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## Porcine circovirus: An old virus in a new guise causes an emerging disease through a novel pathogenesis

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Postweaning multisystemic wasting syndrome (PMWS) is an emerging disease that was first identified at the Western College of Veterinary Medicine (WCVM), and is now recognized worldwide. The cause of this condition is a newly discovered small, single-stranded DNA virus called porcine circovirus-2 (PCV-2). Although newly discovered, the virus is not new to pigs and is widespread in pig populations. The diagnosis of PMWS and other PCV-2 associated diseases, including respiratory disease and reproductive failure, is based on identifying viral DNA or viral protein in diseased tissue. Why an old virus should suddenly emerge as a disease-causing agent is not currently understood. Numerous putative infectious and non-infectious co-factors (eg, husbandry practices and vaccination strategies) have been implicated in the pathogenesis of PCV-2-associated diseases. Apparently, for full expression of disease, PCV-2 infection must be combined with some other factor that activates the immune system and amplifies PCV-2 replication. This issue of *Large Animal Veterinary Rounds* discusses the emergence of PCV-2 associated disease and current information on diagnosis and control.

### A brief natural history of the virus

Porcine circovirus was first "discovered" in 1974 as a contaminant of a pig kidney tissue culture cell line, PK-15, used in laboratories throughout the world.<sup>1</sup> Based on its size and appearance, porcine circovirus was initially described as a "picornavirus-like virus particle," meaning that it was thought to be in the same family of viruses causing foot and mouth disease. However, after a period of 8 years, characterization of the genetic material from purified viral particles demonstrated that the virus contained a unique, circular, very small, single-stranded DNA. Based on those findings, the virus was renamed porcine circovirus (PCV) by the German virologist, Dr. Irene Tischer, who first described the agent.<sup>2</sup> In 1995, the *Circoviridae* were designated as a separate virus family by taxonomists based on the unique structural features of the agents in the group. Two important viral pathogens of birds, psittacine beak and feather disease and chicken anemia are also members of this family, as well as a similar virus found in pigeons, pigeon circovirus.<sup>2</sup>

The PCV found in contaminated tissue culture cells was subsequently shown to be nonpathogenic following experimental infection in pigs.<sup>2</sup> However, in the mid-1990's a number of western Canadian practitioners and diagnosticians recognized a new condition of pigs. Further investigations by Drs. John Harding, Ted Clark, and Debbie Haines suggested the involvement of a new PCV in this condition, that came to be known as postweaning multisystemic wasting syndrome (PWMS).<sup>3,4</sup> The causative agent was first isolated by Lori Hassard in the Diagnostic Laboratory at the WCVM.<sup>5</sup> Together with Dr. Gordon Allan and his colleagues, at Queens University, Belfast, Northern Ireland, the group at the WCVM showed that the circovirus from pigs with PMWS was different from the tissue culture contaminant virus in several important respects.<sup>5,6</sup> The genetic sequences of the tissue culture contaminant virus and the virus from pigs with PMWS are only approximately 70% the same. However, PCVs isolated from pigs with



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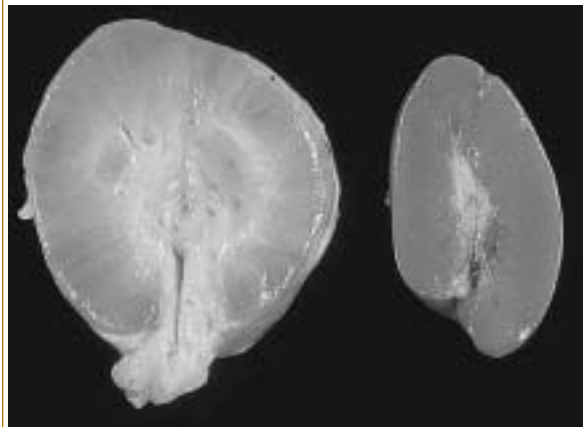


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**Figure 1: Circovirus infected lung showing interstitial pneumonia, interlobular edema, and bronchial lymphadenopathy**



**Figure 2: Enlarged kidney with lymphocytic interstitial nephritis from pig with PMWS (left) and a normal kidney (right)**



