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Epidemiological and virological characterization of mpox cases in Venezuela during the multinational 2022-2023 outbreak.

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Keywords: mpox; poxvirus; monkeypox; outbreak; Venezuela.

Abstract. Mpox (formerly known as monkeypox) is an infectious disease caused by MPXV, a member of the family *Poxviridae*. On July 23, 2022, the WHO declared the first Public Health Emergency of International Concern of Mpox due to an escalating global outbreak with low intensity. Two clades of MPXV and several lineages within each of these clades have been described. Clade I, also known as the Central African clade, causes a more severe and lethal disease than clade II, which circulates in West Africa. MPXV clade IIb caused the first international outbreak (2022), while clade Ib caused a more recent one (2023-2024). Venezuela reported 12 cases during the 2022-2023 outbreak. This study aims to describe the epidemiological and virological characteristics of these cases. The first three cases were from men infected outside Venezuela, while most of the subsequent ones were from men who acquired the disease in the country. All the cases were from men who have sex with men, and frequently also people living with HIV-1/AIDS. No critical outcome was observed in any of the patients. Sequence analysis showed that most of the MPXV belonged to clade IIb lineage B.1. The recurrent emergence of mpox epidemics warrants the further implementation of molecular epidemiology surveillance and vaccination programs.

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Caracterización epidemiológica y virológica de los casos de mpox en Venezuela durante el brote multinacional 2022-2023.

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Palabras clave: mpox; poxvirus; viruela símica; brote; Venezuela.

Resumen. La mpox (antes conocida como viruela símica) es una enfermedad infecciosa causada por el virus MPXV, miembro de la familia *Poxviridae*. El 23 de julio de 2022, la OMS declaró la primera Emergencia de Salud Pública de Importancia Internacional de mpox, debido a un brote mundial en escalada, actualmente de baja intensidad. Se han descrito dos clados de MPXV y varios linajes dentro de cada uno de estos clados. El clado I, también conocido como clado centroafricano, causa una enfermedad más grave y letal que el clado II, el que circula en África occidental. El primer brote internacional (2022) fue causado por el clado IIb de MPXV, mientras que uno más reciente (2023-2024) es causado por el clado Ib. Venezuela notificó 12 casos durante el brote de 2022-2023. El objetivo de este estudio es describir las características epidemiológicas y virológicas de estos casos. Los primeros tres casos fueron de hombres que se infectaron fuera de Venezuela, mientras que la mayoría de los siguientes fueron de hombres que adquirieron la enfermedad en el país. Todos los casos fueron de hombres que tuvieron sexo con hombres y que viven con VIH-1/SIDA. No se observó ningún desenlace crítico en ninguno de los pacientes. El análisis de secuencias mostró que la mayoría de los MPXV pertenecían al linaje B.1 del clado IIb. La aparición recurrente de epidemias de mpox justifica una mayor implementación de programas de vacunación y vigilancia epidemiológica molecular.

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INTRODUCTION

Mpox (formerly known as monkeypox) is an infectious disease caused by MPXV, a member of the *Poxviridae* family. MPXV belongs to the genus *Orthopoxvirus*. MPXV is an enveloped 200-250 nm virus with linear double-stranded DNA of approximately 200 kb. MPXV interacts with glycosaminoglycans at the surface of the susceptible cells to enter and replicate in the cytoplasm of the infected cell [1-3].

This infection causes a variety of clinical manifestations, particularly skin lesions and lymphadenopathy, but also can present with musculoskeletal pain, ocular manifestations, and malaise [4]. The infection spreads mainly through contact with infected humans or animals or contaminated materials. However, frequent cases and deaths have been observed in children, suggesting that routes of transmission other than sexual contact may also be effective in this new outbreak [5,6]. The likelihood of aerosol transmission seems to be low [7].

The disease has been known to infect humans since 1970. Several cases have been reported in Africa since then, with a few documented cases until 2022 in other countries outside the continent, primarily due to zoonotic transmission. On July 23, 2022, the WHO declared the first public health emergency of international concern of mpox due to an escalating global outbreak, which

is still ongoing at present, with low intensity [2,8]. By August 2024, nearly 100,000 cases have been reported in 122 countries, with a relatively low mortality rate (207 deaths) [9]. This outbreak has been characterized by human-to-human transmission, frequently among men who have sex with men (MSM). HIV co-infection is also frequent [1].

