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An emerging public health threat: Mayaro virus increases its distribution in Peru

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ABSTRACT

Background: The infection caused by Mayaro virus (MAYV), which presents as an acute febrile illness, is considered a neglected tropical disease. The virus is an endemic and emerging pathogen in South America and the Caribbean, responsible for occasional and poorly characterized outbreaks. Currently there is limited information about its expansion and risk areas.
Methods: A cross-sectional study was performed in 10 urban primary care health centers in the Cajamarca region of Peru from January to June 2017. A total of 359 patients with suspected febrile illness were assessed. RNA was extracted from serum samples, following which MAYV real-time reverse transcriptase PCR (RT-PCR) for the detection of the *nsP1* gene was performed.
Results: MAYV was detected in 11.1% (40/359) of samples after RT-PCR amplification and confirmatory DNA sequencing. Most infections were detected in the adult population aged 18–39 years (40%) and 40–59 years (32.5%). Headache was the most frequent symptom in patients with MAYV infection (77.5%), followed by fever (72.5%), myalgia (55.0%), and arthralgia (50.0%). During the study, most of the MAYV cases were seen in May (47.5%) and April (35.0%), corresponding to the dry season (months without rain).
Conclusions: This study is novel in describing the presence of MAYV in Cajamarca, an Andean region of Peru. Symptoms are non-specific and can be confused with those of other arbovirus or bacterial infections. Molecular biology methods such as RT-PCR allow the timely and accurate detection of MAYV and could thus be considered as a tool for surveillance in endemic areas.

Introduction

The infection caused by Mayaro virus (MAYV) is considered a neglected tropical disease by the World Health Organization (WHO) and represents an important public health challenge (Marcondes et al., 2017). MAYV cases in humans have been limited to Central and South America, particularly to regions around the Amazon basin, with some cases exported by travelers (Mackay and Arden, 2016). It was first isolated in Trinidad and Tobago from the blood of five symptomatic infected humans in August and September of 1954 (Anderson et al., 1957), and native human cases were later reported from Brazil (1955), Bolivia (1959), Suriname (1964), Peru (1965), Ecuador (1997), Venezuela (2000), Mexico (2001), and Haiti (2015). Imported cases in North America

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from Peru (Tesh et al., 1999) and Bolivia (Taylor et al., 2005) have also been reported. In Europe, the first imported case was observed in the Netherlands in 2008 in a patient who had come from Suriname (Hassing et al., 2010).

MAYV is a member of the Semliki complex, which includes seven other viruses: Bebaru virus (BEBV), chikungunya virus (CHIKV), getah virus (GETV), Semliki Forest virus (SFV), Ross River virus (RRV), o'nyong-nyong virus (ONNV), and Una virus (UNAV); these make up a serological group within the *Alphavirus* genus that share some common antigenic sites. Consequently, there is cross-reactivity with polyclonal immune sera among the species (Acosta-Ampudia et al., 2018), affecting not only hemagglutinin inhibition and complement fixation assays (Esposito and Fonseca, 2017), but also antibody assays (such as ELISAs) (Hassing et al., 2010), which makes diagnosis a challenge.

Although the number of reported Mayaro fever cases and outbreaks has been low compared to those of other arboviruses, it is possible that considerable misdiagnosis and underreporting might have led to inaccurate estimates of the public health burden of MAYV (Alva-Urcia et al., 2017). The Semliki complex viruses usually cause a human disease characterized by fever, arthritis, and skin rash (Acosta-Ampudia et al., 2018; Esposito and Fonseca, 2017). Accurate diagnosis of Mayaro fever may be complicated by this clinical similarity seen in endemic arboviruses (Mackay and Arden, 2016; Alva-Urcia et al., 2017; Izurieta, 2018). In addition, co-infection with dengue virus (DENV) has been described previously (Acosta-Ampudia et al., 2018).

