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Emergent Arboviruses: A Review About *Mayaro virus* and *Oropouche orthobunyavirus*

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Arthropod-borne viruses have a significant impact on public health worldwide, and their (re) emergence put aside the importance of other circulating arboviruses. Therefore, this scoping review aims to identify and characterize the literature produced in recent years, focusing on aspects of two arboviruses: *Mayaro virus* and *Oropouche orthobunyavirus*. The Mayaro and Oropouche viruses were isolated for the first time in Trinidad and Tobago in 1954 and 1955, respectively, and have more recently caused numerous outbreaks. In addition, they have been incriminated as candidate diseases for human epidemics. These viruses have been drawing the attention of public health authorities worldwide following recent outbreaks. To determine the global epidemiological profile of these viruses, we used the Dimensions Database, which contains more than 100 million publications. In general, we identified 327 studies published from 1957 to 2020 for *Mayaro virus*, and 152 studies published from 1961 to 2020 for *Oropouche orthobunyavirus*. Interestingly, we observed that Mayaro and Oropouche had a significant increase in the number of publications in recent years. Thus, this comprehensive review will be helpful to guide future research based on the identified knowledge gaps.

Keywords: arbovirus, neglected diseases, arthropod-borne diseases, tropical disease, public health

INTRODUCTION

New pathogens, vectors, and diseases are constantly discovered; which is therefore applied the concept of "emerging disease" (1, 2). In this context, the arthropod-borne viruses (arboviruses) stand out due to their explosive global distribution, transmission capacity, close relationship with changes in the environment, and human behavior (3). However, even though arboviruses infect millions of humans and other animals and cause great economic impact on public health worldwide, most remain neglected. These viruses correspond to an extensive group of viral vector borne infections, for example the *Dengue virus* (DENV), *Zika virus* (ZIKV), and *Chikungunya virus* (CHIKV) viruses that are globally spreading (4). The (re)emergence of these "already known" pathogens put aside the importance of other lesser known circulating arboviruses, such as *Mayaro virus* (MAYV) and *Oropouche orthobunyavirus* (OROV). The first one was isolated in Trinidad and Tobago (1) and quickly spread outside its original geographical range because of its

vector's vast distribution and competence. In addition, this virus has drawn the attention of public health authorities worldwide following recent outbreaks in the Americas (5).

Lastly, OROV is a poorly studied pathogen responsible for some outbreaks since the early 1960s, representing a public health burden to Brazil, Panama, and Peru (6). Therefore, this review aims to summarize the state of the entomo-epidemiological literature about these two arboviruses, gathering the information published in recent years, focusing on the virus and vector dispersion, symptoms, and clinical issues.

METHODS

Search and Data Management Process

The present review was performed on the Dimensions Database (Digital Science and Research Solutions Inc.), which contains more than 100 million publications available to consult. Our research has been composed of two Phases: I) The first group of documents was accessed using the following inclusion factor criteria/keywords: 'Mayaro Virus' in the title and abstract + Publication Year: 1957-2020; and 'Oropouche Virus' in the title and abstract + Publication Year: 1961-2020. In addition, all documents published were considered; Open and Closed Access; Publication Type: Article, Preprint, Chapter/Thesis, and Proceeding.

Thus, the search results composed a database in electronic spreadsheets (Google Sheets) related to each keyword and organized by Title, DOI, Type and Year of Publication, Authors, and Abstract. Following that, the results were analyzed, and the second and final phase was subsequently applied. II) In this phase, we performed a filtered analysis considering the following exclusion criteria: Any data not covered by the date range of MAYV (1957–2020) and OROV (1961–2020); any study that was not in the English language; any document that was not a Scientific Article (except Letter to Editor, Editorial, Note, Short Communication, Etc.); any duplicated file; any article which did not present at least one piece of information about viral biology, epidemiology (virus/vector distribution), clinical manifestations and disease prevention/treatment in its abstract.

RESULTS

The scope of this review included studies focused on different aspects of two arboviruses: MAYV and OROV. As a result of Phase I, a constant, although low, number of publications were observed for MAYV between 1957 and 2009, with no more than five documents published per year. Subsequently, the numbers of reports fluctuate until 2016, followed by an exponential upward curve that peaked in 2019, with more than 60 documents (**Figure 1**). Those papers were mainly published in open access platforms, with emphasis on articles (n= 295), followed by preprints (n= 17), chapters (n= 10), proceedings (n= 5) and edited books (n= 1) (**Figure 2**).

