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Porcine reproductive and respiratory syndrome developments: An in-depth review of recent findings

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ABSTRACT
The porcine reproductive and respiratory syndrome (PRRS) virus (PRRSV) belonging to the Arteriviridae family is the cause of PRRS disease. After being discovered for the first time in the United States in 1987, this illness quickly expanded to Canada. The disease was initially discovered in late 1990 in Germany, from where it quickly spread throughout Europe. The consequences of PRRSV lead to a number of epidemiological issues, including a sickness with a delayed immune response that permits extended viremia, which facilitates viral transmission. The virus penetrates the nasal epithelium, tonsils, lung macrophages, and uterine endometrium through the oronasal and genital pathways. Abortions performed late in pregnancy and premature or delayed deliveries resulting in dead and mummified fetuses, stillborn pigs, and weakly born piglets are indicative of reproductive syndrome. In the meanwhile, dyspnea, fever, anorexia, and lethargic behavior are signs of respiratory syndrome. The virus can be isolated from the tissue or serum of animals that have been infected to confirm the diagnosis. Pig movements and potential airborne dissemination are two ways that the virus can enter new herds and propagate through nose-to-nose contact or aerosols. Various supportive therapies may enhance infant survival, and antibiotics may or may not lessen the impact of secondary bacterial infections. The absence of simple diagnostic tests, the virus's airborne transmission, the occurrence of subclinical infections, and the virus's persistence in infected populations have all contributed to the failure of control efforts for PRRS.
Keywords: Disease, Pig, PRRS, PRRSV, Virus.

Introduction

Porcine reproductive and respiratory syndrome (PRRS) is an infectious disease that affects pigs of all ages and is characterized by respiratory issues and reproductive failure in pigs (Raymond *et al*., 2017). After being discovered for the first time in the United States in 1987, this illness quickly expanded to Canada (Chae, 2021). The disease was initially discovered in late 1990 in Germany, from where it quickly spread throughout Europe (Balka *et al*., 2018). The illness first surfaced in the Netherlands in 1991 and has since spread to every province that practices extensive pig raising (Dortmans *et al*., 2019). In 1994, PRRS received official recognition in 16 nations across three continents (America, Asia, and Europe) (Franzo *et al*., 2022).

The spread of the illness has actually been considerably more widespread than has been reported. The illness is

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currently listed on list B of the OIE infectious disease index (Zhang *et al*., 2022a). Because its cause is unknown, this illness is known in America as "swine mystery disease" or swine infertility and respiratory syndrome (SIRS) (Zheng *et al*., 2024). The condition is also referred to as porcine epidemic abortion and respiratory syndrome (PEARS) in Europe and as blue-eared pig illness in the United Kingdom (Lunney *et al*., 2010). The term that most appropriately captures this disease's characteristics is PRRS, which has been agreed upon internationally.

The PRRS virus (PRRSV) belonging to the Arteriviridae family is the cause of PRRS disease (Wahyuningtyas *et al*., 2021). The first isolates of PRRSV were made in 1991 at the Central Veterinary Institute in Lelystad, Netherlands, and then in the USA in 1992 (Sinn *et al*., 2016). This virus is classified as a positive-strand RNA virus, and its biology has been thoroughly studied. The PRRSV can spread by feces, urine, and semen in addition to direct contact with sick pigs (An *et al*., 2011). In swine-intensive locations, the disease can also be transmitted by aerosol, which can lead to chronic reinfection of livestock (Prieto and Castro, 2005). It is also possible that mechanical vectors could carry the disease. There might be substantial fatality rates and a common increase in secondary infections (Cai *et al*., 2023).

Abortions performed late in pregnancy and premature or delayed deliveries resulting in dead and mummified fetuses, stillborn pigs, and weakly born piglets are indicative of reproductive syndrome (Pena *et al*., 2019). Rare cases of early to mid-pregnancy reproductive failure have been reported. The harm that PRRSV causes to the placenta and endometrium is most likely the reason for reproductive abnormalities associated with the virus (Novakovic *et al*., 2016). In the meanwhile, dyspnea, fever, anorexia, and lethargic behavior are signs of respiratory syndrome (Pei *et al*., 2023). Compared to mature animals, younger pigs are more influenced. Other than wild boars, laying pigs, and domestic pigs, no other species is known to naturally infect PRRSV.

To date, PRRS disease has spread quickly throughout the world. This, together with a lack of scientific understanding of the disease, has caused the pig farming sector to become concerned (Sun *et al*., 2023). This review aims to provide an explanation of the etiology, history, epidemiology, pathogenesis, immune response, pathology, clinical symptoms, diagnosis, differential diagnosis, transmission, risk factors, economic impact, treatment, vaccination, and control of PRRS.

