

GloPID-R report on chikungunya, o'nyong-nyong and Mayaro virus, part 3: Epidemiological distribution of Mayaro virus

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GloPID-R report on chikungunya, o'nyong-nyong and Mayaro virus, part 3: Epidemiological distribution of Mayaro virus

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1. Introduction

Mayaro virus (MAYV) is a mosquito-borne alphavirus (family *Togaviridae*), transmitted mainly by *Haemagogus* species in the American continent. The first MAYV strains were isolated from the blood of infected, symptomatic humans in Trinidad and Tobago in 1954 (Anderson et al., 1957). Since then, MAYV was repeatedly detected in humans and mosquito vectors in Central and Southern America (Mackay and Arden, 2016; Acosta-Ampudia et al., 2018). Two unique reports from Haiti raises the issue of circulation in the Caribbean and requires further confirmatory investigations (Lednicky et al., 2016; White et al., 2014). MAYV is transmitted by *Haemagogus* species in an enzootic cycle using non-human primates (NHPs) as the main amplification and maintenance hosts, and humans becoming sporadically infected when venturing in or nearby forest habitats. Currently, three MAYV genotypes have been described (namely: D, L and N).

MAYV shares with other arboviruses, in particular the related chikungunya virus (CHIKV), a clinical presentation typically characterized by fever, headache and rash during the acute case, together with a polyarthralgia that can persist for months or even years (Mackay and Arden, 2016; Hassing et al., 2010; Halsey et al., 2013; Thiberville et al., 2013; Heath et al., 2018; Taylor et al., 2005). This makes accurate diagnosis based on clinical presentation difficult and it is expected that cases of MAYV infection are being misdiagnosed and/or underreported because of the massive circulation of CHIKV (or even dengue virus (DENV), Zika virus (ZIKV) and oropouche virus (OROV)) in the Americas in recent decades. Laboratory testing is necessary for differential and confirmed diagnosis. Cross-reactivity between antibodies against MAYV and those against related alphaviruses such as CHIKV exist and can lead to a difficult interpretation of serological results (Paniz-Mondolfi et al., 2016; Pezzi et al., 2019).

2. GloPID-R chikungunya (CHIKV), o'nyong-nyong (ONNV) and Mayaro virus (MAYV) Working Group

This work has been accomplished by experts of GloPID-R (Global Research Collaboration for Infectious Disease Preparedness, www.glopid-r.org) chikungunya (CHIKV), o'nyong-nyong (ONNV) and Mayaro virus (MAYV) Working Group. The interest of this group is focused on the natural history, epidemiology and medical management of infection by these viruses, in order to identify knowledge gaps and to propose recommendations for direct future investigations and rectification measures. Here, the experts of the GloPID-R Working Group performed an assessment of the available information regarding the epidemiological distribution of MAYV. This work complements other previous or ongoing reports of the GloPID-R Working Group on chikungunya, o'nyong-nyong and Mayaro virus epidemiology (submitted paper, under review), diagnosis (Taylor et al., 2005), ecology (submitted paper, under review) and clinics.

3. Sources of data

Data from the first virus isolation until December 2018 were collected, including both acute cases in humans (confirmed by RT-PCR and/or presence of IgM) as well as results of serological studies showing past infections in humans (presence of IgG).

Data on MAYV infections were obtained from health organizations and the peer-reviewed literature concerning all the New World countries.

To identify MAYV cases in humans, firstly we consulted different public health alert systems and websites, including:

World Health Organization (WHO) - 'Disease outbreak news (DON)' section
Program for Monitoring Emerging Diseases (ProMED);
European Centre for Disease Prevention and Control (ECDC) through 'Communicable disease threats report (CDTR)';
Institute of health of each American country, through periodic bulletins on viral infections (when available).

A comprehensive review of literature on PubMED was conducted using the search terms 'mayaro virus' and the name of each American and Caribbean country. Finally, viral sequences available in GenBank were checked, in order to assess the countries where MAYV-positive human samples were collected. The lineage of MAYV strains (D, L or N) is indicated in Tables 1–5 of Supplementary data according to information present in GenBank or in articles linked to the viral sequence; otherwise, it was defined through phylogenetic reconstruction.

In the article and in Supplementary data we reported details about MAYV detection: number of cases, year, localization and technique(s) used to confirm the infection. We classified the sources of our data in 6 categories:

Declared outbreaks
Single case reports (mainly about returning travelers)
Surveillance studies, aiming to identify the etiology of acute illnesses confirmed by PCR and/or serology
Serosurveys (to evaluate previous exposure to the virus, confirmed by serology)
GenBank sequences, present on the database without additional information on the isolated strains
Annual report from health authorities.

In this report, experts provided a picture of MAYV geographic spread through Americas; they identified gaps of knowledge and proposed recommendations in order to suggest research priorities in the field.