The lowest number of documents was observed for OROV, rarely exceeding five documents per year from 1961 to 2014. From 2015, the number of documents rose significantly, reaching a peak in 2017 with 16 documents (**Figure 3**). Among those reports, we retrieved articles (n= 134), chapters (n= 12), preprint (n= 4) and proceedings (n= 2) (**Figure 4**).

As a result of Phase II (**Table 1**), after applying all of the predefined filters, we obtained a total of 168, and 82 articles for MAYV and OROV, respectively. Despite the lower number for filtered OROV data, the scientific content was rich, which provided an interesting discussion. Curiously, despite OROV first being isolated in 1955, the first article was published only six years later. Below, we present our review of the compiled data.

Mayaro Virus
Virus Information
Jordi Casals and Whitman described MAYV as a representative of the *Alphavirus genus*, belonging to the *Togaviridae* family (1, 7, 8), and it has been isolated in the 1950s by Charles Anderson
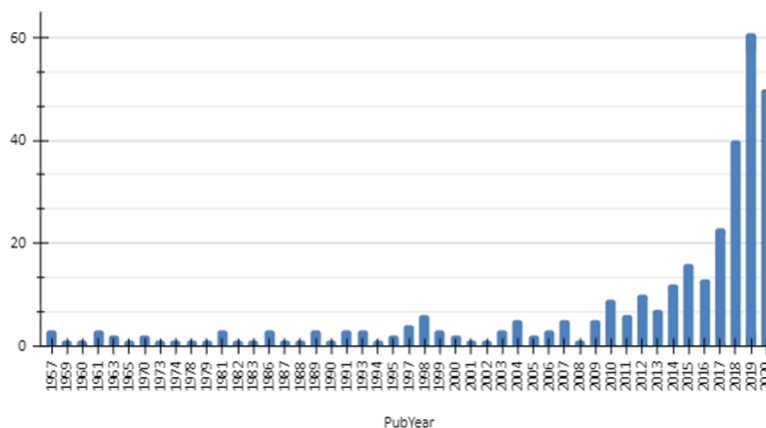

FIGURE 1 | Graphical representation of the number of documents published about MAYV by year from 1957 to 2020 resulted from a search performed at Dimensions.io Database and exported on Jan 15, 2021.
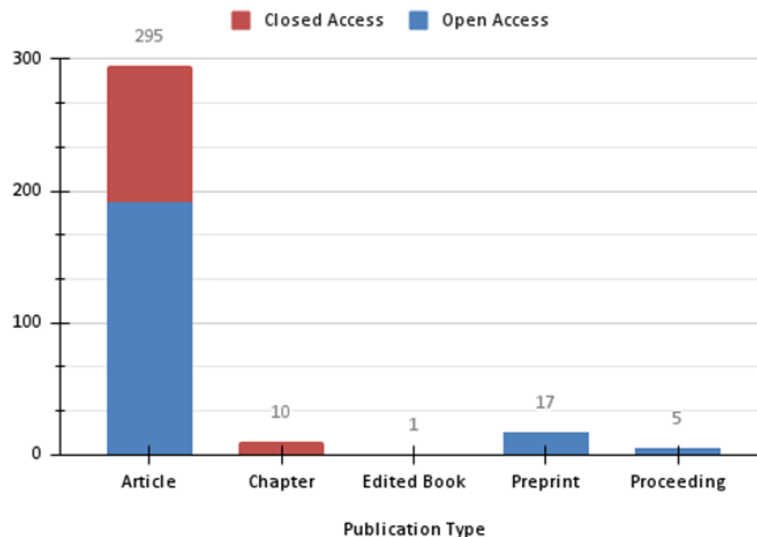
FIGURE 2 | Graphical representation of the number of documents published about MAYV by type and access platform resulted from a search performed at Dimensions.io Database and exported on Jan 15, 2021.
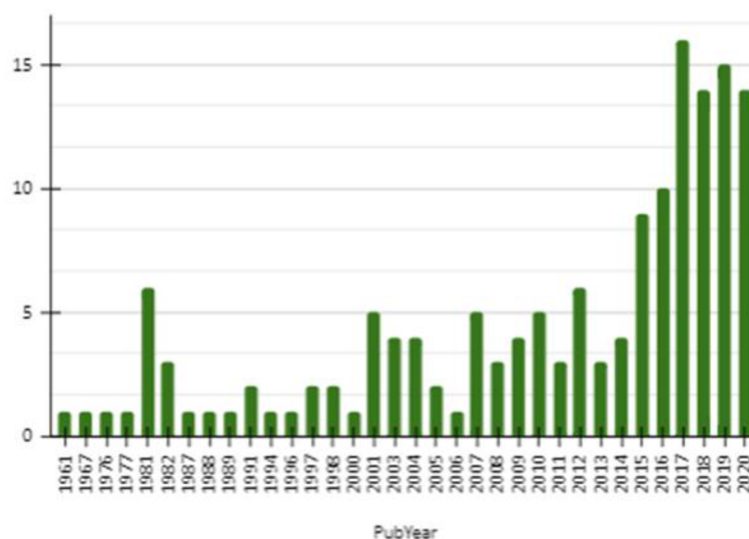

