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Layout
David Brown

Logo Design
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Inducing sterilizing immunity against PRRSV in breeding-age, female swine

Laura Batista, DVM, Scott A. Dee, DVM, MS, PhD, Diplomate ACVM
Swine Disease Eradication Center, University of Minnesota, St. Paul, MN, USA

Introduction

Porcine reproductive and respiratory syndrome virus (PRRSV) constitutes one of the most important disease problems that the swine industry faces today. PRRSV is an RNA virus classified in the Arteriviridae family, order Nidovirales. Other viruses in this family include lactate dehydrogenase elevating virus and simian haemorragic fever virus. These viruses replicate primarily in macrophages and are known to establish asymptomatic persistent infections in their host. The persistence of PRRSV involves a continuous, low level of viral replication but is not a true steady-state persistent infection.[2] Persistent infection, defined as "the continued presence of a pathogen in a host beyond the acute symptomatic phase of infection"[3,4] has been detected up to 157 days post-experimental-infection in weaned pigs.[5] Persistence in adult sows may be shorter, up to 86 days.[6] If such animals shed, naïve animals may become infected, resulting in irregular periods of viral circulation and clinical PRRS. The main risk factors for the introduction of the virus into naïve herds or reintroduction to previously infected farms are the purchase of semen and/or breeding stock. Naïve gilts introduced into a seropositive herd as well as seronegative and even seropositive sows, exposed to an heterologous strain of the virus, are susceptible to PRRSV. Different approaches such as gilt acclimatization,[5] partial depopulation,[1] herd stabilization,[7] and test and removal[8] have been described in order to control and eradicate PRRSV infection from pig farms. Gilt acclimatization is the single most important and effective management scheme to control the infection.[9,10] Gilt acclimatization is also necessary as a preamble to eradication, since it prevents recirculation of the virus in the sow herd.

For those involved in the swine industry and who are attempting to control and/or eradicate PRRSV, some solid answers in relationship to PRRSV shedding and persistence in adult populations are indispensable. Two questions needing immediate answers for adult populations are the following:

- For how long do PRRSV-positive animals shed the virus?
- How long does persistence last after initial infection?

Answers to these questions are important because, among the most important control and/or eradication strategies proposed for PRRSV, farm closure and intentional exposure/injection of PRRSV to naïve gilts during acclimatization have proven to be extremely successful.[11]

The intentional exposure/injection of PRRSV to naïve gilts (not boars) during the acclimatization period is a management tool that is becoming more and more popular in different swine production areas. This management consists of exposing the naïve replacement to the farm's homologous strain(s) in order to achieve protection against PRRSV in these animals, therefore avoiding subpopulations of negative animals and thus limiting the virus ability to replicate.[11]

These two strategies, farm closure and intentional exposure/injection, are widely used in the swine industry around the world, and both have a common base: a relatively long interval of isolation of the infected pigs in order to avoid shedding and/or persistence. The time issue related to shedding and persistence have been extrapolations from very good science done by other groups such as Osorio's, Zimmerman's, and Allende's. The only problem with doing this extrapolation was that this research was done with young animals (3-week-old pigs at the time of inoculation) and our research group suspected important differences between younger and older populations. The isolation period of the farm or the quarantined animals has very important economic implications if these strategies are not well planned and will lead to a decreased output (number of pigs weaned or sold per group) issue that has been discussed thoroughly by several authors.

Results and discussion

In one of our latest persistence experiments,[12] we attempted to reproduce two very common population dynamics/situations in swine production—either the natural injection of PRRSV-homologous strain(s) to replacement animals in an all-in/all-out acclimatization unit or a population that has recently experienced an outbreak of PRRSV. The results of our experiment on persistence and shedding on 120 four-month index gilts and 30 sentinels concluded that, under the conditions of our study, PRRSV persistence appears to be limited to < 120

days and shedding to < 90 days within a large population of experimentally infected breeding age female swine (**Table 1**).