4. MAYV distribution

An account of the epidemiological findings about MAYV human cases is shown below. Further details are presented in Tables 1–5 of Supplementary data (Central America, Caribbean, Brazil, Peru and rest of South America).

4.1. Central America

4.1.1. Mexico

4.1.1.1. Surveillance study. The study was performed on patients with probable diagnosis of DENV in 2001 (Navarrete-Espinosa and Gómez-Dantés, 2006). 2 cases were found positive with ELISA IgM, one from northern Mexico (Tamaulipas state), the other from western Mexico (Veracruz state).

4.1.2. Panama

4.1.2.1. Serosurvey. Serosurvey conducted retrospectively on samples collected during the construction of canals in Panama and Colombia in 1904–1914 (Srihongse et al., 1973).

4.1.2.2. Surveillance study. During an encephalitis outbreak in 2010, a household study was performed testing sera for several arboviruses (Carrera et al., 2018). One case was positive with ELISA IgM in Darien region (southern Panama).

4.2. Caribbean

4.2.1. Haiti

4.2.1.1. Case report. One MAYV strain isolated in 2014 from a patient co-infected with CHIKV living in rural Haiti (White et al., 2014).

4.2.1.2. Case report. Acute case confirmed in 2015 by virus isolation in a patient living in the western part of Haiti (Lednicky et al., 2016).

4.2.1.3. Outbreak (NOT CONFIRMED). Febrile undiagnosed fever suspected of being caused by MAYV in 2018 according to clinical presentation, not supported by biological evidence (ProMED: 20180909.6018117).

4.2.2. Trinidad and Tobago

4.2.2.1. Outbreak. First isolation of MAYV during an outbreak of febrile illness in 1954 (Anderson et al., 1957).

4.2.2.2. GenBank sequence (no additional information). 2 MAYV strains isolated in 1957, both belonging to genotype D. GenBank accession numbers available in Table 2-Supplementary data.

4.3. Brazil

4.3.1. Outbreak

A MAYV outbreak was detected in Pará state, northern Brazil, among forest workers (Causey and Maroja, 1957). 6 MAYV strains were isolated.

4.3.2. Serosurvey

Antibodies against MAYV were detected in sera from Indians living in the Amazon Basin in Mato Grosso state when tested with HI test in 1963–1964 (Neel et al., 1968).

4.3.3. Serosurvey

Sera from military troops in different areas of the country were tested by HI and VNT in 1964 (Niederman et al., 1967). 1% of samples was positive for antibodies against MAYV.

4.3.4. Serosurvey

The survey was performed on sera collected from tribes living in the Amazon Basin, Brazil (Black et al., 1974). Sera were tested by HI test, with 42% of positive rate.

4.3.5. GenBank sequence (no additional information)

Two MAYV strains isolated in 1970, both belonging to genotype D. GenBank accession numbers available in Table 3- Supplementary data.

4.3.6. Outbreak

MAYV outbreak was detected in a small village in Pará state, northern Brazil, in 1977–1978 (Pinheiro et al., 1981; da Rosa et al., 1981). It was estimated that 20% of the 4000 inhabitants were infected.

4.3.7. GenBank sequence (no additional information)

3 MAYV strains isolated in 1981, all belonging to genotype D. GenBank accession numbers available in Table 3- Supplementary data.

4.3.8. GenBank sequence (no additional information)

2 MAYV strains isolated in 1984–1988, both belonging to genotype L. GenBank accession numbers available in Table 3- Supplementary data.

4.3.9. GenBank sequence (no additional information)

6 MAYV strains isolated in 1991. 5 belong to genotype D, one to genotype L. GenBank accession numbers available in Table 3- Supplementary data.

4.3.10. Case report

Three MAYV cases were detected in the state of Mato Grosso, western Brazil, in 2000 (Coimbra et al., 2007). Samples were tested by haemagglutination inhibition test (HI).

4.3.11. Case report

The infection was acquired in Acre state, north western Brazil, in 2004 and detected by PCR (Terzian et al., 2015).

4.3.12. Surveillance study

Survey of acute febrile illness in Manaus, northern Brazil, in 2007–2008 (Mourão et al., 2011). 33 cases were confirmed by ELISA IgM, and in one of them viral genome was detected by PCR.

4.3.13. Outbreak

The outbreak was detected in a very small village in Pará state, northern Brazil, in 2008 (Azevedo et al., 2009). Cases were diagnosed by ELISA IgM, and 3 MAYV strains were isolated.

4.3.14. Case report

Imported case- France ex Brazil, 2009 (Receveur et al., 2010). The patient was infected in Amazonas state, northern Brazil. ELISA detected presence of IgM in the serum of the patient.