On August 14, 2024, the WHO declared a second public health emergency of international concern for mpox due to an ongoing global outbreak, this time developing in Africa, with the majority of cases in the Democratic Republic of Congo [4,10]. By the end of August 2024, the only cases described out of Africa were in Sweden and Thailand, with a history of travel from Africa. Both viral sequences were already available in the GISAID database on August 28, 2024 [11].

Two clades of MPXV and several lineages within each of these clades have been described. Clade I, also known as the Central African clade, is associated with higher severity and lethality (up to 10%) compared to clade II, which circulates in West Africa [12-14]. MPXV clade IIb caused the first international outbreak (2022), while the more recent one is caused by clade Ib.

The USA exhibited the highest number of mpox cases of the first outbreak worldwide: more than 33,000 by August 2024. In Latin America, Brazil, Colombia, Mexico, and Peru, there was also a high number of cases: more than 11,000 cases in Brazil, more than 4000 cases in Colombia and Mexico, and more than 3,500 cases in Peru until August 2024 [9].

Venezuela reported 12 cases during the 2022 outbreak [15,16]. This study aims to describe the epidemiological and virological characteristics of these cases.

MATERIALS AND METHODS

This is a descriptive study of the cases of mpox detected in Venezuela. The Instituto Nacional de Higiene Rafael Rangel (INHRR) is responsible for the molecular diagnosis of MPXV in Venezuela. It implemented an algorithm for the molecular detection of MPXV cases, previously discarding other confusing exanthema-inducing infections, Varicella-Zoster and Herpesvirus, by detecting IgM/IgG antibodies in the sera of suspected patients [16]. The presence of MPXV DNA was detected by qPCR, as previously described [16]. Based on the WHO/PAHO recommendations on strengthening surveillance, the country has decentralized molecular diagnosis since January 2023 into four states, and surveillance was intensified through the use of the Vesicular Eruptive Febrile Syndrome surveillance protocol.

Once qRT-PCR identified the cases, MPXV genomic DNA was amplified using ARTIC primers [17] for complete genome sequencing. Multiple libraries were prepared from the same sample to increase sequence coverage, using the DNA Prep library preparation kit with the Nextera DNA CD Indexes (Illumina, Inc. San Diego, CA, USA) for next-generation sequencing (NGS). The libraries were pooled and quantified (Qubit DNA HS, Thermo Scientific, Waltham, MA, USA). Their quality was checked (Bio-Fragment Analyzer, Qsep1-Lite, BiOptic, New Taipei City, Taiwan) before sequencing, and sequencing was carried out using an iSeq 100 platform and a 300-cycle V2 kit with paired-end sequencing.

The viral genome sequence assembly was performed using the Genome Detective Virus tool (https://www.genomedetective.com/). Nucleotide sequences of three partial complete genomes with more than 60% coverage have been deposited into the GISAID database with the accession IDs EPI_ISL_15014548 and EPI_ISL_19370098. The other two sequences (MPXV6 and MPXV10), with lower coverage and are not acceptable for GISAID, are available upon request.

FASTA file obtained from Genome Detective was analyzed using the Nextclade web tool Nextclade Web 1.14.1 (https://clades.nextstrain.org). MPXV genomes were aligned using MAFFT v.7 (https://mafft.cbrc.

jp/alignment/server/). Mega [18] was used for sequence identity determination.

RESULTS

Twelve cases of mpox were reported in Venezuela between June 2022 and March 2023 (Table 1). Five corresponded to imported cases, and seven were community-acquired. All patients were male, acquired through sexual contact (MSM), and 7/10 (70%) corresponded to people living with HIV-1/AIDS (PLWHA). The mean age was 30 years (range 24-37). Most of the cases corresponded to the capital region, 42% (5/12) of the Bolivarian State of Miranda, 25% (3/12) of the Capital District, and the remaining 8% one each from Barinas, Carabobo, Guarico and Zulia states (Table 1).

A complete genome sequence could be obtained for only one isolate (MPXV7, with 92.7% coverage), while partial sequences were obtained for three more isolates (Table 2). Even with the low coverage, it could be confirmed that all isolates were from MPXV clade IIb. A discrepancy was found for the isolate MPXV1 for lineage assignment between the different web algorithms available online (Table 2).

Most MPXV isolates detected in Venezuela belonged to the B.1 lineage. Ten thousand three hundred fifty-four total sequences were available in the GISAID database until August 29, 2024 [11]. From these, 8868 sequences belong to the B.1 lineage and its sublineages (3848 to the B.1 lineage and 5020 to the B.1.1 to the B.1.22 sublineages), being the B.1 lineage prevalent globally during the first international outbreak of mpox.

