

# Chikungunya crisis in the Americas: a comprehensive call for research and innovation

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Chikungunya virus (CHIKV) remains a major public health problem in the Americas, with alarming numbers of infected.<sup>1</sup> Even after decades of engaging with health issues related to arboviruses, healthcare systems continue to struggle to contain new epidemics of this virus.<sup>2</sup> This underscores the complexity of the challenges faced by affected countries in the control and prevention of these mosquito-borne diseases.

With 1,659,167 cases recorded since 2016, translating to a rate of, 25.37 per 100,000 people, the Brazilian Health Minister has highlighted a substantial surge in chikungunya fever cases, maintaining Brazil as the epicentre for the disease in the Americas.<sup>1,3</sup> Florida and Texas have reported CHIKV infections, highlighting the virus's reach beyond traditionally endemic areas.<sup>1</sup> The climate changes and the large immunologically naïve population in North America and Europe may be a combination of factors for future epidemics and new risk areas. A study published in "The Lancet Regional Health–Americas" emphasises that chikungunya infection frequently results in chronic arthralgia, affecting the quality of life of those infected and posing a substantial burden on healthcare systems in affected regions.<sup>1</sup>

In 2018, chikungunya was added to the World Health Organization (WHO) shortlist for priority research and development as a neglected tropical disease due to the lack of an approved vaccine and the potential for chronic dysfunction. The problems regarding chikungunya could not be stopped with the end of the acute phase.<sup>4</sup> Chronic arthritis is likely to lead more than half of the patients into a chronic phase of their condition, persisting for over three months and resulting in long-term pain that could continue for years.<sup>5</sup> Musculoskeletal disorders are present in 95% of chronic cases and can be incapacitating.<sup>2</sup> It is possible to

find immune disturbance with high levels of inflammatory cytokines, persistent bony erosion, joint effusions, and tendonitis.<sup>2</sup> This can lead to a significant decline in quality of life and physical function.<sup>6</sup> This scenario impacts the health and well-being of the affected individuals and has significant economic implications.<sup>6</sup> Chronic pain due to CHIKV leads to increased absenteeism from work, resulting in decreased productivity and a substantial economic burden on societies.<sup>7</sup> While chikungunya poses a significant health risk in the Americas, strategies for managing chronic pain and rehabilitation lack standardised consensus.<sup>1</sup>

In the face of this escalating issue, scientists have been investigating potential treatments for chronic pain caused by chikungunya. On a search in PubMed (terms: "Chikungunya virus" OR "Chronic chikungunya infection") AND ("Pain management" OR "Pain treatment" OR "Pain relief" OR "Pain control" OR "Analgesics" OR "Physical therapy"), there are only seven articles regarding chikungunya and medications, four about physical rehabilitation, and 14 about vaccine studies. A search on [clinicaltrials.gov](https://clinicaltrials.gov) showed a limited selection of trials targeting this area, with two completed studies focusing on the effectiveness of chloroquine and methotrexate. Currently, there are two active trials seeking participants: a phase 1 trial exploring SAR440894 and another studying the effect of methotrexate. Meanwhile, the Brazilian Registry of Clinical Trials (ReBEC) listed only one trial recruiting participants to study the impact of dexamethasone combined with methotrexate. No studies on rehabilitation methods for chikungunya are available on [clinicaltrials.gov](https://clinicaltrials.gov), whereas ReBEC lists three studies on rehabilitation for chronic chikungunya arthralgia. [Table 1](#) summarize the clinical trials information from [clinicaltrials.gov](https://clinicaltrials.gov) and ReBEC.

The current state of research into therapies for chronic pain caused by the CHIKV reveals a concerning scarcity of published and ongoing studies, with an emphasis on methotrexate, a drug whose effectiveness and safety has previously fallen short of expectations.<sup>8</sup> This focus suggests cautious optimism in the scientific community about its potential efficacy. However, the