4.3.15. Surveillance study

During a large DENV outbreak in the state of Mato Grosso (2011–2012), some DENV- samples from acute febrile patients tested positive by PCR for MAYV (Zuchi et al., 2014).

4.3.16. Surveillance study

Seroprevalence study conducted in Goias state, central Brazil, in 2011–2013. DENV- patients were tested with an enzyme immunoassay on infected cultured cells (EIA-ICC) (Costa et al., 2017).

4.3.17. Case report

Imported case- The Netherlands ex Brazil, 2013 (Slegers et al., 2014). After a travel in Pará state, northern Brazil, the patient tested positive for anti-MAYV IgM and IgG by IFT; the result was confirmed by VNT.

4.3.18. Case report

One MAYV infection was acquired in Pará state, northern Brazil, in 2014 (Mota et al., 2015). Virus was detected by PCR and isolated.

4.3.19. Surveillance study

Study performed in 2014–2015 on CHIKV- patients from Goias state (central Brazil), tested for anti-MAYV IgM by ELISA (Brunini et al., 2017).

4.3.20. Outbreak

MAYV cases were detected in Goias state, central Brazil, in 2015 (ProMED: 20150705.3485723).

4.3.21. GenBank sequence (no additional information)

Virus isolated from human serum in Mato Grosso state, western Brazil, in 2015, belonging to genotype L. GenBank accession number available in Table 3- Supplementary data.

4.3.22. Surveillance study

The survey was performed in Mato Grosso state, western Brazil, on samples from acute febrile patients in 2015–2016 (de Souza Costa et al., 2019). Cases were detected by PCR.

4.3.23. Surveillance study

The study was conducted in Amazonas state in 2016 testing samples from patients with acute febrile illness (ProMED: 20161128.4658296).

4.4. Peru

4.4.1. GenBank sequence (no additional information)

8 MAYV strains isolated in 1995, all belonging to genotype D.

GenBank accession numbers available in Table 4- Supplementary data.

4.4.2. Case report

Cases of MAYV infection reported from different sites in Peru in 1995–1998 (Tesh et al., 1999). 25 cases were detected during seroepidemiological studies on surveillance of acute febrile illnesses; 2 were imported cases (USA ex Peru). MAYV was isolated from 21 patients, 6 were diagnosed by serology.

4.4.3. GenBank sequence (no additional information)

18 MAYV strains isolated in 1995–2000, all belonging to genotype D. GenBank accession numbers available in Table 4- Supplementary data.

4.4.4. Surveillance study

Study performed on samples from febrile patients from different sites in Peru in 2000–2007 (Forshey et al., 2010). 73 cases were confirmed by virus isolation, PCR or IgM seroconversion. 77 additional cases were classified as presumptive cases (high IgM without seroconversion). 25 MAYV strains were isolated.

4.4.5. GenBank sequence (no additional information)

12 MAYV strains isolated in 2002–2006, all belonging to genotype D. GenBank accession numbers available in Table 4- Supplementary data.

4.4.6. GenBank sequence (no additional information)

One MAYV strain isolated in 2010, classified as genotype N. GenBank accession number available in Table 4- Supplementary data.

4.4.7. Surveillance study

Study performed on sera of febrile patients from different sites of Peru in 2010–2012 (Halsey et al., 2013). Positive cases were confirmed by virus isolation and/or PCR and/or ELISA IgM.

4.4.8. GenBank sequence (no additional information)

3 MAYV strains isolated in 2011, all belonging to genotype D. GenBank accession numbers available in Table 4- Supplementary data.

4.4.9. Case report

Imported case- Switzerland ex Peru, after a travel in northern Peru in 2011 (Neumayr et al., 2012). Anti-MAYV IgM and IgG were detected by IF test and diagnosis was confirmed by VNT.

4.4.10. Case report

Imported case- Canada ex Peru, 2018. Viral genome was detected by PCR (ProMED: 20180518.5804085).

4.4.11. Annual report from health authorities

For the year 2018, Peruvian Health authorities declared 35 MAYV cases (ProMED: 20190503.6454329).

4.5. Rest of South America

4.5.1. Bolivia

4.5.1.1. Outbreak. An epidemic of jungle fever was detected in eastern Bolivia in 1955. 192 people got infected; MAYV was responsible for 10–15% of the cases (Schaeffer et al., 1959).

4.5.1.2. Case report. One case of MAYV infection was detected in 1999 and confirmed by serological test (Taylor et al., 2005).

4.5.1.3. Surveillance study. The study was performed in 2000–2007 on samples from febrile patients from different sites in Bolivia (Forshey et al., 2010). 24 cases were confirmed by virus isolation, PCR or IgM seroconversion. 22 additional cases were classified as presumptive cases (high IgM without seroconversion). 15 MAYV strains were isolated.

