SENECA VALLEY VIRUS

Etiology

- Seneca Valley virus (SVV, also known as Senecavirus A) is a small, non-enveloped picornavirus discovered incidentally in 2002 as a cell culture contaminant.
- Only a single species is classified in the genus Senecavirus. The family Picornaviridae also contains foot-and-mouth disease virus (FMDV) and swine vesicular disease virus (SVDV).

Cleaning and Disinfection

- The efficacy of most disinfectants against SVV is not clearly known. Because vesicular diseases are clinically indistinguishable, disinfection protocols for FMDV should be followed even if SVV is suspected. This includes use of: sodium hydroxide, sodium carbonate, 0.2% citric acid, aldehydes, and oxidizing disinfectants including sodium hypochlorite.

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Epidemiology

- The survival of SVV in the environment has not been reported. Most cases of idiopathic vesicular disease, which is associated with SVV, seem to occur between spring and fall.
- Neutralizing antibodies to SVV have been detected in small populations of swine, cattle, and wild mice in the United States. Since July 2015, isolates have been identified in pigs from Minnesota, Iowa, South Dakota, Nebraska, Illinois, Indiana, Missouri, Oklahoma, and North Carolina. SVV has also been linked to recent vesicular disease outbreaks in Brazil.
- There is no record of SVV causing symptomatic human disease. The virus has potent oncolytic abilities which are currently being explored in human cancer treatment research.

Transmission

- The transmission route(s) for SVV are not well understood. Another picornavirus, FMDV, is known to spread readily by direct contact with infected individuals, fomites, or exposure to aerosolized virus, but it is unknown if these same modes of transmission also apply to SVV.

Infection in Swine/Pathogenesis

- The pathogenicity of SVV in swine remains unclear. Experimental infections in swine have failed to produce signs of disease and SVV has been isolated from healthy pigs in the United States. However, the virus is linked to idiopathic vesicular disease, and multiple cases of vesicular disease in swine in the United States have been reported in which SVV was the only detected pathogen. SVV has also been linked to idiopathic vesicular disease during concurrent infection with porcine circovirus and porcine enterovirus.
- SVV has been recovered from vesicular lesions in pigs that are clinically indistinguishable from foreign animal diseases such as FMD, SVD, vesicular stomatitis, and vesicular exanthema of swine virus. Lameness is commonly observed. In Brazil, SVV has also been associated with epidemic transient neonatal losses (ETNL) syndrome, although further study is needed.
- Gross lesions include multifocal, round, discrete erosive and/or ulcerative lesions on distal limbs, especially around the coronary bands. Crusting and sloughing of the hoof wall may also be observed. Similarly, fluid filled vesicles and multifocal chronic superficial and/or deep ulcers have been described in and around the oral mucosa, snout, and nares.

Diagnosis

- SVV can be grown in human retinoblast (PER.C6®) cells and human lung cancer cell monolayers (NCI-H1299®), producing high virus titers. SVV replicates readily in certain human tumor cells with neuroendocrine properties that are most sensitive to killing by the virus, while leaving normal adult human cells relatively unscathed.
- Electron microscopy, immunohistochemistry (IHC), reverse transcription polymerase chain reaction (RT-PCR), and quantitative real-time RT-PCR have been used in the study and diagnosis of SVV.
- Monoclonal antibodies have been developed in an attempt to develop more rapid and sensitive immunoassays for diagnosis, leading to the creation of a successful competition enzyme linked immunosorbent assay (cELISA) for specific detection of anti-SVV antibodies.

Immunity

- Serological studies have revealed the natural occurrence of neutralizing anti-SVV antibodies in swine, cattle, and mice, but rarely in humans. Both humans and mice have developed neutralizing antibodies after intravenous treatment with SVV-001.
- No vaccines are currently available for SVV.
- Swine SVV isolates are genetically similar to the prototype species, SVV-001.
**Prevention and Control**
- Proven methods for prevention and control of SVV are lacking. Vaccination and stamping out have been used to control FMD, which is caused by a similar virus.
- Common industry biosecurity practices should also be in place.
- There is no national surveillance for SVV, although the state of California classifies SVV as a monitored condition.

