PORCINE RESPIRATORY DISEASE COMPLEX (PRDC)

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Abstract

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Respiratory disease has an important impact on swine producers worldwide. A disease pattern has emerged that has been designated as the porcine respiratory disease complex (PRDC). PRDC is a common term for pneumonia in finishing or fattening pigs caused by a multifactorial etiology. This article focuses on three major swine respiratory pathogens, including Porcine Reproductive and Respiratory Syndrome virus (PRRSV), Mycoplasma hyopneumoniae and swine Influenza virus (SIV) and their interaction. Several control strategies are discussed.

Keywords: porcine respiratory disease complex, porcine reproductive and respiratory syndrome virus, Mycoplasma hyopneumoniae, swine influenza virus.

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Introduction

In recent years, a number of emerging and changing pathogens have been found to be important in the development of porcine respiratory disease complex (PRDC). PRDC is economically significant for pork producers throughout the world. PRDC is characterized clinically by slow growth, decreased feed efficiency, anorexia, lethargy, fever, cough and difficult breathing and is common in pigs around 10 to 20 weeks of age. Because PRDC is not caused by a single organism but is multifactorial the pathogens isolated from pigs vary between and within production units (Dee, 1996). The three pathogens most commonly isolated from pigs with clinical disease consistent with PRDC at the Iowa State University-Veterinary Diagnostic Laboratory (ISU-VDL) include Porcine Reproductive and Respiratory Syndrome virus (PRRSV), Mycoplasma hyopneumoniae and Swine Influenza virus (SIV). Other pathogens such as Pasteurella multocida, Actinobacillus pleuropneumoniae, Streptococcus suis, and Haemophilus parasuis are also important in the induction of pneumonia associated with PRDC. Pneumonia associated with Porcine Circovirus type 2, the cause of post weaning multisystemic wasting syndrome (PMWS) is also increasing. Similar scenarios have been observed in Thailand. At the Chulalongkorn University-Veterinary Diagnostic Laboratory, Bangkok, Thailand, PRRSV and M. hyopneumoniae were the most commonly isolated pathogens from pigs showing disease consistent with PRDC. In addition,
over 50% of viral pneumonia found at the Thai diagnostic laboratory in the last three years (1999-2001) was attributed to PRRSV (Pirarat et al., 2002).

**Porcine Respiratory and Reproductive Syndrome Virus (PRRSV)**

The emergence of PRRSV in the swine population resulted in significant changes in the health status of pigs throughout the world (Zimmerman et al., 1997). PRRSV is often considered the most serious pathogen to the swine industry. In addition, the emergence of porcine circovirus type 2 and new strains of swine influenza virus play a role in the increase of respiratory disease associated with pig production. Other well-known organisms, such *Mycoplasma hyopneumoniae, Actinobacillus pleuropneumoniae, swine influenza virus, Haemophilus parasuis, Pasterella multocida* and *Streptococcus suis* remain problematic. Understanding how each of these pathogens cause disease helps to understand the strategies needed to control their impact on the pig's respiratory system.

Although the shift to intensive production systems occurred at the same time that PRDC appeared as a serious health concern, the emergence of PRRSV can be equally correlated with the increase in respiratory disease in many swine units. PRRSV is a virus that first emerged in the United States in 1987, Europe in 1992 and in Southeast Asia sometime in the late 1980’s to early 1990’s (Zimmerman et al., 1997). Research performed in Thailand by Damrongwatanapokin et al in 1996 demonstrated that in Thailand, the virus resembles the North American strain of PRRSV, more than the European strain (Damrongwatanapokin et al., 1996). Subsequently, both strains were commonly isolated from PRRSV infected herds throughout Thailand (Thanawongnuwech et al., 2002). However, since much of Southeast Asia has historically and presently imported breeding stock from both North America and Europe, the presence of both strains of PRRSV is likely to be common in many countries.

Respiratory disease induced by PRRSV can vary from clinically non-apparent and mild to acute, severe pneumonia characterized by labored and increased rates of breathing, lethargy and fever (Halbur et al., 1995). No cough is observed with PRRSV infection alone. Diagnosis of PRRSV is carried out by serology, virus isolation or demonstration of the virus in lung tissue using immunohistochemistry. Although seroconversion to PRRSV is rapid and typically observed within 7 days of infection, the initial antibodies are fairly ineffective and the virus can remain in the blood for up to 150 days (Meier et al., 1999; Allende et al., 2000). Neutralizing antibodies appear in the serum a minimum of 35 days after experimental challenge.

