




# Clinical, Epidemiological, and Laboratory Features of Mayaro Virus Infection: a Systematic Review

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## Abstract

**Purpose of Review** Mayaro virus is an arbovirus that circulates in a wild cycle transmitted by *Haemagogus janthinomys*; however, case reports in urban areas suggest that other arthropods could be acting as vectors. It shares several similarities with Chikungunya virus, being highly probable that many cases are being misdiagnosed. The disease caused by this pathogen is known as Mayaro fever, which is restricted to regions of Central and South America, mainly the Amazon rainforest. Cases of Mayaro fever have continuously been increasing, suggesting that Mayaro virus would become another major epidemic arbovirus in America.

**Recent Findings** Four electronic databases were searched for articles in English and Spanish using the keywords “Mayaro” and “case.” A total of 234 cases were retrieved in the 23 selected manuscripts. Of all cases, most of them were male young adults, reported as autochthonous cases occurring mainly in Peru and Brazil, who were performing activities in wild rural areas. Fever, arthralgia, headache, myalgia, and retro-orbital pain were the main clinical manifestations. Most of the patients had laboratory parameters within the normal range, joint complications were evidenced in few cases, and all of them recovered without specific treatment.

**Summary** Mayaro fever appears to be a mild self-limited disease that affects mainly males at productive age that are in contact with wild environments. However, further studies are required to establish its true pathogenic potential of Mayaro virus.

**Keywords** Arbovirus · Alphavirus · Mayaro virus · Systematic review · Latin America

## Introduction

Arboviral infections, or arthropod-borne viral infections, are one of the most important causes of disease in tropical and subtropical regions worldwide and one of the most critical global public health problems [1]. Arboviruses belong to five families: Bunyaviridae, Flaviviridae, Orthomyxoviridae, Reoviridae, and Togaviridae, and they are transmitted by a wide range of arthropod vectors such as mosquitoes and ticks, which can be circulating in an urban environment or their biological cycle is restricted to wildlife [2–4]. Dengue virus (DENV), Chikungunya virus (CHIKV), and Zika virus (ZIKV) are the most known and the main arboviruses of public health importance for local surveillance systems worldwide [2, 5]. However, there are several other neglected arboviral species for which particular attention must be given due to their fast spreading as a result of the geographical expansion of mosquitoes due to climate change and the increase in land use [6, 7].

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Three arboviruses, Venezuelan equine encephalitis virus (VEEV), Oropouche virus, and Mayaro virus (MAYV), have been proposed as candidates for the next arboviral epidemic, at least in the Americas [8]. MAYV (*Alphavirus* genus, *Togaviridae* family) is a single-stranded RNA virus that forms part of the Semliki complex along with CHIKV, Bebaru, Getah, O'nyong-nyong, Ross River, Semliki Forest, and Una viruses [9]. This arbovirus circulates in a natural wild cycle among different animal species through the bite of female mosquitoes of the genus *Haemagogus*, being *Haemagogus janthinomys* its main important vector [10]. However, reports of the disease in urban areas have suggested that MAYV might have been introduced into urban environments in which other mosquito species, such as *Aedes* and *Culex* spp., could be acting as vectors, since vector competence has already been evaluated and demonstrated for some species [11].

MAYV was first detected in 1954 in Trinidad and Tobago in the serum of forest workers [12]. It shares biological, epidemiological, and clinical similarities with other arboviruses from the Americas, of which the most closely related is CHIKV; being highly probable that cases due to MAYV may have been misdiagnosed as CHIKV for a long time as both of them share similar geographical distribution and other features [13, 14]. The disease caused by MAYV is usually denominated as Mayaro fever, and it has been restricted to several countries of Central and South America, which territories form part or surrounds the Amazon rainforest, which is considered the main important region where MAYV is actively circulating [15, 16]. During the last years, cases due to MAYV have continuously been increasing, and reports of the disease have been more frequent, suggesting that MAYV is close to becoming another major epidemic arbovirus in Americas soon [17].

