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Cache Valley virus isolation from a horse in Veracruz State, Mexico

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Cache Valley virus (CVV) was isolated from a clinically presenting horse in the Mexican Gulf region. CVV is linked to neuroinvasive disease in humans and fetal demise and defects in sheep. This is the first association between CVV and disease in horses. Implications for public and veterinary health are discussed.

KEYWORDS

orthobunyavirus, arbovirus, Cache Valley virus, encephalitis, horse

Introduction

Cache Valley virus (CVV) is an arbovirus first isolated in 1956 from *Culiseta inornata* mosquitoes and named after the Cache Valley region in Utah, USA (1). It is a member of the Bunyamwera serogroup in the genus *Orthobunyavirus*, family Peribunyaviridae (2, 3). CVV is endemic in North and Central America, having been detected in various Culicidae species (4–6), wild and domesticated animals (6), and humans (7). Infections in people are linked to the central nervous system and are associated with lethal aseptic meningitis (8). Ovine epizootics lead to spontaneous abortions and congenital defects of the musculoskeletal and central nervous systems (4, 6, 8, 9). Here, we report for the first time the isolation of CVV from a horse in Mexico including clinical observations and the documentation of its phylogenetic analysis and relationships.

Materials and methods

Sampling site and horses

Seven female horses (*Equus ferus caballus*) born in the highlands near Mexico City, Mexico, were included in this study. All mares were verified by plaque reduction neutralization tests (PRNTs) to be seronegative to Venezuelan equine encephalitis virus (VEEV). Blood samples were obtained with a 10-mL Becton Dickinson Vacutainer ® (NYSE). An iButton chip (EDS, Lawrenceburg, KY) was implanted in their left hip to facilitate temperature monitoring. After 30 days, on 3 August 2014, the mares were transported 633 km away to a test site in the suburban periphery of Minatitlan City, Veracruz, Mexico (Figure 1). Horses were allowed to roam freely in an open pasture for grazing and monitored daily for signs of disease, temperature, and blood counts over a 22-day period (Table 1).

Results

Mosquito collection

We used Hamster Trinidad bait traps and collected the following mosquito species (N = 250): *Culex* (*Melanoconion*) *taeniopus* (10%), *Culex* (*Melanoconion*) *iolambdis* (10%), *Culex nigripalpus* (50%), *Coquillettidia nigricans* (10%), *Culex quinquefasciatus* (10%), *Aedes taeniorhynchus* (2%), *Mansonia titillans* (2%), *Anopheles albimanus* (2%), and unidentified species (4%).

Clinical observations

On 15 August 2014, one of seven mares presented the following symptoms: it developed profuse ocular discharge, jaundice, and pale mucous, accompanied by a mildly elevated heart rate and a high respiratory rate. The elevated respiratory rate persisted through 20 August 2014, measuring at least double the normal range on 3 of those 6 days and accompanied by a heart rate either at or slightly above the expected range throughout this period (Table 1). The mare displayed peristaltic movements with hyperactivity disorders on 19–20 August 2014, with symptoms worsening and the onset of diffuse diarrhea on the second day. By 22 August 2014, the mare was in prostration more than usual. The mare then recuperated, with no detectable illness on 26 August 2014 and no sequelae noted in a 2-month post-illness analysis. The mare had low hemoglobin and hematocrit measurements and elevated platelet counts throughout the study period, indicative of anemia and reactive thrombocytosis (Table 1).