4.5.1.4. GenBank sequence (no additional information). 10 MAYV strains were isolated in 2002–2006, belonging to genotype D. GenBank accession numbers available in Table 5- Supplementary data.

4.5.1.5. Case report. Case report- Germany ex Bolivia, 2012 (Theilacker et al., 2013). The patient probably got infected in Rurrenabaque region (norther Bolivia). Immunofluorescence test (IFT) and seroneutralization test were used to diagnose MAYV.

4.5.1.6. Case report. Case report- Germany ex Bolivia, 2014 (Tappe et al., 2016). Immunofluorescence test (IFT) was positive for IgG anti-MAYV; result was confirmed by virus neutralization test (VNT).

4.5.2. Colombia

4.5.2.1. Serosurvey. Serosurvey conducted retrospectively on samples collected during the construction of canals in Panama and Colombia in 1904–1914 (Srihongse et al., 1973).

4.5.2.2. Serosurvey. Seroprevalence study conducted in Santander state, northern Colombia, in 1959 (Groot et al., 1959). Samples were tested by HI.

4.5.2.3. Serosurvey. Seroprevalence study performed in different sites of Colombia in 1966 (Evans et al., 1969). Samples from military recruits were tested by HI test.

4.5.3. Ecuador

4.5.3.1. Serosurvey. Seroprevalence study performed in south-eastern Ecuador in 1997 (Izurieta et al., 2011). People native to rainforest had higher IgG prevalence (46,2%) compared to people from coastal or mountain areas (2,4%). Samples were tested with ELISA.

4.5.3.2. Surveillance study. Study performed on samples from febrile patients from western Ecuador (2000–2007) (Forshey et al., 2010). 1 case was confirmed by PCR or IgM seroconversion.

4.5.3.3. Case report. Imported case- Germany ex Ecuador, after a travel in the jungle in 2014 (Tappe et al., 2016). IF test was positive for both IgM and IgG anti-MAYV.

4.5.4. French Guiana

4.5.4.1. Case report. A febrile patient tested positive by HI and ELISA IgM in 1995; the virus was isolated (Talarmin et al., 1998).

4.5.4.2. Serosurvey. Sera from different areas of the country were tested with HI test in 1995–1996 (Talarmin et al., 1998).

4.5.4.3. GenBank sequence (no additional information). 4 MAYV strains isolated in 1996–1998, belonging to genotype D. GenBank accession numbers available in Table 5- Supplementary data.

4.5.4.4. Case report. Imported case- Germany ex French Guiana, 2013. IgM and IgG anti-MAYV were detected by IF test, and PCR was positive (Friedrich-Jänicke et al., 2014).

4.5.4.5. Case report. Imported case- France ex French Guiana, after a travel in the eastern part of the country in 2015. Diagnosis of MAYV infection was confirmed by PCR and ELISA IgM and IgG (Llagonne-Barets et al., 2016).