Likely, the global burden of Mayaro fever is still underestimated, mainly due to the health personnel's lack of accurate diagnostic methods and clinical suspicion [18]. MAYV laboratory confirmatory diagnosis can be made using different virological, serological, or molecular methods. The virus can be detected through viral isolation in cell cultures; however, this method can only be performed in reference laboratories [19]. Another alternative is the detection of the viral RNA through reverse transcription (RT) polymerase chain reaction (PCR), being highly useful during the acute phase of infection [20]. Additionally, the detection of antibodies to MAYV through serological methods such as enzyme-linked immunoassay (ELISA) and indirect immunofluorescence assay (IFA) can be used as indirect diagnosis; however, its interpretation must be carefully made since cross-reactivity can occur with other alphaviruses; thus, usually, detection of antibodies needs a confirmation method such as plaque reduction neutralization testing (PRNT) or the evidence of

seroconversion between acute and convalescent serum samples [21, 22].

Descriptions of clinical, epidemiological, and laboratory features of MAYV infection have been done in some narrative reviews; however, since its first description, several reports of cases of the disease were done by many authors contributing to the knowledge of the disease behavior; nevertheless, to our knowledge, no systematic review related to MAYV infection has been published to date, being essential to characterize the disease before its burden to improve its suspicion among clinicians. Thus, this systematic review aims to evaluate all available evidence regarding the clinical, epidemiological, and laboratory features of MAYV infection.

## Methods

### Search Strategy and Selection Criteria

We followed the recommendations made by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) to guide all the steps of this review. Searching for scientific literature was carried out on June 8th 2023, in four scientific literature databases: PubMed MEDLINE, EMBASE, Scopus, and BVS. A search using the terms ["Mayaro" AND "case"] was performed in all four databases. The references of all the articles were extracted and collected in a library created in the "EndNoteX8" program combining all different searches. Once the reference list was created, the elimination of duplicate articles was carried out using the automatic tool of the program. The procedure results provided a list of potentially valuable articles for analysis and selection.

We reviewed all the literature managed in the eligible list to choose those that would be part of this review. The inclusion criteria were case reports, clinical cases, and other papers written in English or Spanish, with reports of confirmed human cases of Mayaro fever and information regarding epidemiological data, clinical manifestations, and laboratory results available. Those publications that did not fulfill inclusion criteria were excluded.

### Data Extraction

We independently screened the titles and abstracts to identify relevant reports. Possible disagreements were resolved through the author's discussion. Data were extracted from all the included studies and tabulated in Excel. For each article, we extracted information related to the clinical features of all confirmed cases. Additionally, we also performed the data extraction related to the country of the patient's origin, country of travel where the infection was presumed to have

occurred, sex and age of the reported patients, working and leisure activities, hematological and biochemical laboratory findings, complications, treatment, need for hospitalization, and clinical outcome.

## Definitions

Following the recommendations of the Pan American Health Organization (<https://www.paho.org>, accessed on June 8th 2023), we defined a confirmed case of Mayaro fever as a disease caused by MAYV, which diagnosis was made by at least one of the following methodologies recommended: detection of viral RNA in serum samples through conventional or real-time RT-PCR, viral isolation with later confirmation by molecular methods, detection of IgM or IgG antibodies through ELISA or IFA in a single serum sample confirmed by PRNT panel with negative results against other alphaviruses, or seroconversion of IgG antibodies of more than four titers (fourfold change) between paired acute and convalescent serum samples without seroconversion against other alphaviruses.

## Results

### Scientific Literature Search

Figure 1 summarizes our search procedure. Using the terms ["Mayaro" AND "case"], 28, 44, 107, and 311 publications were found in the PubMed MEDLINE, EMBASE, Scopus,

and BVS databases, respectively, giving a total of 490 scientific manuscripts, which were extracted and loaded in the EndNoteX8 program to eliminate duplicate publications, giving a total of 410 eligible scientific manuscripts.