Viral isolation and genome sequencing

Viral isolation from serum collected on 4–16 August 2014, as well as on 23 August 2014, was attempted in Vero cells. The mare's

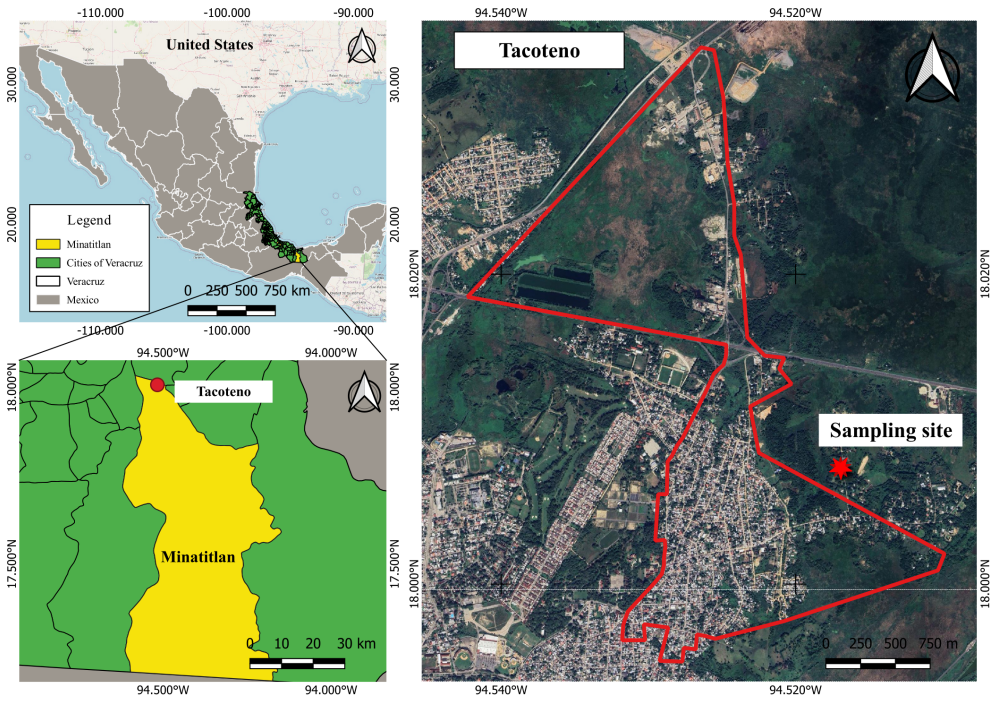

FIGURE 1
Geographical localization of Minatitlan City, state of Veracruz, Mexico. The map shows the location of the sampling site, near urban settlements and areas with wetlands, swamps, and grassland patches. The primary maps were generated using QGIS 3.16.6 (https://www.qgis.org). Free geographic data of administrative areas of Mexico were downloaded from the National Institute of Statistics and Geography, Mexico (INEGI, https://www.inegi.org.mx/app/mapas). Satellite images and street maps were obtained from Google Maps (https://www.google.com/maps).

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TABLE 1 Clinical and viral characterization of a horse infected with Cache Valley virus.

