Vesicular Stomatitis Virus

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KEYWORDS

• Vesicular stomatitis • Livestock disease • Equine • Vector-borne disease outbreak

KEY POINTS

- Vesicular stomatitis (VS) is a disease reportable to state and federal animal health officials in the United States. Veterinarians suspecting VS in a clinical animal should contact either the State Veterinarian or the federal Area Veterinarian in Charge (AVIC) for the state in which the animal is located.
- Diagnostic confirmation of vesicular stomatitis virus (VSV) infection at an approved laboratory is required for the first equine case in a county and in all suspected cases in ruminants and swine.
- Isolation of animals with lesions and implementation of aggressive vector control measures are imperative to reduce the spread of VSV during an outbreak.
- VSV is a zoonotic pathogen that can be transmitted to humans through direct contact with animals with lesions. Personal protective equipment and good biosecurity practices should be used by veterinarians and animal handlers when handling horses and other livestock with active VS lesions.

INTRODUCTION

Vesicular stomatitis (VS) is a viral, vector-borne disease of livestock caused by *Vesiculoviruses,* vesicular stomatitis New Jersey virus (VSNJV) or vesicular stomatitis Indiana virus (VSIV), referred to collectively as vesicular stomatitis viruses (VSV). The disease is confined to the Americas where it occurs annually in endemic cycles in Mexico, Central America, and northern regions of South America and only in sporadic epizootic outbreaks every 2 to 10 years in the United States.[1] Equids, such as horses, mules, and donkeys, are the most commonly affected species in US outbreaks, followed by cattle and camelids, such as llamas and alpacas[2]; however, the disease can also occur in other ruminants and swine. Clinical signs of the disease in affected species are produced by the development of vesicular (blister-like) lesions that occur on the muzzle, nostrils, lips, oral mucosa, tongue, teats, udder, sheath, ventral abdomen, ears, and/or coronary bands (**Fig. 1**).[3] Lesions in the mouth and on the tongue usually cause hypersalivation and anorexia, whereas coronary band lesions often produce lameness. The disease is self-limiting and the lesions in most affected

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Fig. 1. Vesicular stomatitis. (*Courtesy* of Jason E. Lombard, DVM, MS.)

livestock heal within a couple of weeks without veterinary intervention; however, some older animals or those with underlying health conditions may require supportive care, especially in cases with severe oral lesions where the animals cease to eat or drink.[3] The disease is also zoonotic, transmitted to humans through direct contact with infectious lesions in livestock, and typically causes fever, headache, fatigue, and myalgia lasting 3 to 5 days.[3] The appearance of VSV-caused lesions in ruminants and swine is clinically indistinguishable from lesions of foot and mouth disease (FMD), one of the most economically devastating viral diseases of livestock[1]; therefore, immediate reporting to state and federal animal health officials of VSV-like lesions is required in the United States to first rule out FMD infection using appropriate diagnostic assays.

Transmission of VSV to horses and other livestock species occurs mainly through biting insects[4]; however, the spread can also occur through direct contact with virus-containing fluids from infectious lesions and saliva or through indirect contact with contaminated fomites, such as shared water, feed, feeders, lick tubs, tack, or veterinary supplies, like oral drenching equipment or dental floats.[5,6] Suspected vectors of VSV include black flies (Simuliidae), sand flies (Psychodidae), and *Culicoides* biting midges (Ceratopogonidae) as species from all three of these families have been found naturally infected with VSV in the wild.[7–9] However, other biting insects have been experimentally infected with VSV and may also be involved in transmission. Proximity of affected livestock premises to water has been indicated as a significant risk factor, which is likely reflective of nearness to prime habitat for competent vectors.[10] Black flies, hatching from moving waterways, and *Culicoides spp*., hatching from muddy areas around standing water, move directly to nearby livestock to feed, thus initiating VSV transmission in the area if those vector populations are carrying the virus.