Considering that MAYV has been co-isolated along with yellow fever virus from the same invertebrate (Hoch et al., 1981) and that *Aedes* spp. have been reported to be able to transmit MAYV in certain laboratory conditions (Smith and Francy, 1991; Long et al., 2011), the urbanization of MAYV is likely and it has the potential to represent a real threat to the region of the Americas, especially if viral changes lead to more effective transmission by arthropods, such as urban mosquitoes (Mackay and Arden, 2016; Izurieta, 2018). Molecular epidemiology surveillance in South and Central America suggests that recent recombination events confirm the preference of MAYV for human hosts over non-human primates, with no effect on MAYV adaptation to mosquito vectors such as *Aedes aegypti* and *Culex quinquefasciatus*, to which the virus is nonetheless well adapted (Mavian et al., 2017).

The principal reservoirs for MAYV are sylvatic vertebrates, maintaining the zoonosis in the rainforest. Epizootics and epidemics of the disease occur periodically, as the virus is spread during the wet season and is limited in the dry season — trends that follow the mosquito population in the jungle (Izurieta, 2018). MAYV has been isolated from several genera of mosquitoes, including *Culex* spp., *Haemagogus* spp., *Mansonia* spp., *Aedes* spp., *Psorophora* spp., and *Sabethes* spp. *Haemagogus janthinomys* is considered the main vector, as it is competent in transmission, with a rate of 70% in laboratory experiments (Long et al., 2011). A potential three-cycle transmission dynamic for MAYV has been proposed by Izurieta et al., who explained that the virus is transmitted in the jungle by *Haemagogus* spp. in a sylvatic cycle, which may then reach urban areas through people living in urban or peri-urban areas and working in or visiting the forest fringe (intermediate cycle); once in the urban setting, MAYV could potentially be spread by *Aedes aegypti* in an urban cycle. It is likely that these three dynamic transmission cycles occur currently and that MAYV might be misdiagnosed as DENV (or another locally transmitted pathogen) given their close clinical and immunological profiles (Izurieta, 2018).

The emergence of Mayaro fever cases in Mexico (Navarrete-Espinosa and Gomez-Dantes, 2006) and Haiti (Lednicky et al., 2016) suggests that the virus is expanding its geographical range of activity. This geographical distribution could pose a threat to south-eastern and south-western states of the USA (including Florida, Louisiana, Georgia, Alabama, Texas, and California), areas well within the estimated range of *Aedes* mosquitoes (Izurieta, 2018).

The possibility of MAYV expanding its host and vector range represents an additional concern regarding its potential as an emergent threat to public health in the Americas. As both CHIKV and Zika virus (ZIKV) infections emerged in the Americas and spread rapidly to several countries, affecting millions of people from 2013 to 2016, these countries could now become high-risk areas for MAYV infection, which may likely be misdiagnosed as CHIKV, ZIKV, DENV, or Oropouche virus (OROV) due to their similarities (Acosta-Ampudia et al., 2018; Silva-Caso et al., 2019).

Materials and methods

Study location

Ten urban primary care health centers within Cajamarca's Regional Health Direction participated in the study, between January and June 2017. The Department of Cajamarca is located in the northern part of the Peruvian territory, at an altitude between 319 m above sea level (Contumazá Province) and 4496 m above sea level (Cajabamba Province). It has a territory of 33 318 km^2 with an average annual temperature of 15.6 °C. In 2017, the urban population was 475 680 inhabitants (35.4%), while the rural population was 865 944 inhabitants (64.6%). Public health insurance coverage reaches 70.5% of the population, and health care is conducted through health networks made up of health facilities, which are easily accessible to the population (Instituto Nacional de Estadística e Informática, 2018; Instituto Nacional de Estadística e Informática, 2014). The health facilities that participated in this study had a basic laboratory and qualified personnel, which allowed sampling from the associated urban areas, as well as from the rural population who were referred to these facilities if necessary. These establishments are strategically located near the largest population centers in the province.