Etiology

An RNA virus known as PRRSV was discovered and isolated. It belongs to the genus Arterivirus, family Arteriviridae, and order Nidovirales (Chaudhari and Vu, 2020). PRRSV has been determined through electron microscopy examinations to be a spherical, enveloped virus with a core measuring 25–35 nm and a diameter of 45–80 nm (Duan *et al*., 2024). Surface projections at small sizes are plainly evident. After being pretreated with ether or chloroform, the virus is rendered incapable of replicating, guaranteeing the existence of an envelope that contains lipids (Yang *et al*., 2015). The buoyant density of PRRSV is 1.19 in CsCl and 1.14 in sucrose (Carlsson *et al*., 2009). When comparing the pure CsCl preparation to the sucrose preparation, the infectivity peak was larger in the former. Treatment with substances that prevent DNA production (5-bromo-2-deoxyuridine, 5-iodo-2-deoxyuridine, and mitomycin C) had no effect on the replication of the PRRSV, suggesting that RNA is the nucleic acid (Zhang *et al*., 2022a).

Viral proteins of about 15, 19, and 24–26 kDa were identified using polyclonal antiserum immunoblotting (Chaudhari *et al*., 2020). The 19 kDa protein is probably a coat-associated protein, the 24–26 kDa protein is probably a glycosol coat-associated protein, and the 15 kDa protein is a nucleocapsid protein (Diao *et al*., 2023). The PRRSV infectivity titer was reduced 10-fold when maintained under conditions of 15–20 minutes at 56°C, 10–24 hours at 37°C, 6 days at 20°C, and more than 1 month at 4°C (Hou *et al*., 2020). The infectivity titer was stable for more than 4 months at −70°C. Virus infectivity titers are reduced by more than 90% at pH levels less than 5 or greater than 7 (Robinson *et al*., 2018). The erythrocytes of guinea pigs, sheep, goats, cattle, mice, rats, rabbits, type O people, ducks, and chickens are not hemagglutinate by PRRSV (Bougon *et al*., 2021).

PRRSV grew to titers of 10^5 to 10^7 $TCID_{50}$ in three cell types: primary porcine alveolar macrophages (PAMs), continuous cell line CL 2621, and MA 104 (Yan *et al*., 2022). In PAM cultures, cytotoxic effects lead to fast (1–4 days) clumping, rounding, and lysing of the cells (Cafruny *et al*., 2006). Cross-reactivity with sera against 39 enveloped RNA viruses that infect vertebrates was not seen, including viruses that are believed to be most closely related to PRRSV (equine arteritis virus and lactate dehydrogenase receptor virus) (Snijder *et al*., 1999). Serum polyclonal or monoclonal antibodies have shown differences in antigenicity between isolates from North America and Europe. Furthermore, it has been demonstrated that isolates from North America and Europe reflect two distinct genotypes (Nelsen *et al*., 1999).

The genome of PRRSV is a single-stranded, unsegmented, positive-sense RNA (Wang *et al*., 2024). The RNA genome is roughly 15 kilobases in size and has at least ten open reading frames (ORFs) (Zhou *et al*., 2022). The RNA-dependent RNA polymerase, helicase, endoribonuclease, four proteases, and two poly-proteins (pp1a and pp1b) are produced by the translation of ORFs 1a and 1b downstream of the 5'-UTR. These poly-proteins then undergo cleavage to yield fourteen non-structural proteins (Nsp) (Zhang *et al*., 2022a). This protein does not exist in the virion; it is only expressed during replication. The eight viral

structural proteins are encoded by ORFs 2-7. Virus structural proteins are encoded by eight ORFs (ORF3, ORF4, ORF5, ORF5a, ORF6, ORF7, ORF2a, and ORF2b) located downstream of ORF1b to the 3' end (You *et al*., 2022).

They consist of structural proteins, both major and minor. The tiny structural protein is composed of one non-glycosylation (E or 2b) and three N-glycosylations (GP2a, GP3, and GP4) that combine to create a trimeric coat protein complex (Wu *et al*., 2005). Trimeric complexes are necessary for viral infectivity, either on their own or in conjunction with GP5 (Van Breedam *et al*., 2010). Viral cellular tropism and replication depend on the E protein, which also interacts with the trimeric complex (Kappes and Faaberg, 2015). The primary structural proteins are the nucleocapsid protein N, the membrane non-glycosylated protein M, and the major envelope glycoprotein GP5 (Dokland, 2010). The generation of virion and viral infectivity depend on the heterodimer formed by GP5 and M (Luo *et al*., 2023). Recently, a novel structural protein named ORF5a was identified; it may play a role in virion survival, replication mechanisms, and cell tropism (Ma *et al*., 2021). In the process of assembling infectious particles, the N protein, encoded by ORF7, interacts with viral RNA (Zheng *et al*., 2024). Because of its high expression and antigenicity, it is mostly utilized as an antigen in diagnostic procedures.

