VESICULAR EXANTHEMA OF SWINE VIRUS

Prepared for the Swine Health Information Center
By the Center for Food Security and Public Health,
College of Veterinary Medicine,
Iowa State University
September2015

SUMMARY

Etiology

- Vesicular exanthema of swine virus (VESV) is a non-enveloped RNA virus in the family *Caliciviridae.*
- There 40 known serotypes within the VESV species, collectively known as marine vesiviruses. These include Sam Miguel sea lion virus, which is morphologically indistinguishable from VESV.

Cleaning and Disinfection

- Caliciviruses are stable in the environment and resistant to heat.
- They are generally susceptible to sodium hypochlorite (0.1%), sodium silicate (2%), citric acid (2%), acetic acid (5%), and phenol (5%).

Epidemiology

- VESV was first detected in swine in California in 1932. The virus was eradicated and is now considered a foreign animal disease.
- In addition to swine, marine vesiviruses can infect pinnipeds (seals), cetaceans, cattle, horses, skunk, primates, reptiles, and fish.
- VESV has occasionally been isolated from humans with blisters; however, the virus is not considered to be a serious public health threat.
- VESV does not currently exist in swine anywhere in the world. Other marine vesiviruses remain prevalent along the Pacific coast of the United States.
- VESV is highly infectious in swine and can cause morbidity of up to 90%.

Transmission

- The 1932 outbreak was linked to feeding of uncooked garbage and fish scraps to pigs. VESV can also be spread via direct contact with vesicular fluid, oral and nasal secretions, and vesicle coverings.

Infection in Swine/Pathogenesis

- VESV-induced vesicular disease is clinically indistinguishable from vesicular disease caused by foot-and-mouth disease virus, vesicular stomatitis virus, swine vesicular disease virus, or Seneca Valley virus.

- In swine, vesicles form on the snout, oral mucosa, soles of the feet, coronary bands and between the toes. Lesions may also occur on teats.
- VESV has also been associated with reproductive failure in swine and mild encephalitis.

Diagnosis

- VESV can be grown in cell culture. Electron microscopy, reverse transcriptase polymerase chain reaction (RT-PCR), and real-time RT-PCR can be used to detect antigen and nucleic acids respectively.
- Available serological tests include complement fixation, virus neutralization, and enzyme-linked immunosorbent assay (ELISA).

Immunity

- There are currently no available vaccines for VESV.

Prevention and Control

- To prevent infection with VESV, all garbage and fish fed to swine must be cooked to 100°C for 30 minutes.
- Standard biosecurity practices should also be in place.

Gaps in Preparedness

- Development of a vaccine for VESV is complicated by the presence of multiple serotypes.
- Better understanding of the host range of marine vesiviruses is needed.

OVERVIEW

Vesicular exanthema of swine virus (VESV) is a non-enveloped, positive-sense, single-stranded RNA virus belonging to the genus *Vesivirus* in the family *Caliciviridae.* There are two species within the *Vesivirus* genus: feline calicivirus (FCV) and VESV. There are approximately 40 serotypes of VESV: 13 are referred to as VESV, 17 are referred to as San Miguel sea lion virus (SMSV), and the remaining serotypes are named after the species they were discovered in. Serotypes are genetically similar and non-host-specific. Collectively, VESV, SMSV, and others within the VESV species are considered marine vesiviruses, although they are capable of causing pathogenic infections in several terrestrial animals.

VESV is known for causing a highly infectious, vesicular disease in febrile swine and is clinically indistinguishable from foot-and-mouth disease, swine vesicular disease, and vesicular stomatitis disease. VESV originated in a swine herd in California in 1932 and spread throughout the United States in the early 1950s. Efforts to eradicate VESV were successful and it was declared "exotic" in 1959. VESV in swine has not been documented in any other regions of the world. In 1972, San Miguel sea lion virus (SMSV) was isolated from California sea lions with vesicular and reproductive disease. SMSV is biophysically indistinguishable from VESV and is capable of producing vesicular disease in swine. In retrospect, VESV is believed to have originated from SMSV. SMSV serotypes continue to circulate in wild and domesticated animals along the California Pacific coastline.

