



Understanding PCV2 Pathogenesis

Brad Thacker, DVM, PhD, MBA, DABVP
Merck Animal Health, De Soto, KS

Introduction

Understanding porcine circovirus type 2 (PCV2) pathogenesis – how the disease develops within a pig – is critical when choosing a PCV2 vaccine. Following exposure to the virus, viremia (presence of PCV2 in the blood) starts building with low levels of virus in the blood, and is the initial step in the development of the disease in the pig.

Even low levels of PCV2 viremia can have a metabolic cost. A pig's energy and resources are directed to the immune system rather than growth, affecting average daily gain and feed efficiency.^{1,2} Severe disease can result in death. Controlling PCV2 disease by utilizing vaccines that are labeled to help prevent viremia is a highly effective approach because the cycle of the disease is broken and the damage caused by infection is limited or essentially eliminated.

PCV2 is a very tiny, hardy and durable virus that is found worldwide in nearly all swine operations. While vaccination has been effective in most situations due to the fact that it reduces virus shedding, it does not eliminate the virus, so it will persist in the environment. PCV2 is ubiquitous because it is:

- Resistant to common disinfectants
- Resistant to inactivation even at a low pH
- Stable at high temperatures
- Highly infectious and transmissible via oronasal secretions and feces

Because PCV2 infects cells of the pig's immune system, the impact of the disease goes beyond the direct infection. PCV2 can potentiate the impact of other pathogens, including porcine reproductive and respiratory syndrome virus (PRRSv), *Mycoplasma hyopneumoniae* and swine influenza virus (SIV). PCV2 vaccination can serve as the foundation for helping control these other diseases.

Economic impact

According to Darin Madson, DVM, Iowa State University Veterinary Diagnostic Laboratory, PCV2 is one of the top three economically important swine diseases behind PRRSv and *Mycoplasma pneumoniae*.³ If pigs are left unvaccinated, producers could see up to a \$20 loss per pig, which equates to losses that could exceed \$2 billion in the U.S. alone.⁴

With 92 percent of operations vaccinating for PCV2,³ the disease is being controlled, but it is important to continue vaccination because PCV2 is a constant that threatens productivity, morbidity and mortality. Plus, pigs vaccinated for PCV2 can deliver a sizable return on investment, as high as 10:1, or up to approximately \$20 per pig over unvaccinated pigs.⁴

PCV2 clinical signs

PCV2 infections can be subclinical, showing no outward signs of infection but greatly impacting average daily gain and overall performance. The clinical manifestations of the disease include:

- Rapid weight loss in early finishing, with reduced feed and water consumption
- Labored breathing (pneumonia)
- Diarrhea
- Enlarged lymph nodes
- Skin and kidney lesions (PDNS)
- Jaundice
- **High mortality**
- Abortion and weak-born pigs

