Porcine Reproductive and Respiratory Syndrome: Diagnosis, Management, and Current Treatment and Prevention

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Abstract

Porcine Reproductive and Respiratory Syndrome (PRRS) is currently the most financially devastating disease in the swine industry globally, and is estimated to cost the United States alone $560 million dollars annually. The PRRS virus (PRRSv), a nidovirus infamous for its genetic complexity and rapid mutation, causes the disease. Infection with PRRSv results in reproductive failure in breeding stock and respiratory disease in young stock. Weaned piglets exhibit fatigue, labored breathing, and a high fever, eventually dying from interstitial pneumonia. Despite active research, disease prevention efforts remain relatively ineffective and mortality rates remain high. Vaccinations of various types have been commercially available for decades, but vaccine efficacy remains low. In addition, both vaccinated swine and swine that recover from previous infection often remain susceptible when exposed to another viral variant or variant subtype. The disease is highly transmissible. Viral shedding is present in all bodily fluids with some research indicating that aerosolized PRRSv travels and causes pathogenesis in swine. Disease prevalence is high throughout the majority of the Midwest, but PRRS surveillance has not previously been performed in the Upper Peninsula. For these reasons, research in the Upper Peninsula must be performed to establish infection level in our area in order to implement proper prevention and control protocols.

Background

The first reports of PRRS occurred in Iowa in the 1980s, but the disease spread quickly. Within one decade of the disease’s first discovery in Iowa, animals presented with clinical PRRS
symptoms in Europe, Canada, Asia, and the Czech Republic (Holtkamp et al., 2013). The mechanisms of disease are relatively unknown and adequate forms of disease prevention have yet to be established. Initial emergence of the disease in the commercial swine industry may have resulted from transmission from wild boars, which have tested positive for the PRRS antigen throughout Europe and other countries (Stadejek, Stankevicius, Murtaugh, & Oleksiewicz, 2013).

Each swine herd presents uniquely with varying signs and symptoms within the first month of PRRSv infection. Signs of disease include pneumonia in weaned piglets and abortion in breeding sows. Due to an overwhelming amount of diverse clinical presentation, PRRS diagnosis was inconsistent surrounding its discovery. Disease names across the globe were variable, such as ‘swine mystery disease,’ ‘swine infertility and respiratory syndrome,’ ‘porcine epidemic abortion and respiratory syndrome,’ and ‘blue-eared pig disease’ (Nodelijk, 2002). Clinicians now understand that PRRS is caused by viral infection at various porcine life stages, resulting in respiratory and reproductive failure in swine. The disease is highly communicable and very difficult to manage (Li et al., 2016). Some measures of prevention such as vaccination have been established but are not entirely effective. Understanding the structure and mechanisms of the PRRSv and its communicability is vital in establishing herd health protocols to protect farms from PRRS infection (Murtaugh & Genzow, 2011).

**PRRS Etiology**

The PRRSv is classified in the *Arteriviridae* family, and in the order *Nidovirales*. Structurally, PRRSv is a single stranded RNA virus surrounded by a lipid bilayer. Six proteins are embedded in the viral envelope. Three proteins are considered to be major proteins, and three are classified as minor proteins due to their relative abundance (Van Breedam et al., 2011).
These proteins are classified as envelope proteins (E), membrane proteins (M), nucleocapsid proteins (N), and glycoproteins (GP2, GP3, GP4, GP5), along with a newly discovered protein 5a (Becares, Sanchez, Sola, Enjuanes, & Zuñiga, 2014). Understanding the prevalence and function of these viral proteins is important in development of efficient PRRS vaccines because immunity to the PRRS virus is achieved by producing antibodies to these viral proteins.

In addition to swine, nidoviruses are known to cause severe respiratory infection in humans, small animals, and other livestock (Perlman, Gallagher, & Snijder, 2008). RNA nidoviruses are known for their genetic complexity and inherent intricacy of replication and transcription (Perlman et al., 2008). Subsequently, the mechanisms of PRRSv infection are difficult to understand and replicate. Three main viral variants exist regionally throughout the globe with each viral variant containing subtypes. The two main viral variants include type I, which was initially isolated in Europe, and type II, which was isolated in North America. Type I PRRSv are further subdivided into three determined subtypes with some evidence contributing toward establishing a fourth subtype (Stadejek et al., 2013). Viral types I and II differ significantly in genetic sequence while subtypes of PRRSv type I differ in sequence length and presence of insertions and deletions. A newly discovered, highly pathogenic variant of PRRSv type II (HP-PRRSv) is found in China, Vietnam, Cambodia, and other Asian countries. Infection of HP-PRRSv results in high mortality, typically killing more than half of piglets and adult pigs in a herd (Tornimbene et al., 2015; Wang et al., 2013).