FIGURE 3 | Graphical representation of the number of documents published about OROV by year from 1961 to 2020 resulted from a search performed at Dimensions.io Database and exported on Jan 15, 2021.

from rural workers in Trinidad Island. It has three identified genotypes (D, L, and N), and the virus comprises a simple RNA strand with positive polarity, with a genome sequence of approximately 11.5 kilobases (kb).

In general, the life cycle of MAYV is poorly known and needs further study. However, some aspects of its life cycle are like several arthritogenic alphaviruses. The cycle starts with the fusion of the viral envelope and the target cells' plasma membrane *via* specific receptors on their surface. After that, the virus invades the cell and

reaches the cytoplasm simultaneously when the pH of the endosome decreases (9).

Subsequently, the basic virus structure is disassembled, and the genomic RNA is released and translated into nonstructural proteins, which generate messenger RNA and various structural proteins (5). Finally, it generates the nucleocapsid, and its glycoproteins, combined with the plasma membrane, lead to the release of new viral particles outside the cell (5). The released viral particles can then infect new cells and start their cycle again.
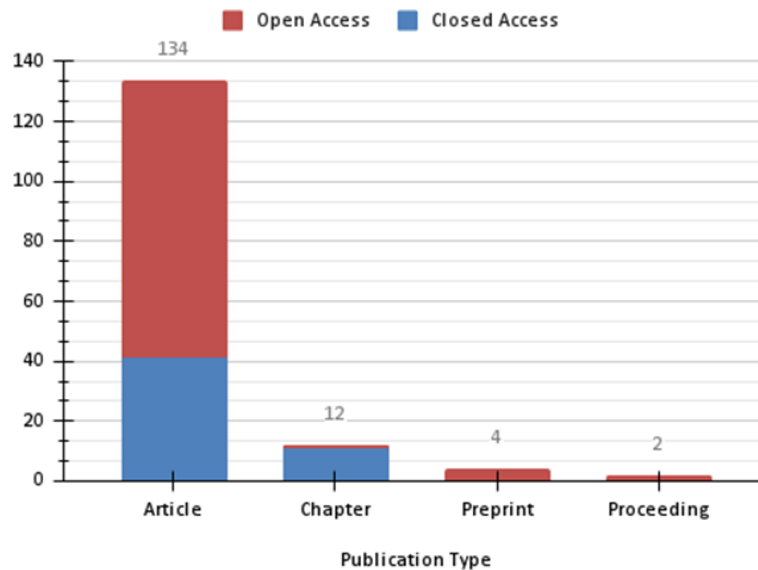
FIGURE 4 | Graphical representation of the number of documents published about OROV by type and access platform resulted from a search performed at Dimensions.io Database and exported on Jan 15, 2021.

In addition, the MAYV presents remarkable genetic plasticity due to the high rate of mutation, which increases the likelihood of adaptation to new hosts, both vertebrates and invertebrates (10).

Vectors and Reservoir Hosts

The primary vectors of MAYV are mosquitoes belonging to the genus *Haemagogus* (11, 12), while the secondary vectors may vary between different genus like *Culex* sp., *Sabethes* sp., *Psorophora* sp, *Coquillettidia* sp. and *Aedes* spp (8, 13). Furthermore, in a laboratory-controlled environment, studies show that mosquitoes such as *Ae. aegypti, Ae. albopictus, Anopheles* spp. and *Cx. quinquefasciatus* can also harbor and transmit MAYV (14–18). Considering the potential of those mosquitoes playing a role as vectors for MAYV, the importance of this virus in urban areas is increasing.