The MPXV1 isolate was classified as lineage B.1 by Nextclade, as were most isolates from this study, but B.1.6 by GISAID [11]. The B.1.6 assignment by GISAID is somehow unexpected since this lineage is strongly associated with mpox cases in Peru [19], and the country of infection for patient C1 was Spain.

Five hundred thirty-three B.1.6 MPXV sequences were available at GISAID on August 29, 2024 [11] (5.1% of the total sequences). Of the 439 B.1.6 sequences (82%) were from Peru (Fig. 1). Some B.1.6 isolates were also found in Colombia and Chile, while this isolate was utterly absent from Brazil (0/353 sequences), Bolivia (No MPXV sequence available), Argentina (0/11 sequences) and only 1/102 B.1.6 isolates in Ecuador. How-

Table 1
Demographic characteristics of patients infected with MPXV reported in Venezuela in 2022.

Patient ID	Sex and age	Date of diagnosis	Travel from	MSM	HIV-1	Outcome
C1	Male, 32	12/6/22	Spain	Yes	Negative	Good
C2	Male, 28	25/8/22	Brazil	Yes	Positive	Good
C3	Male, 31	23/8/22	Peru	Yes	Negative	Good
C4	Male, 24	10/9/22	None	Yes	Positive	Good
C5	Male, 30	6/9/22	None	Yes	Positive	Good
C6	Male, 36	19/9/22	None	Yes	Positive	Good
C7	Male, 31	20/9/22	None	Yes	Positive	Good
C8*	Male, 37	23/9/22	None	Yes	N/A**	Good
C9*	Male, 25	26/9/22	None	Yes	N/A	Good
C10	Male, 30	13/10/22	Colombia	Yes	N/A	Good
C11	Male, 26	9/12/22	None	Yes	Positive	Good
C12	Male, 33	3/3/23	Panamá	Yes	Positive	Good

*Reported contact with patient C7. **N/A: not available. Did not reported HIV status nor accepted an HIV test.

Table 2
Sequence analysis of MPXV Venezuelan isolates.

Isolate ID*	Patient ID	Accession ID	Genome coverage**	Clade	Lineage***
MPXV1	C1	EPI_ISL_15014548	64.2 %	IIb	B.1 or B.1.6
MPXV6	C6	NA****	37.3 %	IIb	B.1.19
MPXV7	C7	EPI_ISL_19370098	92.7 %	IIb	B.1
MPXV8	C8	NA****	56.8 %	IIb	B.1
MPXV10	C10	NA****	39.0 %	IIb	B.1

*For the other MPXV isolates, sequence information could not be obtained. **Percent nucleotides effectively sequenced along the whole genome. ***Lineage assignment according to the Nextclade algorithm. In the case of MPXV1, GISAID assigned this isolate to the B.1.6 lineage. ****NA: not available. Not submitted to GISAID because of low coverage.

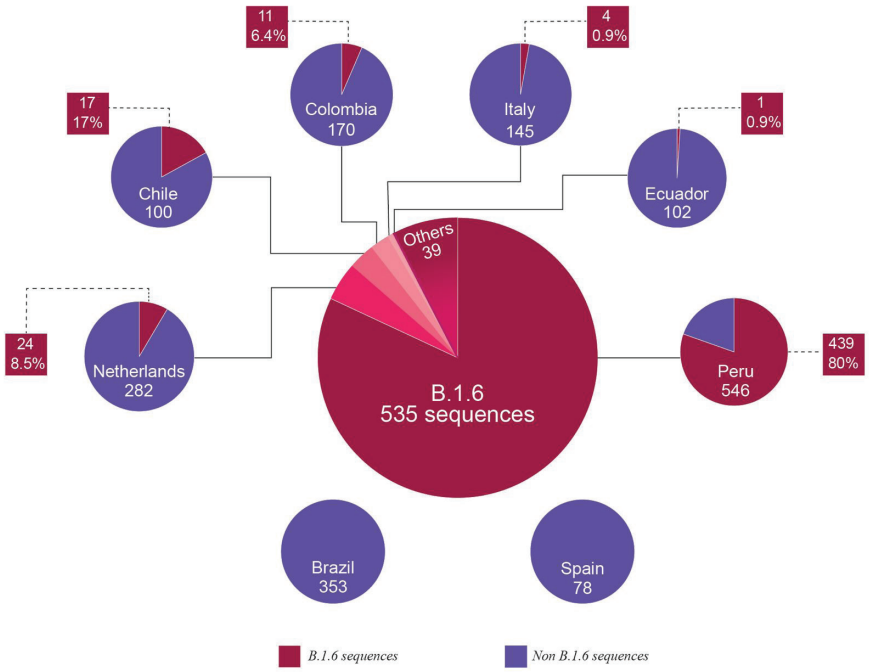

Fig. 1. Distribution of the MPXV lineage B.1.6 in the world. (GISAID, 2024).