In clinical application, the genetic complexity of PRRSv makes the disease hard to manage. The PRRSv has been established as one of the most highly mutating RNA viruses (Renukaradhya, Meng, Calvert, Roof, & Lager, 2015). For example, sows that recover from infection are known to develop immunity to PRRS. However, the immunity seems to be limited
to the original isoform of the virus. When sows are exposed to a heterogeneous isoform of the PRRS virus, they develop clinical signs (Neumann et al., 2009). This implies that many isoforms of the virus are present, and more research will be needed to discover all isoforms of the virus in order to produce an effective and efficient vaccine for PRRS.

**Disease Mechanisms**

Upon infection, PRRS\textsubscript{v} attacks pulmonary intravascular macrophages and pulmonary alveolar macrophages, which it utilizes as a host for reproduction and replication. PRRS infection has also been shown to significantly decrease T lymphocyte cells in the immune system, providing opportunity for secondary bacterial and viral infection, for example: co-infection with *Streptococcus suis*, *Mycoplasma hyopneumoniae*, and Porcine Circovirus (Li et al., 2016). This mechanism likely suppresses immune response in infected pigs, as shown in a study by Jung et al. (2009), in which PRRS\textsubscript{v} infected weaned piglets were exposed to Porcine Respiratory Coronavirus ten days after infection with PRRS\textsubscript{v}. Pigs previously infected with PRRS\textsubscript{v} developed more severe pneumonia, were more febrile, and experienced significantly reduced weight gain in comparison to pigs infected only with respiratory coronavirus (Jung et al., 2009).

Furthermore, Jung et al. (2009) provided evidence that the exacerbated infection in the PRRS\textsubscript{v} pigs was due to a decreased immune response by measuring decreased antiviral cytokine (IFN-\(\alpha\)) production after initial PRRS\textsubscript{v} infection. IFN-\(\alpha\) is known to mediate immune response to viral infection by activating macrophages in the body (Biron, 1998).

In addition to long term infection, the depressed immune system induced by PRRS\textsubscript{v} delays the production of neutralizing antibodies 3-5 weeks post-infection (Van Breedam et al.,
Neutralizing antibodies produced by swine following infection are mainly against the GP5 protein, one of the glycoproteins of the virus (Becares et al., 2014). It is known that GP5 forms a disulfide bridge with the M protein of other PRRS virions that are necessary for swine infection (Eck et al., 2016). In addition, the GP4 and GP5 proteins are known to elicit the strongest immune response with the most neutralizing antibodies. These proteins are also the most genetically diverse proteins in the virus (Eck et al., 2016). Understanding the role and mechanisms of these viral proteins is vital in understanding the mechanisms of disease transmission and acquired immunity.

Disease Transmission

The virus passes through the placenta in late gestation, resulting in infected piglets prior to farrowing (Dee, 2016). In addition, infected piglets can transmit the virus for 112 days post infection. The communicable period for PRRSv is crucial to spread of disease, and due to typical housing conditions, PRRSv circulates easily through a herd of weaned piglets. Since piglets are typically weaned at 3-6 weeks of age and then housed in a communal setting, this provides the ideal opportunity for the PRRSv to spread through a herd and infect any healthy piglets (Dee, 2016). The virus is highly communicable and spreads through viral shedding between pigs. The virus is shed in almost all bodily fluids including nasal secretions, semen, breastmilk, urine, and feces. This provides easy routes for viral transmission in a farm setting. For example, semen collected from infected boars can infect sows that are artificially inseminated (Neumann et al., 2009). The lack of adequate biosecurity in the porcine artificial insemination industry is just one example of the factors that have led to an increase in PRRSv infection of breeding sows, which provides a direct route to infecting piglets.
While it is known that PRRSv exists in bodily fluids and is highly communicable, recent research also demonstrates that PRRSv is transmissible through contaminated air. Both the amount of aerosolized virus detected and the number of viral variants detected are positively correlated with pig farm density in an area (Brito, Dee, Wayne, Alvarez, & Perez, 2014). However, a study by Brito et al. detected many variants of PRRSv even in areas with low farm density (2014). In addition, aerosolized modified live PRRSv was detected in the study, which could lead to positive ELISA testing on PRRS negative farms (Brito et al., 2014). Consideration of vaccination protocols and infection rates of surrounding swine farms is important in diagnosis and control of PRRS.