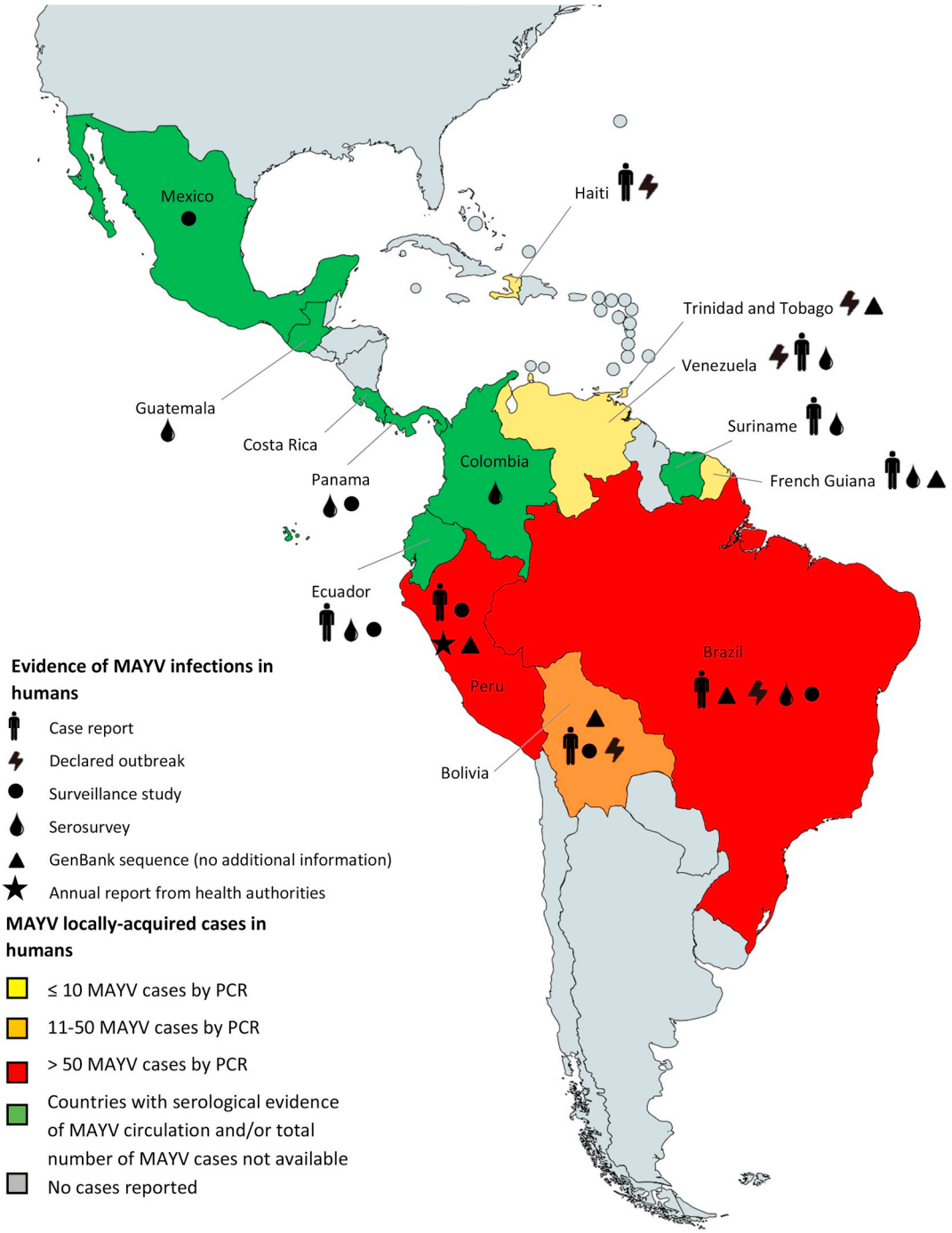


Fig. 1. Acute MAYV cases in humans confirmed by PCR or virus isolation. Countries (in green) where MAYV infections have been suggested based on HI, VNT, PRNT, IF or ELISA are not classified in the map since cross-reactivity with related alphaviruses may have affected serological assays.

4.5.5. Suriname

4.5.5.1. Serosurvey. Seroprevalence study conducted on Dutch soldiers stationed in Suriname in 1984 (Karbaat, 1965).

4.5.5.2. Case report. Imported cases- The Netherlands ex Suriname, after a travel in the central part of the country, 2008 (Hassing et al., 2010). IgG were detected by ELISA in both patients, IgM in one patient only. The infection was confirmed by VNT.

4.5.6. Venezuela

4.5.6.1. Serosurvey. Seroprevalence study performed in northern Venezuela in 1965 (Jonkers et al., 1965). Samples were tested with HI and VNT.

4.5.6.2. Case report. Four cases of MAYV infection in Central Venezuela (2000). Tested by ELISA, 3 patients were positive for IgM anti-MAYV and all of them had IgG anti-MAYV (ProMED: 20010428.0825).

4.5.6.3. Outbreak. Outbreak detected in Portuguesa state, north western Venezuela, in 2010 (Auguste et al., 2015). Distribution of



Fig. 2. Distribution of MAYV genotypes.

MAYV cases and MAYV genotypes are presented in Fig. 1 and Fig. 2

5. Discussion

According to the 9th report of the International Committee on Taxonomy of Viruses (ICTV) (Genus, 2019), MAYV belongs to the Semliki Forest complex and is related to Una virus, previously considered a subtype of MAYV (Genus, 2019). MAYV strains have been classified, on the basis of E1-E2 partial sequences, into three genotypes: (1) genotype D, largely distributed in South America; (2) genotype L, supposedly limited to Brazil but recently detected in Haiti, and (3) genotype N, a newly described clade accounting for just one MAYV strain isolated in Peru in 2010 (Auguste et al., 2015). We performed a phylogenetic analysis using 56 MAYV complete genomes and we observed the same subdivision (Fig. 3). Genotype D includes several clades that segregated by geographic region (Venezuelan, Peruvian, Bolivian and Brazilian clades); all these isolates are highly conserved (< 3% nucleotide divergence) but are quite distinct from the other genotype isolates (5–6% nucleotide divergence with genotype N and 12–13% nucleotide divergence with genotype L). The wide distribution

