Vesicular Stomatitis

Sore Mouth of Cattle and Horses, Indiana Fever

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Importance

Vesicular stomatitis is an important viral disease of livestock in the Americas. It can affect ruminants, horses and pigs, causing vesicles, erosions and ulcers on the mouth, feet and udder. Although deaths are rare, these lesions can result in pain, anorexia and secondary bacterial mastitis, and some animals may lose their hooves after developing laminitis. Vesicular stomatitis viruses are endemic from southern Mexico to northern South America, but regularly spread north and south from these regions, causing outbreaks and epidemics. While these viruses are no longer endemic in the U.S., they are introduced periodically into the southwestern states, and can sometimes spread farther north. These outbreaks end after freezing temperatures kill the insect vectors that transmit vesicular stomatitis; however, the introduced viruses may overwinter for a year or two, re-emerging in the spring. Vesicular stomatitis is clinically indistinguishable from several other vesicular diseases of livestock including foot-and-mouth disease (FMD). Prompt diagnosis is important not only for containing vesicular stomatitis outbreaks, which can restrict international trade, but also in preventing major livestock diseases such as FMD from spreading undetected. People who work with vesicular stomatitis viruses or come in close contact with infected animals sometimes become infected and develop an influenza-like illness.

Etiology

Vesicular stomatitis can be caused by four named viruses in the genus Vesiculovirus (family Rhabdoviridae): vesicular stomatitis New Jersey virus (VSV-NJ), vesicular stomatitis Indiana virus (VSV-IN), vesicular stomatitis Alagoas virus (VSV-AV) and Cocal virus. The viruses that cause vesicular stomatitis have been divided into two major serotypes, New Jersey and Indiana. VSV-NJ belongs to the New Jersey serotype. The remaining three viruses are members of the Indiana serotype, which is currently subtyped serologically into 3 groups. VSV-IN belongs to the Indiana 1 subtype, Cocal virus to the Indiana 2 subtype, and VSV-AV to Indiana 3.

The genus Vesiculovirus also contains several related viral species, which, as of 2014, included Piry virus, Maraba virus, Isfahan virus and Chandipura virus. Chandipura virus has been associated with influenza-like illnesses and encephalitis in humans in India. This virus may also infect ruminants and pigs in the area, based on serological studies, although there is currently no evidence that it causes disease in these species. Isfahan virus may circulate between gerbils, sandflies and people in the Middle East, but it is not thought to infect domesticated animals. Piry and Maraba viruses were found in South America. Experimental infection with Piry virus caused vesicular lesions at the inoculation site in horses but not in any ruminant species. Maraba virus has only been isolated from insects. None of these viruses, including Chandipura virus, is currently considered to be an agent of the livestock disease vesicular stomatitis. However, they are thought to be pathogens or potential pathogens for people working in laboratories.

Additional vesiculoviruses have been reported in the literature, but have not yet been officially accepted as separate viral species.

Species Affected

Vesicular stomatitis mainly affects equids, cattle and swine. Sheep and goats can develop clinical signs, although this is uncommon, and South American camelids have also been affected. Antibodies to vesicular stomatitis viruses (VSV) have been found in many other species including deer, pronghorn (Antilocapra americana), bighorn sheep (Ovis canadensis), bats, raccoons (Procyon lotor), opossums (Didelphis marsupialis), anteaters (Tamandua tetradactyla), bobcats (Lynx rufus), bears, wild canids, dogs, non-human primates, rabbits, various rodents, fruit bats (Artibeus spp.), turkeys and ducks. Additional non-livestock species (e.g., guinea pigs, hamsters, mice, ferrets, opossums, chickens) have been infected experimentally.

Livestock are not thought to maintain vesicular stomatitis viruses long term, and their reservoir or amplifying hosts are unknown. Deer mice (Peromyscus sp.) can become viremic, and small rodents have been proposed as possible reservoir hosts;
however, this remains speculative. Some authors have even suggested that vesicular stomatitis viruses might be plant viruses found in pastures, with animals at the end of an epidemiological chain.

**Zoonotic potential**

Humans can be infected with vesicular stomatitis viruses, and may become ill.