Study subjects

Patients with a suspected acute febrile illness (AFI) who attended the healthcare facilities within 7 days of a quantified or not quantified patient-reported fever were included. For the patients in whom the fever could be corroborated, it had to have been higher than 38 °C for <7 days, without an identifiable source of infection and associated with one or more of the following signs and symptoms: headache, myalgia, arthralgia, retro-ocular pain, lower back pain, rash, hyperoxia, odynophagia, nausea, emesis, abdominal pain, asthenia, syncope, hypothermia, jaundice, and others. The exclusion criteria were patients with an incomplete record of their medical data and patients with an identifiable source of infection, such as acute upper respiratory tract infections, pneumonia, and urinary tract infections, among others.

Ethics statement

The study protocol was approved by the Research Ethics Board of the Hospital Regional de Cajamarca, Peru. The samples were obtained in the context of the epidemiological/syndromic surveillance program according to the health directives of the National Center for Epidemiology, Disease Control and Prevention of the Ministry of Health of Peru. Therefore, it was exempt from informed consent.

Samples

A total of 359 samples were collected using Vacuette TUBE Serum Separator Clot Activator (Vacuette; Greiner Bio-One, Kremsmünster, Austria). The amount of blood extracted was 3 ml. Samples were transported by car and plane following cold chain procedures, using coolers and ice packs, with strict temperature monitoring performed (temperature maintained between 4 °C and 8 °C) until transfer to the Instituto de Investigación Nutricional in Lima, Peru, where they were stored at −80 °C until further molecular analysis.

RNA extraction

RNA extraction was performed using the High Pure RNA Isolation Kit (Roche Applied Science, Mannheim, Germany) following the manufacturer's instructions; 200 μl of the serum samples was used. The viral RNA obtained was stored at −80 °C until use.

*Real-time reverse transcriptase PCR (real-time RT-PCR) amplification for the detection of non-structural protein gene 1 (*nsP1*) and diagnosis of MAYV*

First, the Transcriptor High Fidelity cDNA Synthesis Kit (Roche Applied Science, Mannheim, Germany) was used according to the manufacturer's instructions: denaturation for 10 min at 65 °C, cDNA synthesis for 30 min at 55 °C, and inactivation at 85 °C for 5 min. Then, the real-time RT-PCR assay was performed using TaqMan probe with TAMRA quencher at 50 μM and 100 μM of primers in a final volume of 20 μl. Five microliters of the cDNA was mixed with 15 μl of the Master solution. PCR conditions for MAYV were 95 °C for 10 min and 45 cycles of 15 s at 95 °C, 30 s at 52 °C, and 30 s at 72 °C. All procedures were performed in a Light Cycler 2.0 instrument and data were analyzed with the Light Cycler software version 4.1 (Roche Diagnostics, Mannheim, Germany). The primers and the probe used were provided by the US Centers for Disease Control and Prevention (CDC, Fort Collins, CO, USA); these were recently designed and will detect both genotype L and genotype D. Each primer is an equimolar mixture of the following two primers: forward primers *MAY896* (5′-CAA TCG TAT ACG TGC CGT TG-3′) + *MAY896L* (5′-CAA TCA TAT ACG TGC CGT TG-3′), reverse primers *MAY1001c* (5′-CGG CGT AAC CTG ATG TTT TT-3′) + *MAY1001cL* (5′- CGG CGT ACC CTG ACG TTT TT -3′), and TaqMan probes *MAY960FAM* (5′- FAM-CGA TGA GCC CAG GGG TAT TCGG-TAMRA-3′) + *MAY960FAML* (5′- FAM-CGA TGA GCC CAG GGG TTT TTG G-TAMRA-3′). The RNA control with genotype L and D was also provided by the CDC (Fort Collins, CO, USA). An internal control reaction was run for each of the samples, as mentioned in the CDC instructions, to confirm the integrity of the extraction reagents and the successful recovery of RNA. PCR products were purified using the SpinPrep Gel DNA Kit (EMD Biosciences, Inc., Novagen, Madison, WI, USA) and were sequenced by Sanger method (Macrogen, Seoul, South Korea).