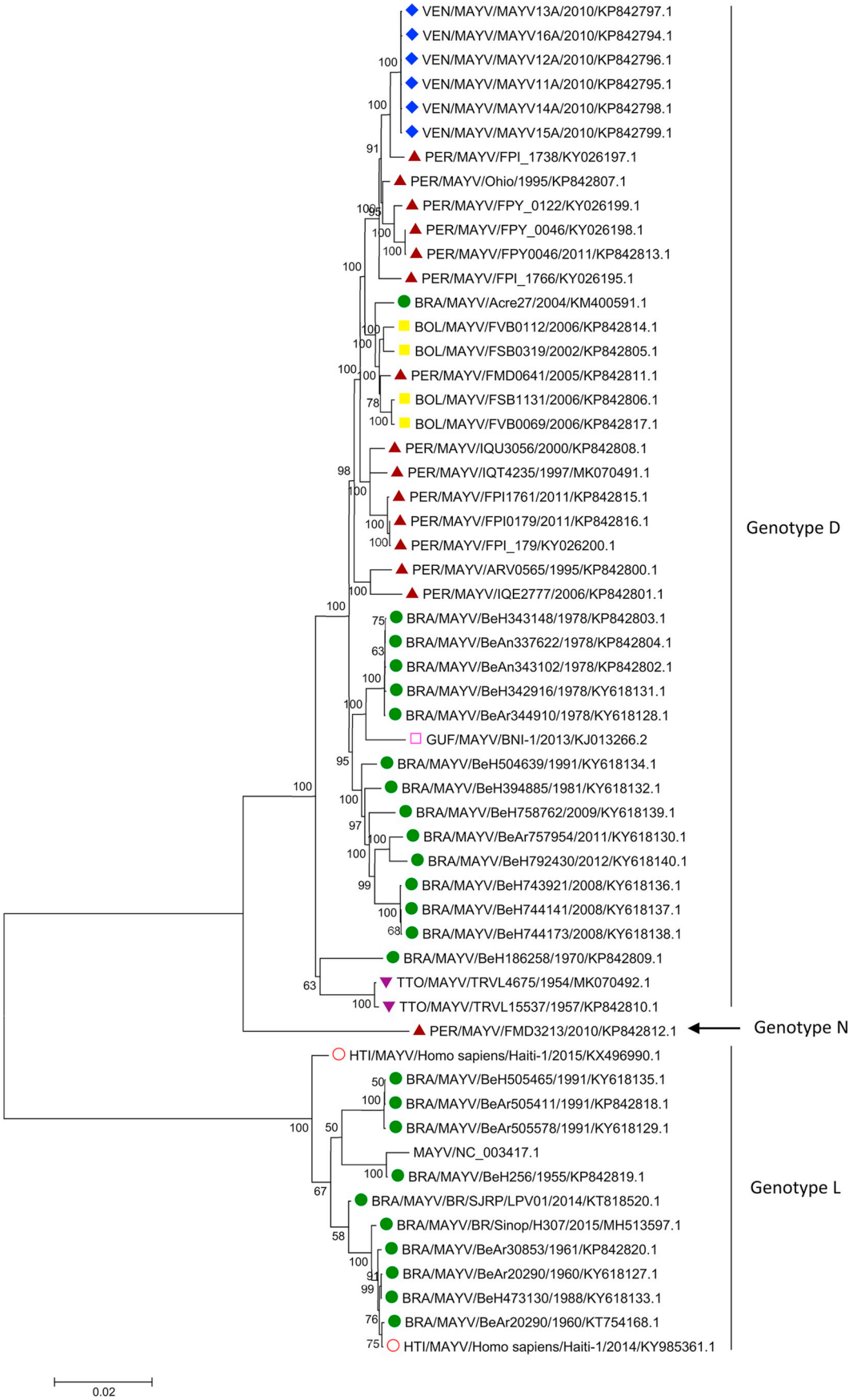


Fig. 3. Phylogenetic analysis of 56 complete MAYV genomes present in GenBank. Neighbor-joining phylogenetic tree was generated with MEGA 6 using Tamura-Nei model (Gamma distribution) with 1000 bootstrap replication. 10,999 sites were included. All positions containing gaps and missing data were eliminated (complete deletion). The best substitution model was selected with jModeltest. Tip labels indicate GenBank accession number, strain name, country and year of isolation (when available).

of genotype D is in contrast to the apparent restriction of genotype L to Brazil. This may be explained by a sampling bias rather than the existence of a specific barrier to MAYV dispersal. It would be of interest to investigate other factors that could be part of genotypic segregation, such as vector competence, vector distribution or presence of alternative amplification hosts. Of note, no clear epidemiological (apart from geographical distribution), clinical or ecological patterns have been associated to date with the different genotypes. This obviously deserves further investigations.