**Gaps in Preparedness**
- Continued research on the epidemiology of SVV and idiopathic vesicular disease is needed.
- The development of more rapid, cost-effective diagnostic assays, combined with screening and monitoring of swine herds prior to the appearance of vesicular lesions, will be important in the future.
Seneca Valley virus (SVV, also known as Senecavirus A) is a small, non-enveloped picornavirus, unknown until 2002 when it was discovered incidentally as a cell culture contaminant. Only a single species, Senecavirus A, is currently classified in the Senecavirus genus of the family Picornaviridae, although sporadic serologically similar isolates have been identified in porcine samples spanning almost three decades. Naturally occurring antibodies against the virus have been detected in swine, cattle, mice, and a single human sample, though the virus is not known to cause disease in humans. Pathogenicity in swine remains unclear. Outbreaks of idiopathic vesicular disease have been linked to SVV in the absence of other identified etiologic agents and also during concurrent infection with porcine circovirus and porcine enterovirus. In contrast, the virus has also been identified in healthy pigs, and experimental infection has failed to produce clinical signs thus far.

Swine SVV infection has occurred across the United States and Canada, and idiopathic vesicular disease has been reported globally from Europe to South America to Australia and New Zealand. Transmission of picornaviruses is generally very rapid and occurs in the cytoplasm of host cells. Clinical signs of SVV, when present, are indistinguishable from those of swine vesicular disease (SVD), vesicular stomatitis virus (VSV), vesicular exanthema of swine virus (VESV), and foot-and-mouth disease virus (FMDV), all more serious and economically devastating foreign animal diseases (FADs). Erosions, ulcerations, and vesicular lesions of the snout, oral mucosa, and distal limbs, especially around the coronary band, may be observed. Hoof sloughing and lameness can also occur, as well as more general symptoms of illness such as fever, lethargy, and anorexia. In Brazil, SVV has also been associated with epidemic transient neonatal losses (ETNL) syndrome, although further study is needed.

Cultivation and purification of SVV can be performed in the laboratory using human retinoblast (PER.C6®) cells and human lung cancer cell monolayers (NCI-H1299a), yielding high virus titers. Replication of SVV occurs readily in certain human tumor cells with neuroendocrine properties that are most sensitive to killing by the virus, while leaving normal adult human cells relatively unscathed. Electron microscopy, immunohistochemistry (IHC), reverse transcription polymerase chain reaction (RT-PCR), and quantitative real-time RT-PCR have been used in the study and diagnosis of SVV. Monoclonal antibodies have been developed in an attempt to develop more rapid and sensitive immunoassays for diagnosis, leading to the creation of a successful competitive enzyme-linked immunosorbent assay (cELISA) for specific detection of anti-SVV antibodies.

Understanding the epidemiology of SVV and potential role of other species in virus transmission and origin, combined with continued development of rapid and specific diagnostics and elucidation of the link between viral infection and clinical disease in swine, will be crucial to our knowledge and ability to manage this newly discovered and little understood virus.
LITERATURE REVIEW

1. Etiology
1.1 Key Characteristics
Seneca Valley virus (SVV, also known as Senecavirus A) is a small, non-enveloped virus containing a single strand of positive-sense RNA within a protein capsid.\(^1,2\) It was originally discovered as a cell culture contaminant, presumed to have been introduced through bovine serum or porcine trypsin during the cultivation of human retinoblast (PER.C6\(^\circ\)) cells.\(^3\) This first reported isolate of SVV was identified in Maryland in 2002.\(^4\) Only a single species is currently classified in the new genus Senecavirus, closely related to the genus Cardiovirus, within the family Picornaviridae.\(^1,2\) Other prominent members of Picornaviridae include poliovirus, rhinovirus, hepatitis A virus, foot-and-mouth disease virus (FMDV), and swine vesicular disease virus (SVDV).\(^4\) In addition to its clinical resemblance to vesicular foreign animal diseases (FADs),\(^5\) SVV is known for its ability to replicate in tumor cells and is being studied for treatment of neuroendocrine cancers.\(^1\) It is currently marketed by Neotropix under the trade name NTX-010.\(^6\)