PCV2 diagnosis

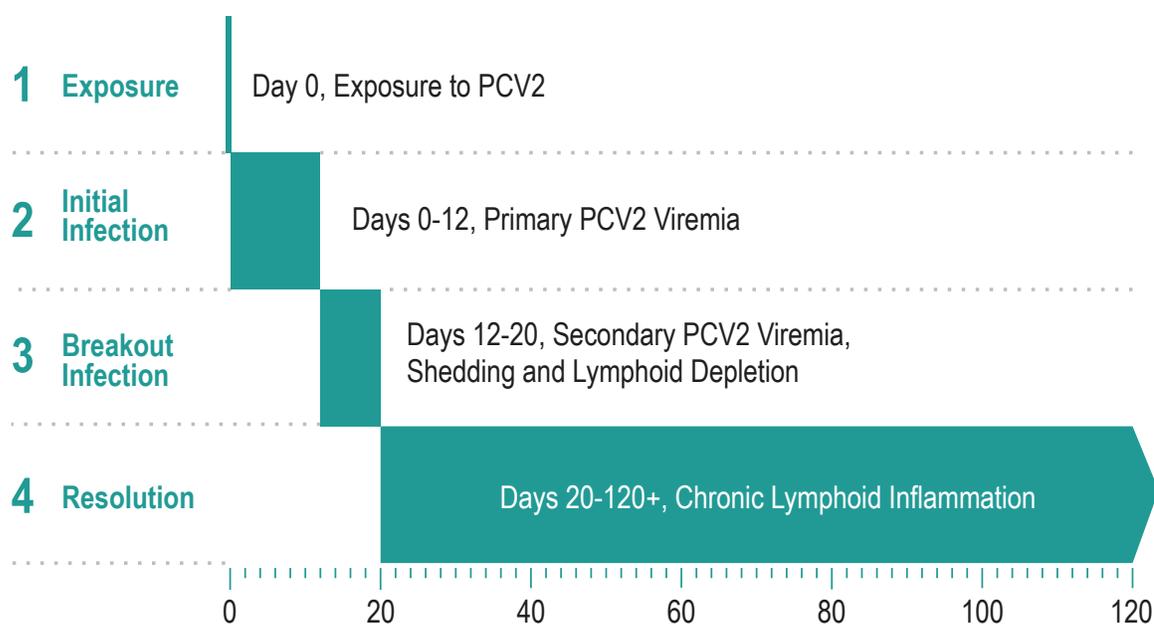
The American Association of Swine Veterinarians (AASV) has developed a case definition for PCV2 disease. They recommend that a veterinary diagnostic laboratory must confirm the following histopathological or microscopic tissues changes in the pig:

- Depletion of lymphoid cells in lymphoid tissues of growing pigs
- Identification of disseminated granulomatous inflammation in one or more tissues (spleen, lymph nodes, lung, kidney, tonsil, etc.)
- Detection of PCV2 virus in lesions of growing pigs
- Reproductive disorders confirmed by presence of antigen in fetal myocarditis lesions

PCV2 pathogenesis

Pathogenesis is the mechanism by which a disease develops and includes where the pathogen goes and what it does within the body, and how the body reacts to that pathogen. The steps in the PCV2 disease process include: 1) exposure, 2) initial infection, 3) breakout infection and 4) resolution. See Figure 1.

Figure 1: Time line of the PCV2 disease progression



Step 1: Exposure

Pigs are exposed to PCV2 by contact with a contaminated environment, such as the floor, feeders, waterers, fences and possibly the air. The virus is transmissible from an infected pig to a healthy one by oronasal secretions or fecal matter.

Step 2: Initial infection resulting in primary viremia

PCV2 infects susceptible lymphocytes in surface-located lymphoid tissues, such as the tonsil and the Peyer's patches, which are found in the small intestine. At the cell level, susceptible lymphocytes must be permissive and allow the virus to enter the cell. In addition, the lymphocytes must be actively dividing in order for PCV2 to replicate. This replication can be enhanced by immune stimulation from other co-infections like PRRSV or *Mycoplasma hyopneumoniae*.

After sufficient virus replication in the lymphocyte, the lymphocyte dies and releases infectious PCV2 to the surrounding tissues. From there, the virus gains access to blood and lymph vessels, resulting in primary viremia or relatively low-level, non-detectable viremia. The primary viremia spreads the virus throughout the body causing infection of lymphocytes in multiple lymphoid tissues, including lymph nodes, spleen, liver and possibly bone marrow. The number of lymphocytes that become infected and die is relatively small. Microscopically, no obvious lesions or aggregation of virus are detected.

Step 3: Breakout infection resulting in secondary viremia, shedding and lymphoid depletion

This secondary viremia is readily detectable in a large number of lymphocytes and leads to an overwhelming level of infection in the pig. This secondary viremia is readily detectable in samples from the field or experimental studies. Shedding of PCV2 via feces and oronasal secretions starts at this point.