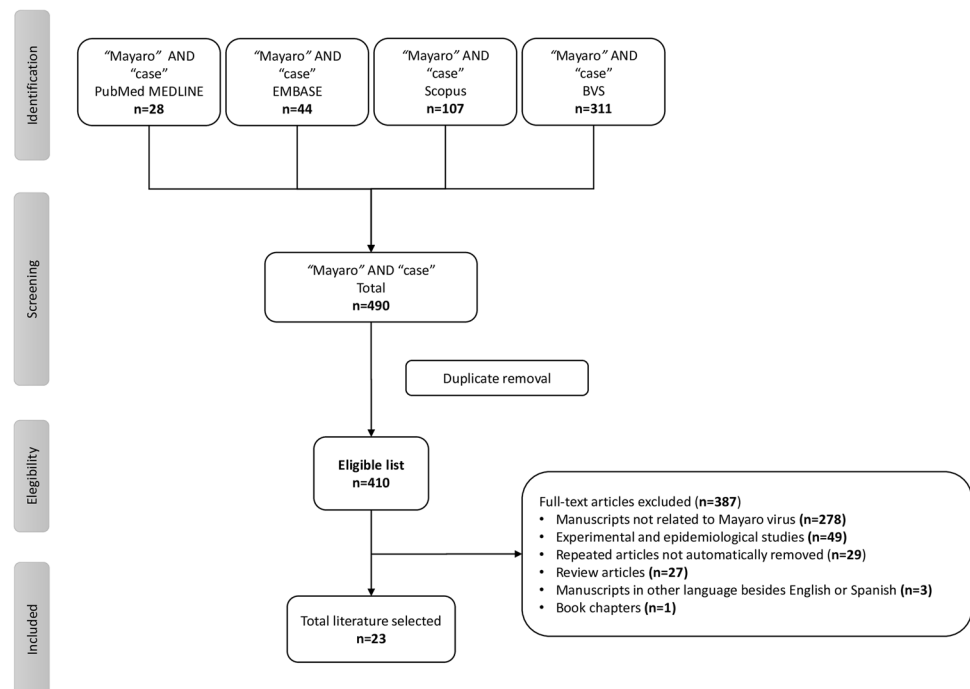
### Literature Selection

From the eligible list of 410 scientific manuscripts, we selected 23 as they fulfilled our inclusion criteria and case definition. A total of 387 publications were discarded as they were manuscripts in which the central topic was not MAYV, studies regarding the biology or epidemiology of MAYV or its vectors, repeated publications which were not automatically removed by the EndNoteX8 tool, review articles, publications in a language other than English or Spanish, and book chapters.

### Demographic and Epidemiological Data

A total of 234 clinical cases were reported in the 23 selected publications [12, 19, 23–40, 41•, 42, 43]. Data related to age, sex, autochthonous cases, imported cases detailing country of origin and country of travel, and working and leisure activities are shown in Table 1. Regarding age, 39% were young adults, 25.8% were middle-aged adults, 10.1% were teenagers and senior adults, 8.1% were children, and 6.9% were infants. Most patients, 56.1%, were males, and the remaining 43.9% were females. Almost all (96.6%) were autochthonous cases, occurring mainly in Peru (54.9%) and Brazil (38.1%), followed by Venezuela (4.4%), Trinidad and

**Fig. 1** Search strategy for the systematic review



**Table 1** Demographic and epidemiological features of Mayaro virus infection cases

	Total cases (%), <i>n</i> = 234
<b>Age<sup>a</sup></b>	
Infant (<5)	11/159 (6.9)
Children (5–11)	13/159 (8.1)
Teenagers (12–17)	16/159 (10.1)
Young adults (18–39)	62/159 (39)
Middle-aged adults (40–59)	41/159 (25.8)
Senior adults (≥60)	16/159 (10.1)
<b>Sex<sup>b</sup></b>	
Male	111/198 (56.1)
Female	87/198 (43.9)
<b>Autochthonous cases</b>	
Peru	124/226 (54.9)
Brazil	86/226 (38.1)
Venezuela	10/226 (4.4)
Trinidad and Tobago	5/226 (2.2)
Haiti	1/226 (0.4)
<b>Imported cases</b>	
<b>Country of origin</b>	
Netherlands	3/8 (37.5)
France	2/8 (25)
Germany	2/8 (25)
Switzerland	1/8 (12.5)
<b>Country of travel</b>	
Brazil	2/8 (25)
French Guiana	2/8 (25)
Surinam	2/8 (25)
Bolivia	1/8 (12.5)
Peru	1/8 (12.5)
<b>Working and leisure activities<sup>c</sup></b>	
Housekeeper	9/40 (22.5)
Eco-tourism	5/40 (12.5)
Forest worker	5/40 (12.5)
Lumberjack	5/40 (12.6)
Farmer	4/40 (10)
Fishing	4/40 (10)
Camping	3/40 (7.5)
Butterfly hunting	2/40 (5)
Military	2/40 (5)
Biologist	1/40 (2.5)
Wildlife volunteer	1/40 (2.5)