Virion RNA can directly encode proteins because it serves as a messenger for the viral genome and RNA (Chaudhari and Vu, 2020). PRRSV virions have a spherical form and range in diameter from 45 to 80 nm (Dokland, 2010). Recent research using cryo-electron tomography revealed that contrary to earlier assumptions, the viral nucleocapsid possesses an asymmetric form (Asarnow *et al*., 2024). The RNA genome and N protein combine to produce the nucleocapsid, which is encased in a lipid-containing envelope.

History

In late gestation sows, clinical outbreaks of an unidentified disease with substantial reproductive loss were initially identified in the late 1980s (Lunney *et al*., 2010). Piglets are also affected by the disease, which lowers growth performance, causes severe pneumonia, and increases the frequency of poor births and fatality rates in newborn piglets (Papakonstantinou *et al*., 2023). In 1987, there was the first documented outbreak of this novel disease in North Carolina, USA (Chae, 2021). Because of the severity, duration, combination of respiratory and reproductive symptoms, and the fact that no known swine infection is implicated in the majority of cases, veterinarians and researchers believe this illness to be unique. This syndrome was given the moniker "mystery swine disease (MSD)" because the etiology is uncertain (Zheng *et al*., 2024).

A similar outbreak took place in Münster, Germany, just a few years later in 1990 (Balka *et al*., 2018). There was no discernible connection between the outbreaks in North America and Europe. The illness quickly spread to other nations in the ensuing years. The names and acronyms used to refer to MSD expanded globally along with the disease. SIRS and MSD are widely used in the USA (Chae, 2021). Common names in Europe include "blue-eared pig disease" and PEARS (Zaulet *et al*., 2012). Participants consent to use the European Commission's PRRS name at the 1992 International Symposium on Disease in St. Paul, Minnesota, USA (Done *et al*., 1996). PRRS is also acknowledged by the International Office of Epizootics. PAM are used at the Lelystad, Netherlands-based Institute; the strain is known as the Lelystad virus (Delputte and Nauwynck, 2004).

These viruses are identical, according to the preliminary genetic investigation; however, they now have two distinct genotypes, which are known as PRRSV1 and PRRSV2, which are two distinct virus species (Torricelli *et al*., 2023). Furthermore, both species share characteristics with other members of the Arterivirus genus, which was previously known as Porarterivirus until 2016 (Balka *et al*., 2018). Antibodies have been found in serum in Canada since 1979; the first proof of PRRSV was obtained by retrospective serological tests (Seo *et al*., 2016). Retrospective research conducted in the US revealed no signs of infection until 1985. After then, it became much more common in North America until clinical epidemics were first documented in 1988–1989 (Plagemann, 2003). In Europe, there might be a comparable pattern.

In Asia, the first outbreak was reported in Japan in 1988, but the presence of antibodies in serum has been documented retrospectively in South Korea since 1985 (Lee *et al*., 2023). These findings imply that the PRRSV might have been present in farmed pigs for a number of years prior to the first epidemic being documented.

Epidemiology

The consequences of PRRSV lead to a number of epidemiological issues, including a sickness with a delayed immune response that permits extended viremia, which facilitates viral transmission (Franzo *et al*., 2022). A silent viral infection that is limited to specific lymphoid tissues affects some pigs. It has been demonstrated that this virus has minimal replication and continues to cause infection on the farm (Li *et al*., 2024a). Because of the genetic diversity of PRRSV, the disease has resurfaced in livestock, presumably as a result of weak immunological effects (Franzo *et al.*, 2022).

In endemic farms, a number of animal groups can be distinguished due to distinct immune responses and genetic variability: uninfected animals, animals undergoing infection and virus excretion, animals recovered from infection and protected, and animals recovered from infection but having passed the protection stage and are therefore vulnerable to recurrence (Clilverd *et al*., 2023). PRRSV only infects a small number of animals on endemic farms that mostly

house protected species and issues arise when there are abrupt changes in the composition of the infected group or when a vulnerable animal group predominates (Sanchez *et al*., 2023).

At the moment, PRRSV is classified as two distinct viral species: PRRSV1 and PRRSV2 (Fiers *et al*., 2022). Both species are widely distributed worldwide, and nearly every country that produces pigs is affected by this disease, with the exception of certain South American, Australian, New Zealand, Scandinavian, and Swiss nations that do not have PRRSV (Carlsson *et al*., 2009). PRRSV2 is the extremely pathogenic PRRS virus that first appeared in China (Wang *et al*., 2022). This virus quickly spread throughout Asia. It is currently found in Asian nations such as the Philippines, Singapore, Vietnam, Malaysia, Myanmar, Laos, Cambodia, China, Indonesia, Bhutan, and the Philippines (Zhang *et al*., 2022b). The global distribution map of the PRRSV indicates that there is a very real chance of any strain, including the highly virulent strain seen in Asia, spreading across continents. Furthermore, the return of PRRSV to nations that are PRRSV-free could have disastrous effects, as it did recently in Chile (Neira *et al*., 2017).