1.2 Strain Variability
As of 2014, the single species of the Senecavirus genus is known as Senecavirus A.\(^7\) The complete genome sequence was analyzed for the original SVV isolate, SVV-001, and published in 2008.\(^2\) The genome is believed to be fairly stable, as intentional repeated passage in non-permissive cell lines has been unable to produce a progeny virus. However, the genetic variability of picornaviruses is still generally high.\(^3\) Distance of the SVV genome from those of known cardioviruses does not support the theory that SVV-001 originated as a recombinant virus derived from cardioviruses.\(^2\) However, a similar comparison of the SVV and classical swine fever (CSF) genomes suggests the possibility of previous genetic exchanges between members of Picornaviridae and Flaviviridae.\(^8\)

Since the initial discovery of SVV-001, at least 12 additional serologically similar isolates from pigs have been identified in samples submitted to the National Veterinary Services Laboratory (NVSL).\(^2\) These samples were isolated between 1988 and 2005 in various locations across the United States. Analyses of the different isolates suggests the existence of a common ancestor within the last three to four decades and a relatively recent introduction into United States swine herds.\(^3\)

2. Cleaning and Disinfection
2.1 Survival
Survival of SVV in the environment has not been reported.

Idiopathic vesicular disease outbreaks in swine appear to follow a seasonal pattern with most cases occurring between spring and fall.\(^9\) Little is known about SVV in particular and its potential role in vesicular disease, but a connection between the two has been suggested.

2.2 Disinfection
Until an FAD can be ruled out, an initial response to vesicular disease outbreaks in swine should follow protocols in place for such events.\(^9\) Heat and alkaline or acidic disinfectants, such as sodium hydroxide, sodium carbonate,\(^1\) and 0.2% citric acid, can deactivate FMDV, although efficacy may decrease when the virus is dried.\(^10\) Aldehydes and oxidizing disinfectants, including sodium hypochlorite, are also effective. Detergent and organic solvents are less effective in FMDV disinfection, though these are occasionally used in conjunction with a disinfectant to solubilize organic material.\(^1\) More research is needed on disinfection protocols specific to SVV to determine the effectiveness of existing methods.
3. Epidemiology

3.1 Species Affected
Neutralizing antibodies to SVV have been detected in small populations of swine, cattle, and wild mice in the United States, suggesting exposure to the virus without overt clinical signs. Similar serological testing of four primate species revealed no anti-SVV antibodies.\(^4\)

However, another study in mice showed no horizontal transmission, as measured by seroconversion, between infected and naïve mice during a 30 day period.\(^3\) Swine are thought to be a natural host of SVV, though further confirmatory evidence is needed.\(^3,11\)

3.2 Zoonotic Potential
There is no record of SVV causing symptomatic human disease,\(^12\) and normal primary human cells tested in vitro demonstrate resistance to infection. Presence of neutralizing anti-SVV antibodies is rare in humans, suggesting that SVV exposure is not common or that the virus does not typically replicate enough in humans to stimulate a detectable humoral immune response. Further, SVV-001 does not bind human erythrocytes and is not inhibited by other components of human blood.\(^11\)

However, SVV can be readily propagated in human tumor cells showing neuroendocrine features. Due to its efficacy as an oncolytic agent, some attention should be given to the potential for viral adaptation and zoonotic infection in humans.\(^3\) Though picornaviruses do not commonly produce a change in tropism,\(^6\) if the virus acquired the ability to spread horizontally and become pathogenic in humans, other patients in the hospital, health care workers, and others in contact with infected patients could potentially be at risk.\(^3\)

SVV has also been identified as a virus of concern with porcine and human host range (able to infect humans or human cells in culture) in the preparation of biological products such as porcine trypsin that may be used in the production of vaccines or other human treatments. This suggests the need for revised and improved diagnostic testing of any and all reagents used for the production of products being given to humans.\(^13\)

