Combining limited evidence on chikungunya: a systematic literature review and meta-analysis on clinical outcomes

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Introduction

Disease background

- Chikungunya is a viral disease caused by a mosquito-borne alphavirus, the chikungunya virus (CHIKV).[1]
- The virus is characterized by an <u>acute phase</u> (commonly presenting with fever, arthralgia, and myalgia), with a variable proportion of individuals (30%-40%) also developing <u>chronic symptoms</u> that can be present for months or even years (including chronic arthritis, fatigue, stiffness, and depression among others).[2,3]
- Due to global warming and mosquito vector spread, the disease has rapidly expanded, and <u>currently over three-quarters of the world's population lives in the areas at risk of CHIKV transmission.</u> [4,5]

Problem statement

- The increased frequency of chikungunya outbreaks in recent decades, along with the ongoing spread of the virus, has led to a <u>substantial adverse impact on societies and healthcare systems</u>. Despite these challenges and the high morbidity rates associated with chikungunya, specific treatments or <u>preventive vaccines for the disease are currently unavailable, and the evidence is limited</u>.

Objective:

- The study aimed to improve the current evidence on chikungunya by combining clinical data on the disease through a meta-analysis.

Methods

Clinical systematic literature review (cSLR)

- The process to identify sources that could be used in meta-analysis consisted of two stages: <u>initial</u> and <u>updated</u> cSLR.
- The cSLR <u>data search</u> was performed following the requirements of global health technology assessment (HTA) agencies, with the searches conducted in MEDLINE In-Process, Embase and MEDLINE.
- Strict <u>PICOS criteria</u> were created to ensure only relevant articles would be identified through the cSLR.
- The cSLR identified relevant articles for meta-analysis, extracting key information on study design, patient characteristics, and clinical presentation into a standardised data extraction table shell in Microsoft Excel.

Feasibility assessment and meta-analysis

- A <u>feasibility assessment</u> was carried out to ensure the comparability of selected studies for meta-analysis.
- We conducted a <u>manual assessment</u> to check the comparability of the populations in any identified outlier group.
- <u>Meta-analyses</u> were performed for various endpoints related to the frequently reported clinical symptoms of chikungunya, including mortality rates, incidence of symptoms, and frequency of hospitalization.
- The results of each meta-analysis were presented using a <u>forest plot</u>, which displayed the effect size for each study along with the numerical and graphical representation of the confidence interval.

Results

A total of 316 articles were included in the cSLR and considered in the meta-analysis.

Acute hospitalization

- On average, 17% of symptomatic adults with confirmed chikungunya are hospitalized during the acute phase.

Mortality

- In populations with a <u>normal mortality risk</u>, the estimated death rate from CHIKV infection is 0.32%.
- In <u>high-risk populations</u>, the estimated death rate from CHIKV infection is 15% (Figure 1).

Chikungunya symptoms

- It is estimated that 73.8% of individuals infected with CHIKV experience a <u>symptomatic disease</u>.
- <u>Arthralgia and fever</u> are the most frequently reported symptoms of chikungunya.
- On average, 43.4% of patients with acute chikungunya transition to chronic disease, and about 50% of these chronic patients do not recover from the disease.
- The chronicity rate is projected at 43.89% after three months, declining to 34.39% after six months, and further decreasing to 31.87% after 12 months.