Mayaro virus circulation has been documented only in the Americas. Data about MAYV cases in humans provide a picture of the regular spill over events leading to human infections in Central and South America in the last 65 years. The Amazon region of Brazil provides the higher number of sporadic cases and epidemics, followed by Peru and Bolivia. This is not surprising, because these countries share borders with Brazilian regions where MAYV has been more frequently detected (Amazonas, Acre and Mato Grosso States). Returning travellers got infected after stays in several countries such as Ecuador, Suriname and French Guiana providing evidence of virus circulation (Hassing et al., 2010; Tappe et al., 2016; Friedrich-Jänicke et al., 2014; Llagonne-Barets et al., 2016). Data from Central America (Panama, Costa Rica, Guatemala) are outdated and should be updated to reflect the recent circulation of the virus in the area. This is valid also for the Caribbean, especially after a recent report of two cases in Haiti (Lednicky et al., 2016; White et al., 2014). Overall, seroprevalence and surveillance studies are urgently needed in both Central and South America to better assess the actual scale of MAYV diffusion.

Several factors may have contributed to underestimating the actual prevalence of MAYV infections in humans. First, the widespread circulation of pathogens with an overlapping clinical picture such as dengue virus (DENV), Zika virus (ZIKV) and CHIKV in the American continent, makes probable that MAYV infections have commonly been underreported. Cases of MAYF have been observed during DENV outbreaks or in patients with DENV-like illness, highlighting the fact that similar symptoms make several other arboviral diseases indistinguishable without laboratory testing. In additions, MAYV RT-PCR diagnosis remains poorly available and the cross-reactivity observed between antibodies against MAYV and the closely-related alphaviruses (especially viruses belonging to Semliki forest complex) is a significant barrier to specific serological diagnosis.

Second, since epidemiological data on related alphaviruses has been commonly obtained based on serological tests that also detect to a various extent antibodies to MAYV, MAYV infections may be more common than is generally reported (Pezzi et al., 2019). For example, a seroprevalence study performed in the Amazon Valley of Brazil in 1953–1954 revealed that 18.9% of the samples tested by virus neutralization test were positive for Semliki Forest virus (SFV) (Causey and Theiler, 1958). Since SFV is confined to Africa and in the same period MAYV was detected in the Amazon Valley (Causey and Maroja, 1957), it is possible that such "Semliki Forest-positive" sera actually reflected exposure to MAYV or related variants. Cross-reactivity with chikungunya virus (CHIKV) was also observed in MAYV infected returning travellers, which made the diagnosis late and difficult (Hassing et al., 2010; Friedrich-Jänicke et al., 2014).

According to available data on MAYV distribution, experts identified several gaps of knowledge and provided adapted recommendations (Paragraphs 5 and 6). The aim was to identify and suggest research priorities in the field.

6. Gaps of knowledge

6.1. Entomological and environmental surveillance

Since *Haemagogus* species are the mosquito transmitter of MAYV in the American continent, detailing the spatial distribution of the vector through the continent, especially in border areas between forest and human habitations, is necessary to inform about regions of increased risk for human cases. The different aspects relating to entomology and natural cycle are further developed and discussed in the ongoing report "entomological aspects and vector control" of the GloPID-R chikungunya, o'nyong-nyong and Mayaro virus Working Group.

6.2. Disease surveillance and epidemiology

In the last 65 years, the circulation of MAYV in central and southern America has been proven through circumscribed outbreaks, sporadic serosurveys and case reports of returning infected travellers. The available information concerning MAYV diffusion is insufficient to assess the actual burden of MAYV in the American continent.

6.3. Laboratory tests for seroprevalence studies

High-performance serological assays are needed to overcome the issue of antigenic cross-reactivity between member viruses of the Semliki forest virus serocomplex. In particular, the close phylogenetic relationship among MAYV and CHIKV explains why MAYV and CHIKV antibodies commonly cross-react in ELISA or immunofluorescence testing (Pezzi et al., 2019). Moreover, multiple exposures to various alphaviruses reduce specificity to all serological assays including ELISA, HI, CF, and even the gold standard of specificity, seroneutralisation assys (Pezzi et al., 2019). It is doubtful that adapted and routine serological tools and interpretation algorithms are currently available to expedite accurate and large-scale seroepidemiological studies for MAYV. Better diagnostics are therefore essential to confirm viral transmission.

6.4. Laboratory algorithm and case definition for clinical care

The current situation is characterized by the absence of a clear laboratory algorithm ensuring that MAYV is part of differential diagnosis in specific cases (*e.g.* dengue like syndrome with negative DENV laboratory testing); there is no discriminatory routine and specialist serological assays for clinical care; there is no international case definition for probable and confirmed MAYV cases.

