

HIGHLY PATHOGENIC PORCINE REPRODUCTIVE AND RESPIRATORY SYNDROME VIURS



The mission of the Swine Health Information Center is to protect and enhance the health of the United States swine herd through coordinated global disease monitoring, targeted research investments that minimize the impact of future disease threats, and analysis of swine health data.

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SUMMARY

IMPORTANCE

- Porcine reproductive and respiratory syndrome (PRRS) emerged in the late 1980s nearly simultaneously in the United States and Germany, causing severe illness in pigs. Since then, PRRS has become an economically devastating disease of pigs found in many, but not all, swine-producing areas of the world.
- Highly pathogenic PRRS (HP-PRRS) was first described in China in 2006, and new variants continue to appear. Chinese strains have not been detected in the United States to date; however, there is ongoing concern about transboundary spread.

PUBLIC HEALTH

- PRRS virus (PRRSV) is not zoonotic.

INFECTION IN SWINE

- Clinical presentation is variable. In breeding animals, anorexia, fever, lethargy, depression, respiratory distress, and vomiting can be seen, as well as cyanosis of the ears, abdomen, and vulva.
- Transplacental transmission results in reproductive failure (stillborn, autolyzed, and/or mummified fetuses) or birth of viremic piglets.
- In young, growing, and finishing pigs, acute viremia is followed by respiratory disease including pneumonia, sneezing and expiratory dyspnea. Fever, lethargy and depression can also be seen.
- HP-PRRS virus (HP-PRRSV) causes similar clinical manifestations; however, infections with highly virulent strains are characterized by increased disease severity. Additionally, neurological signs have been associated with HP-PRRSV, as well as an erythematous blanching rash.
- HP-PRRSV causes clinical disease and death in all ages, including adult pigs and pregnant sows.

TREATMENT

- There is no treatment for PRRS. Antibiotics may be used to treat secondary bacterial infections.

CLEANING AND DISINFECTION

- PRRSV is stable over a pH range of 6.0–7.5, and the virus can survive for years at temperatures of -70°C to -20°C (-94°F to -4°F). Experimentally, PRRSV has been shown to survive in pork under various conditions, but the introduction of the virus through importation of pork has been deemed unlikely.
- PRRSV is susceptible to phenol, formaldehyde, and many common disinfectants such as sodium hypochlorite (bleach), iodine, and quaternary ammonium compounds. No information on survival or disinfection specifically for HP-PRRSV was found.

PREVENTION AND CONTROL

- PRRS is an OIE-listed disease and must be reported internationally according to the Terrestrial Animal Health Code.
- Methods to prevent the entry of PRRSV into a naïve swine herd include quarantine and testing of new breeding animals; sanitation and drying of transport/supply vehicles; shower-in, shower-out or use of Danish entry systems; and implementation of insect control programs (e.g., screening, habitat management, and insecticide use). Air filtration systems can also reduce the risk of PRRSV transmission.
- In PRRS-endemic herds, control programs can be implemented to limit adverse effects of the disease. Best control strategies will vary depending on specific farm situations. Control programs often involve a combination of gilt acclimatization, restricted entry of incoming breeding stock, restricted cross-fostering, euthanasia of affected pigs, all-in/all-out pig flow, partial or total herd depopulation and repopulation, segregated early weaning, test and removal, and herd closure.
- Vaccination has been the main control measure implemented in China against HP-PRRSV.

TRANSMISSION

- Infected pigs shed PRRSV in respiratory secretions, saliva, urine, semen, mammary secretions, and feces.
- PRRSV is transmitted directly via intranasal, oral, intrauterine/transplacental, and vaginal routes. The virus can enter through breaks in the skin such as bites, cuts, or scrapes, as well as husbandry practices like ear notching and tail docking. Experimentally, intramuscular inoculation induces disease in pigs.
- Aerosol transmission has been demonstrated and may serve as an important means of virus spread between farms. Fomites and mechanical insect vectors have also been implicated in PRRSV transmission.
- PRRSV endemicity in a herd is driven by carrier animals and the continuing presence of susceptible animals (usually suckling piglets). Vertical transmission is a major contributor to within-herd PRRSV transmission as is comingling of infected and susceptible pigs.
- It is not known how transmission of HP-PRRSV differs from PRRSV, if at all.

PATHOGENESIS

- PRRSV replicates mostly in the lymphoid tissues and lungs. HP-PRRSVs may have a wider tissue tropism compared to other strains.

DIAGNOSIS

- PRRSV can be detected via direct fluorescent antibody, immunohistochemistry, or nucleic acid-based assays. Several variations on the reverse transcriptase polymerase chain reaction (RT-PCR) assay have been developed. Loop-mediated isothermal amplification (LAMP) tests and rapid point-of-care immunochromatographic strip tests have been described, but are not widely available or routinely used in the United States.
- Although traditional assays cannot distinguish PRRSV from HP-PRRSV, newer RT-PCR variations available in China are capable of differentiation. These tests are not widely available in the United States.
- Serological tests for PRRSV antibody include indirect fluorescent antibody and enzyme linked immunosorbent assay (ELISA) targeting the nucleocapsid (N) protein.
- Samples suitable for virus detection include serum, lung, lung lavage, lymph nodes, spleen, heart, kidney, thymus, and tonsil (especially in carrier pigs). PRRSV can also be detected in oral fluids.