Pathogenesis

The virus penetrates the nasal epithelium, tonsils, lung macrophages, and uterine endometrium through the oronasal and genital pathways (Wahyuningtyas *et al*., 2021). The latency time for PRRS disease varies depending on the age, immunity, and infectious dosage of the pig and can range from three days to several weeks in endemic instances (Butler *et al*., 2014). Once the virus enters local lymphoid tissues, it spreads throughout the body through the blood and lymphatics, where it either circulates unhindered or attaches itself to circulating monocytes, which causes leukopenia (Beyer *et al*., 2000). Cells from several organs and tissues can replicate PRRSV; the primary cell types where this might happen are monocytes, dendritic cells, and alveolar macrophages; these cell types are also the most important for pathogenesis (Ma *et al*., 2021). The virus can cause lymphadenopathy, pneumonia, myocarditis, encephalitis, rhinitis, and vasculitis, depending on its virulence (Meng, 2000). The main ways that the virus is expelled are by feces, milk secretions, urine, semen, saliva, and trans placenta (Pileri and Mateu, 2016). Infections due to PRRSV seldom persist longer than 200 days (Ma *et al*., 2021).

Immune response

Immunologically, PRRSV elicits a robust and swift humoral response; however, these primary antibodies do not offer defense and might even be detrimental, as they trigger an event known as antibody-dependent enhancement (ADE), which amplifies viral replication by coating the virus and enabling its entry into macrophages, as demonstrated *in vitro* in target cells (Mateu and Diaz, 2008).

Considering that IgG opsonizes viral particles and facilitates their entry into monocytes and macrophages through these receptors, and possibly the CD163 receptor against PRRSV on macrophages, which determines replication efficiency and pathogenicity PRRSV next, it has been observed that cells infected with PRRSV significantly induce IgG and Fcg receptors (Su *et al*., 2021). This kind of virus internalization can increase sensitivity to PRRSV by eliciting interleukin-10 production, which can then cause surrounding differentiated monocytes to produce CD163 (Singleton *et al*., 2016). The immune response depends on the infection of macrophages, monocytes, and dendritic cells, but infection of these cells also seems to be a major factor in PRRSV pathogenicity (Cai *et al*., 2023).

While it is well known that type I interferons (IFN-1) such as IFNα and INFβ produced by virus-infected cells stimulate the production of an innate antiviral response and that INFα prevents PRRSV multiplication (An *et al*., 2020). According to a number of studies, PRRSV causes interleukin-10 and suppresses IFN-1, particularly INFα and INF-β and "short porcine type I interpheron", or spI IFN (Huang *et al*., 2015; Gong *et al*., 2024).

In PRRSV-infected cells, there was a decrease in IRF3 transcript abundance, which is known to be crucial for INF I gene expression, as well as a suppression of spI IFN expression and a decrease in INFα transcript abundance (Pröll *et al*., 2017). IRF3 was inhibited in PRRSV-infected cells, which led to a decrease in INFβ gene expression (Luo *et al*., 2008).

Theoretically, a typical course of some PRRSV infections involves an increase in pro-inflammatory molecules followed by an increase in anti-inflammatory molecules. Numerous investigations on PRRSV-infected cells show that pro-inflammatory molecules are overexpressed, which aids in the pathophysiology of PRRSV (Montaner-Tarbes *et al*., 2019; Su *et al*., 2021). The CASP1, NF-κB, and IL-1β genes are overexpressed in cells that have been experimentally infected in vivo; NF-κB causes strong activation of the iflamoma CASP1 gene, which then releases IL-1b, causing fever and inflammation (He *et al*., 2022). Additionally, PRRSV-infected cells exhibit increased production of matrix metalloproteinases (MMP2 and MMP9) due to NF-κB (Lee and Kleiboeker, 2005). MMP overexpression promotes the invasion of inflammatory cells and exacerbates inflammation. In addition to PRRSV-infected cells, after acute infection, there is a striking overexpression of IL8 (CXCL8) which results in infiltration of neutrophils and other polymorphonuclear leukocytes (Liu *et al*., 2017). Other chemokines, which are equally critical for macrophages and lymphocyte infiltration, such as CCL2 (MCP1), CXCL9, and CXCL10 (IP10), were also shown to be markedly elevated (Xiao *et al*., 2010). Finally, the quantity of anti-inflammatory chemicals

such as PGE2 and IL10 (mRNA and protein) increased (van Reeth and Nauwynck, 2000).

The protective immune response of Th1 cells can be changed into a non-protective Th2 response by over-expression of IL10, which inhibits the loss of virus that promotes viral infection (Loving *et al*., 2015). Reduced allogeneic activation of T cells and downregulation of CD80/86 expression (costimulatory molecules and major histocompatibility molecule class II, or MHC-II) have been noted in experimental infection techniques (Flores-Mendoza *et al*., 2008).