<sup>a</sup>Seventy-five cases were excluded due to missing data

<sup>b</sup>Thirty-six cases were excluded due to missing data

<sup>c</sup>One hundred ninety-four patients were excluded due to missing data

Tobago (2.2%), and Haiti (0.4%) (Fig. 2). The remaining 3.4% were imported cases among patients from the Netherlands (37.5%), France, Germany (25%), and Switzerland (12.5%), which acquired the disease while traveling to

Brazil, French Guiana, Surinam (25%), Bolivia, and Peru (12.5%) (Fig. 3). Several working and leisure activities were identified among some patients as follows: 22.5% were housekeepers; 12.5% were forest workers, lumberjacks, and people who were doing ecotourism; 10% were farmers and people fishing; 7.5% were having dinner outside while camping; 5% were people doing butterfly hunting and military personnel; and 2.5% were biologists performing research and wildlife volunteers.

## Clinical Data

The most frequent clinical manifestations are included in Table 2. Of all reported cases, 90.6% had fever, 63.7% had arthralgia, 61.5% reported headache, 50% had myalgia, and 47.4% reported retro-orbital pain. Other relevant signs and symptoms included body pain in 33.3%, nausea in 26.5%, any rash in 23.9%, chills and hyporexia in 15.4%, vomiting in 15%, joint swollen and sore throat in 12.4%, abdominal pain in 10.3%, diarrhea in 6.8%, and cough in 6.4%. Several other clinical manifestations such as jaundice, conjunctival injection, joint tenderness, fatigue, nasal congestion, asthenia, somnolence, and dizziness, among others, were also reported in some patients, but they were present in less than ten patients; therefore, they were not considered in the present review.

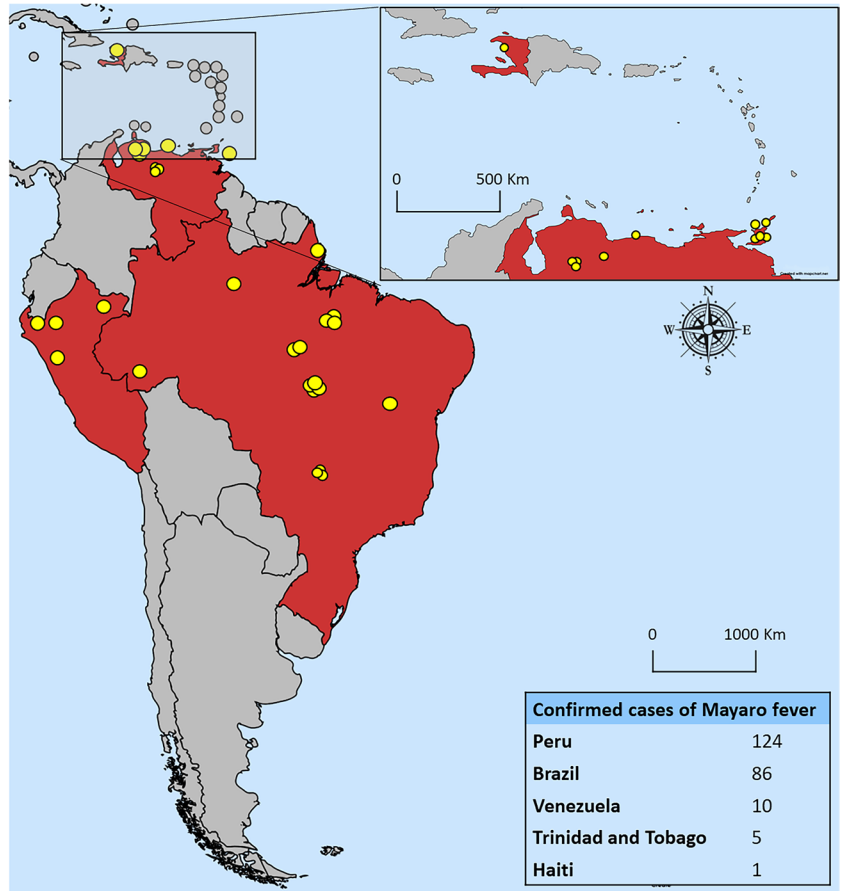
## Laboratory Features

Hematologic and biochemical laboratory available data were extracted from all Mayaro fever cases included in the present study (Table 3). From all reported cases, excluding those in which data were unavailable, most of the patients (82.8%) had their laboratory parameters within the normal range. Only 17.2% of cases had an abnormal alteration in any of these hematologic or biochemical parameters, which included leukocytosis (39.1%), leukopenia (34.8%), elevated alanine aminotransferase, thrombocytopenia (21.7%), prolonged erythrocyte sedimentation rate, lymphocytosis (17.4%), elevated aspartate aminotransferase (8.7%), elevated C-reactive protein, hematocrit, lactate dehydrogenase, and lymphopenia (4.3%).