The MAYV seropositivity in different vertebrates such as arboreal mammals, birds, and even alligators, has already been demonstrated. Reports of this range of potential hosts indicates replication and circulation of the virus, which is likely using them as reservoirs (19). In addition, birds, marsupials, and rodents combined with primary and secondary vectors further increase the chances of spreading the virus (20–22).

Geographic Distribution

After the first report, it was suggested that MAYV could be restricted to forest areas in the tropical region of South and Central America. However, over the years, many countries such as French Guiana, Bolivia, Peru, Suriname, Trinidad, Tobago, Argentina, Colombia, Caribbean, Venezuela, and Brazil have reported cases of MAYV (1, 23–25). Furthermore, in 2015, the virus was disclosed in an outbreak in Venezuela. Recently, the presence of the virus was recorded in two new Brazilian states: São Paulo and Rio de Janeiro (26), indicating that the virus continues to spread. In the wild cycle, MAYV is kept in a similar way as the sylvatic cycle of YFV, being transmitted mainly by mosquitoes of the genus *Haemagogus* (12). However, it is believed that MAYV can also be transmitted by secondary vectors, since the isolation of MAYV from other Culicidae species such as *Aedes, Culex, Psorophora, Coquillettidia, Sabethes*, and *Haemagogus* spp. has been reported (11, 13, 27).

Regarding the MAYV genotypes, until now, three genotypes (D, L, and N) have already been identified. The genotype D has a wide geographical distribution, occurring in Brazil, and other countries such as French Guiana, Bolivia, Peru, Surinam, Trinidad, Tobago, Argentina, Colombia, and Venezuela (28–30). On the other hand, the L genotype has a more limited distribution and has being described in Haiti and Brazil (27, 29). Lastly, the N genotype was first reported in 2015 in Venezuela (28).

The relevance of MAYV as a human pathogen and its potential for emergence in urban areas is of great concern, for example, Lorenz et al. (31), highlighted that environmental variations, mainly due to global warming, may contribute in the coming years to expand the distribution of MAYV. Furthermore, population growth, demographics, and other factors combined with the vectorial competence of different species of mosquitoes suggest that MAYV infection can reach an even larger scale in a short time, along with other arboviruses.

TABLE 1 | Summary of the number of documents analyzed in each phase.

	MAYV	OROV)
Total Raw Metadata (Phase I)	327	152
Total Cleansed Data (Phase II)	168	82

MAYV has already been registered in different parts of the world in isolated cases or small outbreaks, which indicates that the virus continues to spread. In this context, a significant number of published articles have arisen since this virus obtained greater visibility, both in the media and the scientific environment. Another factor contributing to the spread of the virus may be related to negligence towards this disease and its suspected and confirmed vectors, such as mosquito *Ae. albopictus*. In the last years, this species has been highlighted in studies which presents its ability to play a role as a potential bridge between the sylvatic and urban cycles of several arboviruses (32–35).

Clinical Aspects

To date, few studies are available on MAYV infection, and those which are provide a favorable general clinical aspect. However, inflammation and joint pain can persist for a long time, limiting or incapacitating the infected person. In general, the symptoms are very similar to those of other arboviruses; for this reason, MAYV is often misdiagnosed (8, 19, 23, 24, 36, 37). In humans, MAYV is considered an accidental infection and presents a greater risk for individuals who developed activities inside or close to forests. MAYV infection is not fatal, and its symptoms resemble those of DENV and CHIKV, causing an acute and self-limiting febrile illness with a short viremic period.

When in the viremic phase, the infected individual may have a viral amount of RNA (detected by RT-qPCR) between $2.7{\times}10^2$ and $1.9{\times}10^5$. For CHIKV (virus close-related to MAYV), symptomatic individuals present between $1.3{\times}10^1$ and $2.9{\times}10^8$ pfu/mL. Individuals infected with MAYV and/or CHIKV, presenting the described titers, may be potential disseminators of the virus (27, 38, 39).

The acute phase of the disease lasts for 3-5 days and includes fever, headache, eye pain, rash, myocarditis, hemorrhagic and neurological manifestations (37, 40, 41). Arthralgia and myalgia account for 50–89% and 75% in infected patients, respectively. The arthralgia can be accompanied by joint swelling, which is the main symptom in severe infection that occasionally persists for several months, incapacitating the patient (24, 42).