Endpoints without data availability

- The meta-analysis estimation of several endpoints proved to be infeasible due to their infrequent reporting in the studies identified through the cSLR. Among others, these endpoints include the duration of each symptom, length of acute and chronic illness, and hospitalization of chronic patients.
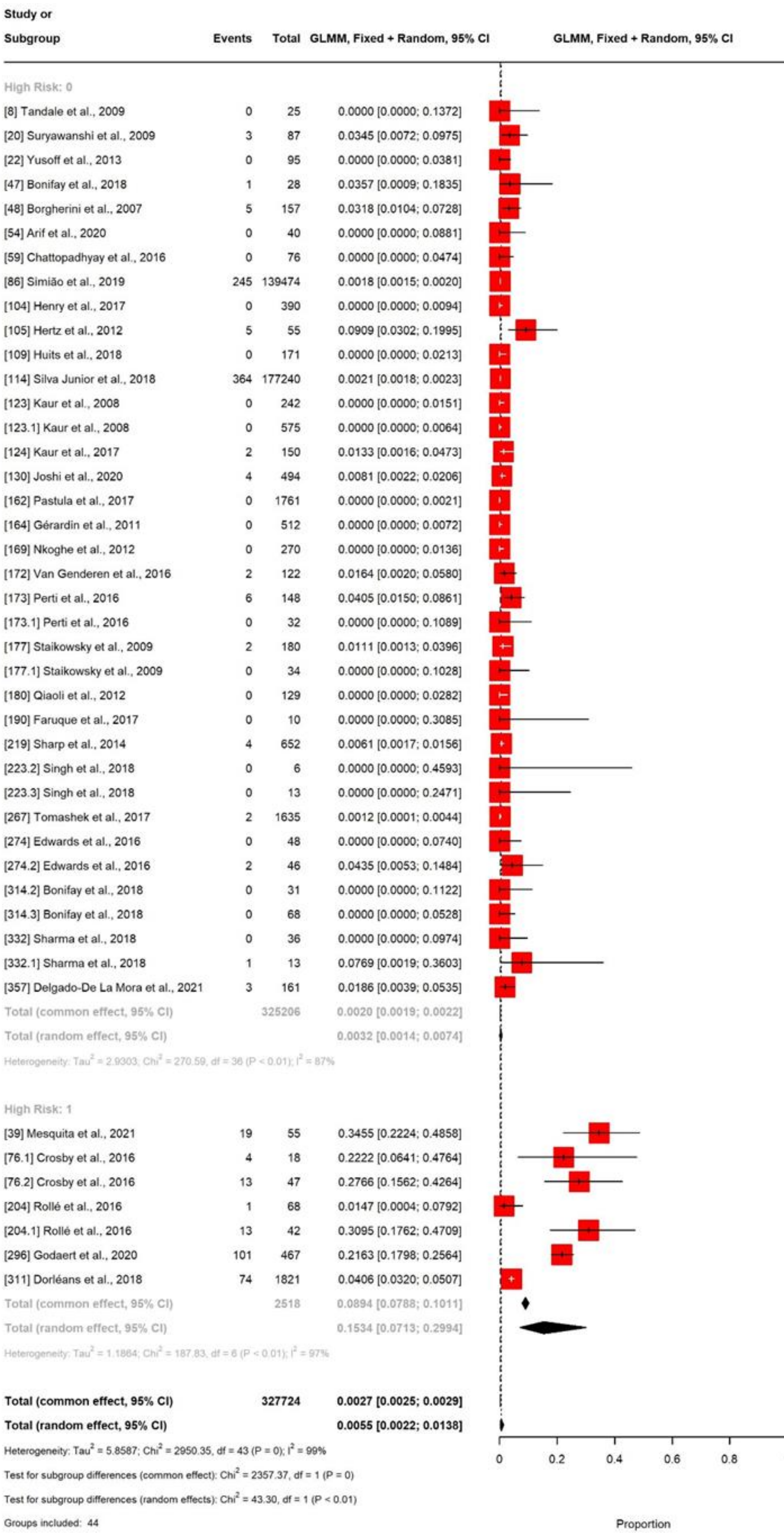

Figure 1. Forest plot for the subgroup analysis for mortality based on expected risk of mortality following a CHIKV infection

Discussion

- Chikungunya is associated with a <u>significant disease burden</u>: 73.8% of infected individuals experience symptomatic disease, with <u>arthralgia, fever, and joint pain</u> constituting the <u>most frequently reported symptoms</u> of CHIKV infection.
- Patients <u>65 years or older</u> presented a relatively <u>higher mortality rate</u>, increased <u>hospitalization rates</u>, and a lower incidence of symptoms compared to other age groups. To gain a deeper understanding of the potential influence of this demographic, future analysis could try to assess the overall impact of age on disease outcomes in CHIKV infection.
- This <u>study included all reported (sub)groups rather than just the studies themselves</u>. This approach provided the advantage of including more populations reporting the desired endpoint, resulting in a sufficient number of groups for meta-analysis and <u>better control of heterogeneity</u>.
- A <u>limitation</u> of this study was the presence of <u>heterogeneity among studies</u>. This can be explained by the collection of data on chikungunya, which is predominantly conducted during outbreaks, limiting the ability to establish strict scientific protocols and control various parameters, and by lack of consensus regarding the standardized reporting of endpoints.
- The field of chikungunya is characterized by novelty and uncertainty, reflected by the unexpectedly low number of 15 meta-analyses that could be conducted out of the 33 endpoints of interest. Therefore, <u>more structured research is essential to understand chikungunya comprehensively</u>.

- Chikungunya is associated with high morbidity rates that have adverse effects on societies and healthcare systems
- Subgroup analysis allowed for including more populations for endpoints and better control of heterogeneity
- More research with long-term follow-up is needed to further develop our understanding of chikungunya

References

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