former. There are two simple steps that can help in the diagnosis. First, during the initial phase of any outbreak, before the spread of one or both viruses is known, it is necessary to advise a CBC and dengue serology in all patients. These tests are widely available, are very economical, and can reliably confirm or rule out dengue within the first week. Second, once the information regarding a specific outbreak becomes available, a presumptive diagnosis can be made. It is advisable to start with CHIK V PCR test initially and also consider CBC and dengue serology to rule-out co-infections. Hypotension, hemoconcentration, moderate to severe serositis and severe thrombocytopenia are clinical features that can indicate dengue fever.

In the present study, ankle swelling was a common feature present in almost 60% of patients. The characteristic nasal hyperpigmentation was uncommon, occurring in less than 10% of cases. Generalized erythema, swelling and itching were common, but they are often seen in dengue also, although facial erythema or hyperpigmentation are more suggestive of CHIK F. Oral ulceration is another feature which is usually not seen with dengue, but was present in almost 17% patients. Combination of these features, with a normal CBC and epidemiological support can safely make a diagnosis even in the absence of CHIK V PCR or IgM.

Paracetamol is the recommended medication for fever control in dengue and is largely effective in controlling the symptoms. However, in the case of CHIK F, PCM may not be as effective. Most guidelines suggest the use of PCM over NSAIDs in the

acute phase of CHIK F and advise against the use of steroid [3, 5, 11]. But in the present study, almost all patients required NSAIDs for symptomatic relief and some even required steroid right from the beginning. None of the patients in this group were benefited by PCM. There is no evidence to suggest that using NSAIDs or steroids is harmful in CHIK F even in the early stages of the disease. In fact, early treatment can help alleviate symptom and improve outcomes, especially for those with disabling articular symptoms. In the chronic phase, dengue is not a consideration, and in majority of patients, joint pains dominate the clinical picture. The guidelines recommend use of NSAIDs initially and steroid and /or HCQ in those with inadequate control, with later addition of other DMARDs, although the evidence supporting this is largely based on expert opinion and safety considerations with only a few trials available. The patients in this group were advised steroid, HCQ and MTX without much adverse effects. Extrapolating the evidence from early RA, which used to be treated previously in a step up pyramidal approach using NSAID, steroid and DMARDs sequentially, the paradigm shift in approach there can very well be utilized in viral arthritis as well by using all three simultaneously and then following a step-down approach as the symptoms are resolved. The excellent safety profile of both HCQ and MTX, at least in short term, coupled with their proven role in chronic arthritis of different etiologies, is strong argument in using these drugs early on, which can help in rapid taper of steroid. There is some evidence that combination DMARD therapy is better than HCQ alone in CHIK V chronic arthritis [12], and the same can be employed much earlier, provided one can exclude other diagnosis like dengue and there are no comorbidities or extra-articular complications.

In the present study, only 12% patients required daily steroid, rest all were managed with weekly or biweekly steroid regimen. The adverse effects were minimal and easily managed with dose reduction. Although this was not a prospective study and no statistical analysis were done to compare treatments, on clinical grounds alone, coupled with the experience in managing rheumatological patients, MTX was somewhat better drug than HCQ alone and majority of patients on HCQ alone were later also given MTX so as to achieve the symptom control and to reduce the requirement of NSAIDs and steroids. Also, patients seen in the later months were not given HCQ at all and still had good outcomes using only MTX and bi-weekly steroids.

In patients with chronic arthritis, the main differential diagnosis is RA. Unlike the typical description of small joint involvements in RA [13, 14], the pattern of joint involvement in this study was somewhat different. Knee, shoulder and ankle were the most commonly affected joints in the patients with CHIK V arthritis. Although most patients were in the subacute (<3 months) phase at presentation, the persistence of symptoms during follow up is an indication of chronicity of disease in a large majority. The typical history of acute onset arthritis with fever and rash, along with the background of an outbreak, are indicative of CHIK V. The results suggest that joint swelling is very uncommon in CHIK V arthritis (22%) and even tenderness is not present in all patients (91%). Coupled with the finding of low values of repeat CRP, this might suggest that the systemic inflammation may not remain chronically high. On the other hand, no response to PCM and other analgesics like tramadol and exquisite response to NSAID and steroid is a pointer towards inflammatory nature of arthritis. The CTS like symptoms were observed in very few patients, although one study from Western India reported this symptom in almost one-third of patients [15].

Future Direction*:*

Two areas of interest can be identified which need larger and long-term prospective studies. First, it is important to identify patients early on, and PCR is an expensive test not available or feasible for every patient. Either some clinical features or some easily available and economical blood investigation may help in this. Alongside, better standardization of IgM kits and their availability will help in recognizing an outbreak in early stage and differentiating with other acute febrile illnesses. Second, the question of early and aggressive treatment with DMARDs remains to be explored to determine if it can prevent long-term arthritis.