EPIDEMIOLOGY

- PRRSV occurs in many parts of the world. Countries thought to be PRRS-free include Sweden, Norway, Finland, Switzerland, New Zealand, Australia, Argentina, Brazil, and Cuba.
- HP-PRRSV first emerged in China and continues to circulate there. The virus has spread to other countries in Asia, including Vietnam, Bhutan, Cambodia, Laos, Malaysia, Myanmar, the Philippines, Thailand, Singapore, and India.

- To date, Chinese HP-PRRSV variants have not been detected in the United States.
- HP-PRRSV causes high morbidity and mortality compared to other strains. In the 2006 Chinese outbreak, morbidity rates ranging from 50–100% were noted. An overall mortality rate of nearly 20% was observed, with up to 100% mortality in individual herds. Mortality rates were highest in suckling pigs (100%), followed by nursery pigs (70%), finishers (20%), and pregnant sows (10%).

ETIOLOGY

- PRRSVs are single-stranded RNA viruses belonging to the family *Arteriviridae*. Viruses affecting pigs are found in the genus *Betaarterivirus*.
- There are two PRRS genotypes that share only 60% homology. PRRSV-1 (species name *Betaarterivirus suis 1*) is known as the European type, and PRRSV-2 (species name *Betaarterivirus suis 2*) is known as the North American type.
- ORF5 and NSP2 are the most variable parts in the PRRSV genome and are commonly used for phylogenetic analysis. However, they are not indicators of pathogenicity.

HISTORY IN SWINE

- PRRS emerged in the United States and Germany around 40 years ago, but its origin remains unknown.
- In 2006, HP-PRRS caused a Chinese outbreak in which two million pigs were affected and 400,000 died. The virus originated from a type 2 (North American) PRRSV already circulating in China. New HP-PRRSVs continue to emerge, and highly pathogenic forms of the virus are now dominant in China.

IMMUNITY

- PRRSV suppresses innate immunity in infected pigs. Although PRRSV can persist in carrier pigs, it seems that most infected pigs become immune and viral shedding stops around 60 days post-infection.
- PRRSV vaccination may moderate clinical signs and reduce virus shedding. Inactivated and modified live vaccine (MLV) formulations are available. PRRSV vaccination is challenging because the virus mutates rapidly, and many vaccines perform poorly following heterologous challenge.
- Problematically, MLVs may revert to virulence under field conditions. And, since MLVs can replicate in the host inducing viremia and virus shedding, they play a role in the emergence of recombinant PRRSVs.

GAPS IN PREPAREDNESS

- PRRS is economically devastating for swine producers in many parts of the world, and new PRRSV variants—causing high morbidity and mortality—continue to emerge in Asia.
- Potential entry routes into the United States should be investigated. Strict biosecurity measures should be in place on swine operations to prevent an HP-PRRSV incursion.
- To advance our understanding of PRRSV, future studies on basic viral biology, pathogenesis, host genomics, viral genomics, and immunology must continue.
- Prolonged carriage in pigs makes PRRS elimination difficult. Control programs are hampered by the virus' rapid evolution and lack of heterologous protection by current vaccines. New vaccine technologies must be developed to enhance cross-protective immunity and protection. Additionally, diagnostic tests that can differentiate infected from vaccinated animals (DIVA) are urgently needed.

LITERATURE REVIEW: HIGHLY PATHOGENIC PORCINE REPRODUCTIVE AND RESPIRATORY VIRUS

IMPORTANCE

Porcine reproductive and respiratory syndrome (PRRS) emerged in the late 1980s nearly simultaneously in the United States and Germany, causing severe illness in pigs. Since then, PRRS has become an economically devastating disease of pigs found in many, but not all, swine-producing areas of the world. Highly pathogenic PRRS (HP-PRRS) was first described in China in 2006, and new variants continue to emerge. Chinese HP-PRRS variants have not been detected in the United States to date; however, there is ongoing concern about transboundary spread.

PUBLIC HEALTH

There is no evidence that PRRS viruses are zoonotic.

INFECTION IN SWINE

CLINICAL SIGNS

The clinical presentation of PRRS is variable and influenced by the virulence of the infecting strain, host immune status and susceptibility, exposure to lipopolysaccharides (bacterial endotoxin), presence of concurrent disease, and management factors.¹

In breeding animals, anorexia, fever, lethargy, depression, respiratory distress, vomiting, and cyanosis of the ears, abdomen, and vulva may be seen.² Transplacental transmission results in reproductive failure (stillborn, autolyzed, and/or mummified fetuses) or the birth of viremic piglets.¹ In young, growing, and finishing pigs, acute viremia causes clinical respiratory disease. In addition to pneumonia, sneezing, expiratory dyspnea, fever, lethargy, and depression may occur.¹ The peak age for respiratory disease is 4–10 weeks. Where PRRS is endemic, illness is seen mostly in nursery pigs (when maternal antibody wanes) or replacement gilts or sows.¹ Epidemics occur when the virus enters an immunologically naïve herd or when antigenic variation leads to the emergence of a new PRRS virus (PRRSV) variant.¹