When PRRSV infection is present, neutralizing antibody (NAb) induction is significantly delayed and NAb levels stay low, which prevents the effective removal of infected cells (Hsueh *et al*., 2021). Although NAb does not cure viremia, it is crucial for preventing infection. In the first four weeks after infection (PI), virus neutralization tests are unable to identify NAb; for types 1 and 2, detection occurs on day 28 PI or later (Vu *et al*., 2011).

Intriguingly, PRRSV-infected cells may exhibit a balance between apoptotic and non-apoptotic processes at the same time (An *et al*., 2020). It is feasible that PRRSV deliberately creates an antiapoptotic state to finish the cycle of viral replication before inducing apoptosis to release the viral (Li *et al*., 2024b). The antiapoptotic genes BCL2A1, MCL1, CHFR, NF-kB, ADM, and IL10 were shown to be expressed in PRRSV-infected cells (Xiao *et al*., 2010). Perforin (PFR) and granzymes are released by activated CTL and NK cells, and together, they cause target cells to undergo apoptosis (Osińska *et al*., 2014). PFR1 and granzyme transcript abundance have been found to be elevated in PRRSV-infected cells, along with overexpression of proapoptotic markers XAF1, BID, CytoC, CASP 10 AIFM2, and others that can cause PRRSV-infected cells to undergo apoptosis (Miller *et al*., 2010).

Apoptosis-infected cells produce immunosuppression by reducing the quantity of immune cells, which interferes with innate and adaptive immune responses and prevents the primary infection from being eradicated (Zhai *et al*., 2024). It also has an immunosuppressive effect on surviving cells.

Pathology

Reproductive tract pathological alterations are indicative of PRRS but not pathognomonic. At autopsy, cases of field-acquired PRRSV infection that do not result in a serious subsequent bacterial infection typically appear normal (Butler *et al*., 2014). Piglets that are born weak may have clear fluid in their chest cavity, and occasionally there may be pulmonary consolidation (Papakonstantinou *et al*., 2023). More widespread lesions of the respiratory tract, such as rhinitis, are more common than minor microscopic alterations, which are only seen in mild to severe interstitial pneumonia and infrequently catarrhal pneumonia (Ruedas-Torres *et al*., 2024). Furthermore, there are thymic tonsillar crypts, thymic alterations, perivasculitis, mononuclear myocarditis, splenitis with decreased lymphocytes, and thinning of the lymph nodes (Agliani *et al*., 2023). There have been no reports of inflammatory lesions in pig placentas infected with PRRSV or of virus-like structures in fetal and placental capillary endothelial cells (Barrera-Zarate *et al*., 2022). This might be a result of PRRSV's comparatively low pathogenicity in the UK.

In the USA, the prototype VR-2332 virus causes interstitial pneumonitis, lympho-mononuclear encephalitis, and lymphoid mononuclear myocarditis, but no lesions in the central nervous system (CNS) or heart have been seen following naturally acquired or experimentally induced viral infections (Rossow *et al*., 1994). Other symptoms include ultrastructural alterations, such as the loss of ciliated epithelial cells in the bronchioles and the degeneration of alveolar macrophages, along with excessive endoplasmic reticulum vacuolation (Saade *et al*., 2020a). There have been reports of fetal lesions in other investigations, which include extensive localized pulmonary bleeding along with bronchial buds that have degenerated and necrotized (Wagner *et al*., 2011).

A decrease in the quantity of alveolar macrophages obtained from bronchoalveolar lavage is brought about by PRRSV infection (Renson *et al*., 2017). Alveolar macrophages make up 90% of recovered cells in healthy pigs, but with an acute PRRSV infection, this percentage decreases to approximately 50%, with a corresponding surge in neutrophils and lymphocytes (Chaudhari and Vu, 2020). Following an experimental PRRSV infection, blood lymphocytes and monocytes, particularly T lymphocytes, decreased within three days of the infection, but by day fourteen, levels had recovered to normal (Wu *et al*., 2022). Leukocyte recovery is finished by day 28 after infection, and there might even be a stronger reaction to foreign antigens. As a result, after infection, there is a chance that sensitivity to further diseases will grow. Young pigs from cattle with PRRS have also been found to have high serum levels of alpha-I acid glycoprotein, an acute phase reactive protein that indicates tissue damage (Zhou *et al*., 2021).

Clinical symptoms

The symptoms of PRRS in a pig include fever, chills, dyspnea, eyelid edema, flushed skin, coarse hair, conjunctivitis, depression, anorexia, and diarrhea. These symptoms are comparable to different stages of pneumonia, myocarditis, encephalitis, rhinitis, vasculitis, and lymphadenopathy (López-Heydeck *et al*., 2015).

On farms, there is a rise in piglet mortality, a decline in the quality of sow semen, and an increase in abortions, mummification, stillbirths, weak births, and recurrent estrus rates in the reproductive area (Torrents *et al*., 2021). In developing animals, respiratory problems caused by PRRSV itself are due to the increased prevalence of viral infections that cause respiratory

symptoms and also lead to overall low weight gain (Ruedas-Torres *et al*., 2024).