Date	CPE	VEEV $PRNT_{50}$	HR	RR	Temp (°C)		WBC (no.)	Lym (no.)	Plt (no.)	RBC (no.)	Hgb (no.)	Hct (%)
					Avg	Max						
Normal range	Neg.	<20	28–44	10–24	37.2–38.3		4.9–10	1.6–4.6	81–240	6.9–10.7	11.3–17.9	31–48
8/3/2014	ND	<20	49	30	38.3	39.6	ND	ND	ND	ND	ND	ND
8/4/2014	Neg.	<20	44	22	37.5	40.3	ND	ND	ND	ND	ND	ND
8/5/2014	Neg.	<20	44	20	37.2	38.5	10.7	4.6	903	6.22	10.4	26.9
8/6/2014	Neg.	<20	54	20	37.9	40.1	10.7	4.5	860	5.61	10.5	24.9
8/7/2014	Neg.	<20	42	22	37.5	40.1	9.7	4.3	753	6.34	10.5	28.7
8/8/2014	Neg.	<20	42	12	37.5	39.5	9.3	3.7	705	5.77	10.1	25.8
8/9/2014	Pos.	<20	48	28	37.6	40.3	9.3	3.0	819	5.34	9.5	23.5
8/10/2014	Pos.	<20	48	22	38.5	39.8	7.1	2.8	688	5.29	9.1	23.4
8/11/2014	Pos.	<20	48	20	37.4	39.7	6.4	2.2	622	5.21	9.2	22.9
8/12/2014	Pos.	20	42	18	38.4	39.7	7.6	3.0	641	5.41	8.7	24.1
8/13/2014	Neg.	20	48	20	37.8	39.2	7.2	2.7	641	5.41	8.7	24.1
8/14/2014	Neg.	20	ND	ND	37.7	39.8	6.7	2.8	541	5.12	8.3	22.8
8/15/2014	Neg.	40	45	37	37.5	39.1	8.3	3.1	546	5.46	8.7	24.4
8/16/2014	Neg.	20	48	56	38.4	39.7	9.2	5.3	778	4.54	8.3	19.6
8/17/2014	ND	40	48	30	37.3	39.6	8.6	3.4	555	5.10	8.3	22.3
8/18/2014	ND	80	44	48	37.5	39.5	9.1	3.7	630	4.61	8.9	22.5
8/19/2014	ND	20	44	48	37.8	40.2	11.1	3.7	527	5.13	8.4	25.8
8/20/2014	ND	80	48	36	38.5	39.6	11.8	4.0	595	4.61	8.2	22.7
8/21/2014	ND	>640	42	18	37.5	39.2	11.5	4.7	694	4.46	8.4	21.8
8/22/2014	ND	>640	48	20	37.4	39.2	10.6	3.6	674	4.97	8.6	24.8
8/23/2014	Neg.	>640	42	18	37.6	38.3	ND	ND	ND	ND	ND	ND
8/24/2014	ND	>640	ND	ND	ND	38.3	11.2	2.7	676	4.45	8.4	21.7

Cytopathic effect (CPE) in assay Vero cells is reported as a binary positive (Pos.) or negative (Neg.) outcome. Neutralizing antibody titers against Venezuelan equine encephalitis virus (VEEV) as measured by the plaque reduction neutralization 50% ($PRNT_{50}$) assay are reported as reciprocal serum dilution values. Heart rate (HR) is reported as beats per minute. Respiratory rate (RR) is reported as breaths per minute. White blood cell (WBC), lymphocyte (Lym), and platelet (Plt) counts are reported as $\times 10^3$ cells/μL. Red blood cell (RBC) counts are reported as $\times 10^6$ cells/μL. Hemoglobin (Hgb) is reported as g/dL. ND, no data. Normal values are derived from Robinson et al. (10).

primary serum obtained directly from the field was inoculated in the cells. From 9 to 12 August 2014, a cytopathic effect (CPE) was induced, and RNA was harvested from the cell culture supernatant and eluted in 50 μL of water using the QIAamp Viral RNA Mini Kit (Qiagen, Hilden, Germany) according to the manufacturer's instructions for viral species identification. This was followed by RNA extraction, and a cDNA library was generated using SuperScript III Reverse Transcriptase (Invitrogen, Carlsbad, CA) with random hexamers according to the manufacturer's instructions. This cDNA, along with cDNA generated from water and a stock of the TC-83 strain of VEEV to serve as negative and positive controls, respectively, was subjected to PCR with the VEEV 7894(+) and VEEV 395(−) primers as previously described (11). Upon discovering that VEEV was not detected from any of the cell culture supernatants obtained from CPE-positive isolation attempts from the mare in question, the RNA was subjected to next-generation sequencing using the Illumina NextSeq550 platform.

Samples were negative for VEEV by RT-PCR. The viral isolate derived from the sample from 11 August 2014, designated strain Mx14Eq03, was subjected to next-generation sequencing (NGS) using Illumina NextSeq. *De-novo* sequence assembly performed with ABySS version 2.03 (12) yielded a single viral species: CVV (GenBank accession OP137174-137176).

The L, M (Gc), M (Gn), and S segments of CVV Mx14Eq03 were aligned with all available CVV sequences as representative strains of closely related viruses (Table 2) using the MUSCLE algorithm in MegAlign Pro v17.2.1 (DNASTAR, Madison, WI). Alignments were trimmed to 528, 1,803, 525, and 754 nucleotide regions of the L, M (Gc), M (Gn), and S segments, respectively. The trees were generated from 62 L segments, 65 M (Gn) segments, 113

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TABLE 2 Historical CVV strains isolated and closely related strains used in the phylogenetic analysis.