The first HP-PRRS epidemic, described in China in 2006, was characterized by a fever of 40–42°C (104–107.6°F), neurological signs, petechiae, an erythematous blanching rash, and blue ears.³ Reported signs include lameness, respiratory distress, diarrhea, depression, anorexia, and lethargy. Similar clinical signs have been described in other HP-PRRS outbreaks. Signs consistent with the original outbreak have also been reproduced in pigs experimentally infected with HP-PRRS virus (HP-PRRSV).^{4–6} Unlike older variants, HP-PRRSV causes clinical disease and death in adult pigs, including pregnant sows.³

POSTMORTEM LESIONS

Most experimentally infected pigs develop lesions in the lungs and lymph nodes, where viral replication predominantly occurs, at 4 to ≥ 28 days post-infection (dpi).¹ Interstitial pneumonia, which varies from multifocal to lobular to diffuse in distribution, is most severe from 10–14 dpi, and lungs may appear mottled and tan.^{1,2} Lung lesions may be complicated by concurrent bacterial and/or viral infections.^{1,2} Enlarged, tan, edematous lymph nodes are also commonly seen.^{1,2}

Endometritis, myometritis, and placental lesions can be seen in infected sows. In aborted fetuses and stillborn pigs with uncomplicated PRRS, no lesions may be detected. However, umbilical cord arteritis and hemorrhage may be seen in addition to lung and lymph node lesions.^{1,2}

Microscopic lesions associated with PRRS include nonsuppurative interstitial pneumonia, mild nonsuppurative encephalitis, myocarditis, rhinitis, and possible depletion of germinal centers of lymph nodes.^{1,2} Although these lesions are suggestive of PRRS, they are not pathognomonic.

In the 2006 Chinese outbreak, HP-PRRSV infection led to severe, multiorgan damage. Lesions described by Tian et al. include foci with pathological changes and hyperplasia in the lungs, with hemorrhagic spots and lung edema; splenic infarcts and bladder dilatation, filled with reddish-brown urine, and frequent blood spots in the kidney; putrescence of cardiac muscle; foci of yellow-white necrosis or hemorrhage in the liver; slightly softened encephala, blood egression emission, and effusion of jelly from the brain putamen; obvious hemorrhagic spots in the lymph nodes; arthritis with swollen joints; and intestinal ulceration.³

Pigs experimentally infected with HP-PRRSV have demonstrated acute lung injury, including distortion of lung structure and diffuse fibrosis.⁵ Severe histopathological lesions have been described, including destruction of lung structure with extensive hemorrhage and a large number of inflammatory cells infiltration, severe dropout of alveolar epithelial cells with exudation of inflammatory cells and erythrocytes into the alveolar spaces, vasculitis, and thrombus, alveolar lumens flooded with edema fluid and pulmonary interstitial edema accompanied vascular trauma, and formation of multinucleated giant cells and epithelioid cells.⁵ Lung lesion scores in experimentally infected domestic pigs are significantly higher than in wild pigs.⁷ Experimental studies of recombinant HP-PRRSVs have confirmed their pathogenicity in pigs.⁸⁻¹⁹

TREATMENT

There is no treatment for PRRS. Antibiotics may be used to treat secondary bacterial infections.

CLEANING AND DISINFECTION

SURVIVAL

PRRSV is inactivated by heat and drying. At temperatures of -70°C to -20°C (-94°F to -4°F), the virus can survive months to years.¹ PRRSV is stable at pH 6.0–7.5 but inactivated at high or low pH levels.^{1,20} There is some evidence that PRRSV can persist in pork.

- In one study, PRRSV was detected in experimentally contaminated fresh sausage for up to 15 days at 4°C (39.2°F) and for 30 days at -20°C (-4°F).²¹ However, PRRSV could not be isolated from experimentally contaminated ham, bacon, or acidified sausage.
- A similar study found that PRRSV could be detected for up to 48h at ambient temperature in experimentally contaminated fresh pork.²² At 4°C (39.2°F), PRRSV survived for 3–6 days (depending on the virus concentration used to contaminate the pork). When pork was frozen, PRRSV was detectable for 7–60 days, again varying according to virus concentration.²²

It may be possible for exsanguinated carcasses held at 4°C (39.2°F) to retain infective doses of PRRSV.²³ Despite these findings, the likelihood of PRRSV introduction through the importation of pork is unlikely.²⁴ No information was found on the survival of HP-PRRSV.

DISINFECTION

Lipid solvents including chloroform and ether reportedly inactivate arteriviruses.²⁰ Detergent solutions can disrupt the viral envelope.^{1,20} PRRSV is susceptible to phenol, formaldehyde, and common disinfectants including sodium hypochlorite (bleach).² Experimentally, room temperature inactivation of PRRSV has been achieved with chlorine (0.03% for 10 minutes), iodine (0.0075% for 1 minute), and a quaternary ammonium compound (0.0063% for 1 minute).¹ No information was found on disinfectants specifically recommended for HP-PRRSV.