**Geographic Distribution**

Vesicular stomatitis viruses are endemic in southern Mexico, Central America, and northern South America. VSV-NJ was also endemic on Ossabaw Island, Georgia in the U.S for decades; however, recent surveys could find no evidence for its presence. Reductions in the feral swine population on this island may have resulted in its eradication.

VSV-NJ and VSV-IN regularly cause outbreaks in areas of North and South America where they are not endemic. However, viruses are not maintained in these regions long term. VSV-AV and Cocal virus have been only been detected in limited areas of South America, to date.

Vesicular stomatitis is not thought to be endemic outside the Western Hemisphere, although other vesiculoviruses do circulate in the Eastern Hemisphere.

**Transmission**

The transmission of vesicular stomatitis is incompletely understood. The relative importance of the various transmission routes in each situation is also sometimes unclear.

Insect vectors are thought to introduce VSV into populations of domesticated animals. Sand flies (Lutzomyia sp.), blackflies (family Simuliidae) and Culicoides midges can act as biological vectors. Sand flies seem to be important vectors in endemic areas, but have a limited flight range and are not thought to spread these viruses long distances. Blackflies are believed to be particularly important vectors in parts of the western U.S. Where the virus originates, before entering livestock populations, is still uncertain. Once animals develop lesions, however, insects may become infected by feeding on viruses in these lesions or contaminated secretions. In addition, infected blackflies can transmit VSV to other blackflies feeding at the same time on a host, even if the host is not infected. Transovarial transmission has been demonstrated in sandflies and blackflies in the laboratory, and may be possible in Culicoides. It might contribute to virus overwintering in cold climates.

Vesicular stomatitis viruses have also been found in other insects including Aedes mosquitoes, Chloropidae (eye gnats), and flies in the genus Musca or family Anthomyiidae. These insects may act as mechanical vectors. Migratory grasshoppers (Melanoplus sanguinipes) have been proposed to play a role in spreading VSV. In laboratory experiments, these grasshoppers could be infected from plants or other sources, and cattle that ate grasshoppers developed clinical signs. In the field, cattle may ingest large numbers of molting grasshoppers while grazing, as these insects are immobile during that stage.

Once it has been introduced into a herd, vesicular stomatitis can spread from animal to animal by direct contact. Broken skin or mucous membranes may facilitate entry of the virus. Infected animals shed VSV in vesicle material. Viruses from lesions in the mouth and on the muzzle can contaminate saliva, and to a lesser extent, nasal secretions. However, VSV has also been detected in the saliva of some experimentally infected horses that did not have oral lesions. Vesicular stomatitis viruses are not considered to be shed in feces, urine or milk, although they have been detected occasionally in the feces of symptomatic, experimentally infected swine. Livestock can be infected experimentally by aerosols in the laboratory, but this route did not result in skin lesions in most species. VSV does not appear to cross the placenta or cause fetal seroconversion.

Contaminated fomites such as food, water and milking machines are also thought to play a role in transmission. VSV in saliva was reported to survive for 3-4 days on milking pails, mangers and hay. Viruses dried onto glass, plastic or stainless steel in the laboratory lost a great deal of infectivity within the first 1-6 days at 22°C, although some infectious virus was still recovered after 2-8 days. However, survival in liquid medium that contained organic material (i.e., cell culture medium with 5% fetal bovine serum) was prolonged, especially at cold temperatures. These suspensions did not lose significant infectivity for at least 4 weeks at 4°C. Approximately 90% of infectious virus disappeared during the first 8 days in such suspensions incubated at 28°C, but some viable viruses were still present after 4 weeks. At 37°C, 90% of infectivity had been lost by 3 days, and no live viruses could be detected after 21 days. Only 10% of the viruses suspended in cell culture medium without serum were still viable by 4-12 days at 4°C.

People can be infected by contact with lesions or secretions from infected animals, particularly vesicular fluid and saliva, or when manipulating VSV in the laboratory. Aerosol transmission has been reported in laboratories, and some cases occurred after accidental inoculation (needlestick injuries). Some people are probably infected through insect bites, as antibodies to these viruses are common in endemic regions.