Natural VESV infections have occurred in a variety of marine and terrestrial animals including pigs, pinnipeds (seals), cetaceans, cattle, horses, skunk, primates (including humans), reptiles, and fish. Over half of the marine vesiviruses have induced vesicular disease in pigs experimentally. Oceanic fish are the suspected reservoir species for VESV. Marine vesiviruses are not considered a public health threat, but occasional human infections have been documented.

VESV is a highly infectious disease but seldom results in death. It can be introduced in swine herds through untreated garbage and fish or by direct contact with vesicle fluid, vesicle coverings, or oral and nasal secretions from infected animals. Vesicles form within 24 hours post-infection and rupture 24-48 hours after formation. Ruptured vesicles ulcerate and begin healing approximately ten days post-infection. Infected pigs become febrile coincident with vesicle formation and return to normal after most vesicles have ruptured. Reproductive failure has also been associated with VESV. Diagnosis is confirmed using serology, electron microscopy, or reverse transcriptase polymerase chain reaction (RT-PCR).

There is no treatment or vaccine for VESV. Mortality is uncommon with VESV-induced infections and animals generally heal one to two weeks after the onset of clinical signs. Despite VESV eradication from swine, SMSV and other serotypes are likely still circulating along the North American Pacific coastline. Neutralizing anti-SMSV antibody has been documented in several species including marine mammal species, feral swine, and a donkey. The presence of marine vesiviruses in wild and marine mammals indicates that VESV is still a threat to the United States swine industry. Further research is needed to definitively determine the reservoir hosts for VESV.

LITERATURE REVIEW

1. Etiology

1.1 Key Characteristics

Vesicular exanthema of swine virus (VESV) is a non-enveloped, positive-sense, single-stranded RNA virus belonging to the genus *Vesivirus* in the family *Caliciviridae.*

1.2 Strain Variability

The *Vesivirus* genus is comprised of two species: feline calicivirus (FCV) and VESV. Several additional viruses, distinct from VESV and FCV, may be classified as vesiviruses but have not been recognized as a species. These include canine calicivirus and mink calicivirus.[1,4]

There are 40 estimated serotypes within the VESV species that are phylogenetically referred to as marine vesiviruses.[1] Thirteen serotypes are known as VESV (i.e., VESV-A48, VESV-B34), 17 as San Miguel sea lion virus (SMSV) (i.e., SMSV-1, SMSV-2), and the remainder are named by the host they were isolated from: for example bovine calicivirus Bos-1 (BCV Bos-1) and Stellar sea lion virus V810 (SSLV-V810).

2. Cleaning and Disinfection

2.1 Survival

Caliciviruses are generally stable in the environment and resistant to inactivation by heat.[1] Vesiviruses are labile below pH of 4.5–5.0.[4]

2.2 Disinfection

Caliciviruses are resistant to inactivation by heat and some chemicals (ether, chloroform, and mild detergents).[1] Exposure to the following chemicals for at least 2 minutes at 4°C, 25°C, and 37°C will completely inactivate VESV: sodium hypochlorite (0.1%), sodium silicate (2%), citric acid (2%), acetic acid (5%), and phenol (5%). VESV serotypes are more resistant to disinfectants than SMSV serotypes.[6]

3. Epidemiology

3.1 Species Affected

VESV first emerged in swine in California in 1932, and spread throughout the United States in the early 1950s. Although the original source of VESV remains unknown, the outbreak was linked to feeding uncooked garbage and fish scraps to swine. The US Secretary of Agriculture declared a national emergency and enforced eradication efforts, including requirements for proper treatment of garbage and fish fed to swine. Efforts were successful and VESV was declared “exotic” in 1959. However, in 1972 a pathogenic virus causing vesicular disease in California sea lions was isolated from throat and rectal swabs. The virus was named San Miguel sea lion virus (SMSV) and is morphologically indistinguishable from VESV.