PREVENTION AND CONTROL

DISEASE REPORTING

PRRS is an OIE-listed disease and must be reported internationally according to the *Terrestrial Animal Health Code*. Any suspicious clinical or necropsy findings should always be reported to the USDA and your State Animal Health Official.

DISEASE PREVENTION AND CONTROL

Methods to prevent the entry of PRRSV into a naïve swine herd include quarantine and testing of new breeding animals; sanitation and drying of transport/supply vehicles; shower-in, shower-out, or use of Danish entry systems; and implementation of insect control programs (e.g., screening, habitat management, and insecticide use).¹ Air filtration systems have been shown to reduce the risk of PRRSV transmission on sow farms, boar studs, and nurseries,²⁵⁻²⁷ though initial investment can be costly.²⁸

In PRRS-endemic herds, control programs can be implemented to limit the adverse effects of the disease.¹ Control strategies and specific farm situations are variable but include:²

- Gilt acclimatization—using replacement gilts that have developed immunity prior to herd introduction through contact with PRRSV-infected animals, intentional exposure to PRRSV (e.g., feedback of PRRSV-contaminated tissues or exposure to serum from acutely infected pigs), or vaccination;¹
- Breeding herd control—application of acclimatization protocols for all incoming breeding stock as described above, plus use of PRRSV-negative semen, limiting the frequency of new stock introductions, and consideration of herd closure for at least 200 days following an outbreak;¹
- Pig management—limiting transmission by restriction of cross-fostering; euthanasia of affected pigs; and use of all-in, all-out pig flow in the nursery. Partial depopulation can prevent lateral spread of PRRSV, but in herds where that is not possible, mass vaccination can also be employed;¹
- Eradication—eliminating PRRSV from a herd via total herd depopulation/repopulation, partial depopulation, segregated early weaning, test and removal, and herd closure.¹

In China, HP-PRRSV control programs have mostly centered on vaccination, although vaccines may provide only partial protection.²⁹ Acclimatization of pigs (through exposure to serum from PRRS-positive pigs) has also been done, but whole herd depopulation/repopulation, test and removal, and herd closure strategies have not been implemented widely in China.²⁹

An epidemiological study of PRRSV infection in Heilongjiang, China, including backyard farm, specialized pig farms, and commercial pig farms, found that increased risk of infection was associated with unrestricted movement of external people (presumably non-employees), close proximity (<1 km) to another house, road or farm, and sale of farm products at both local and provincial markets.³⁰

TRANSMISSION

Infected pigs shed PRRSV in nasal secretions, saliva, urine, semen, mammary secretions, and feces.^{1, 31} PRRSV is transmitted directly via intranasal, intramuscular, oral, intrauterine/transplacental, and vaginal routes.¹ The most effective route of PRRSV transmission seems to be parenteral. Any break in the skin, including those related to husbandry practices, such as ear notching, tail docking, teeth clipping, and injection, can facilitate virus entry.¹ PRRSV can also be spread via bites, cuts, scrapes, or any other activity involving blood and oral fluids.¹ PRRSV can be shed in semen for up to 92 dpi, making sexual transmission possible during natural breeding or artificial insemination.² Aerosol transmission has also been established.¹ PRRSV can survive in pork. However, the likelihood of transmission via ingestion is thought to be quite low, especially if meat is cooked.^{23, 24, 32} Indirect transmission occurs following exposure to fomites, including contaminated needles or personnel contaminated with blood or oral fluids, as well as mechanical insect vectors such as houseflies and mosquitoes.¹

PRRSV endemicity in a herd is driven by infection in carrier animals (more than 200 days)² and the presence of susceptible animals in a herd.¹ Vertical transmission is a major contributor to within-herd PRRSV transmission, as is comingling of infected and susceptible pigs.¹ Between herds, PRRSV transmission occurs mainly following exposure to infected pigs, contaminated semen, or infective aerosols.¹ Proximity to infected herds is a known risk factor for PRRSV transmission.¹

It is not known how transmission of HP-PRRSV differs from PRRSV, if at all.

PATHOGENESIS

Primary viral replication occurs in macrophages and then spreads to lymphoid tissues (spleen, thymus, tonsil, lymph nodes), lungs, and other tissues, where replication continues in monocyte-derived cells.¹ These cells display the glycoprotein receptor sialoadhesin and the transmembrane protein CD163, which mediate virus entry and release of internalized virus to the cytoplasm (a prerequisite for viral replication).¹ Specific cells known to support PRRSV replication include pulmonary alveolar macrophages and pulmonary intravascular macrophages in the lungs and macrophages in lymphoid tissues.¹ PRRSV crosses the placenta after day 72 of gestation.²

HP-PRRSV has a broader tissue tropism *in vivo* than other variants;³³ the immune organs and lungs are severely affected.^{34, 35} Viral antigen has been detected in the trachea, esophagus, liver, mandibular gland, and thyroid gland in pigs inoculated with HP-PRRSV.³³ Similarly, epithelium in tissues including the interlobular bile duct in the liver, distal renal tubule of the kidney, esophageal gland, and tracheal gland have been positive for viral antigen only in HP-PRRSV-inoculated pigs.³³ HP-PRRSV is also known to cross the blood-brain barrier and induce damage to neurons and neuroglial cells.³⁶ In an experimental study comparing HP-PRRSV pathogenicity in wild and domestic pigs, HP-PRRSV-positive cells were found in the bronchiolar, gastric, and renal tubular epithelial cells in wild pigs but not in domestic pigs.⁷

DIAGNOSIS

PRRS may be suspected when reproductive disease occurs in breeding swine, and respiratory disease is present in pigs of any age. However, presentation is variable and may be complicated by the presence of other pathogens.