3.3 Geographic Distribution
Early studies of SVV-001 and closely related isolates suggest that SVV may be common with a wide distribution in the United States.\(^2\) From 1988–2005, seven SVV isolates were identified from pigs in the United States (Minnesota, North Carolina, Iowa, New Jersey, Illinois, Louisiana and California).\(^4\) Since July 2015, SVV has been detected in pigs from Minnesota, Iowa, South Dakota, Nebraska, Illinois, Indiana, Missouri, Oklahoma, and North Carolina.\(^14\) SVV has also been linked to recent vesicular disease outbreaks and outbreaks of sudden death in neonatal pigs (known as epidemic transient neonatal losses [ETNL]) in Brazil.\(^15,16\)

Idiopathic vesicular disease in swine has previously been reported in Australia\(^17\), New Zealand\(^18\), Canada\(^19\), Florida\(^20\), and Indiana\(^21\), as well as Iowa and nearby states.\(^22\) Cases of idiopathic vesicular disease are thought to result from infection with SVV, swine enteroviruses, teschoviruses,\(^23\) porcine parvovirus, or calicivirus. Vesicular lesions in swine have also been reported in connection with mycotoxins, contact dermatitis, and feed containing marine products or the fungus *Sclerotinia sclerotiorum*.\(^5\) The potential involvement, if any, of SVV in many of these incidents is unknown, but the clinical resemblance to more contagious and deleterious FADs certainly warrants further investigations of any potential connection.

3.4 Morbidity and Mortality
Pathogenicity of SVV remains unclear, and very limited data are currently available on associated morbidity and/or mortality in swine.
SVV was diagnosed in a group of 187 pigs arriving in the US from Canada in 2007; twelve had erosions of the snout, 25–30% had vesicular lesions along the coronary band, and approximately 80% were lame. Fifteen of the pigs had lesions deemed significant by a USDA veterinarian. No mortality was reported in this case. However, a single reported case of SVV in a pig with vesicular lesions in 2010 resulted in euthanasia of the animal due to the progression of clinical disease.

4. Transmission

Replication of picornaviruses is rapid and occurs in host cell cytoplasm. Transfection of SVV-resistant cell lines with genomic viral RNA leads to production of the virus in cells, suggesting the permissibility of cells to the virus is related to receptor expression, interaction, or internalization during attempted viral entry. The life cycle of SVV-001 can be completed in 12 hours, expediting the spread to neighboring cells. Replication of SVV occurs successfully in pigs and the spread of some SVV isolates to naïve individuals has been demonstrated, even in the absence of clinical signs.

Ultrastructural analysis (transmission and negative staining) of oral and skin lesions has failed to demonstrate a viral presence. This may be attributed to the chronic nature and actual absence of the virus in these lesions or to the difficulty of identifying picornaviruses when they are not aggregated into crystalline arrays. Another picornavirus, FMDV, is known to spread readily by direct contact with infected individuals, fomites, or exposure to aerosolized virus, but it is unknown if these same modes of transmission also apply to SVV.

Detectable levels of infectious virus have been found in nasal secretions, sputum, blood, urine, and stool in human cancer patients treated with intravenous SVV-001 in clinical trials. The virus is also able to cross the blood-brain barrier in humans.

5. Infection in Swine/Pathogenesis

5.1 Clinical Signs

Lesions observed in pigs infected with SVV cannot be distinguished clinically from those caused by FMDV or other vesicular diseases. Several SVV-infected pigs arriving in the United States from Canada in 2007 displayed erosions on the snout, swollen coronary bands with blanching and broken vesicles, and sloughing of hooves and dewclaws. A greater number, close to 80%, of the herd was lame. In a separate incident, another pig naturally infected with SVV exhibited vesicles and erosions in or around the oral cavity, nares, and coronary bands, with ulcers present on fore limbs and hind limbs. Anorexia, lethargy, lameness have also been reported, as has fever up to 105°F in early stages of the disease. In Brazil, SVV has been associated with sudden death in neonatal pigs (epidemic transient neonatal losses [ETNL]), although further study is needed.

5.2 Postmortem Lesions

Gross lesions include multifocal, round, discrete erosive and/or ulcerative lesions on distal limbs, especially around the coronary bands. Crusting and sloughing of the hoof wall may also be observed. Similarly, fluid filled vesicles and multifocal chronic superficial and/or deep ulcers have been described in and around the oral mucosa, snout, and nares. Serofibrinous peritonitis and pericarditis, locally extensive hemorrhagic jejunitis, and a focal gastric ulcer have also been reported in an infected individual.