Species	GenBank accession	Strain name	Country	Specific location	Collection date	Host
Cache Valley virus	KX100135.1	6V633	USA	Cache Valley, Utah (near Wellsville)	1956	Mosquito (*Culiseta inornata*)
Cache Valley virus	KX100141.1	W308-67	USA	Myalusing, Wisconsin	1967	Mosquito (*Aedes trivittatus*)
Cache Valley virus	KX100138.1	W728-67	USA	Mazomanie, Wisconsin	1967	Mosquito (*Aedes communis*)
Cache Valley virus	KP835801.1	69V2152	USA	Oregon	1969	Mosquito (*Culiseta inornata*)
Cache Valley virus	KX100144.1	MPB1-1551	Mexico	Palo Blanco, Tamaulipas	1971	Mosquito (*Psorophora confinnis*)
Cache Valley virus	KP835815.1	CtAr560-79	USA	New Haven, Connecticut	1979	Mosquito (*Ochlerotatus triseriatus*)
Cache Valley virus	KX100150.1	MI80-1-450	USA	Cass County, Michigan	1980	Horse
Cache Valley virus	KX100147.1	CK-102	USA	San Angelo, Texas	1980	Sheep (sentinel)
Cache Valley virus	KP835819.1	MN550	Canada	Manitoba	1981	Mosquito (*Culiseta inornata*)
Cache Valley virus	KP835820.1	RU68	USA	Dennisville, New Jersey	1982	Mosquito
Cache Valley virus	KP835811.1	3178	USA	New London, Connecticut	1998	Mosquito (*Anopheles punctipennis*)
Cache Valley virus	KX100153.1	WI-03BS7669	USA	Wisconsin	2003	Human
Cache Valley virus	KP835807.1	10951	USA	New Haven, Connecticut	2003	Mosquito (*Anopheles punctipennis*)
Cache Valley virus	KP835813.1	9122	USA	Fairfield, Connecticut	2005	Mosquito (*Ochlerotatus taeniorhynchus*)
Cache Valley virus	MZ612422.1	W08491	USA	North Dakota	2005	Mosquito (*Culex tarsalis*)
Cache Valley virus	KP835805.1	10311	USA	Litchfield, Connecticut	2008	Mosquito (*Ochlerotatus trivittatus*)
Cache Valley virus	KP835810.1	10625	USA	Hartford, Connecticut	2008	Mosquito (*Ochlerotatus trivittatus*)
Cache Valley virus	JN848543.1	CVV-111	Mexico	Celestún, Yucatan	December 2008	Mosquito (*Aedes taeniorhynchus*)
Cache Valley virus	JN848544.1	CVV-189	Mexico	Celestún, Yucatan	December 2008	Mosquito (*Aedes taeniorhynchus*)
Cache Valley virus	JN848545.1	CVV-198	Mexico	Celestún, Yucatan	December 2008	Mosquito (*Aedes taeniorhynchus*)
Cache Valley virus	JN848546.1	CVV-207	Mexico	Celestún, Yucatan	December 2008	Mosquito (*Aedes taeniorhynchus*)
Cache Valley virus	JN848548.1	CVV-255	Mexico	Celestún, Yucatan	December 2008	Mosquito (*Aedes taeniorhynchus*)
Cache Valley virus	JN848549.1	CVV-262	Mexico	Celestún, Yucatan	December 2008	Mosquito (*Aedes taeniorhynchus*)
Cache Valley virus	JN848550.1	CVV-283	Mexico	Celestún, Yucatan	December 2008	Mosquito (*Aedes taeniorhynchus*)
Cache Valley virus	JN848552.1	CVV-417	Mexico	Celestún, Yucatan	December 2008	Mosquito (*Aedes taeniorhynchus*)
Cache Valley virus	JN848553.1	CVV-464	Mexico	Celestún, Yucatan	December 2008	Mosquito (*Aedes taeniorhynchus*)
Cache Valley virus	JN848554.1	CVV-471	Mexico	Celestún, Yucatan	December 2008	Mosquito (*Aedes taeniorhynchus*)
Cache Valley virus	JN848556.1	CVV-548	Mexico	Celestún, Yucatan	December 2008	Mosquito (*Aedes taeniorhynchus*)
Cache Valley virus	JN848557.1	CVV-600	Mexico	Celestún, Yucatan	December 2008	Mosquito (*Aedes taeniorhynchus*)
Cache Valley virus	JN848541.1	CVV-002	Mexico	Celestún, Yucatan	December 2008	Mosquito (*Aedes taeniorhynchus*)
Cache Valley virus	JN848542.1	CVV-078	Mexico	Celestún, Yucatan	December 2008	Mosquito (*Aedes taeniorhynchus*)
Cache Valley virus	JN848547.1	CVV-213	Mexico	Celestún, Yucatan	December 2008	Mosquito (*Aedes taeniorhynchus*)
Cache Valley virus	JN848551.1	CVV-390	Mexico	Celestún, Yucatan	December 2008	Mosquito (*Aedes taeniorhynchus*)
Cache Valley virus	JN848555.1	CVV-478	Mexico	Celestún, Yucatan	December 2008	Mosquito (*Aedes taeniorhynchus*)