## Treatment and Outcomes

Treatment, complications, need for hospitalization, and clinical outcomes data were retrieved and analyzed for the present manuscript (Table 4). From all reported cases, data regarding treatment (96.2% [*n* = 225]), complications (95.7% [*n* = 224]), need for hospitalization (82.9% [*n* = 194]), and clinical outcome (64.1% [*n* = 150]) were not reported in most of the cases. When information was available, supportive therapy with hydration and

**Fig. 2** Countries and regions where autochthonous cases of Mayaro fever have been reported. Countries in red are the ones in which cases of Mayaro fever occurred. Yellow dots refer to specific sites where one or more autochthonous cases of the disease were reported



**Fig. 3** Countries where imported cases of Mayaro virus infection have been reported and region where the disease was probably acquired. Countries in emerald green marked with a yellow cross refer to the patients' origin. Countries in red are the ones in which the infection may have acquired. Yellow dots refer to specific sites where

the infection may have acquired. Segmented lines with the figure of an airplane refer to the pathway from the probable site of infection to the site where the disease was imported. Asterisk (\*) symbol means two cases



**Table 2** Clinical features of Mayaro virus infection cases

Clinical feature	Total cases (%), <i>n</i> = 234
Fever	212/234 (90.6)
Arthralgia	149/234 (63.7)
Headache	144/234 (61.5)
Myalgia	117/234 (50)
Retro-orbital pain	111/234 (47.4)
Body pain	78/234 (33.3)
Nausea	62/234 (26.5)
Rash <sup>a</sup>	56/234 (23.9)
Chills	36/234 (15.4)
Hyporexia	36/234 (15.4)
Vomiting	35/234 (15)
Joint swollen	29/234 (12.4)
Sore throat	29/234 (12.4)
Abdominal pain	24/234 (10.3)
Diarrhea	16/234 (6.8)
Cough	15/234 (6.4)

<sup>a</sup>Maculopapular (7 cases); macular (2 cases); not specified (47 cases)

**Table 3** Laboratory findings of Mayaro virus infection cases

Laboratory features	Total cases (%), <i>n</i> = 234
In normal range (normal) <sup>a</sup>	111/134 (82.8)
With alterations (abnormal) <sup>a</sup>	23/134 (17.2)
↑ WBC	9/23 (39.1)
↓ WBC	8/23 (34.8)
↑ ALT	5/23 (21.7)
↓ PLT	5/23 (21.7)
↑ ESR	4/23 (17.4)
↑ Lym	4/23 (17.4)
↑ AST	2/23 (8.7)
↑ CRP	1/23 (4.3)
↑ Hct	1/23 (4.3)
↑ LDH	1/23 (4.3)
↓ Lym	1/23 (4.3)

*AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *CRP* C-reactive protein, *ESR* erythrocyte sedimentation rate, *Hct* hematocrit, *LDH* lactate dehydrogenase, *Lym* lymphocytes, *PLT* platelet count, *WBC* white blood cells

<sup>a</sup>One hundred cases were excluded due to missing data

anti-inflammatory drugs was administered in 88.9% of cases, and 11.1% did not receive any therapy; persistent chronic arthralgia and joint symptoms were reported as the only complications identified; most of the patients, 95% in total, did not require hospitalization, and only 5% were hospitalized during the course of their disease; and finally, total recovery was reported in all cases without any evidence of the fatal outcome.