In addition, severe cases can present encephalitis (inflammation in the brain), although the disease is self-limiting in most cases, with the symptoms disappearing within a week (23, 37). Since 2011, the Brazilian Ministry of Health has included MAYV as a compulsory notification disease within the National Health System (Ministério da Saúde, Portaria N°104, de 25 de Janeiro de 2011).

Diagnostic and Treatment

Neutralization and reverse-transcription polymerase chain reaction (RT-qPCR) tests are now available in most laboratories and can help to confirm MAYV infection (43). Molecular studies have advanced towards the detection of MAYV in plasma and urine samples with promising results, being a potential tool for diagnosis of patients with MAYV (44). Currently, the absence of a specific test for diagnoses contributes to the underreported number of cases. Furthermore, since the diagnosis is mainly based on symptoms, the infection can be easily misdiagnosed with other arboviruses, such as CHIKV, DENV, and ZIKV infections, due to the possible co-circulation of these viruses in the same area (10, 23, 30).

In this sense, we must consider other factors that limit MAYV diagnosis, as the possibility of cross-reaction, in particular with CHIKV and *O'nyong-nyong virus* specific antibodies and the high prevalence of asymptomatic cases, thus underestimating the number of cases (25, 40, 45). In addition, it is important to mention that cross-reactivity for both MAYV with ZIKV and CHIKV has already been reported in Zambia (46). Furthermore, to date, there is no vaccine or specific therapy for this illness, although there are studies working towards vaccine development (47, 48).

Oropouche orthobunyavirus
Virus Information

OROV is a member of the *Peribunyaviridae* family, *Orthobunyavirus* genus, and is part of the Simbu serogroup. OROV is an emerging virus that causes a Dengue-like illness known as Oropouche fever. It is an enveloped virus with a tri-segmented single-stranded negative-sense RNA genome, typical of the *Orthobunyaviruses* (49). The large segment (L) encodes the viral RNA-dependent RNA polymerase. The medium segment (M) encodes a polyprotein originating the envelope glycoproteins and the nonstructural protein (NS). Additionally, the small segment (S) encodes the nucleocapsid protein that protects viral RNA from degradation (49, 50).

In this context, OROV NSm and NSs proteins have started to be exploited by the generation of OROV recombinant viruses (51–54). In addition, Aquino et al. (55), described the complete nucleotide sequence of the OROV L RNA segment. OROV can interchange segments of RNA with other strains through genetic reassortment, which is common in viruses with segmented genomes, allowing the incorporation of genes and development of novel virulent viral strains (36, 56), such as Iquitos Virus (36) and Jatobal (57). These reassorted strains together with the "original strain" are the only zoonotic virus of the Simbu serogroup present in South America. The genome of these reassortment viruses contains an L and S segment from OROV and an M segment from an unknown virus. Since the M segment encodes for viral attachment and entry proteins, it could potentially change the virus tropism and expand the host range of OROV (58).

Studies on the molecular biology of the OROV small RNA segment have suggested its monophyletic origin and the existence of at least three genotypes (I, II, and III) (57). In addition, Vasconcelos et al. (59) suggested that OROV emerged in Brazil ≈223 years ago. Furthermore, based on the N gene analysis, these authors suggested that genotype I was responsible for the emergence of all other genotypes and virus dispersal, besides the observed distinct patterns of OROV strain clustered according to each RNA segment (59). However, their results suggest that each has a different evolutionary history and that the classification in genotypes must consider each particularity.

Vectors and Reservoir Hosts

Studies have suggested that South and Central America OROV has two distinct transmission cycles: sylvatic and urban. In the first, the transmission occurs between its insect vectors and wild

host such as birds and mammals like *Proechimys* sp., *Bradypus tridactulus, Allouatta caraya*, and *Callithrix penicillata* (50, 60, 61). During this cycle, the virus is transmitted by vector culicids such as *Aedes serratus* and *Coquillettidia venezuelensis*, from which OROV has been isolated in the Brazilian Amazon region and Trinidad, respectively (62–64, 66).

In contrast, the urban cycle involves humans as the only vertebrate hosts, excluding domestic animals (66), and hitherto uncertain mosquito species. In this cycle, the role of *Culicoides paraensis* (Goeldi) as a main vector has been supported by experimental and epidemiological data (50, 63). Besides that, anthropogenic actions on forest areas and the presence of *C. paraensis* in urban areas can facilitate the vector's contact with humans (67–71).