6.5. Diagnosis of acute cases

Very few molecular assays are currently available for MAYV detection. Their performances, as well as their adequacy to detect the different MAYV lineages, have not been assessed through comparative studies. No commercial tests exist except for one anti-MAYV ELISA (IgM and IgG) by EUROIMMUN which has not been clinically evaluated. Multiplex molecular and serological tests for discrimination of MAYV and CHIKV in areas of co-circulation are missing, making differential diagnosis a challenging task. Our information about kinetics of viral load are limited and derive just from sera (kinetics in different body fluids have never been investigated). No International Standards (IS) are available and External Quality Assessment (EQAs) have never been organized to evaluate laboratories capacity to diagnose MAYV infection. The different aspects relating to diagnosis of MAYV infection are further developed and discussed in the report "Biological diagnostics" of the GloPID-R chikungunya, o'nyong-nyong and Mayaro virus Working Group (Pezzi et al., 2019).

6.6. Cross-protection

It is unknown whether individuals infected by MAYV or CHIKV are efficiently protected against secondary infection by the other virus, as well as by other clinically related alphaviruses. It is also unknown whether previous infection by MAYV or CHIKV may be responsible for a potentially more severe infection by the other virus as suggested in the case of successive infection by different serotypes of DENV. This

remains to be firmly established from humans or from relevant animal models.

6.7. Natural history

The natural history of MAYV infection is not accurately characterized, as well as the clinical spectrum of the disease, from acute to long-term sequelae. Few case reports and just one longitudinal study documented persisting arthralgia post MAYV infections (Hassing et al., 2010; Halsey et al., 2013; Taylor et al., 2005). Our knowledge on this subject needs to be increased to determine if a "post-MAYV" syndrome exists, similar to the "post-CHIKV" syndrome that includes a variety of long-term (mostly rheumatologic) complications of CHIKV.

6.8. Molecular epidemiology

Convenient genotyping and sequencing techniques are needed to assist the development of molecular epidemiology studies. Moreover, clear cut-off of percent identity and criteria allowing a clear classification of MAYV strains into genotypes do not exist.

7. Expert recommendations

7.1. Entomological and environmental surveillance

It is necessary to determine the pattern of spatial distribution of *Haemagogus* species, to investigate the vector species range involved in MAYV transmission through field studies and laboratory competence studies, and to characterize the natural transmission cycle and animal reservoirs.

7.2. Disease surveillance and epidemiology

Specific efforts are required to better characterize MAYV circulation and epidemiology at large scale (including clinical epidemiology). MAYV should be more frequently included in molecular proficiency panels for febrile illnesses of unknown origin in the Americas, and seroprevalence studies should be performed. This obviously requires improved diagnostic assays.

7.3. Laboratory tests for seroprevalence studies

Accurate assays and algorithms allowing to detect IgG antibodies specific to MAYV and to distinguish them from IgG to CHIKV should be developed. At this stage, performing seroneutralization tests is essential for confirmation after performing a screening assay (*e.g.* ELISA, haemagglutination inhibition test or immunofluorescence assay); however, a proportion of samples remains without clear identification, in particular in case of co-circulation of related viruses. Clear interpretation guidelines or new specific assays are required and reference serological standards are needed (possibly produced from non-human primates (Pezzi et al., 2019)).

7.4. Laboratory algorithm and case definition for clinical care

Case definitions (for probable and confirmed cases) and a clear diagnostic laboratory algorithm should be set-up.

7.5. Diagnosis of acute cases

For diagnosis at the acute stage of the disease, virus co-circulation requires the development of molecular multiplex tools and specific IgM assays to differentiate MAYV from related alphaviruses in the Americas. Viremia kinetics and viral loads in different body fluids should be better documented, as well as the kinetics of immune response. International Standards (IS) should be made available, taking into account the MAYV genetic heterogeneity. Moreover, External Quality Assessments (EQAs) should be organized in order to assess laboratory capacity of detecting MAYV with both molecular and serological tools.

7.6. Cross-protection

Cross-protection studies between MAYV and related alphaviruses, in particular CHIKV, should be implemented. Moreover, it is necessary to investigate the possible effect of a previous infection by MAYV or CHIKV on a subsequent infection of MAYV. Both aspects could be clarified using samples from naturally exposed humans and experimentally infected non-human primates.

7.7. Natural history

Natural history of infection should be better investigated. Longitudinal studies would prove useful to identify long-term complications.

7.8. Molecular epidemiology

Genotyping and sequencing protocols should be selected and proposed in order to quickly identify the lineage of circulating viral strains. The region of the genome that gives the highest information for genotyping should be identified and this choice standardized in order to allow comparisons across laboratories. Cut-off of percent identity should be standardized to define genotype accurately. Moreover, a genomic reference database should be made available similar to those existing for other arboviruses (e.g. the sites of the Virus Variation Resource (Virus Variation) or the Virus Pathogen Resource (Virus Pathogen Database and Analysis Resource). It would allow to store sequence data, gene and protein annotations as well as information about isolation hosts, country and year.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.antiviral.2019.104610.

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