Statistical analysis

Qualitative variables were reported as frequencies in percentages. Fisher's test (*F*-test) and the Chi-square test were used to determine the significance of differences, with a *p*-value of $\leq$0.05 representing statistical significance. A correlation matrix was constructed to analyze the associations of signs and symptoms. All analyses were processed with Minitab software version 18.1 (Minitab Inc., USA). The graphical representation of the data was performed using OriginPro version 10 software (OriginLab Corp., USA).

Results

A total of 359 patients with a suspected AFI were included in the study. MAYV was detected in 11.1% (40/359) of samples after RT-PCR amplification of *nsP1* from MAYV RNA and confirmatory DNA sequencing. There were no failures in the internal control in any of the samples analyzed, which allowed all 359 samples to be included in the study. This number of positive MAYV cases versus the hypothetical non-presence of the virus in the study area was statistically significant ($p < 0.01$, Chi-square test).

The demographic characteristics of the 359 patients are summarized in Table 1. The infection ratio was similar in male (52.5%) and female (47.5%) patients. The main age groups affected were adults between 18 and 39 years old (40%) and between 40 and 59 years old (32.5%). However, there was no difference in age distribution between MAYV-negative cases and MAYV-positive cases ($p = 0.057$, Chi-square test); only one borderline difference was detected for the group less than 5 years of age ($p = 0.045$, *F*-test), which is possibly because the frequency of negative cases (2.8%) is outside the confidence interval (4.0–23.0%) of the positive cases.

The seasonality of infections is depicted in Figure 1, showing an increasing rate between March and June, corresponding to the dry season (without rain) in the study area. It is also interesting to note that the seasonal distribution of MAYV-positive cases coincided with the distribution of AFI cases (Figure 1, inset).

Regarding the clinical presentation, the most frequent symptom in MAYV cases was headache (77.5%, 31/40), followed by fever (72.5%, 29/40), myalgia (55%, 22/40), and arthralgia (50%, 20/40).

Table 1
Demographic characteristics of patients tested for Mayaro virus (MAYV).

Characteristics	Total		MAYV-negative		MAYV-positive			
	n	%	*n*	%	*n*	%	95% CI	*p*-Value[a]
Age (years)								
<5	13	3.6	9	2.8	4	10.0	4.0–23.0	0.045
5–11	50	13.9	48	15.0	2	5.0	1.4–16.5	0.093
12–17	34	9.5	32	10.0	2	5.0	1.4–16.5	0.401
18–39	121	33.7	105	32.9	16	40.0	26.4–55.4	0.379
40–59	95	26.5	82	25.7	13	32.5	20.0–48.0	0.348
>60	46	12.8	43	13.5	3	7.5	2.6–19.9	0.450
Total	359	100.0	319	100.0	40	100.0		
Sex								
Male	167	46.5	146	45.8	21	52.5	37.5–67.1	0.502
Female	192	53.5	173	54.2	19	47.5	32.9–62.5	0.502
Total	359	100.0	319	100.0	40	100.0		

[a] The *p*-value was determined by *F*-test between positive and negative MAYV cases. The confidence interval (CI) is for positive cases.