Additionally, laboratory settings have shown the susceptibility of culicids species such as *Aedes scapularis, Aedes albopictus, Culex fatigans,* and *Psorophora ferox* to OROV (58). Mendonça et al. (72) recently showed that OROV is restricted by the midgut barrier of *Ae. aegypti, Ae. albopictus,* and *Cx. quinquefasciatus* in a laboratory-controlled environment. However, the authors highlight that if this restriction is overcome, OROV could be efficiently transmitted to vertebrate hosts. In this context, besides *Cx quinquefasciatus* having been frequently detected with OROV during outbreaks (73), to date, it appears to have a low efficiency as a vector for OROV.

The link between the sylvatic and urban cycles is probably due to humans entering the forests, becoming infected, and returning to urbanized areas (63). Additionally, it is essential to mention that wild and domestic birds have tested positive for OROV antibodies during outbreaks, but their importance to OROV spread remains to be determined (58).

Geographic Distribution
OROV is an endemic virus which was isolated in 1955 in Trinidad and Tobago from a pool of *Coquillettidia venezuelensis*. Simultaneously, antibodies against OROV were detected in a 24-year-old male field worker and non-human primate. All of these discoveries were in 1955, with data from a village called Vega de Oropouche on the Oropouche river from which the virus acquired its name (64, 65). This virus has caused several outbreaks, mainly in Brazil, the Amazon region, Panama, and the Caribbean (50, 52, 68, 73, 74).

Other South American countries also faced the presence of OROV, such as Ecuador (Guayaquil) (10, 75); Peru (Martin, Santa Clara, Cajamarca, Cusco, Yurimaguas, Madre de Dios, Iquitos - Loreto, Bagazan-Pachiza, Huánuco, Leoncio Prado, Puerto Maldonado (62, 76–79), Panama (Chame/San Miguelito, Bejuco, Chilibre), Venezuela, Argentina and Bolivia (64, 73, 78, 79). Given the current situation of OROV, it is possible to note the silent expansion of this virus.

Clinical Aspects
It is estimated that 63% of OROV infections are symptomatic (36, 56, 67). The most common clinical symptoms reported among the patients with OROV infections are acute febrile, headache, myalgia, arthralgia, malaise, photophobia, exanthema, polyuria, anorexia, dizziness, chills, joint pain (64), retro-ocular pain, hypoxia (79),

muscle pain and skin rash. In addition, many infections develop into meningitis or encephalitis (69), as well as spontaneous bleeding (in rare cases: petechiae, epistaxis and gingival bleeding) and aseptic meningitis (66).

Most of these clinical symptoms are observed in around 60% of patients resembling classical arboviral infection and highlighting the importance of laboratory diagnostic tests (65), being challenging to diagnose and distinguish from other co-occurring infectious diseases (80).

In addition, it was not uncommon to find studies reporting the identification of OROV in patients with suspected other viral infections, as well as co-infections with DENV, ZIKV and CHIKV (77). Simultaneous co-infection with two or three different viruses alters the immune response but does not imply more clinical severe symptomatology than single viral infections (81). Specifically, in the Peruvian region, OROV infections and co-infections were more frequent in May, June, and July, corresponding to the region's dry season (77).

In the Amazon region, OROV infections are challenging to distinguish from undifferentiated febrile illness associated with group C *Orthobunyaviruses* or Candiru complex. Furthermore, the symptoms present no differences even in patients with co-infections between different arboviruses (82), and they can reappear one or two weeks after recovery in about 60% of the patients. Additionally, there are reports of patients that showed hemorrhagic symptoms or neurological complications associated with OROV infection (50, 67, 77).

Although fatal cases have not been reported, OROV is known for causing dramatic human epidemics (83). In addition, it is essential to mention that the segmented nature of the OROV genome enhances the likelihood of genome reassortment events. This phenomenon has been associated, in some cases, with a significant increase in disease severity to other viruses (84).