Genetic analyses of VSVs from US outbreaks have indicated that they arise from viruses circulating in Mexico.[11–13] Both VSV serotypes and multiple lineages are found circulating in southern and south-central Mexico annually.[1,13,14] It is hypothesized that specific climatic and environmental factors occur in certain years that favor expansion of VSV-carrying vectors northward from these endemic regions. In those years, VS cases are seen in states in northern Mexico just a few months before outbreaks being recognized in Texas, New Mexico, and/or Arizona in the United States. These years have been termed incursion years for US outbreaks, and the dominant climatological and ecological variables supporting this movement have been modeled and reported.[15] After an incursion year, the virus may overwinter and resurge to cause cases the following year, termed an expansion year, with slightly different climatological and

ecological conditions identified as supporting this resurgence.[15] Northward expansion has been documented in horses as far north as Montana [https://www.aphis.usda.gov/vs/nahss/equine/vsv/vsvmaps/MT_2005_Cumulative_Final_121105.pdf]. If no VS outbreak is identified in the year following an incursion year, then it is hypothesized that the environmental variables supporting the vectors for an expansion year may not have been present and therefore, the continued transmission did not occur. Research is ongoing to further evaluate and understand how climate and ecology affect insect vector populations and the potential for VSV transmission in a given year.

VS outbreaks in the United States cause significant trade disruptions and economic impacts, mainly through cessation of international and interstate movement of livestock, but also through reduced participation in or cancellation of equine and livestock shows and events.[16] The seasonality of disease occurrence also has an impact. VS outbreaks occur during the height of vector activity, usually late spring through early fall, which is also the time of year where a high volume of equine shows/events and county fairs are scheduled to occur. In addition, the large numbers of cattle in the western United States that move through livestock markets and sales in the fall can be held up by VS outbreaks and associated quarantines. States without VS cases issue specific movement restrictions on susceptible livestock species from VS-affected states which may bar movement from affected counties altogether or require a certificate of veterinary inspection within just a few days of movement that includes statements by the veterinarian attesting to the examination of the animal and the absence of VS lesions. International export of livestock from VS-affected states is halted until at least 30 days after the last quarantine release in the state or longer depending on the requirements of the receiving country. International export of livestock from non-affected US states is usually able to proceed; however testing for VSV may be required by the receiving country which adds additional planning and expense to the exporters. Although the World Organization for Animal Health (WOAH) (formerly Office International des Epizooties [OIE]) removed VS from its list of internationally reportable diseases in 2015, the United States remains bound by bilateral trade agreements with its trade partners to immediately report the occurrence of VS and provide information on response measures and updates on the outbreak.

History and Management of the Disease in the United States

Over the past 20 years, VS outbreaks in the United States have been geographically confined mainly to the southwestern and Rocky Mountain regions of the country, have primarily involved the VSNJV serotype of the virus, and large multi-year outbreaks have been temporally separated in 4- to 8-year increments with smaller, single incursion outbreak years occurring sporadically in between. A summary of outbreak years, affected states, virus serotype, and number of affected livestock premises during this time period is presented in **Table 1**. Historically, equine premises make up the majority of the affected premises identified during each outbreak year. Several factors may be involved in why equine premises are most impacted during an outbreak, such as vector preference for equids and/or common management practices on equine premises. For example, daily feeding and handling practices on equine premises make it more likely that clinically affected horses will be noticed by owners or barn managers, as opposed to grazing cattle operations where the animals may not be observed directly for days or weeks at a time, and even when observed, may not be noticed to have a clinical abnormality. In the Rocky Mountain region of the United States, many cattle herds are moved to high mountain pastures for the summer months and will not be physically observed until gathered again in the fall. Equine

Table 1
Summary of vesicular stomatitis outbreaks in the United States within the past 20 y including outbreak year, affected states, virus serotype, and number of affected livestock premises

Outbreak Year	Number of States Affected	States	VSV Serotype	Number of Affected Premises
2004	3	CO, NM, TX	VSNJV	294
2005	9	AZ, CO, ID, MT, NE, NM, TX, UT, WY	VSNJV	445
2006	1	WY	VSNJV	13
2009	2	NM, TX	VSNJV	5
2010	1	AZ	VSNJV	2
2012	2	CO, NM	VSNJV	36
2014	4	AZ, CO, NE, TX	VSNJV	435
2015	8	AZ, CO, NE, NM, SD, TX, UT, WY	VSNJV	823
2019	8	CO, KS, NE, NM, OK, TX, UT, WY	VSIV	1,144
2020	8	AR, AZ, KS, MO, NE, NM, OK, TX	VSIV, VSNJV (TX)	326

Abbreviations: AR, arkansas; AZ, arizona; CO, colorado; ID, idaho; KS, kansas; MO, missouri; MT, montana; NE, nebraska; NM, new mexico; OK, oklahoma; SD, south dakota; TX, texas; UT, utah; WY, wyoming.

owners are also more likely to seek veterinary care in response to noticing a clinical abnormality in their horse(s).