Furthermore, large numbers of lymphocytes die, leading to depletion of lymphoid follicles or lymphocyte numbers in lymphoid tissues, which is visible by immunohistochemistry (IHC) under the microscope. Lymphoid depletion follows secondary viremia by a week or so. PCV2 infection is now in multiple lymphoid tissues, and large amounts of virus are produced and circulating through the pig's system.

Step 4: Resolution resulting in chronic (granulomatous) inflammation

Following depletion of lymphocyte populations that were susceptible to infection, the body mounts an inflammatory response to clean up the dead lymphocytes and fill in the space previously occupied by those lymphocytes. This chronic inflammatory response is carried out by an infiltration of histiocytes, which are tissue-located macrophages that engulf and digest the dead cells.

With PCV2 infection, the lymphocyte death is a relatively quiet process. There is minimal acute inflammation, meaning that there is not the typical, early and acute inflammatory response characterized by infiltration of neutrophils (pus cells) and fluid (edema). Because PCV2 is so durable, histiocytes can contain inactive PCV2 virus particles, which are picked up during the cleaning process and unable to actively replicate. Chronic inflammation always lags behind lymphoid depletion by a week or so. If a pathologist identifies lymphoid depletion, chronic inflammation is also present.

Because PCV2 is a chronic disease, secondary viremia, shedding, lymphoid depletion and lymphoid inflammation can persist for months. This chronic disease occurs despite the emergence of PCV2 antibodies, as measured by indirect immunofluorescence assay (IFA), at two to three weeks post-exposure.

Figure 2: Diagnosis of the disease

What Can Be Measured and How:	Viremia (Polymerase Chain Reaction [PCR])	Shedding (PCR)	Lymphoid Infection (IHC)	Lymphoid Depletion (Histopathology)	Lymphoid Inflammation (Histopathology)
1 Exposure					
2 Initial Infection					
3 Breakout Infection	■	■	■	■	
4 Resolution	■	■	■	■	■

Discussion

When reading PCV2 vaccine label claims, it is important to understand which parts of the PCV2 disease process the vaccine is targeting. Those that prevent viremia help break the disease cycle in the critical period following exposure to the virus. It is much more effective to control the disease early on so that damage caused by infection is limited or essentially eliminated. Vaccines labeled to help prevent PCV2 viremia are effective because they help break the cycle of disease early. Merck Animal Health believes viremia is the most important measure of PCV2 vaccine efficacy, as prevention of viremia stops the infection early on in the disease process before tissue damage can occur.

Also important are subsequent claims on the label. Those vaccines that reduce virus shedding and reduce lymphoid infection caused by PCV2 help stem the impact of infection that occurs later in the disease progression. The "aid in reduction" label claims mean that virus shedding and lymphoid infection occurred in vaccinates, but with significantly less severity than in controls.

1. Kekarainen T, Montoya M, Dominguez J, Mateu E and Segales J. Porcine Circovirus type 2 (PCV2) viral components immunomodulate recall antigen responses. *Vet Immunol Immunopathol*. 2008. Jul 15;124 (1-2):41-9.
2. Colditz I.G. Effects of the immune system on metabolism: implications for production and disease resistance in livestock. *Livestock Production Science*. 2002. Vol. 75, Issue 3. 257-268.
3. Darin Madson, DVM, Iowa State University Veterinary Diagnostic Laboratory Seminar, speaking at the 2010 World Pork Expo.
4. Gillespie, J., Opriessnig, T., Meng, X.J., Pelzer, K. and Buechner-Maxwell, V. Porcine circovirus type 2 and porcine circovirus-associated disease. *J. Vet. Intern. Med*. 2009. Vol. 23, 1151-1163.

Merck Animal Health

Summit, New Jersey 07901

www.merck-animal-health-usa.com Technical Service: 1-800-211-3573 Customer Service: 1-800-521-5767

Copyright © 2013 Intervet Inc., doing business as Merck Animal Health, a subsidiary of Merck & Co., Inc.
All rights reserved. SW-PCV-TB-013-1 (08-13)