**Disinfection**

Vesicular stomatitis viruses are susceptible to numerous disinfectants including 1% sodium hypochlorite, 40-70% ethanol, 2-propanol, aldehydes (e.g., 0.5%-2% glutaraldehyde, formaldehyde), 1% cresylic acid, phenolic disinfectants and detergents. These viruses appear to be more susceptible to inactivation by acid (e.g., pH 2) than alkaline conditions. VSV are also susceptible to UV light including sunlight, or heat (e.g., 4 minutes at 55°C, or one minute at 60°C).
Infections in Animals

Incubation Period

The incubation period is usually 3-7 days, but longer or shorter incubation periods have been reported. During one outbreak in California, the average incubation period was approximately 9 days. Lesions and/or fever developed in 1-3 days in some experimentally infected livestock.

Clinical Signs

Vesicular stomatitis is characterized by vesicles, papules, erosions and ulcers. These lesions occur mainly in and around the mouth, and on the feet, udder (especially the teats) and prepuce. The predominant sites affected may differ between outbreaks, and are probably influenced by the feeding preferences of the insect vectors. In the southwestern U.S., lesions are reported to be more common around the mouth than on the feet. Subclinical infections also seem to be common in livestock.

A transient fever can be seen early in clinical cases, but it may disappear by the time the animal is examined. Excessive salivation is often the first sign noticed. Closer examination may reveal blanched areas and the characteristic raised vesicles (blisters). Vesicles differ widely in size; while some are as small as a pea, others can cover the entire surface of the tongue. They quickly rupture to become erosions or ulcers, and vesicles may be absent by the time the animal is examined. The lips and tongue (especially the dorsal surface) are often affected in the mouth. However, lesions can also be present on the gums and palate. Ulcers and erosions in the mouth frequently coalesce to form large, denuded areas of mucosa with epithelial tags. Severe oral sloughing was unusually common in horses during one recent outbreak in the U.S. Lesions can also occur in other locations on the muzzle or snout, which may swell as a result of tissue damage. When foot lesions are present, they are usually located on the coronary band and/or the interdigital spaces of the hooves. Coronitis, with inflammation and edema extending up the lower leg, is the typical presentation. In pigs, lesions can sometimes appear first on the feet, although the mouth and snout are also affected frequently. In some horses, vesicles and erosions may go unnoticed and the disease may appear as crusting scabs that affect sites such as the muzzle, lips, ventral abdominal wall, prepuce and udder.

Vesicular stomatitis lesions are painful and can cause anorexia, refusal to drink and lameness. Some animals may develop a catarrhal nasal discharge, bleeding from ulcers, or a fetid mouth odor. Lesions on the coronary band may result in laminitis and even loss of the hoof (or claws in pigs). Teat lesions can lead to mastitis from secondary infections. Weight loss may be severe, and milk production can drop in dairy cows. Some infected cattle were reported to be normal but had a poor appetite. Unless secondary bacterial infections or other complications develop, animals usually recover within approximately 2-3 weeks. However, if recovering animals are transported, the stress may cause new lesions to develop.

There is limited information about other species; however, fever and oral lesions also occurred in experimentally infected pronghorn and deer. In one early study, experimental subcutaneous inoculation of VSV-NJ caused fatal illnesses with neurological signs in infant wild mice, hamsters, marmosets, anteaters and opossums. Vesicular lesions were not seen in these young animals. Adults remained asymptomatic when inoculated by the same protocol. In a recent study, opossums experimentally infected with VSV-NJ developed ulcers and erosions at the inoculation site on the tongue, and sometimes had petechiae, ecchymoses and ulcers on the cheeks. Opossums inoculated via snout lesions had inflammation of the nose and erosions on the nasal septum, with or without a serous nasal discharge. A litter of young, nursing opossums remained asymptomatic although their dam had lesions, and they may have been protected by maternal antibodies.

Post Mortem Lesions

Necropsy lesions resemble the lesions in live animals. Heart and rumen lesions, which may be seen in foot and mouth disease, do not occur in cases of vesicular stomatitis.

Diagnostic Tests

Vesicular stomatitis viruses can be found in vesicle fluid, swabs of ruptured vesicles, the epithelium over unruptured vesicles, and epithelial flaps from freshly ruptured vesicles (e.g., epithelial tags from the mouth). Sedation is recommended before sample collection, as the lesions are very painful. If these samples are not available, esophageal/pharyngeal fluid can be collected with a probang cup from cattle, or throat swabs may be taken from pigs. VSV can be detected in oral and nasal secretions for up to 7 days after infection. Electron microscopy of tissue samples may be helpful in distinguishing VSV from some other viruses that cause vesicular lesions, such as foot and mouth disease virus or swine vesicular disease virus.