**Table 4** Treatment, complications, need for hospitalization, and outcomes of Mayaro fever cases

	Total cases (%), <i>n</i> = 234
Treatment <sup>a</sup>	
Supportive therapy	8/9 (88.9)
No therapy	1/9 (11.1)
Complications <sup>b</sup>	
Chronic arthralgia and joint pain	10/10 (100)
Need for hospitalization <sup>c</sup>	
No	38/40 (95)
Yes	2/40 (5)
Clinical outcome <sup>d</sup>	
Recovery	84/84 (100)

<sup>a</sup>Two hundred twenty-five cases were excluded due to missing data

<sup>b</sup>Two hundred twenty-four cases were excluded due to missing data

<sup>c</sup>One hundred ninety-four cases were excluded due to missing data

<sup>d</sup>One hundred fifty cases were excluded due to missing data

## Discussion

MAYV is closest to becoming the next arbovirus of epidemiological importance, at least in the American continent [18]; it is necessary to know more about the pathogen and the disease it causes. The present review analyzed several epidemiological, clinical, and laboratory features among reported cases of Mayaro fever in scientific literature. The analysis revealed that more than half of reported cases were males, young adults, and middle-aged adults, which comprise the majority of the working-age population [44] in tropical rural areas, and are the leading group that is exposed to wild environments due to the economic activities performed in these regions [45]. Rural working activities in the tropics, such as agriculture, farming, and others performed in wild environments (e.g., forest workers, lumberjacks, biologists), have been identified as significant risk factors for the emergence of a wide range of zoonotic pathogens due to extensive land use change, livestock revolution increase, and human invasion of wild ecosystems, which lead to tropical deforestation and displacement of wildlife [46, 47]. Some of these working activities have been identified in the present review among patients with Mayaro fever, and leisure and fun activities related to ecotourism, such as camping, fishing, and butterfly hunting, have also been identified among cases of Mayaro fever. Ecotourism has critical ecological consequences; although activities related to ecotourism do not produce deforestation, human presence in natural environments disturbs the behavior of animals, affecting the structure of ecological communities favoring the contact human-wildlife, which represents a high-risk factor for the emergence of pathogens circumscribed to wildlife to

which humans have never been previously exposed, similar to what probably occurred with MAYV [48, 49].

Although MAYV was first isolated from human symptomatic cases in Trinidad and Tobago [12] and few probable and confirmed cases have been reported in countries of the Caribbean region such as Panama, Mexico, and Haiti [35, 50, 51], the present review identified that most of the reported cases had acquired the disease in the Amazon rainforest and surrounding areas of Brazil, Peru, and Venezuela. Furthermore, imported cases have also been identified among European travelers. They all got infected by MAYV while visiting some countries that form part of the Amazon rainforest (e.g., Bolivia, French Guiana, Surinam). Studies performed in the Amazon rainforest have identified that several arboviruses pathogenic for humans are actively circulating in this region, producing local outbreaks [52•], and incidence rates have increased in recent times due to extensive deforestation [53]. MAYV is usually circulating in a wild cycle within its sylvatic vectors. Several were wild animal species [54], but due to human invasion of wildlife, MAYV is in transition, adapting its biological cycle to an urban ecosystem; this virus may probably be linked to rural and urban autochthonous cases [55]. MAYV may adapt to urban and peri-urban mosquitoes, or the classical vectors change their habits and adapt to an urban ecosystem. In that case, MAYV may become urbanized, establishing and spreading in human settlements [56].

Since its emergence, Mayaro fever has formed part of the etiology of acute undifferentiated febrile illness (AUI), a syndrome caused by a broad range of pathogens which generate a fever of less than 2 weeks of duration accompanied by a great variety of non-specific signs and symptoms, in several regions of Central and South America [43, 57], being essential to understand its clinical presentation. Through the present review, 53 clinical manifestations were identified among reported cases of Mayaro fever, of which 36 were present in less than ten cases. They were not taken into account for the present review. Four of the remaining 17 clinical manifestations (fever, arthralgia, headache, and myalgia) were present in at least half of the cases, being the most frequent and relevant signs and symptoms of Mayaro fever. Among all clinical manifestations described, the development of abrupt fever, arthralgia or arthritis, and maculopapular rash have been described as a clinical triad highly indicative of Mayaro fever [9, 18]; however, this triad may not be helpful as through the present review. It has been identified that only fever and arthralgia are common clinical manifestations, and only less than one-quarter of patients develop any rash. Arthralgia is probably the most essential symptom that could help to suspect the disease.