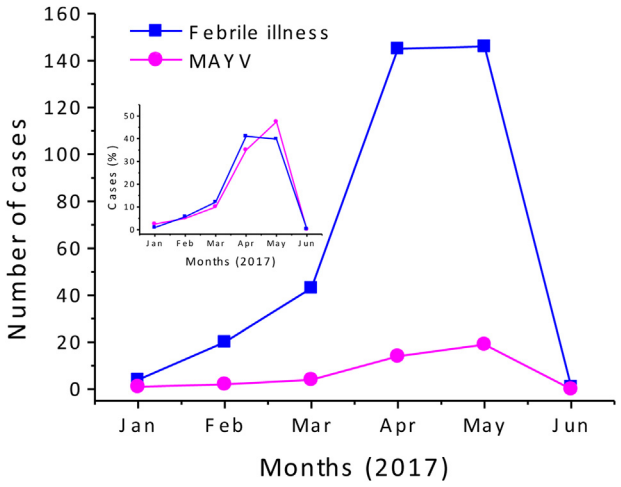

Figure 1. Monthly distribution of the numbers of total cases of acute febrile illness (AFI) and the numbers of MAYV-positive cases. The inset shows the distribution of the cases as frequencies.
MAYV, Mayaro virus; Jan, January; Feb, February; Mar, March; Apr, April; May, May; Jun, June.

The following severe features were detected in the cases: abdominal pain in seven patients and gingival bleeding in one. A list of the symptoms assessed and detected is given in Table 2. However, there were no clear symptoms and signs to establish a clinical diagnosis of MAYV-positive cases. Figure 2 shows the high correlation between the signs and symptoms of MAYV-positive cases and those of MAYV-negative cases (r^2 = 0.9880) and the total AFI cases (r^2 = 0.9902).

Table 2
Clinical presentation of patients tested for Mayaro virus (MAYV).

Clinical	Total n = 359 (%)	MAYV-negative n = 319 (%)	MAYV-positive n = 40 (%)	p-Value[a]
Symptoms and signs				
Headache	302 (84.1)	271 (84.9)	31 (77.5)	0.250
Fever	286 (79.7)	257 (80.6)	29 (72.5)	0.296
Myalgia	249 (69.4)	227 (71.2)	22 (55.0)	0.045
Arthralgia	199 (55.4)	179 (56.1)	20 (50.0)	0.502
Retro-orbital pain	148 (41.2)	133 (41.7)	15 (37.5)	0.734
Lumbar pain	96 (26.7)	85 (26.6)	11 (27.5)	1.000
Nausea	80 (22.3)	71 (22.2)	9 (22.5)	0.972
Cutaneous rash	65 (18.1)	57 (17.9)	8 (20.0)	0.741
Vomiting	54 (15.0)	48 (15.0)	6 (15.0)	0.994
Diarrhea	52 (14.5)	43 (13.5)	9 (22.5)	0.126
Polyarthralgia	29 (8.1)	27 (8.5)	2 (5.0)	0.757
Conjunctival hyperemia	15 (4.2)	13 (4.1)	2 (5.0)	0.678
Hepatomegaly (jaundice)	4 (1.1)	3 (0.9)	1 (2.5)	0.378
Warning signs				
Abdominal pain	93 (25.9)	86 (26.9)	7 (17.5)	0.198
Persistent vomiting	4 (1.1)	4 (1.2)	0 (0.0)	0.014
Gingival bleeding	2 (0.6)	2 (0.6)	0 (0.0)	1.000
Increasing hematocrit	2 (0.6)	1 (0.3)	1 (2.5)	0.211
Edema	2 (0.6)	2 (0.6)	0 (0.0)	1.000
Hematemesis	2 (0.6)	2 (0.6)	0 (0.0)	1.000
Decreasing platelet count	1 (0.3)	1 (0.3)	0 (0.0)	1.000
Weak pulse	1 (0.3)	1 (0.3)	0 (0.0)	1.000
Tachycardia	1 (0.3)	1 (0.3)	0 (0.0)	1.000
Cyanotic or cold limbs	1 (0.3)	1 (0.3)	0 (0.0)	1.000
Arterial hypotension	1 (0.3)	1 (0.3)	0 (0.0)	1.000
Melena	1 (0.3)	1 (0.3)	0 (0.0)	1.000
Gynecological bleeding	1 (0.3)	1 (0.3)	0 (0.0)	1.000
Hematuria	1 (0.3)	1 (0.3)	0 (0.0)	1.000

[a] The p-value was determined by F-test between positive and negative MAYV cases.