Low weight gain, weak births, no birth attainment, reproductive issues, high drug therapy costs from PRRSV alone, or related infectious disorders cause endemic farms to incur ongoing losses (Valdes-Donoso *et al*., 2018). Pigs that are infected may not exhibit any symptoms at all or may exhibit generalized symptoms that are similar to those of swine flu, classic swine fever (CSF), parvovirus, encephalomyocarditis, chlamydiosis, and mycoplasmosis (Labarque *et al*., 2002).

The most frequent secondary infections linked to PRRSV have been identified as Actinobacillus pleuropneumoniae, Salmonella cholerasuis, Pasteurella multocida, Haemophilus parasuis, Aujeszky respiratory coronavirus, encephalomyocarditis virus, and paramyxovirus (Guan *et al*., 2023).

Among the etiologic agents isolated from the porcine respiratory disease complex (PRDC) in the USA, porcine respiratory virus (PRRSV) is one of the most frequently occurring. Other agents that are considered causative etiologic agents include swine influenza A (SIV), porcine circovirus type 2 (PCV2), *Pasteurella multocida*, *Mycoplasma hyopneumoniae*, *Streptococcus suis*, *Actinobacillus pleuropneumoniae*, and Actinobacillus (Hamophylus) parasuis. All of these agents must be isolated from a pneumonic lesion in order to be identified (Saade *et al*., 2020b).

Diagnosis

In acute situations, PRRS is frequently identified just by looking for outward symptoms. The virus can be isolated from the tissue or serum of animals that have been infected to confirm the diagnosis (Xiao *et al*., 2008). It is possible to get serum for viral isolation from many breeding pigs. A diagnostic laboratory can separate the virus if it is present in one of the pigs' bloodstreams (Plut *et al*., 2020). Compared to serological testing, this test is more costly.

Serological detection of antibodies to a disease in an animal's bloodstream indicates whether the animal has been exposed. There are currently four serologic assays available: serum neutralization (SN), enzyme-linked immunosorbent assay (ELISA), monolayer immunoperoxidase assay (IPMA), and indirect fluorescent antibody (IFA) (Pan *et al*., 2023). In the USA, the ELISA test is most frequently utilized (Seo *et al*., 2016).

A veterinarian with knowledge of PRRS and the test is required to interpret serological tests. An animal exposed to PRRSV or a piglet nursing a positive sow could both be indicated by a positive serological test (Fiers *et al*., 2023). Vaccinated animals will also show positive results. There is no test to distinguish between animals that have had vaccinations and those that have not, unlike the pseudorabies serological test. Assessing the significance of a positive test result requires knowledge of the vaccination history of the animal (Fiers *et al*., 2024).

The ELISA test is very sensitive and will detect antibodies as early as 9 days after initial infection. However, because ELISA antibodies are thought to only persist for 5 to 6 months, they may not work well in populations that have had more than 6 months of virus exposure (Young *et al*., 2021). If testing is limited to these animals, the virus may still be prevalent in the herd even if the test results are negative. Pigs with negative ELISA test results could be misdiagnosed because younger animals could test negative or because animals that test negative might start shedding the virus under extreme stress (Ferrin *et al*., 2004). To obtain an accurate picture of the herd's PRRS condition, multiple animals of varying ages should be evaluated (Schoneberg *et al*., 2022). Initiating a PRRS diagnostic and control program requires taking this crucial step.

Differential diagnosis

The disease's symptoms resemble those of other bacterial or viral swine infections, and secondary infection with other pathogens can cause the clinical picture to become hazy. Thus, in addition to laboratory testing, the diagnosis of PRRS should be made based on clinical indicators and post-mortem examination (Zhang *et al*., 2022c). Given the high incidence of newborn mortality, respiratory issues in pigs of all ages, and reproductive failure, this illness should be considered.

The following are included in the differential diagnosis of reproductive diseases: leptospirosis, porcine parvovirus, porcine enterovirus, haemagglutinating encephalomyelitis virus, Toxoplasma gondi, Aujeszky's illness, and CSF, and African swine fever (ASF) (Mengeling *et al*., 2000).

The respiratory diseases that fall under the differential diagnosis category include: myocarditis, swine influenza, enzootic pneumonia, proliferative and necrotizing pneumonia, infection with Haemophilus parasuis, haemagglutinating encephalomyelitis virus, swine respiratory coronavirus, syncitial pneumonia, porcine circovirus-associated disease, and infection with the Nipah virus (Saade *et al*., 2020a).

Transmission

PRRSV can survive relatively poorly in the external environment. While the virus can live for several years in tissue that has been deep frozen, it can only survive for one month at 4°C, 48 hours at 37°C, and less than 45 hours at 56°C (Mesa *et al*., 2024). Although the virus's half-life for survival diminishes at pH values of 5 or above, and live virus can be extracted from cadaver meat that has been kept at 4°C for 48 hours (Blomme *et al*., 2023).