Observed microscopic lesions of the distal limbs, oral cavity, and snout include orthokeratotic and parakeratotic hyperkeratosis, epidermal hyperplasia, and infiltration by neutrophils together with fibrin, edema, acute hemorrhage, and nuclear debris. Occasional colonies of cocci bacteria may be present, along with ulcerative gastritis, lymphoplasmacytic hepatitis, and membranoproliferative glomerulonephritis.
6. Diagnosis

6.1 Clinical History
The pathogenicity of SVV in swine remains unclear. Its relevance lies mainly in its suspected link to idopathic vesicular disease and resemblance to more clinically and economically disruptive vesicular FADs.\textsuperscript{5} Multiple cases of swine vesicular disease in the United States have been reported in which SVV was the only detected pathogen.\textsuperscript{26}

The virus first raised suspicions in a group of pigs brought into Minnesota from Canada in 2007. Out of 187 pigs, 15 displayed significant lesions consistent with a vesicular disease.\textsuperscript{9,28} Tests for FMDV, SVD, vesicular stomatitis virus (VSV), and vesicular exanthema of swine virus (VESV) were negative.\textsuperscript{9} A statement was released by the USDA regarding the findings of porcine circovirus and porcine enterovirus in the affected swine,\textsuperscript{29} and further testing also revealed the presence of SVV.\textsuperscript{9} Unlike FMDV, SVV is not a reportable disease in Canada.\textsuperscript{24}

Also, in 2010, a single six-month-old intact Chester White boar in Indiana exhibiting anorexia, lethargy, and lameness with vesicles and erosions of the oral cavity, snout, and limbs tested positive for SVV in the absence of vesicular FADs or bacterial agents.\textsuperscript{5} Four recent unrelated diagnostic laboratory submissions for cases of vesicular disease in swine – three in Iowa and one in South Dakota – have since tested positive for SVV in the summer of 2015.\textsuperscript{23} Nevertheless, experimental infections of pigs have not resulted in any associated signs of disease,\textsuperscript{1,26,28} and SVV has been isolated from healthy pigs in several areas of the United States.\textsuperscript{5}

6.2 Tests to Detect Nucleic Acids, Virus, or Antigens
During initial diagnosis, other causes of vesicular disease can be ruled out by virus isolation, bacterial culture, histopathology, and ultrastructural analysis of lesions for the presence of virus particles.\textsuperscript{5}

Human retinoblast (PER.C6\textsuperscript{®}) cells\textsuperscript{2} and human lung cancer cell monolayers (NCI-H1299\textsuperscript{®})\textsuperscript{28} can be used for cultivation of SVV. High virus titers are routinely produced, and the virus is purified easily. Thirteen tested human small cell lung cancer, two adrenocortical carcinoma, and seven pediatric neuroendocrine tumor cell lines are also sensitive to killing by SVV. Though the exact mechanism of selectivity is unclear, there is a strong positive correlation between virus-induced cytotoxicity and efficiency of virus replication \textit{in vitro}. In contrast, normal adult human cell lines not killed by SVV produce almost no virus.\textsuperscript{11,12}

Electron microscopy studies of SVV samples reveal the presence of single or aggregate icosahedral particles that are small and indicative of picornavirus infection. Crystalline, lattice-like structures may be observed upon ultrastructural analysis of infected cells at 24 hours post-infection.\textsuperscript{2} Immunohistochemical (IHC) staining of the SVV-001 capsid protein can be used to determine spatial infiltration of the virus into tissues.\textsuperscript{27}

Reverse transcription polymerase chain reaction (RT-PCR) can be used to definitively identify SVV in swine.\textsuperscript{5,9,28} and quantitative real-time RT-PCR (qRT-PCR) has been used to quantify the virus in human patients during cancer clinical trials.\textsuperscript{25} Pan-picornavirus RT-PCR has been used to target the 3′ end of the genomes of six porcine SVV isolates, confirming their close relationship with each other and SVV-001. Sequence analyses of the VP1 and 2C genome regions further support this relationship.\textsuperscript{4}