The presence of joint manifestations in a febrile patient in the tropics is highly indicative of alphavirus infection (e.g., O'nyong-nyong virus, Sindbis virus), and in South America

and the Caribbean region, besides MAYV, CHIKV is another etiology that must simulate an arthritogenic AUI [58, 59]. CHIKV, along with DENV and ZIKV, are the main arboviruses worldwide whose diseases are of significance for the surveillance systems of a large number of countries across the globe, and for which, there are still many challenges to improve their control [5, 60]. Notwithstanding, there are several neglected arboviruses, such as MAYV, which importance remains underestimated. Several cases of Mayaro fever have probably been misdiagnosed as CHIKV due to similar clinical presentation and geographic distribution [61]. Cases of co-infection between MAYV and CHIKV are not rare and can occur [62••]; however, the correct diagnosis is not always performed due to the greater importance of CHIKV over MAYV for epidemiological surveillance systems [18].

Only narrative reviews have suggested that leukopenia and thrombocytopenia are the main laboratory alterations that could suggest a Mayaro infection [9, 63]. The present review is the first one in which the laboratory profile of MAYV infection was characterized, identifying that most cases had their biochemical and hematological parameters within normal ranges, probably due to the mild course of the disease [9, 64]. According to our analysis, if laboratory alterations occur, neither leukopenia nor thrombocytopenia could suggest Mayaro fever and do not help the clinical suspicion. Other altered laboratory parameters, such as prolonged erythrocyte sedimentation rate and elevated liver enzymes, have been identified among a few Mayaro fever cases, which have also been identified during the disease of other alphaviruses [65].

Finally, information regarding treatment, complications, and the need for hospital management was not available in more than three-quarters of reported cases; the authors probably considered this information irrelevant due to the mild course of Mayaro fever. However, available information regarding these topics confirms that Mayaro fever is a mild, self-limited disease. Even without supportive treatment, all patients have recovered completely without needing hospitalization in most cases, with chronic arthralgia the only complication reported in a few patients. Through this review, any fatal outcome due to MAYV infection has been identified; however, in Mexico, a likely fatal outcome due to encephalopathy caused by MAYV infection was reported [50]; nevertheless, evidence regarding its confirmatory diagnosis (positive ELISA IgM in convalescent serum sample without evaluation of other alphaviruses) is insufficient to be considered a Mayaro fever case, being probable that other not evaluated alphaviruses, such as Venezuelan encephalitis virus [66, 67] or even CHIKV [68], were linked to this fatal outcome.

Mayaro fever appears to be a mild self-limiting disease with underestimated importance due to its benign behavior; however, it is very likely that the true potential of MAYV

as a human pathogen is not fully elucidated, as was the case with ZIKV in the past, which was considered a mild and minor disease until cases of congenital malformations and neurodegenerative diseases were reported [69–71]. Thus, MAYV requires further studies to establish its true pathogenic potential and its importance within infectious diseases.

## Conclusions

The present review has identified that Mayaro fever is one of the causes of AUFI in several countries in South America and the Caribbean region, and the Amazon rainforest is the main endemic region in which MAYV is actively circulating. Males at productive age are the higher-risk group due to the economic activities performed in rural areas, such as agriculture and farming. Moreover, leisure activities related to ecotourism are also crucial for acquiring the disease in endemic areas, and imported cases of Mayaro fever in other regions are essential travel medicine diseases. Clinically, it forms part of the etiology of AUFI in South America and the Caribbean region; however, the presence of fever, arthralgia, headache, and myalgia could give a slight suspicion of the disease. Laboratory parameters are usually normal, and when alterations occur, none of them can help to reach the diagnosis or at least suspect Mayaro fever. Fortunately, to date, MAYV is a mild AUFI that can even be self-limited without needing any supportive therapy or hospitalization; however, few patients can develop chronic arthralgia without compromising their life.

**Author Contribution** Conceptualization: C.R.S.-R. and Á.A.F.-M.; writing and preparation of original draft: C.R.S.-R.; writing including review and editing: C.R.S.-R., J.A.M.-F., M.H., A.J.R.-M., and Á.A.F.-M.; visualization: J.A.M.-F.; supervision: Á.A.F.-M. All authors have read and agreed to the published version of the manuscript.

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## Compliance with Ethical Standards

**Competing Interests** The authors declare no competing interests.

**Human and Animal Rights and Informed Consent** This article does not contain any studies with human or animal subjects performed by any of the authors.

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