**Diagnosis**

Pigs diagnosed with PRRS present with reproductive failure in breeding stock and respiratory complications in swine of all life stages (Neumann et al., 2009). Pigs can be cyanotic, anorexic, febrile, lethargic, shivering, and can experience lameness (Holtkamp et al., 2013; Li et al., 2016). Reproductive failure due to infection with PRRSv results in numerous complications surrounding fertility, including increases in abortion, premature births, and prevalence of stillborn and mummified piglets. The Merck Veterinary manual reports that incidence of stillborn piglets can increase by up to 35%, and abortion rates by 10% (2016). Piglets die in utero by hypoxia due to inflammation of blood vessels in the placenta and umbilical cord from the infection. In addition, a high rate of agalactia, or the inability to produce sufficient milk, is found in infected sows, which contributes to the high death rate of piglets.

Respiratory infection due to PRRSv usually presents in young piglets. Piglets demonstrate a characteristic irregular breathing pattern known to be associated with PRRS. Severe lower respiratory tract infection ensues in addition to reduced weight gain, lethargy,
weakness, coughing, and sneezing. Necropsy of piglets reveals interstitial pneumonia of piglets, or infection of the space between lung alveoli and capillaries (Dee, 2016).

Early detection of the virus is necessary for the control of PRRS. Reverse transcription polymerase chain reaction (RT-PCR) is available for early detection and for years was the only source of testing. In the last ten years, both oral fluid-based enzyme-linked immunosorbent assay (ELISA) and serum based (ELISA) testing have become commercially available. Serum-based ELISA has been proven to be a reliable method of diagnosing PRRS infection with accuracy rates of up to 99.9% while oral fluid-based ELISA serves as a convenient and simple test for the consumer while maintaining effectiveness (Díaz et al., 2012).

With the development of highly pathogenic variants of PRRSv (HP-PRRSv) in Asian countries, it has become important to not simply test for PRRSv infection, but to also diagnose the variant of PRRSv. As explained previously, HP-PRRSv infection results in significantly higher fatality and morbidity in swine herds, with death rates of up to 100%. Yang et al. (2013) developed a one-step RT-PCR that takes just two hours to complete. The genetic difference between HP-PRRSv and classical PRRSv (C-PRRSv) is characterized by a 90 base pair deletion in the non-structural polyprotein 2 (NSP2) coding region of the virus (Yang et al., 2013). The one-step RT-PCR utilizes this genetic variation to differentiate between HP-PRRSv and C-PRRSv. Although RT-PCR methods were previously developed to detect PRRSv type I, PRRSv type 2, and HP-PRRSv, the tests were not able to differentiate between the variants at times of co-infection and can take up to weeks to complete (Chai et al., 2013). In addition, the RT-PCR developed by Yang et al. (2013) can detect infection up to two days before symptoms appear. The development of one-step RT-PCR is extremely important in highly sensitive, early detection of HP-PRRSv and C-PRRSv in a clinical setting.
Prevention

Vaccination is the primary form of PRRS prevention in the swine industry. However, PRRS vaccines have been widely ineffective thus far in clinical application. A live vaccine was produced for PRRSv in 1994, but efficacy has not been improved since then (Murtaugh & Genzow, 2011). This is largely due to a minimal knowledge of the multiple variants of the PRRS virus and also due to a scant understanding of porcine immunology (Murtaugh & Genzow, 2011). Developing a herd health protocol is difficult with the use of a live vaccine because pregnant animals cannot be vaccinated, resulting in the inability to prevent infection of piglets in utero.

Current studies aim to establish new vaccines that provide immunity against all isoforms of the virus. Research focuses on determining an efficient viral vector to deliver the PRRS viral RNA into cells to induce immunity. The two current types of available vaccines are modified live vaccines and inactivated vaccines. Alternative vaccines types in clinical trials include DNA vaccines, subunit and peptide vaccines, viral vector vaccines, and plant-derived vaccines (Eck et al., 2016).