Pig movements and potential airborne dissemination are two ways that the virus can enter new herds and propagate through nose-to-nose contact or aerosols (Arruda *et al*., 2019). Within a herd, the disease can spread quickly. During the first 18 months of the UK

epidemic, about 75% of tested pigs tested positive for the virus within three weeks of there being a suspicion of illness (Frossard *et al*., 2017). In tests, it was found that three months after the virus was put into a controlled breeding group, 90% of sows had undergone seroconversion (Batista *et al*., 2002). The virus has been found in both urine and feces, yet fecal isolation is only rarely feasible (Alonso *et al*., 2013). Similar to this, one group has quite easily isolated the virus from the semen of experimentally infected boars, whereas another group has had less success (Nathues *et al*., 2016). Data from experiments and epidemiology indicate that if semen is obtained from wild boars while the disease is still in its acute phase, PRRS may be transmitted by artificial insemination (Wu *et al*., 2011). Although other reservoir species are not known to harbor PRRSV, preliminary data indicate that migratory birds may carry the virus and hence serve as a vector (Wang *et al*., 2013). Contact with older, sick animals is likely the most significant mode of transmission when breeding and finishing pigs (Pileri and Mateu, 2016). There have been cases of isolated contact infections after 99 days, and acutely infected animals can easily spread the virus to other animals by touch for up to 14 weeks following infection (Raymond *et al*., 2017). According to a recent study, the virus could reappear in pigs' oropharynx up to 157 days after infection (Wills *et al*., 2003). In one trial, corticosteroid therapy after infection caused viral re-excretion; however, this was not the case in another (Ison *et al*., 2022).

Depending on group dynamics and management techniques, the virus may or may not spread at the group level. The virus can persist in weaned pigs even in closed herds, and infection happens when colostral antibodies have vanished by the time the pigs are three to six weeks old (Chang *et al*., 2002). Large finishing facilities that buy pigs with a variety of illnesses and immunological problems create the perfect environment for the virus to continue spreading. There is a dearth of evidence in the field about herd damage caused by consistently or latently infected people excreting viruses (Arruda *et al*., 2019).

Risk factor

There are reports of the risk factors for PRRSV infection in livestock, but the majority of these reports are complicated by the absence of objective oversight. In a German study of 150 infected herds, 95% had purchased stock less than 4 weeks before the outbreak or were within 5 km of the infected herd (Hu *et al*., 2023). The following elements were found to have a major impact on PRRSV transmission in various studies: purchase of pork, proximity to infectious livestock herds, absence of quarantine for purchased pigs, and high flock sizes (Hasahya *et al*., 2021).

Scholars continue to gather data concerning the epidemiology of PRRS. According to serological tests, the virus is common in swine populations in Europe and North America, and many infections do not show symptoms right away (Beilage *et al*., 2009). When a flock contracts the PRRSV, the infection typically persists in the flock (Mulligan *et al*., 2022). The most frequent mechanisms of transmission seem to be local airborne dissemination and the movement of sick pigs (Dee *et al*., 2002).

Economic impact

Losses differed greatly in amount and duration. As such, it is critical to distinguish between the disease's effects during the epidemic and endemic stages. The majority of the time, economic losses in the UK are quite minimal, but others claim extremely high losses, ranging from 1 to 25 sows and £65 per sow annually to 0% to 20% of annual production or $18 per space finishing annually in the USA (Valdes-Donoso *et al*., 2018). Losing trade status for seeds that test positive for seropositive could be an extra hardship.

Treatment

Various supportive therapies may enhance infant survival, and antibiotics may or may not lessen the impact of secondary bacterial infections (Odland *et al*., 2022). Although pregnant pigs have been given antipyretic medications, their effectiveness has not been established. It is possible to lower the rate of infection from infected piglets by lowering the size of the herd and eliminating sick pigs (Fano *et al*., 2005). Delaying the rebreeding of afflicted sows, employing artificial insemination to enhance natural service, and postponing iron treatments and tail docking for neonates are other management practices that could lower losses (Pertich *et al*., 2022).

Vaccination

A conventional and essential technique for treating and managing viral infections in pigs is the PRRS vaccination (de Brito *et al*., 2023). PRRS vaccination products are currently offered for sale in a number of nations worldwide. However, the vaccination is ineffective for all PRRSV genotypes due to the great genetic variety and quick viral sequence deposition (Eclercy *et al*., 2021). Put another way, because of the high degree of evolution, the immune response in vaccinated pigs is not entirely cross-protective. Commercial PRRS vaccines are frequently made from subunit components expressing certain proteins, modified viruses (MLVs), and inactivated viruses (made by preparing several virulent isolates or enhanced viral antigens) (Zhou *et al*., 2021).