PRRSV has a predilection to infect macrophages (Thanawongnuwech et al., 1997). PRRSV-infected pigs are usually susceptible to secondary bacterial infection especially with *Streptococcus suis* due to the destruction of macrophages (Thanawongnuwech et al., 2000). In addition, an important factor in disease associated with PRRSV is the ability of the virus to mutate or change its
genetic makeup (Meng, 2000). By changing their genetic appearance, the immune system has to constantly recognize the virus as a foreign one and develop the tools to control and destroy the "new" invader. Each time the virus changes, the immune system must recognize the "new virus", which provides time for the virus to replicate in the host, thus ensuring its survival. This makes the ability to control PRRSV using the immune system difficult.

*Mycoplasma hyopneumoniae*

*Mycoplasma hyopneumoniae*, one of the smallest known bacteria, is the causative agent of enzootic pneumonia. *M. hyopneumoniae* infects the epithelial cells lining the respiratory cells. *M. hyopneumoniae* attaches to the cilia of the epithelial cells of the respiratory tract resulting in clumping, damage and loss of the cilia (DeBey and Ross, 1994; Young et al., 2000). Cilia are an important mechanism used by the respiratory tract to move foreign materials up and out of the airways. The loss of the cilia is thought to be important in the increased incidence of secondary bacterial infections associated with *M. hyopneumoniae* infection. In addition to the damage to the cilia, *M. hyopneumoniae* also induces inflammation and affects the immune system of the respiratory tract (Thanawongnuwech et al., 2001). *M. hyopneumoniae* prevents the immune cells from recognizing it as a foreign invader, resulting in its persistence in the respiratory tract of infected pigs. However, as *M. hyopneumoniae* alters the immune system to ensure its survival, the organism also changes the immune response to a number of other pathogens such as PRRSV (Thacker et al., 1999a) and *P. multocida* (Amass et al., 1994).

Clinical disease associated with *M. hyopneumoniae* infection alone, is minimal with only a mild, non-productive cough being typically observed. Due to the location of *M. hyopneumoniae* on the cilia in the airways, it is difficult for the immune system to respond to the presence of the organism. As a result, serology is a poor tool for diagnostic purposes. Seroconversion to *M. hyopneumoniae* is extremely variable, often occurring 4-10 weeks after infection (Thacker et al., 2000c). Culture of the organism is difficult and impractical. Other diagnostic tools such as immunohistochemistry and PCR are becoming more common, however the significance of identifying the presence of the organism is often unclear. Due to the difficulties in diagnostic testing, the contribution of *M. hyopneumoniae* on an individual pig basis can be difficult to determine. However, if the herd is positive for *M. hyopneumoniae* and has significant respiratory disease, the organism should be considered a major factor in the induction of pneumonia.

**Swine Influenza Virus (SIV)**

Although SIV is commonly isolated from pigs with PRDC and seroconversion is common, its role in the complex is not clear (Thacker et al., 2001). SIV is a virus that infects the epithelial cells that line the airways of the pigs respiratory tract and lungs. Infection of these cells by SIV results in death and loss of these cells. However, these cells
can regenerate quickly and if infection with SIV is not complicated by other organisms, the virus is quickly cleared from the respiratory tract (Thacker et al., 2001). This can happen in as few as 5 days. Once the virus is cleared from the respiratory tract, the epithelial cells quickly regenerate. There is minimal cross-protection between the different subtypes of SIV, all of which cause respiratory disease. Clinical signs typically associated with SIV include fever, lethargy, labored breathing and coughing. Diagnosis of SIV is typically based on serology, which is typically rapid, or the detection of the virus through immunohistochemistry on lung tissue. While virus isolation can be performed, samples must be collected early in the infection as the virus can no longer be isolated after the first 7 days. Increasingly, PCR is becoming available for the diagnosis of SIV (Choi et al., 2002).

