

Vesicular Stomatitis in the U.S.

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Vesicular stomatitis (VS) is a vector-borne livestock disease caused by vesicular stomatitis New Jersey virus (VSNJV) or vesicular stomatitis Indiana virus (VSIV). The disease circulates endemically in northern South America, Central America, and Mexico and only occasionally causes outbreaks in the United States. Over the past 20 years, VSNJV outbreaks in the southwestern and Rocky Mountain regions occurred with incursion years followed by virus overwintering and subsequent expansion outbreak years. Regulatory response by animal health officials is deployed to prevent spread from lesioned animals. The 2019 VS incursion was the largest in 40 years, lasting from June to December 2019 with 1144 VS-affected premises in 111 counties in eight states (Colorado, Kansas, Nebraska, New Mexico, Oklahoma, Texas, Utah, and Wyoming) and was VSIV serotype, last isolated in 1998. A subsequent expansion occurred from April to October 2020 with 326 VS-affected premises in 70 counties in eight states (Arizona, Arkansas, Kansas, Missouri, Nebraska, New Mexico, Oklahoma, and Texas). The primary serotype in 2020 was VSIV, but a separate incursion of VSNJV occurred in south Texas. Summary characteristics of the outbreaks are presented along with VSV-vector sampling results and phylogenetic analysis of VSIV isolates providing evidence of virus overwintering.

Keywords: vesicular stomatitis ; livestock disease

1. 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 2–10 years in the United States ^[1]. Equids, such as horses, mules, and donkeys, are the most commonly affected species in U.S. 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 ^[3]. Lesions in the mouth and on the tongue usually cause hypersalivation and anorexia while coronary band lesions often produce lameness. The disease is self-limiting and the lesions in most affected 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 3–5 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 ^[4]; therefore, immediate reporting to state and federal animal health officials of VSV-like lesions is required in the U.S. to first rule out FMD infection using appropriate diagnostic assays.

Transmission of VSV to livestock occurs mainly through biting insects ^[4]; however, 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, such as 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 to be naturally infected with VSV in the wild ^{[7][8][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 vesicular stomatitis viruses from U.S. outbreaks have indicated that they arise from viruses circulating in Mexico [11][12][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, which 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 prior to outbreaks being recognized in Texas, New Mexico, and/or Arizona in the U.S. These years have been termed incursion years for U.S. 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]. 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 thus 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 U.S. 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 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. Additionally, the large numbers of cattle in the western U.S. 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 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 U.S. 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. While the World Organization for Animal Health (OIE) removed VS from its list of internationally reportable diseases in 2015, the U.S. 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.

2. Vesicular Stomatitis in the United States with Focus on 2019 and 2020 Outbreaks

Over the past 20 years, VS outbreaks in the U.S. 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 4–8 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**.

Table 1. Summary of VS outbreaks in the U.S. within the past 20 years including outbreak year, affected states, virus serotype, and number of affected livestock premises.

Outbreak Year	Number States Affected	States	VSV Serotype	Number 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

Outbreak Year	Number States Affected	States	VSV Serotype	Number Affected Premises
2019	8	CO, KS, NE, NM, OK, TX, UT, WY	VSIV	1144
2020	8	AR, AZ, KS, MO, NE, NM, OK, TX	VSIV, VSNJV (TX)	326

3. Discussions

The 2019 and 2020 VS outbreaks shared some characteristic features of historic outbreaks in the U.S., but also had several unexpected attributes. The factors involved that boosted the 2019 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 2014–2015 were 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 U.S. outbreaks to be dominated exclusively by the VSNJV serotype since the last VSIV outbreak in 1997–1998 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 suggests the occurrence of an overwintering event of VSIV between the 2019 and 2020 outbreaks. While overwintering of the virus was an expected event based on historic occurrences of the same, there were several completely unexpected outcomes that followed. Based on study of the 2004–2006 and 2014–2015 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. We know 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. Additionally, 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 2019–2020 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. While 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. We presented vector collection data here indicating that VSV-infection in central Kansas may have pre-dated the southeastern Kansas cases and been missed, but more study is needed to evaluate how the virus moved and flourished further east than expected. Full genomic sequencing and phylogenetic analysis of the viral isolates from this region are planned to determine the geographic distribution of other closely related lineages from 2020, which might indicate the source of a progenitor virus.

Finally, the new 2020 incursion of a VSNJV serotype virus in south Texas was another unexpected development during the outbreak. Texas, in fact, had cases of both VSIV and VSNJV simultaneously in 2020. While the new VSNJV incursion began in Starr and Zapata Counties along the Mexican border in deep south Texas and moved directly northward to

McMullen and Kerr Counties in south-central Texas, cases of VSIV were simultaneously confirmed in far west Texas in El Paso and Hudspeth Counties. While it stands to reason that west Texas was geographically involved in the same VSIV outbreak as its neighboring state New Mexico, what is more perplexing was the finding of both a VSIV-infected premises and a VSNJV-infected premises with lesion onset dates within 2 days of each other and located approximately 28 miles apart in Zapata County, Texas. No other VSIV affected premises were found in south Texas and the nearest VSIV infected premises in west Texas was approximately 450 miles away. 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 better explain 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.

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