PMWS from many parts of the world, including North America, Europe and Asia are virtually identical, having ~ 96% sequence homology.<sup>7</sup> Examination of the PCV protein content, using polyclonal and monoclonal antibodies to the tissue culture contaminant virus and the viruses isolated from PMWS cases, demonstrated only low-level cross-reactivity between pathogenic and nonpathogenic circovirus strains.<sup>2,5,6</sup> Among pathogenic isolates, there is considerable protein homology, although some antigenic differences have been described.<sup>2</sup> Since the pathogenic and nonpathogenic PCVs were clearly different in terms of DNA sequence and antigenicity, the tissue culture contaminant has been designated PCV-1 and the virus isolated from pigs with PMWS, PCV-2.<sup>2</sup>

### **PCV-associated disease in the field: clinical findings and lesions**

With the possible exception of some cases of abortion, PCV-1 appears to be nonpathogenic in pigs.<sup>2</sup> In contrast, infection with PCV-2 has been consistently associated with the debilitating disease known as PMWS in young weaned pigs. Since its first recognition in western Canada in the early to mid-1990s, it has subsequently been described in the USA, many parts of Europe, and South-East Asia.<sup>2</sup>

Typically, signs of PMWS appear in pigs at 5 to 12 weeks of age. On occasion, new cases are reported in the late grower or finisher pig; this appears to be most common in multiple-source grow-finish barns. In the original description of clinical disease typical of PMWS,<sup>4</sup> Dr. John Harding noted 6 fundamental features that form the basis of clinical diagnosis:

- Wasting and/or unthriftiness that is usually progressive, beginning as subtle weight loss after weaning.
- Lymph node enlargement, a consistent feature that is often missed by the producer. For veterinarians, it has been said, “if you see lymph nodes you don’t know the names of, consider PMWS.”
- Dyspnea is frequently observed. This ranges in severity from mild to life-threatening. It cannot be differentiated clinically from dyspnea associated with the porcine respiratory disease complex (PRDC) in which PCV-2 may or may not play a role.

- Pallor or anemia, often nonregenerative. This may be associated with direct viral effects on the bone marrow or the result of debility.
- Diarrhea that is typically profuse, homogenous brown in color, and often accompanied by dehydration. The etiology of this diarrhea often involves other pathogens, such as *Salmonella* sp, *Brachyspira* sp, and enterotoxigenic *E coli*.
- Jaundice/icterus is a less frequent, but dramatic sign, reported on a sporadic basis by most farms with PMWS.

On a herd level, PMWS usually results in low-grade, but persistent losses. However, the severity can vary and, although rare in the western Canadian experience, severe epidemics resulting in a 3- to 4-fold increase in postweaning mortality have occurred.<sup>2,4</sup> This more severe presentation has been typical of outbreaks in parts of Europe, such as northern France and Spain, and especially recently, in the UK.<sup>2,6,8</sup> In contrast, for some European countries, (eg, Scandinavia and Belgium), very little PMWS has been reported.<sup>2</sup> The reason(s) for the apparent disparity in the severity of PMWS are unknown, but may be attributable to management practices.

Postmortem findings in cases of PMWS show wide variations in organ involvement and lesions may only be recognized on histological examination.<sup>2,3</sup> Gross lesions usually include enlarged lymph nodes and spleen, often with non-collapsed lungs and pulmonary consolidation (Figure 1). There is less consistent evidence of atrophic changes in liver, enlarged kidneys (Figure 2), gastritis and gastric ulcers, and enteritis. The lesions may or may not be reflective of the clinical signs.