The cessation of viremia and detectable shedding of PRRSV is due to the development of a sterilizing immunity that prevents and/or minimizes the replication of the virus. Nevertheless, it has been suggested that the persistence and shedding of PRRSV depends on the age of the pig at the time of the initial contact or infection with the virus. One could speculate that older animals, as well as adults, might have a higher threshold for the establishment of infection compared to younger animals infected in the first month of their life. An explanation for the difference in persistence and shedding between younger, older, and adult animals is that maybe the latter have a more robust cellular and humoral immune response that allows older animals to resolve and recover from the infection in shorter periods of time.

Future work

As always, new information has lead to new questions, such as the following:

- Can the isolation time period be reduced without compromising the health status of the farm in order to reduce the economical impact of the different proposed control and eradication measurement that rely on the cessation of shedding and persistence?
- Is the faster clearance of the virus in older and adult population a question of maturity in the immune response of the pig?
- Is it true that older and adult pigs have a higher threshold in order to establish PRRSV infection?

We are sure that we will be able to answer most of these questions with our recently initiated experiments. The objectives of these new experiments are:

- To document the dynamics of PRRSV persistence in a large population of experimentally infected sows from 0-120 days post-infection
- To characterize the immune response of a large population of experimentally infected female swine over time using multiple diagnostic methods (VI, PCR, ELISA, SN, ELISPOT, flow cytometry)
- To identify changes in immune parameters that correlate with the reduction of the prevalence of persistently infected sows between 90-120 days post-infection

We know that pigs develop both humoral and cell-mediated immunity after PRRSV infection, but their relative importance in protection and clearance of the virus is not yet completely understood. PRRS convalescent animals show specific protective immunity; PRRSV specific antibodies (IgM and IgG) develop approximately 7-14 days after infection and can be detected by indirect fluorescent antibody test (IFA), serum virus neutralization test (SN), immunoperoxidase monolayer assay (IPMA), and enzyme-linked immunosorbent assay (ELISA). There is also an antigen-specific T-cell response to PRRSV infection with field isolates inducing a long lasting (> 1 year) and strong CMI response in pigs; lymphocyte blastogenesis assay, ELISPOT and the delayed-type hypersensitivity test can be used to monitor this immune response. It has also been established that both virus-specific IFN-g-secreting T cells and virus-neutralizing antibodies which have the ability to eliminate the virus are not detected until several weeks after exposure to either wild-type or vaccine virus. Finally, Osorio et al. recently indicated that PRRSV neutralizing antibodies have a significant role in protective immunity against PRRSV. Likewise, solid levels of T cells (represented by IFN-g-secreting T cells) should also correlate with protective immunity. Therefore, the identification of key immune parameters and the basis for this significant delay in the establishment of pro-

Table 1: PRRSV status of sera collected from index gilts following experimental infection and from sentinels during days 90-180 of the study.

Day	Index sows			Sentinals		
	PCR	VI	ELISA	PCR	VI	ELISA
1	0/30[A]	0/30	0/30	NA	NA	NA
3	23/30	0/30	0/30	NA	NA	NA
15	27/30	8/30	30/30	NA	NA	NA
30	0/30	0/30	30/30	NA	NA	NA
60	0/30	0/30	30/30	NA	NA	NA
90	0/30	0/30	29/30	0/30	0/30	0/30
120	0/30	0/30	29/30	0/30	0/30	0/30
150	0/30	0/30	19/20	0/20	0/20	0/20
180	0/30	0/30	9/10	0/10	0/10	0/10

NA = Not available; sentinels were not present until 90-days post-infection of index pigs.
ANumber of animals positive/number of animals tested.

tective immunity in the host following PRRSV infection will lead to the development of differential vaccines and diagnostic assays that could distinguish persistent carriers from those animals that have cleared the virus. Also, the swine industry will then have certainty of PRRSV shedding, persistence, and sterilizing immunity in adult populations, and most certainly sustainable PRRSV control and eradication strategies will be sturdier.

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