TESTS TO DETECT NUCLEIC ACIDS, VIRUS, OR ANTIGENS

Virus isolation can be done in pulmonary alveolar macrophages or African monkey kidney cells (line MA-104, sublines CL-2621 or MARC-145).¹ The optimal time frame for virus isolation from serum and tissues is 1–35 dpi, although the virus may persist in the lymphoid tissues.¹ Following isolation, viral antigen can be visualized via direct fluorescent antibody (using fresh infected tissues, lung preferred) or immunohistochemistry (IHC) on formalin-fixed tonsil or lung.¹ Viral RNA can be detected by reverse transcriptase polymerase chain reaction (RT-PCR) or *in situ* hybridization.¹ Immunochromatographic strip tests for PRRSV detection have been described.^{37, 38} Numerous loop-mediated isothermal amplification (LAMP) assays targeting both type 1 and type 2 PRRSV have been developed for experimental use.³⁹⁻⁴⁵

Traditional RT-PCR assays cannot discriminate between highly pathogenic PRRSV and less pathogenic strains. However, some newer assays are capable of differentiation, including a multiplex quantitative RT-PCR (qRT-PCR) assay⁴⁶ and a one-step RT-PCR method based on changes in the NSP2 gene.⁴⁷ Nested RT-PCR assays detecting NSP2 have also been described.⁴⁸ A SYBR Green-based qRT-PCR assay⁴⁹ and a duplex qRT-PCR assay⁵⁰ capable of differentiating HP-PRRSV from type 2 PRRSV have been developed. An immunochromatographic strip test described experimentally can also detect HP-PRRSV.³⁸ A novel fluorescent probe-based real-time reverse transcription recombinase polymerase amplification (real-time RT-RPA) assay that detects HP-PRRSV has recently been described.⁵¹

TESTS TO DETECT ANTIBODY

Serology is useful to confirm the presence of PRRSV in a herd. Single serum samples have limited diagnostic value since PRRSV is ubiquitous, and results may be confounded by previous vaccination and/or the presence of maternal antibodies. Seroconversion must be demonstrated to diagnose active infections.¹

Indirect fluorescent antibody (IFA) is capable of detecting both IgM (as early as five dpi) and IgG (as early as 9–14 dpi).¹ This test is used mostly to confirm suspected false-positive enzyme-linked immunosorbent assay (ELISA) results. A commercial ELISA targeting the N protein is the reference standard.¹ This test is capable of identifying type 1 and type 2 PRRSV. IgM antibodies are detectable as early as nine dpi; they peak at 30–50 dpi and decline over 4–12 months.¹ Carrier pigs may test negative via ELISA. An ELISA using recombinant NSP7 as antigen has been tested experimentally.⁵² Virus neutralization is highly specific but not a routine diagnostic test.¹

No information was found on the identification of antibodies specific to HP-PRRSV. ELISAs developed for other PRRSVs may also detect antibodies to HP-PRRSV.

SAMPLES

Tissues suitable for virus detection include lung, lymph nodes, spleen, heart, kidney, thymus, and tonsil (especially in chronically infected pigs).¹ Virus can also be detected in serum, oral fluids, and lung lavage. Tissues should be collected from weak-born neonates that have not nursed, nursing pigs that are clinically ill, or febrile, anorectic postweaning pigs or sows.² Virus can also be detected in semen by RT-PCR. Tissues or fluids from aborted, mummified, or stillborn pigs are generally of limited diagnostic value; however, they are sometimes used for RT-PCR or ruling out other infections.¹ Tissue samples appropriate for the detection of PRRSV are also suitable for HP-PRRSV.

Experimentally, PRRSV can be detected in oral fluids by qRT-PCR, and antibody can be detected by ELISA and IFA.^{53, 54} A commercial ELISA to detect PRRSV in oral fluids is available. Pen-based oral fluid sampling may be useful for PRRSV surveillance in swine production systems.^{54, 55}

EPIDEMIOLOGY

SPECIES AFFECTED

Pigs are the natural hosts for PRRSV. In addition to domestic pigs, HP-PRRSV natural infection has been documented in hybrid wild pigs (75% wild boar, 25% domestic Duroc lineage) in China.⁵⁶ Wild pigs have been infected with HP-PRRSV experimentally.⁷

GEOGRAPHIC DISTRIBUTION

PRRSV is endemic in many, but not all, swine-producing regions of the world. Countries thought to be PRRS-free include Sweden, Norway, Finland, Switzerland, New Zealand, Australia, Argentina, Brazil, and Cuba.¹

HP-PRRSV first emerged in China⁵⁷ and continues to circulate there. The virus has spread to other countries in Asia, including Vietnam, Bhutan, Cambodia, Laos, Malaysia, Myanmar, the Philippines, Thailand, Singapore, and India.⁵⁸⁻⁶³ To date, Chinese HP-PRRSV variants have not been detected in the United States.