Natural infections induced by marine vesiviruses can occur in swine, pinnipeds (seals), cetaceans, cattle, horses, skunk, primates (including humans), reptiles, and fish.[3,4,7,8] SMSV serotypes are endemic in many pinniped herds.[8] Over half of the marine vesiviruses have experimentally been capable of producing vesicles in swine, including bovine serotypes.[1,3,4,9] It is speculated that oceanic fish are the natural reservoirs for VESV.[3]

Although the VESV has been eradicated from domestic swine, other marine vesiviruses likely continue to circulate in natural reservoirs and several marine and terrestrial mammals near the California coastal zone. Serum neutralizing anti-SMSV and anti-VESV antibodies been found in feral swine, donkeys,

California sea lions, California gray whales, sperm whales, and sei whales near the California coastal zone.[10]

3.2 Zoonotic Potential

VESV is not thought to be a serious public health threat, but it has occasionally been documented as the causative agent in cases of human clinical disease. A 32-year-old male researcher, working closely with purified calicivirus isolates, developed flu-like illness followed by blister formation on his hands and feet. The fever subsided and blisters healed within one to two weeks. SMSV serotype 5 was isolated from the patient's lesions. The second partially documented human case was a handler of Stellar's sea lions that developed deep, painful blisters on the mouth and facial area. It was originally diagnosed as herpesvirus but 30 days later, a calicivirus closely related to SMSV was isolated from the patient's throat washings.[7]

Humans living on the Pacific Rim have been found to have neutralizing anti-SMSV antibodies. Human infection, neutralizing antibody to SMSV, and the non-specific host range of marine caliciviruses suggests that infection with VESV could extend to humans. [7]

3.3 Geographic Distribution

VESV was originally isolated in 1932 from swine with vesicular disease in California. The disease was contained from 1932–1951, but became widespread throughout the United States in 1952, affecting all major swine production areas. After the initiation of an eradication campaign requiring cooking of garbage and fish fed to swine, the last case of VESV was reported in 1956 in New Jersey. VESV is now considered a foreign animal disease.[2] VESV has not been reported in pigs in any other regions of the world. Although VESV has been eliminated in domestic swine, marine vesiviruses remain prevalent along the Pacific coast of the United States.[2]

3.4 Morbidity and Mortality

VESV serotypes are highly infectious in swine with morbidity of up to 90%.[2] Clinical disease seldom results in death[9] and specific data regarding mortality rates is unavailable.

4. Transmission

Historically, VESV was transmitted through ingestion of untreated garbage and fish scraps. The virus can also spread via direct contact with vesicular fluid, oral and nasal secretions, and vesicle coverings.[4,9]

5. Infection in Swine/Pathogenesis

VESV infection results in the formation of vesicles limited to non-haired portions of the integument and tongue 24 hours post infection.[9] Initially, vesicles are less than 2cm in diameter and thick-walled, containing a small amount of fluid. Two days post-infection (dpi) the vesicles are larger and thin-walled, containing large amounts of fluid. Generally, vesicles rupture three to four dpi or 24–48 hours after vesicle formation.[4,9] Rupture of lingual vesicles causes direct spread to the tonsillar epithelium. Occasionally secondary vesicle formation occurs. Epithelial cells are easily infected when a break in the skin allows exogenous or endogenous virus to access susceptible cells. Fluid released by the rupture of larger primary vesicles may be the source of secondary vesicle formation. Ulceration takes place four to seven dpi. Healing begins ten dpi and is well advanced by 15 dpi.[9] Experimental inoculation of pig kidney cells with VESV serotypes A48 and H54 indicate viral titers peak 8 hours post-infection and virus replication occurs in the cytoplasm of infected cells.[11]

Vesicle formation is accompanied by a fever that peaks at 41–42°C and begins one dpi through five dpi. Once most vesicles have ruptured, around 5 dpi, the fever begins to drop and returns to normal around 11 dpi.[9]

5.1 Clinical Signs
VESV-induced vesicular disease is clinically indistinguishable from vesicular disease caused by foot-and-mouth disease virus, vesicular stomatitis virus, swine vesicular disease virus, or Seneca Valley virus.[1] In swine, vesicles form on the snout, oral mucosa, soles of the feet, coronary bands and between the toes. Lesions may also occur on teats.[4] Both primary and secondary vesicle formation is possible.[9] VESV-induced disease rarely results in death but is highly infectious. VESV has also been associated with reproductive failure in swine.[5] Mild encephalitis can occur in swine with VESV infection. Clinical signs appear four to seven dpi and encephalitis severity does not worsen with time.