Histological examination reveals changes in many lymphoid tissues and organs, including widespread depletion of lymphocytes, particularly in follicles and paracortical zones of the lymph nodes and in the periarteriolar lymphoid sheaths of the spleen. The depletion is often more apparent in lymph nodes that are enlarged. It is accompanied by infiltrations of histiocytes, particularly in the cortical sinuses, which often contain large single, or multiple small, basophilic, cytoplasmic inclusion bodies. Multinucleate syncytia are frequently seen in lymphoid tissues, particularly in lymph nodes, spleen, and gut-associated lymphoid tissue. These are commonly located in the

**Figure 3: Pig with dermatitis and nephropathy syndrome. Note the multiple irregular foci of cutaneous hemorrhage**



Courtesy of Dr. G. Allen

center of follicles depopulated of lymphocytes. In affected lungs, there is commonly a lymphohistiocytic interstitial pneumonia, with destruction of bronchial and bronchiolar epithelium and inflammatory cells in the alveoli. Lymphohistiocytic infiltrations are also found in the liver, kidney, and pancreas. Extensive necrosis of hepatocytes, often with parenchymal collapse, is a feature of liver lesions. In the kidney, there may be multifocal interstitial nephritis with vasculitis. In the stomach, colon, cecum, and duodenum there can be marked gland and crypt necrosis, with mononuclear cell infiltrations.

Immunolabeling of tissue sections from pigs with clinical PMWS, using PCV-2 specific antibodies, often reveals large concentrations of virus antigen in lymphoid tissues, particularly lymph nodes.<sup>2,9</sup> Viral antigen is most frequent in the cytoplasm of cells, but labeling in the nucleus is also observed. Labeled cells appear to be principally mononuclear phagocytes and dendritic cells; epithelial cells and lymphocytes can also contain virus antigen. Retrospective and prospective studies have indicated that while virtually all PMWS cases are associated with the presence of PCV-2 nucleic acid and antigen in lesions, a proportion of cases also contain porcine parvovirus, porcine respiratory and reproductive syndrome virus (PRRSV), or other agents.<sup>2,10,11</sup> These findings, together with experimental infections in the laboratory,<sup>2,12-15</sup> indicate that PMWS is a complex disease in which PCV-2 is the necessary, but not sufficient cause, and that a variety of infectious or non-infectious co-factors aggravate the effects of PCV-2 infection and are required for the development of PMWS disease. As well, it remains controversial whether or not PCV-2 causes immunosuppression in pigs, thereby predisposing them to “secondary” infections.<sup>2</sup>

In addition to its consistent association with PMWS, PCV-2 has also been detected in the organs of some pigs with respiratory disease without other signs of PMWS, including cases of proliferating and necrotizing pneumonia (PNP) and porcine respiratory disease complex in feeder pigs.<sup>11</sup> In cases of respiratory disease, PCV-2 is usually found together with PRRSV, swine influenza (SIV), or other recognized pneumonic pathogens.<sup>2,11,16</sup>

PCV-2 has also been identified in, and isolated from, cases of abortion and fetal death.<sup>17</sup> In these cases, severe myocarditis was often found in association with copious viral antigen in myocardocytes; thus, directly associating the virus with fatal

myocardial failure. In addition to direct fetal damage, PCV-2 was isolated from cases of sow abortion and mortality syndrome (SAMS), although the precise involvement of the virus in causing adult sow death remains to be elucidated.<sup>11</sup> These findings indicate PCV-2 infection should be a differential diagnosis for reproductive disease, especially in first parity gilts that might not be immune.<sup>17</sup>

The virus has also been demonstrated in kidneys and lymphoid tissue from pigs affected with porcine dermatitis and nephropathy syndrome (PDNS), a condition in pigs that appears to be spreading in parts of Europe, and is found sporadically in Canada (Figure 3).<sup>8,18</sup> In a study of pigs with PDNS from the UK, Spain, and the USA,<sup>18</sup> lymphoid depletion was often pronounced, and renal and cutaneous lesions were prominent. PCV-2 nucleic acid was detected in the majority of pigs examined and was found in macrophages, histiocytes, and dendritic cells of several tissues and organs, including lymph nodes, gut-associated lymphoid tissue, tonsil, lung, spleen, liver, kidney, and skin. Many of these pigs were also seropositive for PRRSV. How PCV-2 acts alone or in concert with other pathogens (eg, bacteria) to play a role in the pathogenesis of PDNS is unclear. It may be related to dysfunction of the immune system as a result of PCV-2 infection.

### **Experimental infections reproduce disease lesions seen in the field**

PCV-1 is probably non-pathogenic. No clinical signs, significant gross or histological lesions were observed following inoculation of PCV-1 into “mini” pigs or into conventional colostrum-deprived pigs.<sup>2</sup> The virus was only isolated from nasal swabs and feces. In conventional colostrum-fed pigs, the virus was detected in a wider range of tissues and organs including nasal mucosa, spleen, thymus, liver, lung, small intestine, and in several lymph nodes.