Diagnostic and Treatment
The epidemiological surveillance of OROV is based on detecting the virus genome in the plasma/sera of acutely infected patients or by specific IgM serology during convalescence (50, 55, 57, 64, 85). However, despite genome detection by PCR or RT-qPCR being considered a high-quality detection test, the cost is still high. As an alternative, recent studies have shown arbovirus detection using other body fluids, such as saliva and urine. For example, Naveca et al. (83) found a higher viral load in urine, as suggested by the lower Ct value observed in this specimen, in comparison with results from saliva or plasma.

There is no specific treatment for OROV, only primarily supportive care like prevention and treatment. Adhikari et al. (86) showed novel candidates for epitope-based peptide vaccine design against OROV. Furthermore, they predicted the 3D structure of the most antigenic polyprotein and inhibitor-binding sites for the docking simulation study using various bioinformatics tools.

CONCLUSION

Infectious diseases have a considerable impact on human, animal, and plant health, causing significant morbimortality

and placing a costly burden on global economies. Moreover, arboviruses have become critical threats worldwide due to rapid climatic and geographical changes in urban and peri-urban areas (87). In addition, in many cases, the precarious health conditions favor the reproduction of vectors and, consequently, viral amplification and transmission.

MAYV infection in humans has mainly been reported in rural areas. However, the virus has been registered in urban areas in recent years, making the disease more evident. Given the circumstances and their new worldwide records, it is crucial to monitor the evolution of MAYV since this virus can establish an epidemic scenario, as happened with other viruses such as ZIKV and CHIKV. Currently, the literature reports that *Ae. aegypti* mosquitoes are susceptible to MAYV infection and are potential candidates for the urban life cycle. However, it is essential to emphasize the role of *Ae. albopictus;* this vector can serve as a secondary vector in an outbreak or as a bridge vector between the MAYV or another arbovirus.

Although the MAYV has been neglected for many years and its biology remains poorly understood and largely inferred from related alphaviruses, studies have progressed and for the first time in Latin America, researchers have managed to elucidate the complete molecular structure of MAYV (88). Another critical point is the lack of studies on vaccine development, antiviral treatment, and specific diagnostic tests since the symptoms can be easily confused with other arboviruses.

OROV fever is an emerging and endemic zoonotic disease from some South and Central American areas, with an acute and self-limiting febrile condition. It has long been a neglected disease even though it has infected many people (more than half a million). Although OROV represents a public health concern to some countries, this virus is still poorly studied, and one of the factors that may contribute to the absence of studies on OROV is an underreporting, since its symptomatology can be easily confounded with other febrile illnesses.

The spread of OROV is related to environmental factors, including climate, fauna, and flora changes. For example, Romero Alvarez et al. (62) reported an OROV outbreak in southeastern Peru, where a loss of vegetation was observed at the outbreak site. Indeed, environmental changes, climate and socioeconomic factors could shortly cause the translocation of OROV, as has already been seen for other pathogens. Consistent with climate change, in the case of Culicoides, rising temperatures favor vector spread (89). Like the other viruses mentioned here, there is no vaccine for OROV besides supportive treatment.

The emergence and distribution of vector-borne diseases is a consequence of the disturbance of the ecological balance, which is observed worldwide and to minimize this disturbance, vector control/arbovirus methodologies have emerged in recent years. Although the vector control programs are the best way to reduce vector and the mosquito-borne diseases, the results have not been satisfactory as well as the use of chemical control, which is the most commonly used method in recent times.

On the other hand, some new techniques for urban vector have called attention, for example, the use of the sterile insect technique, which involves the rearing and release of thousands of male mosquitoes carrying a lethal gene for its offspring. The other alternative control method involves the release of *Wolbachia*-carrying mosquitoes for blocking vector-borne pathogens. Studies showed that the introduction of *Wolbachia* into *Ae. aegypti* populations was effective in reducing the incidence of more than 60% of DENV and CHIKV and it is important to emphasize that this is a natural and self-sustaining technique (90–92).

Finally, this review intended to alert public health authorities worldwide to the importance of studies around viruses and their interactions with different vectors, improved methods for the differential diagnosis of arboviruses, mainly to MAYV and OROV, which are diseases that are commonly confused in epidemic outbreaks with other arboviruses. Another essential point that must be prioritized is the integration of different vector control methods, besides the development of vaccines.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material. Further inquiries can be directed to the corresponding author.

AUTHOR CONTRIBUTIONS

TP, FV, and JS contributed to the draft manuscript's conception, design, and writing. LM supervised the research and edited the final version of the manuscript. All authors have read and agreed to the published version of the manuscript.

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