**Interaction Between Pathogens and Control Strategies**

Much of the importance of PRDC is due to the interactions between pathogens. As the number of organisms and pathogens increase, the severity of the pneumonia increases. However, the presence of PRRSV, *M. hyopneumoniae* and/or SIV appears to be important in inducing the conditions in the respiratory tract conducive to the development of PRDC. Under field conditions, pigs infected with both PRRSV and *M. hyopneumoniae*, frequently exhibit an increased severity of pneumonia. In a study designed to investigate the effect the timing of infection had on the severity of disease associated with these two common respiratory pathogens, it was found that the presence of *M. hyopneumoniae* increased the severity of PRRSV-induced pneumonia. No matter when pigs were infected with either pathogen, the clinical disease and pneumonia were more severe (Thacker et al., 1999 a ). This study demonstrated that *M. hyopneumoniae* is an important co-factor in potentiating or augmenting PRRSV-induced pneumonia. In a second study, it was found that infecting pigs with both *M. hyopneumoniae* and SIV, increased the severity of pneumonia and clinical disease associated with the infections (Thacker et al., 2001). While the pneumonia induced by infection with *M. hyopneumoniae* and SIV was not as severe or dramatic as that observed in pigs infected with *M. hyopneumoniae* and PRRSV, the relationship demonstrates that the interaction between these common respiratory pathogens is significant. The findings of these studies demonstrate that understanding the interaction between the various pathogens must be considered if effective intervention strategies are going to be implemented.

Because PRDC is not caused by a single entity, being a multifactorial disease, pathogens isolated from pigs vary between and within production units. This variability in pathogens, in addition to the differing times when the pigs are infected, makes control of PRDC difficult and frequently frustrating. Vaccination plays an integral role in the control of PRDC. Successful immunization for the control of infectious diseases depends on numerous factors including the passive immune status and pig age, the environment conditions in which the pigs are housed, the
condition of the pig's immune system, how well the vaccine induces the appropriate immune response and the potential impact of other pathogens on the host. These factors require the development of individual vaccination programs for each farm. The cause of vaccine failure within a system is often unknown and our basic understanding of the pig immune system, whether humoral (production of antibodies), cell mediated, systemic, local or mucosal is often incomplete. Understanding the immune response, necessary to control a pathogen, as well as the mechanism by which disease is induced and the presence of other potential factors that interfere with mounting an effective immune response, is required to determine the optimal timing and use of a vaccine.

Vaccines for many of the pathogens associated with PRDC are dependent on determining both the pathogen and its specific serotype or subtype. This makes the use of many of these vaccines on a wide scale basis difficult. Individual production systems often require specific vaccines for the control of respiratory disease. It is not in the scope of this article to discuss all potential vaccines that can be used to control respiratory pathogens. It has been determined that the use of a *M. hyopneumoniae* vaccine can be an important tool in the control of PRDC (Thacker et al., 2000c). *M. hyopneumoniae* vaccines are bacterins consisting of inactivated organisms or their components. Protective immunity induced by vaccination has been demonstrated, however protection against clinical pneumonia is incomplete. Immunization may induce the production of serum antibodies but provides minimal local protection against the initial infection and is only slightly effective against colonization. Induction of serum antibodies by *M. hyopneumoniae* vaccine tends to be slow, with seroconversion commonly occurring 2 weeks after the 2nd vaccination. Frequently no serum antibodies are detected following vaccination with a one dose product. No correlation has been found between the presence of serum antibodies and protection against clinical disease (Thacker et al., 2000b). After vaccination, serum antibody levels decline in the absence of infection and pigs frequently become seronegative 4-6 weeks following vaccination. Following infection, vaccinated pigs will demonstrate an excellent memory response to the organism for at least 23 weeks, with antibody levels becoming much higher, compared to non-infected, vaccinated or infected, non-vaccinated pigs. This pattern of serological response can be used to confirm that the herd is actively infected with *M. hyopneumoniae*.

Research in our laboratory has suggested several possible explanations for decreased efficacy (and potential failure) of *M. hyopneumoniae* vaccines. A recent study by Dr. Brad Thacker at Iowa State University demonstrated that maternal antibodies are somewhat protective against clinical disease, as demonstrated by reduced pneumonia and coughing in young pigs at 3 and 6 weeks of age (Thacker et al., 1998). However; the presence of maternal antibodies inhibited the development of both the local and systemic immune responses by the pig and did not decrease the number of
organisms in the respiratory tract (Thacker et al., 2000a). These results suggest that while the presence of maternal antibodies may protect against pneumonia in young pigs, the inhibition of the immune response may simply delay the development of pneumonia. Further studies on the role of maternal antibodies on *M. hyopneumoniae* vaccine efficacy are ongoing in our laboratory (Thacker and Thacker, 2001). In one study, sows never exposed to *M. hyopneumoniae* were vaccinated to induce maternal antibodies. Pigs from these sows showed no decrease in vaccine efficacy when vaccinated in the presence of maternal antibodies. Differing results have been found in the presence of naturally induced antibodies and sow vaccination. One study found that sows, which had been naturally infected with *M. hyopneumoniae* and vaccinated appeared to decrease vaccine efficacy, while a second similar study showed no inhibition of vaccine efficacy. It appears that the level and type (vaccine induced versus naturally induced antibodies) of maternal antibodies may affect their ability to decrease vaccine efficacy. High maternal antibody levels in offspring from naturally infected sows may result in a reduction of *M. hyopneumoniae* vaccine efficacy. These studies suggest that while the presence of maternal antibodies may be somewhat protective in young pigs, their presence may not be beneficial. Herds with extremely high maternal antibody level suggest that the sow herd may also have high numbers of organisms. This will in turn infect the pigs at a younger age and appears to contribute to an increase in respiratory disease in pigs.