The first attempts to experimentally reproduce PMWS were conducted in gnotobiotic pigs in a collaboration between the WCVM and Dr. Steve Krakowka at Ohio State University.<sup>13</sup> These pigs were inoculated with homogenates of lymphoid tissues from field cases of PMWS that contained both PCV-2 and a low level of PPV, which was only detected retrospectively by polymerase chain reaction (PCR). The inoculated pigs developed the spectrum of gross and histological lesions characteristic of PMWS. In subsequent experiments,<sup>14,15</sup> inoculation of PCV-2 alone into gnotobiotic pigs did not result in clinical signs, although histological lesions and PCV-2 antigens were observed in some tissues. In conventionally reared colostrum-deprived pigs, inoculation of PCV-2 alone resulted in typical, mild to moderate lesions of PMWS that were associated with PCV-2 antigen. One of the inoculated pigs developed clinical disease including wasting. Moderately severe lesions were observed postmortem and PCV-2 antigen was present in all examined tissues.

Recognizing the possible role of PPV co-infection provided valuable insight into the pathogenesis of PMWS. In contrast to inoculation of PCV-2 alone, inoculation of gnotobiotic or conventional pigs with PCV-2 and PPV, resulted in severe lesions typical of PMWS.<sup>14,15</sup> Jaundice, enlargement and mottling of the liver, reduction in the size of the thymus, subcutaneous

edema, and ulceration of the stomach were seen in the gnotobiotic pigs, with consolidation of lung tissue in some animals. Histological lesions were observed in many tissues, but were most severe in lymph nodes, liver, kidney, intestine, and lung. PCV-2-infected cells were seen in all tissues examined and seroconversion to PCV-2 and PPV was demonstrated. While PPV clearly enhanced the severity of PCV-2-associated lesions and the quantity and tissue distribution of PCV-2 antigen in the dually infected pigs, PPV antigen was only detected in scattered cells in kidney, liver, and pancreas. Gnotobiotic pigs inoculated only with PPV failed to develop clinical signs of disease, histological lesions were minimal, and no PPV antigen was detected in any of the tissues examined.

The development of typical PMWS lesions in some PCV-2 inoculated pigs, the large concentrations of PCV-2 antigen and nucleic acid in the lesions, as well as the recovery of PCV-2 from the infected animals and the development of PCV-2 antibodies, led investigators to conclude that PCV-2 was the primary viral agent, or necessary cause in PMWS.<sup>14,15</sup> However, co-infection clearly potentiates the effects of this virus.

The non-pathogenicity of PCV-1 was confirmed by inoculating PCV-1 along with porcine parvovirus (PPV). This did not result in any enhancement or amplification of PPV lesions, although in one dually infected pig, a thickening of intestinal surfaces was observed.<sup>14</sup>

### **The role of host and virus differences**

The idea that changes in pig genetics are related to the emergence of PMWS is controversial. There is some evidence, much of it anecdotal, that certain lines of pigs may be more susceptible to the development of disease following PCV-2 infection; however, there are virtually no data that formally address this issue. Significant differences in virulence among PCV-2 isolates or strains have not been supported in recent work by Dr. Gordon Allan and colleagues. They demonstrated that apparently low-virulence PCV-2 isolates from Scandinavia, where little or no PMWS has been reported, can produce fatal PMWS if pigs are experimentally infected with this virus together with PPV.

### **The epidemiology of PCV infections**

Serological studies conducted in the 1980s and early 1990s suggested that infection of pigs with PCV-1 was widespread and probably occurred worldwide.<sup>2</sup> Up to 95% of sera from slaughtered pigs in Germany contained antibodies to PCV-1, and a similar incidence of infection was reported in pigs in the UK. Maternally-derived antibodies disappear by 8-9 weeks after birth, but re-appeared at 13-15 weeks of age, indicating that exposure and natural infection follows rapidly after the decline of maternal antibodies.