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Trial ID	Platform	Treatment	Phase	Comparison	Main outcome	Status	Year of conclusion	Location
NCT00391313	ClinicalTrials	Chloroquine	Completed	Placebo	Not provided	Completed	2007	France
NCT03058471	ClinicalTrials	Methotrexate, NSAID and steroids	Completed	Open label	Swollen or tender joints	Completed	2018	India
NCT04441905	ClinicalTrials	SAR440894	Phase 1	Placebo	Adverse events	Recruiting	2024	USA
NCT04483466	ClinicalTrials	Methotrexate	N/A	Placebo	Disease severity	Recruiting	2027	USA
NCT03090685	ClinicalTrials	Auriculotherapy	N/A	Placebo	Pain	Completed	2017	Brazil
NCT03702348	ClinicalTrials	Resistance exercise	Phase 1	No intervention	Functionality	Unknown status	2019	Brazil
NCT02993952	ClinicalTrials	tDCS	N/A	Sham tDCS	Pain	Completed	2017	Brazil
NCT04455919	ClinicalTrials	Yoga	N/A	No intervention	Quality of life	Completed	2020	Guadalupe <sup>a</sup>
RBR-73fdfq5	ReBEC	Dexamethasone + Methotrexate	N/A	Placebo	Number of painful joints	Recruiting	–	Brazil
RBR-469yd6	ReBEC	tDCS	N/A	Sham tDCS	Pain	Not recruiting	–	Brazil
RBR-25nsk2n	ReBEC	Osteopathic manipulation	N/A	Sham manipulation	Pain	Recruiting	–	Brazil
RBR-4hb9qs	ReBEC	Auriculotherapy	N/A	No intervention	Pain	Completed	2020	Brazil
RBR-99tdpn	ReBEC	Pilates exercise	N/A	No intervention	Pain	Recruiting	–	Brazil
RBR-4qqbps	ReBEC	Auriculotherapy	N/A	Pre and post	Pain	Completed	2020	Brazil
RBR-245rh7	ReBEC	tDCS	N/A	Sham tDCS	Pain	Completed	2023	Brazil

ReBEC: Brazilian Registry of Clinical Trials. tDCS: transcranial direct current stimulation. N/A: not applicable. <sup>a</sup>Ultramarine territory of France.

**Table 1: Clinical trials registered regarding different treatment options for chronic chikungunya arthralgia.**

limited number of studies actively seeking new treatments, including rehabilitation strategies aimed at recovery strengthening the sensorimotor system, points to a significant research gap. This scenario, where two out of three scarce studies concentrate on methotrexate, calls for a renewed and expanded effort, including neuromodulation techniques, to explore a variety of therapeutic options, moving beyond the confines of past approaches to address the challenges of CHIKV-induced chronic pain truly.

#### Contributors

RP and NNMN: conceptualised and wrote the comment. KPB and FF: Writing–review & editing.

#### Declaration of interests

Authors declares no conflicts of interest.

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#### References

- de Souza WM, Ribeiro GS, de Lima STS, et al. Chikungunya: a decade of burden in the Americas. *Lancet Reg Health Am.* 2024;30:100673.
- Bartholomeeusen K, Daniel M, LaBeaud DA, et al. Chikungunya fever. *Nat Rev Dis Primers.* 2023;9(1):17.
- Ministério da Saúde. DE CASOS PROVÁVEIS de dengue por semana epidemiológica, brasil, 2023 E 2024. [www.gov.br/saude/pt/2023](http://www.gov.br/saude/pt/2023).
- Bouquillard E, Fianu A, Bangil M, et al. Rheumatic manifestations associated with Chikungunya virus infection: a study of 307 patients with 32-month follow-up (RHUMATOCHIK study). *Joint Bone Spine.* 2018;85(2):207–210.
- Amaral JK, Taylor PC, Teixeira MM, Tem Morrison TE, Schoen RT. The clinical features, pathogenesis and methotrexate therapy of chronic chikungunya arthritis. *Viruses.* 2019;11(3):289.
- de Souza CG, da Costa JF, de Sousa Dantas D, de Abreu Freitas RP, Lopes JM, Okano AH. Evaluation of pain, functional capacity and kinesiophobia in women in the chronic stage of chikungunya virus infection: a cross-sectional study in northeastern Brazil. *Acta Trop.* 2019;199:104853.
- Adams G, Salomons TV. Attending work with chronic pain is associated with higher levels of psychosocial stress. *Can J Pain.* 2021;5(1):107–116.
- Amaral JK, Sutaria R, Schoen RT. Treatment of chronic chikungunya arthritis with methotrexate: a systematic review. *Arthritis Care Res.* 2018;70(10):1501–1508.