Vaccinating the breeding herd on a regular basis does not appear to be an effective mechanism for controlling mycoplasma pneumonia. Repeated vaccination of sows results in extremely high levels of maternal antibodies, which may affect the efficacy of mycoplasma vaccination of the pigs. Testing pigs at the time of vaccination to determine maternal antibody levels may assist in determining both the status of the sow herd in relation to *M. hyopneumoniae* infection level as well as maternal antibody levels.

The ability of *M. hyopneumoniae* to increase the severity and duration of pneumonia induced by PRRSV has been demonstrated in several studies in our laboratory. A study investigating the effectiveness of *M. hyopneumoniae* and PRRSV vaccines in decreasing respiratory disease, found that PRRSV significantly decreased the efficacy of *M. hyopneumoniae* vaccines, if pigs were infected during or within 2 weeks after mycoplasma vaccination (Thacker et al., 1999b). How PRRSV diminishes mycoplasma vaccine efficacy is unknown, as *M. hyopneumoniae* antibodies were present both systemically and locally in the respiratory tract of infected pigs. This study found that *M. hyopneumoniae* vaccination significantly decreased the increased level of PRRSV-induced pneumonia, observed with co-infection with *M. hyopneumoniae*. Vaccination with a commercial modified live virus (MLV) PRRSV vaccine did not decrease the effect of mycoplasma pneumonia induced by PRRSV or the potentiation of PRRSV pneumonia by *M. hyopneumoniae*. In contrast however, the presence of PRRSV, either through
the use of a MLV PRRSV vaccine or by infection eliminated the reduction in *M. hyopneumoniae* pneumonia by vaccination. In a separate study, we found that administration of a MLV PRRSV vaccine prior to mycoplasma vaccination did not decrease the efficacy of the mycoplasma vaccine (Thacker et al., 2000c). This suggests that timing of mycoplasma vaccination in relation to PRRSV infection and/or vaccination is important to *M. hyopneumoniae* vaccine efficacy.

In order to overcome both maternal antibodies and the effect of PRRSV, new vaccine strategies such as DNA vaccines and special adjuvanted vaccines will need to be developed in order to ensure protection under field conditions. As our knowledge of the immune response required for protection increases, development of new vaccines utilizing that knowledge will follow.

In addition to vaccination, good management practices are required for the successful control of PRDC. Strategically placed anti-microbial therapy and effective management schemes including acclimatization, nutrition, pig flow and environment should be considered in systems experiencing PRDC. Producers may change individual therapeutic strategies one at a time and wait to determine results, or may alter many factors at a time in an effort to control disease. Recently, Thai swine producers have encountered respiratory disease due to feed contaminated with mycotoxins, especially *Fusarium sp*.

Factors such as this must be considered when assessing the causes and appropriate measures to control PRDC. Because PRDC is multifactorial, all aspects of good swine management must be addressed in addition to identifying the pathogens involved.

The information provided in this article attempts to demonstrate how the interaction between pathogens and the immune status of the animal can affect vaccine efficacy. The factors affecting mycoplasma vaccines may also impact the efficacy of other vaccines and should be taken into account when developing strategies for each farm. In addition, management practices must be considered when controlling PRDC. Vaccination alone will not compensate for improper husbandry. Understanding the pathogenesis and factors affecting vaccination efficacy will enable the veterinarian and producer to determine the optimum time for the most effective use of vaccines. These patterns of infection especially in the presence of PRRSV should be taken into account with other vaccine strategies for other pathogens involved in PRDC.

**References**