(Continued)

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TABLE 2 Continued

Species	GenBank accession	Strain name	Country	Specific location	Collection date	Host
Cache Valley virus	KP835803.1	10032	USA	Tolland, Connecticut	2009	Mosquito (*Coquillettidia perturbans*)
Cache Valley virus	KP835804.1	10081	USA	Fairfield, Connecticut	2010	Mosquito (*Anopheles punctipennis*)
Cache Valley virus	KP835812.1	9078	USA	Litchfield, Connecticut	2010	Mosquito (*Anopheles quadrimaculatus*)
Cache Valley virus	KP835814.1	9627	USA	New Haven, Connecticut	2010	Mosquito (*Aedes vexans*)
Cache Valley virus	KF296343.1	NJ3542-10	USA	New Jersey	8/22/2010	Mosquito (*Aedes albopictus*)
Cache Valley virus	KC436106.1	MNZ-92011	USA	Northeast (NY, VT, NH)	9/20/2011	Human (CSF)
Cache Valley virus	KP835806.1	10767	USA	Fairfield, Connecticut	2011	Mosquito (*Anopheles punctipennis*)
Cache Valley virus	KP835816.1	14745	USA	New Haven, Connecticut	2011	Mosquito (*Anopheles punctipennis*)
Cache Valley virus	KP835817.1	16924	USA	Middlesex, Connecticut	2011	Mosquito (*Ochlerotatus canadensis*)
Cache Valley virus	OP137174.1	MX14-Eq03	Mexico	Veracruz	8/11/14	Horse
Cache Valley virus	KP835808.1	12219	USA	Litchfield, Connecticut	2014	Mosquito (*Anopheles punctipennis*)
Cache Valley virus	KP835802.1	9548	USA	Fairfield, Connecticut	2014	Mosquito (*Aedes albopictus*)
Cache Valley virus	MK861967.1	R103016b	USA	Missouri	September 2015	Human (serum)
Cache Valley virus	MZ612423.1	4B	USA	Blacksburg, Virginia	2015	Mosquito (*Aedes japonicus*)
Cache Valley virus	OL555724.1	R132738d	USA	Illinois	Fall 2020	Human (CSF)
Fort Sherman virus	KX100132.1	86MSP18	Panama	Fort Sherman	1985	Not specified
Maguari virus	KX100105.1	BeAr 7272	Brazil	Utinga forest, Para	1957	Mosquito (mixed pool; *Aedes scapularis*, *Aedes serratus*, *Aedes sexlineatus*, *Mansonia* spp., and *Psorophora ferox*)
Maguari virus	KX100108.1	CoAr 3363	Colombia	Buenaventura, Valle del Cauca	1964	Mosquito (*Aedes scapularis*)
Maguari virus	KX100111.1	CbaAr 426	Argentina	Cordoba	1965	Mosquito (*Aedes albifasciatus*)
Maguari virus	KX100114.1	AG83-1746	Argentina	Calchaqui Forest, Santa Fe	1982	Mosquito (*Psorophora varinervis*)
Northway virus	MH484312.1	0234	USA	Northway, Alaska	8/25/1971	Mosquito (*Aedes* spp.)
Playas virus	KX100123.1	75V3066	Ecuador	Playas	1975	Mosquito (*Aedes taeniorhynchus*)
Playas virus	KX100126.1	75V5938	Ecuador	Guayaquil	1975	Mosquito (*Aedeomyia ochler taeniorhynchus*)
Playas virus	KX100129.1	75V5758	Ecuador	La Florida	1975	Mosquito (*Aedeomyia ochler taeniorhynchus*)
Tensaw virus	MH484333.1	A9-171B	USA	Baldwin County, Alabama	9/27/1960	Mosquito (*Anopheles crucians*)
Tensaw virus	FJ943510.1	TSV-FE3-66FB	USA	Everglades National Park, Florida	1963	Mosquito (*Aedes taeniorhynchus*)
Tensaw virus	FJ943509.1	TSV-FL06	USA	Alachua County, Florida	5/23/2006	Mosquito (*Anopheles crucians*)
Tlacotalpan virus	KX100120.1	61D240	Mexico	Tlacotalpan, Veracruz	1961	Mosquito (*Mansonia titillans*)