MORBIDITY AND MORTALITY

There is little information available on PRRS prevalence, and the presence of vaccine-derived antibodies may confound some estimates. According to the Swine Health Monitoring Project, PRRSV incidence in North America decreased to about 25% in 2013–2014 compared to 35% in previous years.⁶⁴ In many countries, 60–80% of pigs are thought to be infected.¹ In a study of U.S. feral swine, only 2.5% were seropositive for PRRSV.⁶⁵ Postweaning mortality can be markedly increased in a PRRSV-infected herd. Mortality in sows ranges from 1–4%, with up to 10% reported in a few severe cases.¹ Dead pigs may account for 0–100% of a congenitally infected litter.¹

HP-PRRSV is known to cause high morbidity and mortality. In the 2006 Chinese outbreak, more than 2 million pigs were affected (morbidity rate of 50–100%).³ An overall mortality rate of nearly 20% was observed, with up to 100% mortality in individual herds.^{3, 66} Mortality rates were highest in suckling pigs (100%), followed by nursery pigs (70%), finishers (20%), and pregnant sows (10%).²⁹ Similar morbidity and mortality rates have been reproduced experimentally.⁶⁷ In wild pigs, experimental infection with HP-PRRSV has resulted in a mortality rate of 25%.⁷ In Chinese pigs infected with the 2013–2014 HP-PRRSV isolates, which resulted from recombination of HP-PRRSV and a recently imported North American virus, morbidity of 100% and mortality of nearly 77% have been reported.⁶⁸

ETIOLOGY

CHARACTERISTICS OF ARTERIVIRUSES

PRRSVs are enveloped viruses belonging to the family *Arteriviridae*. Arteriviruses are single-stranded RNA viruses with a roughly spherical, pleomorphic shape.²⁰ They range from 50–74 nm in size. As of 2021, the family *Arteriviridae* contains six subfamilies, 13 genera, 11 subgenera, and 23 species. Viruses affecting pigs are found in the genus *Betaarterivirus*.²⁰

- PRRSV-1 (species name *Betaarterivirus suis 1*) belongs to the subgenus *Eurpobartevirus*.²⁰
- PRRSV-2 (species name *Betaarterivirus suis 2*) belongs to the subgenus *Ampobartevirus*.²⁰

CHARACTERISTICS OF PORCINE REPRODUCTIVE AND RESPIRATORY SYNDROME VIRUSES

The PRRSV genome consists of about 15,000 nucleotides containing 11 open reading frames (ORFs).⁶⁹ ORFs 1a and 1b encode two nonstructural proteins (NSPs), pp1a and pp1ab, that are further processed into 14 nonstructural proteins (NSPs).⁶⁹ ORFs 2–7 encode eight structural proteins, including the major envelope proteins GP5 and M, the nucleocapsid protein (N), and the minor envelope proteins E, GP2a, GP3, GP4, and ORF5a.⁶⁹ ORF5 and NSP2 are the most variable parts in the PRRSV genome and are commonly used for phylogenetic analysis.

Two genotypes have been identified based on sequencing of ORF5, which encodes the major envelope glycoprotein GP5. PRRSV-1, also known as the European type, is represented by the prototype strain Lelystad virus. PRRSV-2, the North American type, is represented by prototype strain ATCC VR2232.¹ Only 60% nucleotide homology occurs between PRRSV-1 and -2.²⁰

PRRSV in Asia

PRRSV-2 predominates in China; however, there is evidence that PRRSV-1 isolates have also been present since at least 2011.^{70, 71} Whole genome sequencing of HP-PRRSVs isolated from China in 2006 showed that all were type 2 originating from a PRRSV already present in the country.⁷² NSP2 polymorphisms had previously been identified in PRRSV-2 isolates.^{73, 74} However, in highly pathogenic isolates, a hypervariable region was identified in NSP2 containing a discontinuous deletion of 30 aa (a conserved leucine absent at position 482, and a continuous deletion of 29 aa from positions 534–562).³ Additional deletions and insertions have been described in recent HP-PRRSVs, as summarized by Jiang et al.⁷⁵ Since the GP5 region is highly variable, sequence changes there common in addition to NSP2.^{57, 67, 76-85}

HP-PRRSV variants continue to emerge in Asia. PRRSV-2 strains in China belong to four lineages as described by Wang and colleagues, including lineage 1 (NADC30-like), lineage 3 (QYYZ-like), lineage (VR-2332-like), and lineage 8 (JXA1-like).⁸⁶ More recently, Jiang et al. analyzed 353 PRRSV strains collected from mainland China (1996–2017).⁷⁵ They identified four different epidemic periods (*Figure 1*) and eight subgroups, including:

- EU-type isolates, which occurred intermittently from 2006–2015, and were similar to Lelystad strains
- Classic NA isolates, which were prevalent prior to 2006, but mostly disappeared after the 2006 HP-PRRSV outbreak