SVV-specific monoclonal antibodies (mAbs) have been produced that do not cross-react with other vesicular disease viruses (SVD, VSV, and FMDV) as demonstrated by dot blot assay, and they are capable of specifically recognizing viral antigen in SVV-infected cell cultures as confirmed by IHC assay.\textsuperscript{28}
6.3 Tests to Detect Antibody
Creation of the SVV-specific mAbs has contributed to a new competitive enzyme-linked immunosorbent assay (cELISA) for serodiagnosis in pigs. The cELISA is comparable to, or more specific than, indirect IgM ELISA. It is also relatively easy to perform, can detect antibodies from different species and different stages of the immune response, does not require special reagents, and can be modified to screen a large number of samples. All Virus-neutralizing antibody detection is also used in SVV identification.

6.4 Samples
6.4.1 Preferred Samples
Virus isolation from scrapings of vesicular lesions is not always successful, yet the same samples may still test positive for SVV by RT-PCR. Blood, vesicular fluid, and epithelial tissue are typically collected for diagnostic workups in suspected vesicular FAD cases. Urine, feces, and nasal swabs from humans have been used to identify SVV by qRT-PCR.

6.4.2 Oral Fluids
Oropharyngeal fluid has been used successfully in the identification of SVV by RT-PCR, and esophageal/pharyngeal samples may also be submitted for diagnostic workups if FMD is suspected.

7. Immunity
7.1 Post-exposure
Serological studies have revealed the natural occurrence of neutralizing anti-SVV antibodies in swine, cattle, and mice, but rarely in humans.

Human cancer patients in clinical trials have been shown to develop neutralizing antibodies within two weeks of intravenous treatment with SVV-001, with titer and swiftness of immune response dependent upon viral dose. Mice will also develop neutralizing antibodies following intravenous injection of SVV-001.

7.2 Vaccines
No vaccines are currently available for SVV.

7.3 Cross-protection
Subsequent isolates from swine have shown considerable sequence identity with the prototype species, SVV-001. They are also serologically related both to SVV-001 and each other.

8. Prevention and Control
Until more is known about the origins of SVV and its transmission and pathogenesis in swine, some methods of control for other more extensively studied picornaviruses could be utilized. Vaccination (though not currently available for SVV) and stamping out have been successful in curbing FMDV in the United States. Humans also play a significant role in passing the virus from infected animals and contaminated surfaces to susceptible animals, so similar preventive measures should be taken to avoid the possible spread of SVV by this route. Continued vigilance and awareness of the disease is essential.

In the state of California, SVV is classified as a monitored condition by the Department of Food & Agriculture, requiring monthly reporting by diagnostic facilities, and other states might benefit from this as well.
The 2015 OIE Terrestrial Animal Health Code does not cover SVV. There are no recommendations regarding importation of cattle or swine from countries or zones infected with SVV.

10. Gaps in Preparedness
Due to the clinical similarity to FMDV, a devastating and highly contagious FAD affecting pigs, rapid diagnosis of SVV in suspect cases is critical. Continued biological and epidemiological research on SVV and idiopathic vesicular disease is desperately needed to prevent further disruption to swine producers and mitigate consequences in United States markets. The development of more rapid, cost-effective diagnostic assays, combined with screening and monitoring of swine herds prior to the appearance of vesicular lesions could potentially prevent the need for FAD investigations and economic losses.

While pigs are suspected to be a natural host of SVV, little is known about incidence of infection in other species. The close relationship of SVV to cardioviruses, known viruses of rodents, warrants further investigation into the potential for transmission of SVV from rodents to other species. Rodents or other mammals may be alternate hosts of the virus, and it is also possible that SVV exists undetected in swine populations outside of North America. The identification of similar isolates in additional species or locations could help to further our understanding of the origins of the virus.

Due to the seemingly sporadic nature of SVV outbreaks in swine, it will be difficult to develop a clear understanding of the link between viral infection and clinical disease. In future occurrences of idiopathic vesicular disease, SVV must be considered and the presence of additional etiologic or adventitious agents closely monitored as well. Surveillance of healthy herds and diagnostics on individuals without clinical signs may also help to provide a clearer picture of the actual degree of morbidity associated with SVV infection in swine.
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REFERENCES