M (Gc) segments, and 52 S segments. The segments were analyzed separately because bunyaviruses are known to have undergone both recombination and reassortment. Phylogenetic analysis was performed using the phangorn package in R v4.1.3, and the GTR+G+I model of nucleotide substitution was employed (13). A maximum likelihood tree was generated using a rooted UPGMA tree for initialization with 1,000 iterations for bootstrapping analysis. The Mx14Eq03 strain was found by all four analyses to be a lineage 2 member of the CVV species (Figure 2).

Discussion and conclusion

In general, some areas of the south of Mexico have been characterized previously as endemic for VEEV for several orthobunyaviruses including Tlacotalpan virus (TLAV), Patois virus (PATV), and Barrita virus (BITV) (14) and for flaviviruses (11, 15, 16). Thus, the detection of CVV at the test site in the Coatzacoalcos river basin was expected since the virus has been known to circulate widely in the Yucatan Peninsula and also has been suspected to be spread in the lowland region of Veracruz (5, 15). Tlacotalpan virus, a virus considered to be a variant of CVV, was isolated from the Tlacotalpan Veracruz village, a town located 208 km north of our study site, in the 1960s (15).

Reinforcing such observations is the phylogenetic association as demonstrated in our phylogenetic tree and in segment L as shown in Figure 2. Although horses have been found to be seropositive for CVV in the Yucatan Peninsula and elsewhere (5), this is the first viral isolate obtained from this host outside of a single strain obtained from Michigan in 1980 (17).

The period of viremia of the mare showed an elevated heart rate and temperature. Visible signs of illness, including ocular discharge, jaundice, and pale mucus, began 3 days after the viremia and escalated to include additional gastrointestinal symptoms before resolving after