- PRRSV2010 isolates, which were highly pathogenic and reported from 2010–2013; however, none were detected after 2014. This group shows some evidence of recombination but had no unique genetic markers.
- JXA1-P80-like strains, which were highly pathogenic and detected from 2011–2015, especially from 2012–2014. Most isolates contained more than seven unique aa, in addition to some NSP2 deletions that were not consistent with HP-PRRSV.
- NADC30-like isolates, which were first reported in 2011; their prevalence grew rapidly from 2015–2017. Multiple deletions and insertions occurred in these strains, and more than half of the isolates in the study were recombinants.
- Intermediate PRRSV strains, which were divided into several groups. Those isolated before 2006 did not have the 29-aa deletion used as a marker for HP-PRRSV. This group also contained NADC30 recombinants, strains like QYYZ that shared a unique aa deletion (301–302) and insertion (813–848) in NSP2, and some unclassified strains.
- MN184-like isolates, which were identified in 2017 in Liaoning province, shortly before African swine fever emerged there.
- Original HP-PRRSV isolates, which included the 2006 HP-PRRSV outbreak strain and others like it.

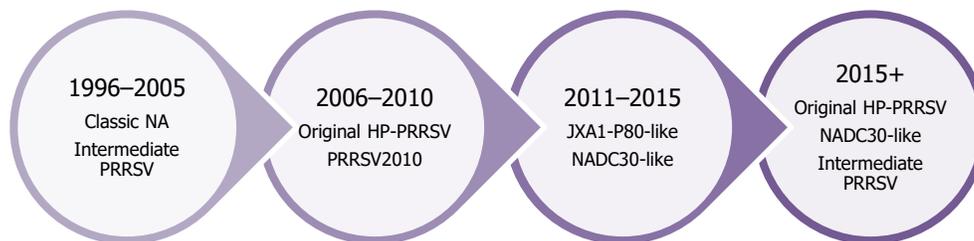


Figure 1. PRRSV epidemic periods (1996–2017) in China as described by Jiang and colleagues.⁷⁵

Recombinant HP-PRRSVs from multiple lineages continue to be characterized in Asia.^{10, 12, 17, 18, 75, 86-96} Because PRRSVs evolve rapidly and recombination is common, the viral population is extremely genetically and antigenically diverse. It is likely that surveillance will continue to identify new variants of HP-PRRSV.

PRRSV in the United States

PRRSV strains with increased virulence (i.e., PRRSV 1-7-4) have been reported in the United States since 2014, but they originated from existing wild-type midwestern PRRSVs, not from Chinese isolates.^{97, 98} An experimental study compared the severity of illness induced by Chinese and U.S. PRRSVs. Interestingly, one U.S. strain (SDSU73) induced moderate clinical disease, similar to the Chinese isolate (rSRV07), while another (VR-2332) caused minimal illness.⁹⁹

Yu and colleagues¹⁰⁰ recently published a comparative analysis of 355 Chinese and U.S. PRRSVs collected from 2014–2018, including 138 strains evaluated using next-generation sequencing and the Sanger method. Chinese PRRSVs belonged to lineages 1, 3, and 8, while U.S. PRRSVs belonged to lineages 1, 5, and 8. In isolates from both regions, interlineage recombination regions in NSP9 and GP2–GP3 were frequently identified. Furthermore, lineage 1 PRRSVs were identified as being most involved in recombination events. The main Chinese recombination patterns found were L1+L8 and L8+L1, while L1+L5 was most common in the United States. Overall, the recombination frequency of recombinants was higher in China than in the United States.

PRRSV Pathogenicity

The significance of the hypervariable NSP2 region is not well understood. It is not correlated with pathogenicity,^{4, 101} but it has recently been linked to PRRSV tropism in porcine alveolar macrophages.¹⁰² Evidence suggests that the NSP9 and NSP10 coding regions contribute to the increased pathogenicity of HP-PRRSV.¹⁰³⁻¹⁰⁵ Virulence determinants are also potentially contained in GPs 2–5.¹⁰⁶ Continued mutations in HP-PRRSVs do not necessarily lead to changes in virus pathogenicity.⁸⁰ However, some variability has been observed between isolates. In one experimental study, a Vietnamese isolate replicated at lower levels and caused fewer fevers and deaths than a Chinese HP-PRRSV.¹⁰⁷ Natural HP-PRRSV recombinants may exhibit higher or lower pathogenicity compared to their parent strains.¹⁰⁶

HISTORY IN SWINE

In the late 1980s, an unknown syndrome emerged in U.S. pigs, causing severe reproductive and respiratory disease.^{108, 109} Around the same time, a similar syndrome was reported in Germany.¹¹⁰ Initially described as "mystery swine disease," the disease was also known as swine infertility and respiratory syndrome (SIRS), porcine epidemic abortion and respiratory syndrome (PEARS), and blue-eared pig disease. Later named porcine reproductive and respiratory syndrome, a viral etiology was confirmed in 1991.¹¹¹

The origin of PRRS remains unknown. However, the virus was likely present in swine long before the original epidemics occurred.¹¹² Through much of the world, PRRS has become an economically devastating disease of swine. In the United States, PRRSV costs the swine industry an estimated \$664 million annually.¹¹³