Many cell lines can be used to isolate VSV from clinical samples. Virus recovery is also possible in embryonated eggs, and animal inoculation (mice) was sometimes employed in the past. The identity of cultured virus can be confirmed with immunofluorescence, complement fixation or ELISAs to detect viral antigens, or with other tests such as reverse transcription polymerase chain reaction (RT-PCR) assays. Antigen capture (indirect sandwich) ELISAs are often used to identify the viral serotype. Some RT-PCR tests can also distinguish New Jersey and Indiana serotypes, and one group in Brazil reported using RT-PCR to confirm the identity of isolated VSV-AV and distinguish these viruses from Cocal virus.

VSV antigens can be detected in tissue samples or vesicle fluid with an antigen capture ELISA, complement fixation or virus neutralization. Descriptions of other antigen detection assays, including lateral flow devices,
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Vesicular Stomatitis can spread between animals by direct contact, as well as via insect-mediated transmission. During outbreaks, uninfected livestock should keep away from any animals that could be infected. Quarantines and animal movement restrictions can help reduce virus spread. There should be no movement of animals from a quarantined property for at least 21 days after all lesions are healed, unless the animals are going directly to slaughter. Isolating symptomatic animals may also be helpful within a herd. Horses appear to be most contagious for the first 6 days after infection. Good sanitation and disinfection can reduce the spread of the virus on fomites. Lower attack rates have been reported on dairies where feed and water troughs were cleaned regularly. Milking equipment should also be disinfected between uses, and cows with lesions should be milked last. The avoidance of hard or abrasive feeds may prevent oral abrasions that could facilitate infections.

Pastured livestock are more likely to become infected than animals with access to a shelter or barn. Stabling animals during outbreaks seems to decrease the risk of disease. During one outbreak in the U.S., animals were also more likely to develop vesicular stomatitis if there were sources of running water (e.g., streams, irrigation canals) within a quarter mile, probably because water sources encourage higher vector populations. If practical (and permitted), moving animals farther from such locations during outbreaks might reduce the risk of infection. Various insect control measures are also thought to be helpful, though their efficacy is not absolute. Insecticide applications should include the inner surface of the pinna, where blackflies tend to feed.

Commercial vaccines are available in some endemic regions of Central and South America. Vaccines are not available in the U.S.

Morbidity and Mortality

Outbreaks of vesicular stomatitis tend to occur each year in endemic areas. Both explosive epidemics and slowly spreading outbreaks with relatively few cases (an endemic pattern) can be seen in these regions. VSV-NJ is involved more often than VSV-IN, while VSV-AV is seen only in limited regions. Outbreaks caused by Cocal virus are reported to occur sporadically in Argentina and Southern Brazil. Vesicular stomatitis is seasonal. Although cases may occur throughout the year, they are particularly common at the end of the rainy season or early in the dry season.

Epidemics occur periodically outside endemic areas, spreading south in South America or north in North America. These outbreaks can sometimes involve hundreds or thousands of farms, as well as wildlife. Outbreaks in the U.S. tend to occur at approximately 5-10 year intervals. In the past, they were seen in the Southwest, the upper Mississippi, and the Rocky and Appalachian mountains; however, most recent epidemics have affected only the western states. These outbreaks appear to be caused by new introductions of viruses from endemic regions, often Mexico. They tend to begin in the spring or early summer in states bordering Mexico, then spread north, often along riverways and in valleys. Some epidemics may extend as far as Canada. The climatic and environmental factors affecting the extent of an outbreak are poorly understood, although transportation of animals has been shown to spread the virus in some cases. Epidemics usually end with the first frosts, but viruses sometimes overwinter outside endemic areas for up to 3 years, re-emerging in the spring. Until the early 1970s, VSV-NJ also affected animals in an endemic pattern in the Southeast; however, the remaining reservoirs of these viruses in wildlife or feral pigs seem to have disappeared.
The morbidity rate for vesicular stomatitis is highly variable, and ranges from 5% to more than 90%. Estimates of typical morbidity differ, and are likely to be affected by the animals’ previous exposure to VSV and other factors. Some authors report that only 10-20% of the animals in a herd are usually symptomatic, with up to 100% seroconverting. In some nonendemic areas, however, morbidity rates may approach 40-60% in susceptible populations. Some outbreaks tend to affect cattle more often than horses, or vice versa. Most clinical cases occur in adults; young cattle and horses under a year of age are uncommonly affected. Deaths are very rare in cattle and horses, but higher mortality rates have been seen in some pigs infected with VSV-NJ. Cattle that develop mastitis or horses with laminitis may be culled due to these sequelae.