The more recent application of PCV-2-specific tests indicates that the prevalence and incidence of PCV-2 infection is also high, affecting up to 100% of pig herds in parts of Canada, the USA, and Europe.<sup>2,19,20</sup> Up to 100%

of pigs within infected herds have PCV-2 antibodies. PCV-2 has also been isolated from pigs in North America, many parts of Europe, and South-East Asia, further indicating that this virus, like PCV-1, is widely distributed in pig populations throughout the world. Moreover, retrospective testing of archived serum going back to the 1970s indicates that infection with PCV-2 is not a recent event; exposure to the virus is detectable in the oldest samples tested from 1974. In addition, it did not arise coincident with the emergence of PMWS, which was first described in mid-1990s.

Infection of pigs with PCV-2 occurs more commonly than the actual incidence of PMWS.<sup>2,19,20</sup> Although the factors predisposing to outbreaks of PMWS have yet to be fully determined, it has been suggested that draughts, overcrowding, poor air quality, mixing of pigs of different age groups, early vaccination, and other environmental “stressors” may be contributing factors. Based on the experimental studies described above, co-infection with other agents has proved to be important.

Both PCVs are likely to be highly resistant to inactivation, indicating that they are capable of surviving in contaminated environments for long periods and are able to survive even stringent decontamination regimes.<sup>2</sup> PCVs may be spread from infected to uninfected pigs both vertically and horizontally; horizontal transmission of PCV-2 has been demonstrated experimentally. Contact with infected pigs, contaminated housing, fomites, and personnel are all probable factors in the horizontal spread of the virus. The association of PCVs with abortions and stillbirths indicates that transplacental spread may also be a factor.<sup>17</sup>

In the case of PCV-1, transmission by contaminated vaccines could also be a means of spread.<sup>2</sup> Several pig virus vaccines are produced in continuous pig cell tissue culture lines and pig serum is used for growth of some cell cultures for vaccine use. Pig trypsin is also widely used for tissue culture. The apparent widespread distribution of PCV-1 in pigs and in continuous porcine cell cultures, combined with its lack of cytopathogenicity, and its small size, which makes particles difficult to recognize in electron microscope preparations, probably makes it an ideal candidate to contaminate vaccine. However, data suggest that contaminated vaccines are not responsible for the spread of PCV-2.

### **Host range**

The host range of PCV-2 has been controversial. Recent studies in farmed wild boar in Saskatchewan indicate that these non-domestic pigs can replicate PCV-2 and develop disease subsequent to infection.<sup>21</sup> Some laboratories have identified PCV-2 nucleic acid in diseased tissue from cattle and other species using suitable primers and the polymerase chain reaction (PCR); however, no gross or histological lesions were observed following inoculation of PCV-2 into lambs or calves, and no antigen was detected in the tissues.<sup>22</sup> One study, as yet

unconfirmed by other investigators, reported lesions in the spleen and multiple lymph nodes of mice inoculated with PCV-2, or with tissue homogenates from pigs with PMWS. Macrophages containing PCV-2 DNA were reported at the centers of inflammatory foci. Concerns about the zoonotic potential of PCV-2 prompted serological studies in swine practitioners, laboratory workers, and hospital patients. None of the humans examined had antibodies to porcine circovirus, but this does not totally alleviate concerns for cross-species transmission in immunosuppressed patients such as transplant patients, especially those who may in the future be candidates for xenotransplantation.<sup>2</sup>

### **The diagnostic approach to PCV-associated disease**

Clinical signs and lesions can be suggestive of PCV-2 infection.<sup>3,4</sup> In the case of PMWS in particular, laboratory testing aimed at demonstrating the virus in affected tissues is recommended to reach a definitive diagnosis. Porcine circoviruses can be isolated from the tissues of pigs affected by PMWS and other disease syndromes in specially treated tissue cultures. Since the virus grows in the cells without producing cytopathic changes, infection has been confirmed by PCR detection of the virus or by staining the cultures using an immunofluorescent or immunoperoxidase technique with polyclonal antiserum.