Discussion

Mayaro virus (MAYV) is an emerging cause of AFI in the Amazon basin region (Acosta-Ampudia et al., 2018). Several cases have been reported in Peru, but it appears that there has been no estimate of its prevalence (Halsey et al., 2013).

In this study, the detection of cases in areas endemic for other arboviruses in northern Peru reached a frequency of 11.1% among those with febrile diseases over a period of 6 months. Patients infected with MAYV showed general symptoms, as described previously in the literature, which include headache, myalgia, arthralgia, fever, retro-orbital pain, and rash (Acosta-Ampudia et al., 2018; Izurieta, 2018). However, there are no specific symptoms or signs to distinguish this infection from other common etiologies of febrile diseases in the jungle area, such as DENV, CHIKV, ZIKV, leptospirosis, and malaria, among others (Acosta-Ampudia et al., 2018; Halsey et al., 2013). In addition, the misdiagnosis of MAYV as other arboviruses (DENV, CHIKV, ZIKV) is a problem, not only due to the similar clinical presentations, as mentioned above, but also due to cross-reactions of similar antigens in conventional serological diagnostic tests (Acosta-Ampudia et al., 2018; Izurieta, 2018). Regarding the epidemiological scenario according to official information, Cajamarca region reported cases of infections due to DENV, CHIKV, and ZIKV during 2017, so the present study brings a new pathogen to this scenario (Centro Nacional de Epidemiología, 2017). A greater number of samples positive for MAYV was observed between the months of March and June; this period corresponds to epidemiological weeks 10–26 during which surveillance centers report an increase in the frequency of arbovirus infections with respect to other months. This corresponds to an epidemic period, related among other factors to an increase in rainfall in the region studied (Alva-Urcia et al., 2017; Centro Nacional de Epidemiología, 2017).

MAYV is described as causing jungle disease, although there is an increasing rate of MAYV in rural areas, which represents a risk for outbreaks and possible urbanization of the virus (Lorenz et al., 2019). Regarding the geographical distribution of MAYV, which would allow us to improve our understanding of the evolution and dispersion of this emerging *Alphavirus* in the Americas (Lorenz et al., 2019), the present work highlights this observation by describing the presence of the virus in a territory where it has not been reported previously.

This situation requires an accurate, rapid, sensitive, and specific diagnostic test for MAYV to allow appropriate and timely diagnosis, which in turn will provide real knowledge of the disease burden. Molecular biology methods allow better identification of MAYV RNA and include real-time RT-PCR, amplification of a region of the 5′ untranslated region and the non-structural protein gene 1 (Waggoner et al., 2018), and real-time reverse transcription PCR multiplexed in a one-step reaction (RT-qPCR) (Naveca et al., 2017).

MAYV has been detected *in Aedes aegypti*, which is a vector for DENV, yellow fever virus, ZIKV, and CHIKV (Mackay and Arden, 2016; Smith and Francy, 1991); therefore, it is possible that its jungle cycle may change and that the infection will spread from rural areas to urban areas, such as coastal cities in Peru. As observed in the CHIKV and ZIKV epidemics in the Americas, both the *Aedes* mosquito and climate change had a fundamental role (Acosta-Ampudia et al., 2018; Levy-Blitchtein and Del Valle-Mendoza, 2016). The infestation of vectors in the study region is determined by the aedic index, and in the region of Cajamarca, this has been described as being constantly high, reaching values between 3.2% and 16% (an aedic index ≥2%) (Organización Panamericana de la Salud, 2011). There is an urgent need for local