IMMUNITY

POST-INFECTION

PRRSV inhibits type I IFN and suppresses innate immunity in infected pigs.¹¹⁴ Cell-mediated immune responses peak around ten weeks post-infection (wpi).⁶⁹ Neutralizing antibodies against the viral proteins N and GP5, and NSPs 1, 2, and 7 appear about four wpi.⁶⁹ Although PRRSV can persist long-term in carrier pigs, it seems that most infected pigs become immune and viral shedding stops around 60 dpi. Declining antibody titers have been observed around 4–8 months post-infection.² In piglets, passive immunity declines soon after weaning. Adult animals are much more resistant to PRRSV infection compared to weaned pigs.¹

HP-PRRSV seems to induce higher levels of anti-PRRSV IgG antibody in wild pigs compared to domestic pigs at 21 dpi.⁷ Experimentally, HP-PRRSV is also a stronger inducer of toll-like receptors (TLR) 3, 7, 8 and IL-1 β , IL-6, TNF- α , IFN- γ production compared to other PRRSVs.⁶

VACCINES

Vaccination against PRRSV may result in protective immunity, moderate clinical signs, and reduced shedding of the virus.¹ However, experience in the field suggests that vaccination is inconsistently effective.¹ Inactivated and modified live vaccine (MLV) formulations are available. MLVs may not provide complete immunity, although they induce a more efficacious immune response than inactivated vaccines. Problematically, they have been known to revert to virulence under field conditions.^{115, 116} And, since MLVs can replicate in the host inducing viremia and virus shedding, they play a role in the emergence of recombinant PRRSVs.^{116, 117} MLVs provide homologous protection, but due to the genetic diversity of PRRSV, cross-protection between vaccine and field strains may not be sufficient to prevent infection.

The development of a universal vaccine has been suggested as a way to overcome current vaccine limitations.¹¹⁸ Vaccine technologies being explored include recombinant vectors (e.g., recombinant adenovirus, attenuated pseudorabies virus, recombinant transmissible gastroenteritis virus, *Mycoplasma* spp.), marker vaccines (differentiating infected from vaccinated animals [DIVA] and compliance marker vaccines), infectious PRRSV cDNA clones, use of as PRRSV as a viral vector (for expression of marker genes, pathogen genes, and cytokine

genes), chimeric PRRSVs, PRRSV attenuation through codon pairs deoptimization of the major envelope gene, and DNA shuffling (rapidly accelerated mimicry of natural recombination).¹¹⁹

Attenuated HP-PRRSV vaccine strains such as JXA1-R, HuN4-F112, and TJM-92 have demonstrated protection against homologous challenge.¹²⁰⁻¹²³ Partial heterologous protection has also been reported following vaccination with attenuated type 1¹²⁴ and type 2^{122, 125-128} MLVs. The HP-PRRSV vaccine strain JXA1-R has been shown to provide heterologous protection against NADC-20.¹²⁹ New vaccine candidates are being continually described. Current candidates include a highly attenuated derivative from the HP-PRRSV strain QY1, showing a 32-aa deletion in NSP2,¹³⁰ and the HP-PRRSV strain HB-XL, suspected to be a novel virus caused by vaccine recombination that results in low morbidity and mortality in pigs.⁸¹

Safety must be considered in HP-PRRSV vaccination programs. In China, at least two instances of natural recombination between a PRRSV vaccine strain and a circulating HP-PRRSV have been documented.^{131, 132} HP-PRRSV revertants of a vaccine strain (JXA1-P80) have also been detected in Chinese pigs.¹³³

CROSS-PROTECTION

PRRSVs evolve rapidly, resulting in a genetically and antigenically diverse population.⁶⁹ Recombination is also a driver of virus change, and it has been linked to the emergence of novel HP-PRRSV strains in China in recent years.^{68, 82, 134} Infection with one PRRSV strain does not prevent infection with another.^{135, 136}

GAPS IN PREPAREDNESS

PRRS is economically devastating for swine producers in many parts of the world, including the United States. New PRRSV variants—causing high morbidity and mortality rates—continue to emerge in Asia. Preventing the spread of PRRSV within and between farms is critical to reducing the disease burden in China and other countries affected by HP-PRRSV. North American PRRSVs have previously been imported into China, and Chinese variants could spread to the United States. Potential transmission routes should be investigated, and strict biosecurity measures should be in place to prevent an HP-PRRSV incursion.

Although PRRS was identified 30 years ago, many knowledge gaps remain. Future studies on basic viral biology, pathogenesis, host genomics, viral genomics, and immunology must continue to advance understanding of PRRSV.⁶⁹ Although PRRSV vaccines are available, control programs are hampered by the virus' rapid evolution and deficient heterologous coverage. New vaccine technologies must be explored to enhance cross-protective immunity and produce products that cannot revert to virulence.⁶⁹ Cost also remains a challenge.¹³⁷ Carrier pigs impede elimination efforts, and diagnostic tests that can differentiate infected from vaccinated animals (DIVA) are desperately needed.⁶⁹ Improved vaccines and diagnostics are critical components in a PRRSV control or elimination program.

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