Recent research in Korea by Park et al. (2014) studied a new modified live vaccine, which resulted in marked improvement over pigs vaccinated with the live vaccine. Vaccinated pigs in the study displayed increased market weight and decreased mortality rate. Necropsy of deceased vaccinated pigs showed fewer lung lesions than deceased non-vaccinated pigs (Park, Seo, Kang, et al., 2014). Extensive research of modified live vaccination is also being conducted by Zoetis and Boehringer Ingelheim to evaluate efficacy against PRRSv challenge (Park, Seo, Han, Kang, & Chae, 2014; Weesendorp et al., 2013).
Eck et al. (2016) utilized propagation-incompetent recombinant vesicular stomatitis virus (VSV) as a viral vector for PRRSv immunity in swine. The virus is packaged in virus replicon particles (VRP) to be utilized as a vector for PRRSv. The recombinant VSV lacks the G protein necessary for viral assembly and expression and is therefore a safe viral vector for PRRSv. However, vaccination trials conducted by Eck et al. (2016) did not induce immune response prior to PRRSv challenge. Although vaccinated pigs did not display a decreased degree of viremia compared to control, vaccinated pigs developed PRRSv-specific antibody responses following viral challenge two weeks earlier than non-vaccinated pigs. As it has been previously established that immune responses typically take at least 3-5 weeks to develop in infected swine, a VSV VRP vaccine could provide an earlier immune response to infection (Eck et al., 2016).

The majority of vaccines available are administered intramuscularly or intranasally, however, the efficacy of intradermal vaccination for PRRS is under research. Intradermal vaccines have been evaluated in swine for pseudorabies but have not been evaluated for the PRRSv. This type of vaccine could provide a new avenue for immunization (Luduec et al., 2016).

**Management**

Management of PRRS-positive animals in a herd depends largely on herd size, strain of virus, and the production system of the farm. If the PRRS positive sows are not culled, cycles of clinical PRRS outbreaks will likely occur on the farm. In a small closed farm, meaning there are few pigs that move to and from the facility, outbreaks may be small and sows may develop immunity to the point that clinical outbreaks do not occur. Although, multiple strains of PRRSv are often present in a single farm and can continue to infect different animals, even in a small-scale farm setting. In large-scale farms that have high swine traffic, positive pigs will continue to
infect others, resulting in cycles of clinical outbreaks of disease. This will make the disease difficult to manage and prevention nearly impossible. In addition, geographical areas with high densities of swine provide an avenue for pigs to come in contact with multiple strains of the virus. Recent research regarding aerosolized PRRSv validates the high communicability of the virus and the risk associated with infection in high swine density areas (Brito et al., 2014).

Biosecure facilities are critical in the management of PRRS. Proper facilities can minimize viral transmission between infected and healthy weaned piglets, as well as between young stock and adult animals. Maintaining clean facilities can aid in management of disease since most disinfectants deactivate PRRSv. In addition, flies and mosquitos are known to spread the virus by mechanical transmission (Neumann et al., 2009). Therefore, clean and biosecure facilities can limit spread of disease by deactivating the virus once viral shedding has occurred, limit transmission between infected and non-infected pigs through nose-to-nose contact, and limit mechanical spreading of viral sheds through insect vectors.

The ability to manage PRRSv is highly debatable. Due to the high genetic variability of the virus, even sows that have gained immunity to one strain of the virus often appear to be naïve to another subtype of the same viral variant. It is evident that we currently have not developed vaccinations that contain all of the viral variants and cannot physically keep up with the rapid rate of viral mutation. Depopulation of an infected herd currently stands as the only method to eliminate disease from a herd, specifically in commercial swine farms. Following depopulation, the facilities must be thoroughly removed of all organic matter and disinfected to remove virion particles. All facilities must be disinfected, including housing pens, hand tools, equipment, and manure pits. In addition to virion particles on surfaces, research demonstrates that aerosolized virion particles remain active in the environment for up to one month. For this reason, it is
recommended to avoid introducing new pigs into the farm before this time has passed (M. Benjamin, personal communication, July 27, 2017).

Conclusion

Determining the infection rate of PRRSv in the Upper Peninsula is vital in implementing prevention and disease management protocols. A complete survey of PRRS infection has not previously been established in our area. Many pig producers in the Upper Peninsula purchase hogs from Iowa, Wisconsin, and Ohio; these states are known to have high PRRSv infection rates. Often, these pigs are brought across state lines unconventionally, without veterinary inspection prior to transfer. This provides an easy method of disease transfer into the Upper Peninsula. In addition, the population of feral swine is increasing in Michigan, potentially adding another avenue of disease exposure to domestic swine (Wyckoff, Henke, Campbell, Hewitt, & VerCauterren, 2009). Immunological surveys of feral swine have confirmed infection of PRRSv, Porcine Circovirus Type 2, and *Mycoplasma hyopneumoniae* (Baroch, Gagnon, Lacouture, & Gottschalk, 2015). Without proper disease management and prevention protocols established in Michigan, PRRS has the potential to spread through the Upper Peninsula’s swine herds and significantly impact swine health in our area. Therefore, it is vital to evaluate PRRSv infection status in the Upper Peninsula and establish routine screening to prevent and manage spread of disease.
Literature Cited