5.2 Postmortem Lesions
Histology and fluorescent antibody examination show intense fluorescence on the snout, tongue, coronary band and tonsillar epithelium. Extracellular fluid accumulation results in separation of individual epithelial cells causing tonofibrils and free-floating cells. Large numbers of inflammatory cells are present in the dermis, concentrated around vessels. Edema and focal necrosis can also be observed in draining lymph nodes.[9] Small, multi-focal, lymphocytic, perivascular cuffs accompanied by mild gliosis can be observed in the medulla oblongata.[9]

6. Diagnosis

6.1 Clinical History
Vesicles in the mouth and on the extremities of febrile swine is suggestive of VESV.[4] Clinical signs are indistinguishable from those caused by other vesicular diseases.

6.2 Tests to Detect Nucleic Acids, Virus, or Antigens
VESV can be readily propagated in mammalian cell cultures (commonly African green monkey kidney or porcine kidney cells).[1,4] Replication results in rapid and destructive cytopathic effects.[4] Electron microscopy can be used on epithelial tissue suspensions or after the passage of swine tissue cultures. RT-PCR and real-time RT-PCR have been developed to detect VESV nucleic acid.[12-14] Detection of antigen in tissues depends on specific antisera for each serotype.

6.3 Tests to Detect Antibody
Anti-VESV antibody can be detected using complement fixation, virus neutralization (VN), and enzyme-linked immunosorbent assay (ELISA). [4,15]

6.4 Samples
6.4.1 Preferred Samples
To detect VESV, viral titers are highest in gross epithelial lesions.[9]

6.4.2 Oral Fluids
VESV titers were found 24 hours after transdermal inoculation of VESV serotype A48 in swine. In oral swabs, virus persisted for three days and in nasal swabs, virus persisted for five days. Virus titers were generally higher in nasal swabs.[9]

7. Immunity

7.1 Post-exposure
Neutralizing anti-VESV antibody increases dramatically three dpi and peaks seven to ten dpi. Virus can only be detected six to seven dpi; therefore, it is presumed that neutralizing antibody formation is protective.[9] Anti-VESV antibody can be detected for six months post-infection. [4]

7.2 Vaccines
There is no vaccine for VESV. As multiple serotypes of VESV result in vesicular disease, developing a multivalent VESV vaccine to protect against all strains may pose a challenge.[4]

7.3 Cross-protection
Research on cross-protection between serotypes is unavailable.

8. Prevention and Control
The most important control measure is prevention of the introduction of VESV by cooking all garbage and fish fed to swine to 100°C for 30 minutes.[4] There is no treatment or vaccine for VESV infection.

When vesicular disease outbreaks occurred in 1932, authorities originally thought foot-and-mouth disease virus was the causative agent. They contained the disease initially through slaughter and burial of all swine, cattle, goats and other exposed animals. Quarantine, disinfection, and a 30 day wait period for restocking were also implemented. These eradication efforts were eventually discontinued and only quarantine was required. It wasn't until regulations on cooking garbage were enforced that VESV infections became scarce and VESV was eventually eradicated.[2]

9. World Organization for Animal Health (OIE) Terrestrial Animal Health Code
Clinical signs consistent with VESV-induced infection should be reported immediately to state and/or federal officials, as the disease is highly infectious and indistinguishable from other vesicular diseases. VESV is not included in the 2015 OIE Terrestrial Animal Health Code.

10. Gaps in Preparedness
VES-like caliciviruses are likely widespread near the North American Pacific Ocean and occasionally appear in domesticated and captive wildlife in the Western United States. This, coupled with the fact that VESV causes an acute and highly infectious vesicular disease, suggests that VESV remains a threat to the United States swine industry. Further research is needed to definitively determine the primary host of marine vesiviruses.