Ongoing surveillance for FMD and other foreign vesicular diseases of concern in the United States requires that United States Department of Agriculture (USDA)-accredited private veterinarians immediately report to state and federal animal health officials on suspected vesicular lesion occurrence in all livestock species, including equids. Follow-up on each report is conducted by a local state or federal veterinary medical officer specifically trained as a foreign animal disease diagnostician (FADD) who deploys to the affected livestock premises, examines the animals, collects the appropriate diagnostic samples, and places a quarantine on the premises. Diagnostic samples are shipped overnight to the USDA's National Veterinary Services Laboratories (NVSL) in either Ames, Iowa, or Plum Island, New York, depending on the species affected. Samples from equids with vesicular lesions, which cannot be infected with FMD, go to NVSL in Ames, Iowa, with diagnostic testing for VS as the primary rule out. Samples from ruminants and swine with lesions go to NVSL on Plum Island for primary rule out of FMD and foreign swine vesicular diseases, followed by secondary rule out of VS, and tertiary testing for domestic vesicular diseases, such as bluetongue, epizootic hemorrhagic disease, and bovine papular stomatitis in cattle and Senecavirus A in swine.

In all suspect cases, samples to be collected from animals with lesions include a serum sample and swabs of the lesions submitted in viral transport media. Diagnostic assays at NVSL used to confirm VSV infection are specific to each VSV serotype and include antibody detection methods on serum samples, such as competitive enzyme-linked immunosorbent assay (cELISA), complement fixation test (CFT), virus neutralization (VN), and virus detection methods on swab samples, such as real-time reverse transcription polymerase chain reaction (rRT-PCR) and virus isolation (VI). Although the cELISA is an early indicator of recent infection and will test positive a few days

before the CFT in a naïve, recently exposed animal, the cELISA may subsequently remain positive for up to 10 to 12 years.[17] Given the number of previously exposed livestock residing in historically affected regions in the United States, the cELISA alone cannot be used to confirm recent infection unless occurring in an animal that was either not geographically present in a previous outbreak region or in an animal too young to have experienced the last US outbreak. The CFT, rRT-PCR, and/or VI are used as reliable indicators of recent infection for the purposes of VS case definition during an outbreak. All case definitions for VS require compatible clinical signs and have several options for diagnostic confirmation using these assays. An IgM capture ELISA has been developed recently at NVSL and may also be used as a reliable indicator of recent infection in future outbreaks. Although the VS index case for the nation, index cases for newly affected states, and VS cases in ruminants and swine require diagnostic confirmation at NVSL, since 2015 the USDA-approved National Animal Health Laboratory Network (NAHLN) laboratories located in historically VS-affected states have been activated during outbreaks to conduct VSV testing in clinically-affected equids. This action has successfully increased laboratory capacity and reduced result turnaround time during an outbreak response.

Once an index case of VS is diagnostically confirmed in the United States, a national situation report is issued first to state and federal animal health officials and bilateral trade partners for their awareness and then the report is publicly posted to the USDA-APHIS website.[2] At least once weekly situation reports are issued and posted throughout the outbreak thereafter until the incident is declared over, usually 30 days after the last quarantine release in the country. A joint state–federal response following standardized response protocols and using local personnel is organized in each affected state. A national-level situation unit leader is activated to provide support, maintain response continuity across states, gather data, and issue situation reports. State animal health officials provide electronic communication by mass email to private veterinarians licensed to practice in the state notifying them of the confirmation of a VS case, recommending increased surveillance and educational outreach to clients, reminding of reporting requirements, and providing instructions on response measures. Information is also posted to state animal health officials' websites, including specifics of any new interstate movement and entry requirements enacted as a response measure.