ever, the earliest sequences for this lineage (earliest collection date June 5, 2022) were from the Netherlands, where 24/182 sequences (13%) were classified as B.1.6 by the GISAID database: the earliest collection date of B.1.6 isolates from Peru was June 25 of this year (from the first reported case in the country). Then, it cannot be discarded that the B.1.6 lineage was also circulating in Spain in June 2022 and not detected because of the relatively low number of sequences available from this country (n=78).

Another Venezuelan isolate was classified as B.1.19 by Nextclade (from patient C6). No information on lineage classification can be obtained from the GISAID database since this sequence could not be submitted due to low coverage (Table 2). A total of 58 sequences of the B.1.19 lineage were available on the GISAID database [11], making it a lineage with a low detection frequency. Most of the sequences are from Europe (n=39), 18 from North America, and none have been reported in South America. However, the

classification of this Venezuelan isolate as B.1.19 may be misleading because of the low coverage of this sequence.

The partial sequence of MPXV8 displayed more than 99.99% identity with the MPXV7 sequence, which agrees with the history of contact between patients C7 and C8 (Table 1).

DISCUSSION

Relatively few cases of mpox were reported in Venezuela. Comegna *et al.*, 2023 [20], suggested several factors to explain the low number of reported cases, including limited diagnostic capacity, particularly outside the capital city. However, as stated before, 4/12 cases were from states outside the capital region, and four diagnostic centers were performing molecular diagnosis of mpox in other states. The fact that many of the community-acquired cases in Venezuela were also PLWHA suggests that the fear of discrimination may have played a role in the low number of cases detected in the country. In addition, the lack of knowledge about this disease (both among patients and among health workers who are not trained to detect cases) may have hampered the identification of cases. Finally, as this outbreak often presented with a mild disease with low severity and cryptic manifestations, often in the genital area, many cases may have gone undetected [21]. Since PLWHA are more likely to seek medical care, with physicians aware of this disease, this increases the likelihood of detecting mpox cases. Most of the MPXV reported in Venezuela belonged to clade IIb lineage B.1.

The high number of mpox cases associated with the first international outbreak led to the evolution of this virus, with the subsequent emergence of lineages inside the clade IIb [2]. An example of this is the emergence of lineage B.1.6, which seems to have emerged in Peru [19]. The importance of genomic surveillance has been stressed with the COVID-19 pandemic. However, the contribution of MPXV genomic sequences to the GISAID database was not proportional to each country's mpox cases [2]. The genome length of this DNA virus (almost 200.000 base pairs) does not contribute to facilitating this task. Only one complete genome with satisfactory coverage could be obtained in our case. The analysis of these complete or partial genomic sequences allowed us to determine the circulation of the lineage B.1 of the clade IIb in the country.

As of the end of October 2024, only three cases of the second mpox outbreak (clade Ib) have been reported outside Africa (with a previous history of being in that continent) [9,10,22]. This second outbreak did not threaten public health in Latin America by the end of 2024. However, the recurrent outbreaks of this disease have shown the emergence of viral lineages with increased ability of human-to-human transmission [23]. This warrants the need for enhancing response interventions and surveillance systems, targeted vaccination, such as vaccination of high-risk individuals, persons in contact with mpox cases, ring vaccination in endemic areas [5,24,25], and educational campaigns on mpox [24,25].

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Conflict of competence

The authors declare that they have no conflict of competence.

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Contributions of authors

Substantial contribution to the conception and design of the study; Critical review of the article; Approval of the final version to be published (all authors). PA: Data collection and molecular diagnosis of cases. CL: Amplification of the viral genome for sequencing. RCJ y YS: Next-generation sequencing. LR,VA,IM, JMG: Data collection and epidemiological analysis of cases. JLZ: Critical review of the manuscript and design of the figure. HRR: Critical review of the study and manuscript. FHJ: Supervision of the study; Writing the first version of the manuscript.

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