In two vaccination trials, Trus *et al*. (2014) used pigs of various ages that had certain immunoperoxidase monolayer assay (IPMA) antibodies. These pigs were partially protected against the severe syndrome (prolonged fever, viremia, and runny nose) after receiving an MLV vaccination based on the European DV subtype 1 strain and contracting the East European PRRSV subtype 3 Lena strain. However, they still perished from a secondary infection in the lungs caused by Trueperella pyogenes and Streptococcus suis. According to Kick *et al*. (2023), the best vaccination

is chosen by taking into account not only the degree of similarity but also specific gene sections linked to virus interactions and genome replication, as well as the usage of chimeric viruses that have been modified to fit into vaccine formulations.

The recommended methods for creating vaccines with greater efficacy include DNA vaccines and recombinant DNA vector vaccines (Weiner and Nabel, 2013). The main structural protein of PRRSV, GP5 glycoprotein, encoded by ORF5, causes pigs to develop neutralizing antibodies (Luo *et al*., 2023). Through the use of a plasmid expressing GP5 from PRRSV, Pirzadeh and Dea (1998) investigated immunized pigs with the generation of particular anti-GP5 neutralizing antibodies. They suggested that GP5 is a good candidate for a subunit recombinant vaccine, despite the fact that the recombinant GST-ORF5 protein produced by *E. coli* might not successfully elicit an immune response to induce neutralizing antibodies due to variations in polypeptide formation or posttranslational modifications. Rompato *et al*. (2006) investigated how the immune response was impacted by the PRRSV-ORF7 (phCMV-ORK7) DNA vaccination and how it related to various adjuvants. The addition of IL-2 to the vaccination has a favorable inductive effect on the activation of virus-specific cellular immunity, but the addition of IL-4 to the ORF7 DNA vaccine has a suppressive effect that generates an immunological response. These findings show that adjuvants for DNA vaccines, in the case of the PRRSV DNA vaccine in particular, and animal vaccinations in general, can strengthen and improve the cellular immune system.

Numerous attempts have been undertaken to develop novel vaccines for PRRS disorders due to the pig's weak innate and adaptive anti-PRRSV immunity, the considerable genetic diversity among PRRSVs, and the unknown link between this syndrome and other pig diseases (Nan *et al*., 2017).

Control

The absence of simple diagnostic tests, the virus's airborne transmission, the occurrence of subclinical infections, and the virus's persistence in infected populations have all contributed to the failure of control efforts for PRRS. Several strategies for managing PRRS include preventing the virus from entering the pig herd through testing and quarantining new arrivals, restricting guest visits, changing shoes and clothes after pigs are marketed, keeping rodents and roaming animals at bay, and cleaning trucks that transport pigs (Alarcón *et al*., 2021). Nevertheless, as PRRS is an airborne illness, there is no certainty that the aforementioned control measures will stop the virus from spreading.

Other control measures recommended by the European Community during acute outbreaks are breeding more sows and rearing more piglets; placentas, fetuses, and deceased piglets from all abortions and early farms should be disposed of carefully because they may carry high concentrations of the virus in the blood, lungs, and other organs; the breeding premises must be thoroughly cleaned after the abortion; farm pigs should not be moved to uncontaminated pens, and farm pens' entrances and exits should be cleaned; and every transport vehicle needs to be completely cleaned and sealed (Colomer *et al*., 2019).

Control measures for this illness have also been proposed, including routine serotin testing to check herd status, on-farm production at two or three locations, and improved management techniques (Magalhães *et al*., 2021). It is advised to use age-separated pig farms and thorough methods to stop the spread of older pigs among younger ones (Butler *et al*., 2014). Early off-site weaning, all-out day care, varying weaning intervals, and early weaning with medicine are strategies that can interrupt the infection cycle in day care settings (Corzo *et al*., 2010). Given the disease's chronic viremia, precautions should be made to keep the negative group from becoming infected again (Kick *et al*., 2023).

Furthermore, the source of replacement pig stock ought to be monitored constantly, and breeding stock must be acquired from animals without a history of PRRS (Fornyos *et al*., 2023). In the event of an early farrowing, sows should be relocated to the farrowing house two weeks in advance (Blavi *et al*., 2021). Supportive care can lower the death rate of newborns (Jeong *et al*., 2021). Due to their poor fertility in the first estrus following abortion or premature calving, sows that lose their litters should only be fed during the regular weaning period in order to avoid disturbance to the "pig flow" (Papakonstantinou *et al*., 2022).

Conclusion

PRRS is an infectious disease that affects pigs of all ages and is characterized by respiratory issues and reproductive failure in pigs. Various supportive therapies may enhance infant survival, and antibiotics may or may not lessen the impact of secondary bacterial infections.

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Author's contributions

TH, ARK, SM, and TDL drafted the manuscript. AP, SMY, IM, and MKJK revised and edited the manuscript. RR, SU, MA, and KAF took part in the preparation and critical checking of the manuscript. RR, RD, SW, and IBM edited the references. All authors read and approved the final manuscript.

Conflict of interest

The authors declare that there is no conflict of interest.

Data availability

All data are provided in the manuscript.

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