Limitations:

The study has several limitations. First and foremost, there is an obvious selection bias as being a rheumatology clinic, patients with predominantly articular symptoms are represented here. Second, there is lack of standardization in CHIK V IgM testing. As the clinic does not have its own laboratory, and patients were not referred to a single lab, the testing was done at different places, which may explain the negative serology results in some cases. To improve accuracy and establish minimum standards, standardization of testing kits is necessary. The female preponderance, although reported in previous studies, may also be due to the presence of old patients of ARDs which definitely are more common in females. The retrospective nature and absence of any protocol makes any conclusion about treatment outcome less meaningful. Additionally, the small sample size limited the ability to perform statistical analysis between different groups. Third, and most important, judging outcome in a disease which is known to be self- limiting is difficult. Despite these limitations, there is a strong argument for treating patients with CHIK V aggressively, contrary to the current

guidelines. In India, the majority of patients are not compliant with a treatment regimen comprising of NSAIDs and steroid alone. . It is very difficult to convince them to keep on taking NSAIDs for weeks. The fear of real and imagined adverse effects, the easy access to internet, and the myriad home remedies make them very fearful of 'painkillers'. Second, as seen in this group of patients, almost all patients had taken PCM and NSAIDs with no relief with former and only partial and transient relief with later. The simple fact that missing the drug, either NSAID or steroid, even for a single day, brings back the pain with full force is very distressing to even those patients who are compliant with the treatment. Therefore, if proper monitoring can be done and the treating physician is well versed with DMARD use, there is some merit in using this therapy right from the beginning.

CONCLUSION:

The ever increasing outbreaks of Chikungunya in different parts of the country and now in the hill state of Uttarakhand is a cause for worry for all healthcare professionals and administrators. The potential to cause severe debilitating pains in the short term and chronic arthritis in the long term can cause significant loss of productivity. Better surveillance and preventive measures are needed to avert this. The present study provides valuable insights into the clinical profile of CHIK V infected patients presenting with predominantly articular symptoms. Despite some limitations like a retrospective design, small sample size and lack of standardization of testing parameters, the study supports the need for identifying the disease at an early stage clinically and instituting aggressive therapy with DMARDs. Long term prospective studies are needed to better identify the subset of patients at risk of chronic arthritis which might benefit from this approach.

Data.
https://doi.org/10.6084/m9.figshare.24324949.v1

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REFERENCES:

1. Chikungunya World Health Organization (WHO). Available at: https://www.who.int/news-room/fact-sheets/detail/chikungunya#:~:text=Chikungunya%20is%20a%20mosquito%2Dborne,meaning%20%E2%80%9Cto%20become%20contorted%E2%80%9D. Accessed on 8th Feb 2023
2. Facts about the Chikungunya. National Centre for Vector Borne Diseases Control. Ministry of Health & Family Welfare, Government of India. Available at: https://nvbdcp.gov.in/index4.php?lang=1&level=0&linkid=488&lid=3764 Accessed on 8th Feb 2023
3. Simon F, Javelle E, Cabie A, Bouquillard E, Troisgros O, Gentile G, et al . French guidelines for the management of chikungunya (acute and persistent presentations). Med Mal Infect 2015; 45: 243-63 .
4. Translational Research Consortia (TRC) for Chikungunya Virus in India. Current Status of Chikungunya in India. Front Microbiol 2021; 12: 695173.
5. Pathak H, Mohan MC, Ravindran V. Chikungunya arthritis. Clin Med (Lond) 2019; 19: 381-5.
6. National Center for Vector Borne Diseases Control: Dengue/DHF situation in India. National Center for Vector Borne Diseases Control, New Delhi; 2022. Available at: https://nvbdcp.gov.in/index4.php?lang=1&level=0&linkid=431&lid=%203715&theme=Blue&font=Increase&Background=Light. Accessed on 30 January 2023
7. National Center for Vector Borne Diseases Control (NCVBDC), Ministry of Health & Family Welfare, Government of India. https://nvbdcp.gov.in/index4.php?lang=1&level=0&linkid=486&lid=3765. [Accessed on 30 Jan 2023]
8. Bhatt, Kamal (2023). CHIK V DATA for submission.xlsx. figshare. Dataset. https://doi.org/10.6084/m9.figshare.24324949.v1
9. Centers for Disease Control and prevention. Dengue. https://www.cdc.gov/dengue/healthcare-providers/clinical-presentation.html#:~:text=Clinical%20findings%20include%20nausea%2C%20vomiting,%2C%20restlessness%2C%20and%20liver%20enlargement. Accessed on 14th March 2023.
10. Ioos S, Mallet HP, Leparc Goffart I, Gauthier V, Cardoso T, Herida M. Current Zika virus epidemiology and recent epidemics. Med Mal Infect 2014; 44: 302-7.
11. World Health Organization Regional Office for South-East Asia .Guidelines on clinical management of chikungunya fever. India. WHO, 2008. Available at: http://apps.who.int/iris/handle/10665/205178 Accessed on 30th Jan 2023.

12. Ravindran V, Alias G. Efficacy of combination DMARD therapy vs hydroxychloroquine monotherapy in chronic persistent chikungunya arthritis: a 24week randomized controlled open label study . Clinical Rheumatol 2017; 36: 1335-40.
13. Senthelal S, Li J, Ardeshirzadeh S, Thomas MA. Arthritis. [Updated 2022 Jun 19]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK518992/
14. Mohammed RH, Bhutta BS. Hand and Wrist Rheumatoid Arthritis. [Updated 2022 Sep 5]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK560890/
15. Pandya S. Methotrexate and hydroxychloroquine combination therapy in chronic chikungunya arthritis: A 16-week study . Ind J Rheumatol 2008; 3: 93-7