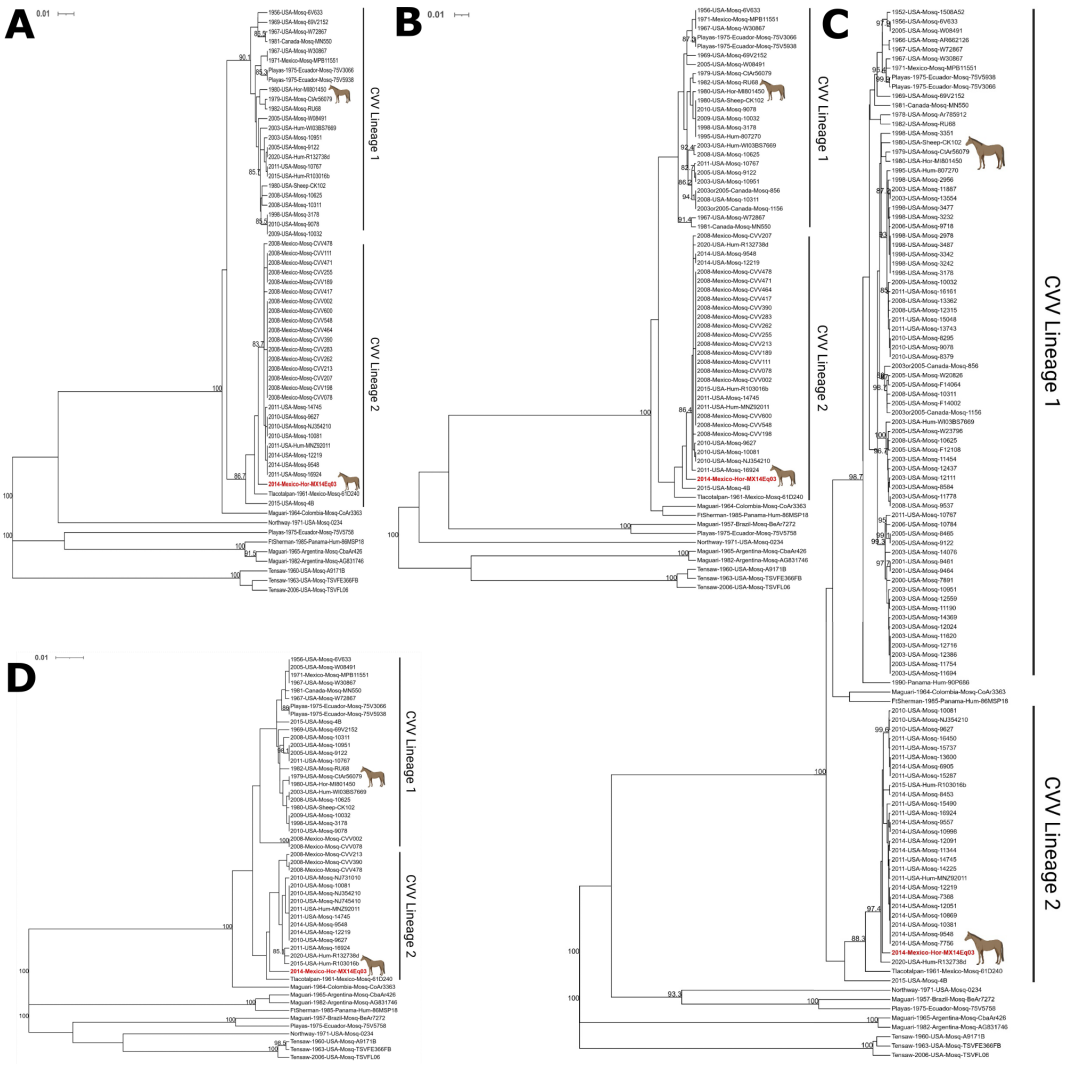

FIGURE 2
Maximum likelihood analysis of the **(A)** L segments, **(B)** Gn gene in the M segments, **(C)** Gc gene in the M segments, and **(D)** S segments of Cache Valley and closely related viruses. The Mx14Eq03 isolate is indicated in red. Equine isolates are indicated with a horse icon. Scale bars and branch lengths refer to the rate of nucleotide substitutions. Bootstrapping values greater than or equal to 80 are indicated at the corresponding nodes. Phylogenetic trees were visualized with iTOL v6.6 and annotated in BioRender.com.