ACKNOWLEDGEMENTS

Funding for this project was provided by the Swine Health Information Center, Perry, Iowa

Authors, Center for Food Security and Public Health, College of Veterinary Medicine, Iowa State University:

- Sarah Horak, BS; 2nd year student,
- Kristin Killoran, PhD; 2nd year student
- Kerry Leedom Larson, DVM, MPH, PhD; Veterinary Specialist

Reviewers, Center for Food Security and Public Health, College of Veterinary Medicine, Iowa State University:

- Pamela Zaabel, DVM; Veterinary Specialist
- James A. Roth, DVM, PhD; Director

To cite:
Horak S, Killoran K, Leedom Larson KR. Vesicular exanthema of swine virus. Swine Health Information Center and Center for Food Security and Public Health, 2016. http://www.cfsph.iastate.edu/pdf/shic-factsheet-vesicular-exanthema-swine-virus.

REFERENCES

1. Virus Taxonomy: Classification and Nomenclature of Viruses: Ninth Report of the International Committee on Taxonomy of Viruses. 2012.
2. Smith AW, Akers TG. Vesicular exanthema of swine. *J Am Vet Med Assoc.*1976;169(7):700-703.
3. Smith AW, Skilling DE, Dardiri AH, Latham AB. Calicivirus pathogenic for swine - a new serotype isolated from Opaleye *Girella nigricans*, an ocean fish. *Science.*1980;209(4459):940-941.
4. Knowles NJ, Reuter G. Porcine Caliciviruses. In: Zimmerman JJ, Karriker LA, Ramirez A, Schwartz KJ, Stevenson GW, eds. *Diseases of Swine*. 10 ed: John Wiley & Sons, Inc.; 2012:493-495.
5. Neill JD, Meyer RF, Seal BS. Genetic relatedness of the caliciviruses: San Miguel sea lion and vesicular exanthema of swine viruses constitute a single genotype within the *Caliciviridae. J Virol.*1995;69(7):4484-4488.
6. Blackwell JH. Comparative resistance of San Miguel sea lion virus and vesicular exanthema of swine virus to chemical disinfectants. *Res Vet Sci.*1978;25(1):25-28.
7. Smith AW, Berry ES, Skilling DE, Barlough JE, Poet SE, Berke T, Mead J, Matson DO. *In vitro* isolation and characterization of a calicivirus causing a vesicular disease of the hands and feet. *Clin Inf Dis.*1998;26(2):434-439.
8. Prato CM, Akers TG, Smith AW. Serological evidence of calicivirus transmission between marine and terrestrial mammals. *Nature.*1974;249(5454):255-256.
9. Gelberg HB, Lewis RM. The pathogenesis of vesicular exanthema of swine virus and San Miguel sea lion virus in swine. *Vet Pathol.*1982;19(4):424-443.
10. Smith AW, Latham AB. Prevalence of vesicular exanthema of swine antibodies among feral mammals associated with the southern California coastal zones. *Am J Vet Res.*1978;39(2):291-296.
11. Zee YC, Hackett AJ, Madin SH. A study of the cellular pathogenesis of vesicular exanthema of swine virus in pig kidney cells. *J Infect Dis.* 1967;117(3):229-&.
12. Reid SM, Ansell DM, Ferris NP, Hutchings GH, Knowles NJ, Smith AW. Development of a reverse transcription polymerase chain reaction procedure for the detection of marine caliciviruses with potential application for nucleotide sequencing. *J Virol Methods.* 1999;82(1):99-107.
13. Reid SM, King DP, Shaw AE, Knowles NJ, Hutchings GH, Cooper EJ, Smith AW, Ferris NP. Development of a real-time reverse transcription polymerase chain reaction assay for detection of marine caliciviruses (genus *Vesivirus*). *J Virol Methods.* 2007;140(1-2):166-173.
14. McClenahan SD, Bok K, Neill JD, Smith AW, Rhodes CR, Sosnovtsev SV, Green KY, Romero CH. A capsid gene-based real-time reverse transcription polymerase chain reaction assay for the detection of marine vesiviruses in the *Caliciviridae. J Virol Methods.*2009;161(1):12-18.
15. Ferris NP, Oxtoby JM. An enzyme-linked immunosorbent assay for the detection of marine caliciviruses. *Vet Microbiol.*1994;42(2-3):229-238.