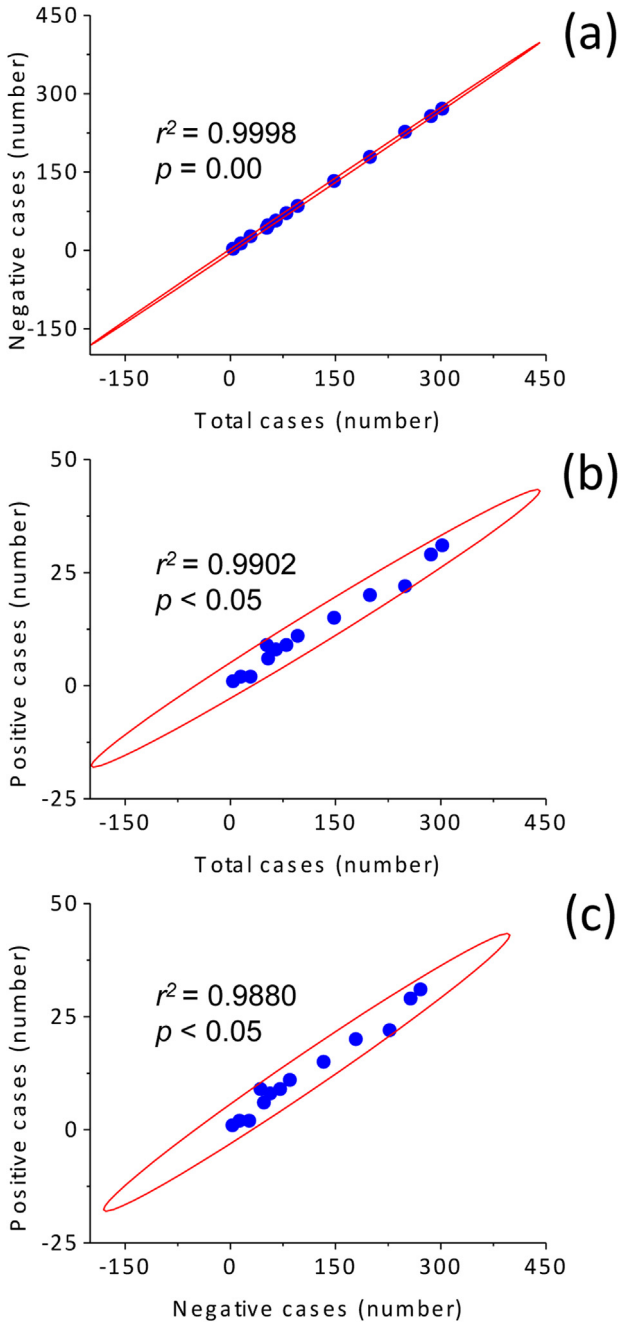

Figure 2. Correlation of the signs and symptoms used in the clinical diagnosis: (a) MAYV-negative cases vs total AFI cases; (b) MAYV-positive cases vs total AFI cases; (c) MAYV-positive cases vs MAYV-negative cases. (MAYV, Mayaro virus; AFI, acute febrile illness).

and international governments to provide resources not only for vector control, but also for accurate detection in the context of epidemiological surveillance of febrile diseases in the Amazon rainforest.

Conclusions

This study is novel in describing the presence of MAYV in Cajamarca, an Andean region of Peru. Symptoms are non-specific and can be confused with those of other arbovirus or bacterial infections. Molecular biology methods such as RT-PCR provide a timely and accurate detection of MAYV, and can thus be considered as a tool for surveillance in endemic areas. This virus should be included in national surveillance programs, and insights into its transmission, pathogenicity, virulence, and local epidemiology are required as a research priority.

Limitations

One of the main limitations of this study was the difficulty in diagnosis, as the symptomatology for MAYV is similar to that of other emerging and reemerging arboviruses in the study area. Mayaro fever is considered a non-fatal disease that often results in a mild clinical presentation (Pilatti et al., 2018). Hence, it may present in a sub-clinical form, leading to incorrect recording and diagnosis of the disease.

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Conflict of interest

On behalf of all authors, the corresponding author states that there are no conflicts of interest related to this study.

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