Livestock premises with laboratory diagnostic results meeting a VS confirmed case definition are categorized as confirmed positive premises. Once a county is confirmed as VSV-positive, new equine premises presenting with clinical signs of VSV in that county are not required to be tested for confirmation of the disease, but the premises are quarantined and classified as suspect premises. Premises are also classified as suspect if clinical animals on the premises fail to meet a confirmed case definition, but have diagnostic evidence of recent VSV infection. All confirmed positive and suspect VS premises are placed under state quarantine for a minimum of 14 days from the onset of lesions in the last affected animal on the premises. The quarantine applies to all VS-susceptible species on the premises and no movement of these species off-site is permitted without approval of the state veterinarian.

Isolation of animals with lesions from clinically healthy animals is instituted to reduce spread of the virus by direct contact, and aggressive vector control recommendations are provided to be instituted by the premises/animal owner to further reduce within-herd spread. Oversight for equine premises is conducted by private veterinarians communicating with state animal health officials in most states, whereas oversight of ruminant and swine premises is conducted directly by state or federal animal health officials. Private veterinarians or animal health officials

overseeing each premises confirm the 14-day countdown after the onset of lesions in the last affected animal. State animal health officials issue a quarantine release once this time period has passed with no new cases presenting. Continuation of aggressive vector control on the premises is recommended throughout the remainder of the outbreak, as re-infection of previously affected animals and lesion development in new animals after quarantine release has occurred occasionally from continued presence of infected vectors in the general area when vector mitigations on the premises are inadequate.

DISCUSSION

Recent outbreaks of VS in the United States have provided evidence that climate change may be impacting the future size, scope, and geographic range of outbreaks. The 2019 and 2020 VS outbreaks shared some characteristic features of historic outbreaks in the United States, but also had several unexpected attributes potentially related to climatic factors. The 2019 VSIV outbreak resulted in identification of 1,144 VSV-affected premises in 111 counties in eight states. The factors involved that boosted this outbreak to become the largest in both size and geographic scope in the past 40 years of recorded history are still a relative mystery, although climatological and ecological conditions affecting vector abundance, dispersal, or habitat quality are suspected to be involved. Indeed, the previous round of outbreaks in 2014 to 2015 was also larger than normal by comparison to other years and may hold the key to identification of climate factors that may have been intensifying into 2019. Questions remain regarding what caused US outbreaks to be dominated exclusively by the VSNJV serotype since the last VSIV outbreak in 1997 to 1998 and, subsequently, what changed that allowed VSIV to appear and surge alone so successfully in 2019. Clinically, the VSNJV and VSIV presented across the outbreaks quite similarly with the full gamut of lesion types represented and neither virus serotype looking any more or less virulent in the animals than the other.

Phylogenetic analysis supports the occurrence of an overwintering event of VSIV between the 2019 and 2020 outbreaks.[18] Although overwintering of the virus was an expected event based on historic occurrences of the same pattern, there were several completely unexpected outcomes that followed. Based on study of the 2004 to 2006 and 2014 to 2015 outbreaks and the dynamics previously described on incursion years versus expansion years, the 2020 outbreak was expected to begin with new cases in all the same states where last observed in 2019 and then expand outward from those saturated regions. It began as predicted with the first cases of 2020 identified early in the season and in previously affected areas in the lower southwestern states before expanding northward, apparently mirroring expected temporal peaks of vector abundance. However, the expected cases in the Rocky Mountain states (Colorado, Utah, and Wyoming) were never observed. This region, with the most cases in 2019, had zero cases confirmed in 2020 despite strong surveillance and testing. It is known that this outcome is not due to an immunity of the previously exposed animals to the virus. High antibody titers to VSV from previous outbreak years have failed to prevent individual animals from developing lesions in the next outbreak year. Anecdotally, horse owners in historically affected VS-regions have reported that the same horse or horses in their herd developed lesions during every outbreak experienced since living there. In addition, several animals in each outbreak are typically identified presenting with new lesions after the previous lesions have healed on premises where the vector control is determined to have been inadequate. These cases suggest no resistance to infected vector re-exposure with the same virus, despite very

high antibody titers, and necessitate the premises be re-quarantined and a more aggressive vector control program administered. There were five such cases documented during the 2019 to 2020 outbreak.