Infections in Humans

Incubation Period

Incubation periods of 1-6 days have been reported in the limited number of human cases described.

Clinical Signs

Some of the most thoroughly documented clinical cases are from a handful of published reports describing infections in laboratory workers. Symptomatic vesicular stomatitis has also been reported in people infected via the environment; however, laboratory confirmation in these reports is sometimes unavailable or inadequate.

In general, vesicular stomatitis is reported to be an acute illness that resembles influenza, with symptoms that may include fever, muscle aches, headache, malaise, enlarged lymph nodes and conjunctivitis. Some authors have suggested that conjunctivitis or cheilitis may be a common early sign. The fever is sometimes but not always biphasic. One person with a needlestick injury developed acute nausea, vomiting and diarrhea, in addition to nonspecific flu-like signs. The gastrointestinal signs resolved spontaneously within 24 hours. Some infected people also had vesicles in the mouth or on the lips or hands; in other cases, no vesicles were present. Most people are reported to recover without complications within 4-7 days. However, one case of severe encephalitis was attributed to VSV in a 3-year-old child in Panama.

Many or most infections with vesicular stomatitis viruses may be subclinical. Seroconversion without obvious signs of illness is reported to be common among laboratory workers, as well as in human populations in endemic regions.

Diagnostic Tests

Most human cases have been diagnosed by serology, using tests such as serum neutralization and complement fixation. Virus isolation can be attempted from the blood, but viremia is very brief and this tends to be unsuccessful.

If vesicles are present, attempts should be made to isolate the virus from vesicle fluid and epithelium.

Treatment

Treatment is supportive, as needed.

Control

Protective clothing and gloves should be used when handling infected animals, and biological safety precautions should be taken in the laboratory.

Morbidity and Mortality

Infections with VSV were seemingly common among laboratory workers and animal handlers before the advent of modern biological safety procedures and equipment. In one study, 54 of 74 laboratory workers or animal handlers had antibodies to these viruses. Some studies have reported that 48–100% of the population in Central America is seropositive, and one study detected antibodies in 25% of the people tested in southeastern Georgia, U.S. when outbreaks were common among livestock there in the 1950s. In contrast, a later study found that the infectivity of a VSV-NJ virus for veterinarians, laboratory workers and other risk groups was relatively low during the 1982-1983 epidemic in the U.S. Evidence of infection was only detected in 17 of 133 people exposed to the virus, and relatively close contact with sources of virus seemed to be necessary.

The percentage of human infections that become symptomatic is unknown. Although some sources suggest clinical cases are rare, others point out that human infections may be underreported as they can easily be misdiagnosed as influenza. In the study above, 31 of the 54 seropositive laboratory workers or animal handlers reported having had a mild, acute illness consistent with vesicular stomatitis. In most cases, clinical cases have had no serious consequences. Laboratory infections have resolved without complications, and no deaths have been reported. Nevertheless, there is one reported serious case, with encephalitis attributed to VSV in a young child.

Internet Resources

Public Health Agency of Canada. Pathogen Safety Data Sheets


The Merck Veterinary Manual

http://www.merckvetmanual.com/mvm/index.html

United States Animal Health Association (USAHA).

Foreign Animal Diseases.


USDA-APHIS

http://www.aphis.usda.gov/
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World Organization for Animal Health (OIE)
http://www.oie.int

OIE Manual of Diagnostic Tests and Vaccines for Terrestrial Animals
http://www.oie.int/international-standard-setting/terrestrial-manual/access-online/

OIE Terrestrial Animal Health Code
http://www.oie.int/international-standard-setting/terrestrial-code/access-online/

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