11 days with no apparent sequelae. We also noticed three distinct clinical signs, namely, depression, high fever, and respiratory distress, observed in other arboviral diseases likewise affecting equines. The disease linked to *Culicoides* mosquito bites is African horse sickness (AHS), known to be endemic in Africa and showing a similar pattern in our Minatitlan mare with the exception that AHS is highly lethal (18). During the study period, the mare seroconverted to VEEV. Low levels of neutralizing antibody against VEEV were first detected on the final day of CVV viremia, 12 August 2014, and the antibody titer steadily increased before reaching the upper limit of the assay on 21 August 2014. Results from the other six mares confirmed the presence of VEEV circulation at the test site during the study period. Sera collected from five of those six mares between 8 August 2014 and 15 August 2014 caused CPE in Vero cells and were subsequently identified as VEEV by RT-PCR and sequencing. Those five mares also seroconverted to VEEV, reaching neutralizing titers of 640 or greater between 13 August 2014 and 21 August 2014. Thus, although VEEV was not isolated from the mare that was infected with CVV, there is persuasive evidence that it was infected with VEEV during the study period. As the previous equine isolate was from a clinically normal animal (17), further study is needed to elucidate any causative relationship between CVV and adverse clinical outcomes in horses.

As expected, the phylogenetic analysis identified the Mx14Eq03 strain isolated in this study as a lineage 2 isolate of CVV. Lineage 1 strains of CVV are generally older and are dominated by strains from the USA and Canada (4, 6). CVV lineage 2, on the other hand, has emerged more recently and was identified in Mexico before its detection in the USA, suggesting possible introduction from Mexico or South America into the USA (4).

From a veterinary standpoint, the importance of our detection of CVV in the Mexican State of Veracruz is highlighted by its association with the sheep industry. The state of Veracruz, after the states of Hidalgo and Mexico, respectively, was recognized in 2021 as the third most important ovine production region of the Mexican Republic, with 730,015 head of sheep (19) that represent an important income source for many farmers. Infections of pregnant ewes can result in severe fetal malformations like arthrogryposis with hydranencephaly and death, with major agroeconomic losses (9). Active CVV circulation in the region also has implications for human health. It is likely that in tropical regions such as Veracruz, both veterinary and human cases are greatly underreported due to the simultaneous circulation of other arboviruses such as VEEV. Accurate, inexpensive, and rapid diagnostics at low containment are needed to improve differential diagnostics. Differential diagnostics should be a medically important component, especially in suspected arboviral diseases in equine herds including humans since the southern Mexican region is affected by other endemic neuroinvasive arboviral diseases such as the equine encephalitis (3, 11) and West Nile virus (16).

All in all, leading among the bunyavirus is the orthobunyavirus genus with more than 170 named viruses, many of them pathogens to humans and distributed worldwide. Among them, CVV is an example considered to be a reemerging zoonosis (3) and can cause serious diseases in humans and domestic animals. CVV disease and its putative impact remain an uncharted scenario in south Mexico worthy of renewed public and veterinary health attention by regional health institutions of the Mexican Republic.

Data availability statement

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found in the article/Supplementary Material.

Ethics statement

The animal study was approved by the IRB protocol from the Facultad de Medicina, Universidad Autonoma del Estado de Mexico (UAEMex) 011/2015. The study was conducted in accordance with the local legislation and institutional requirements.

Author contributions

GO: Investigation, Methodology, Writing – original draft, Writing – review & editing. JP: Investigation, Methodology, Software, Validation, Writing – review & editing. VF: Investigation, Methodology, Writing – review & editing. AG: Investigation, Methodology, Writing – review & editing. MS: Data curation, Methodology, Writing – review & editing. GR: Data curation, Methodology, Writing – review & editing. SW: Investigation, Methodology, Software, Validation, Writing – review & editing. KP: Investigation, Methodology, Software, Validation, Writing – review & editing. SW: Funding acquisition, Methodology, Resources, Validation, Writing – review & editing. JE: Conceptualization, Funding acquisition, Investigation, Methodology, Project administration, Resources, Writing – original draft, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fitd.2024.1456666/full#supplementary-material

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