One hypothesis for the 2020 absence of VS cases in the Rocky Mountain region is that the environmental conditions in the area did not support the high-volume of black flies and *Culicoides* spp. that were present in 2019. Specifically, Colorado, Utah, and Wyoming were experiencing extreme drought conditions throughout 2020, which may have impacted the vector hatch and overall insect populations. Further in-depth study is planned to evaluate this hypothesis and investigate other potential causes.

Another unexpected outcome in the 2020 outbreak was the development of a new outbreak region in the Kansas/Missouri/Oklahoma/Arkansas area. Although Kansas and Oklahoma each confirmed a single VSV-infected premises in 2019 in counties bordering active VSV-infected states, neither state had previously reported cases in at least the past 50 years. Kansas and Oklahoma were anticipated to identify more cases in 2020 in western portions of the states where 2019 cases were found, but instead, the 2020 outbreak erupted far to the east in both states and spilled over into western Missouri and northwest Arkansas. More study is needed to evaluate how the virus moved and flourished further east than expected.

Finally, there was a new 2020 incursion of a VSNJV serotype virus in south Texas during the ongoing VSIV outbreak occurring in the western part of the state hundreds of miles away, which is a rare dynamic last observed in the 1997 to 1998 outbreak and has never been fully explained. It is unknown what, if any, VS cases were occurring on the other side of the border in Mexico at the same time, which could provide better insight to the situation. Full genomic sequencing and phylogenetic analysis are planned to investigate the potential origin of both viruses and the relationship of the 2019 and 2020 isolates to viruses circulating more recently in Mexico. All of these unusual occurrences during the 2019 and 2020 outbreaks may be indicators of changes in climatic and environmental factors inducing a noticeable shift in the epidemiology of a historically-observed vector-borne disease.

SUMMARY

VS is a vector-borne livestock disease caused by VSNJV or VSIV. The disease circulates endemically in northern South America, Central America, and Mexico and only occasionally causes outbreaks in the United States. Veterinarians are required to report suspected cases to state and federal animal health officials. Over the past 20 years, VS outbreaks in the southwestern and Rocky Mountain regions occurred periodically with incursion years followed by virus overwintering and subsequent expansion outbreak years. Regulatory response by animal health officials aims to prevent the spread of disease by animals with lesions and manages trade impacts. Equine practitioners play a significant role during VS outbreaks through initial identification and reporting of cases, diagnostic sample collection and submission, management of affected animals, assisting in premises quarantine count-downs and releases, and advising equine owners on biosecurity and vector mitigation procedures. VSV is a zoonotic pathogen that can be transmitted to humans through direct contact with animals that have lesions. Personal protective equipment and good biosecurity practices should be used by veterinarians and animal handlers when handling all animals with active VS lesions. Recent US outbreaks of VS highlight potential climate change impacts on insect vectors or other transmission-related variables, which may result in shifting epidemiology of the disease in future outbreak years.

CLINICS CARE POINTS

- Vesicular stomatitis (VS) is a disease reportable to state and federal animal health officials in the United States. Veterinarians suspecting VS in a clinical animal should contact either the State Veterinarian or the federal Area Veterinarian in Charge (AVIC) for the state in which the animal is located.
- Diagnostic samples to collect in suspect VS cases include a serum sample and swabs of the lesions in viral transport media. Samples must be submitted to a United States Department of Agriculture (USDA)-approved vesicular stomatitis virus (VSV) laboratory with the authorization of the State Veterinarian or federal AVIC.
- VS is a self-limiting disease and the lesions in most affected horses and other livestock heal within a couple of weeks without veterinary intervention; however, some older animals, or those with underlying health conditions, may require supportive care, especially in cases with severe oral lesions where the animals cease to eat or drink.
- Isolation of affected animals and implementation of aggressive vector control measures is imperative to reduce spread of VSV during an outbreak.
- VSV is a zoonotic pathogen that can be transmitted to humans through direct contact with animals with lesions. Personal protective equipment and good biosecurity practices should be used by veterinarians and animal handlers when handling livestock with active VS lesions.

DISCLOSURE

The author has nothing to disclose.

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