Given the difficulties associated with growing PCV-2 in cell culture, attention has focused on diagnostic methods that rely on the direct detection of DNA or viral antigens.<sup>2,9</sup> PCR, although sensitive and specific when used by itself, can be problematic in routine diagnosis because many pigs can be viremic without developing disease. Diagnosis of PMWS disease is based on the combination of clinical signs, gross and microscopic lesions, and demonstration of PCV-2 antigen or nucleic acid in lesions. *In situ* hybridization and immunohistochemistry have been widely applied to demonstrate infection with PCV-2 in affected tissues.<sup>9</sup>

There are varieties of serological tests that can detect antibodies against PCVs. A new specific test for PCV-2 antibodies has been developed.<sup>20</sup> Since subclinical infections with PCV-2 are known to be widespread in pigs, the use of serology in the diagnosis of PCV2-related diseases is limited. Serology can be used as a management tool, especially when populating or repopulating breeding facilities with gilts. Seronegativity, due either to the decay of maternal antibodies or absence of exposure, may be a risk factor for the development of fetopathogenic PCV-2 infection, especially in gilts.<sup>17</sup>

### **How does PCV-2 cause disease?**

There are many unanswered questions concerning the pathogenesis of PCV-2 infections. The severity of the lesions in experimental infections is substantially enhanced if pigs are co-infected with PCV-2 and PPV or PRRSV.<sup>14,15</sup> This suggests potentiation of PCV-2 replication during co-infection of pigs with other agents. The

mechanism behind this occurrence is not clear. The fact that circoviruses are apparently dependent on host DNA synthesis for their replication and therefore, replicate most efficiently in rapidly dividing cells, may suggest an explanation. If PCV-2 preferentially targets lymphoid cells, its replication may be greatly enhanced by lymphoid stimulation from the potentiating virus (eg, PPV), the immune response to it, or by vaccination against it. Recent studies<sup>23</sup> conducted by Dr. Steve Krakowka support this hypothesis; gnotobiotic pigs inoculated with PCV2 and immunostimulated with a protein-adjuvant combination developed clinical wasting disease. Age-matched gnotobiotic pigs inoculated with PCV2 and not immunostimulated were clinically normal. This seminal observation has been confirmed experimentally in other laboratories using both experimental and commercial vaccines as the immunostimulant. As well, field trials indicate that this phenomenon can occur in the field following administration of commonly used vaccines.

Much remains to be resolved with regard to PCV-2 pathogenesis. The precise identity of the cells targeted by the virus needs to be determined. Virus antigen is observed in the cytoplasm and nuclei of a wide range of lymphoid and non-lymphoid tissues, including smooth muscle cells and fibroblasts. It is not clear if the depletion of lymphocytes is due to direct destruction by the virus or to other mechanisms. Virus antigen is commonly seen within cells of the macrophage/monocyte lineage. Infiltration of lymphoid tissues by large numbers of monocytes is a characteristic lesion and many of these cells contain virus antigen or nucleic acid. The large influx of these cells into tissues containing large amounts of virus antigen indicates local inflammatory responses. The antigen present in the monocytes and macrophages may be due to virus infection, but could also be due, at least in part, to phagocytosis of dead and dying PCV-2-infected cells. This needs to be resolved.

### **Control of PCV-2 infection and PCV-2 associated diseases.**

All available evidence indicates that PCV-2 is an endemic infection in pig populations, probably worldwide; therefore, control of the infection and/or eradication of the virus *per se* are probably not practical.<sup>2</sup> What is more critical in terms of management, is to try and ensure that animals become “immune,” either through natural exposure or vaccination, without developing disease. Currently no vaccine for PCV-2 is available, but some are in the final stages of development and should be commercially available in the near future.

There have been few controlled studies to address ways to limit PCV-2-related disease; however, mounting evidence suggests that management is important. It seems that many modern practices, such as segregated early weaning, neonatal vaccination, and the mixing of pigs at a young age, may have contributed to the emergence of PMWS since immunostimulation in the face of PCV-2 infection is apparently the pivotal event in the evolution

of clinical disease. Reduction in immunostimulatory events in pig husbandry practices will help to alleviate clinical PMWS and other PCV-2-associated diseases and, in fact, has done so in many parts of Europe where PMWS had reached near epidemic proportions.<sup>8</sup> This may include avoidance of mixing of pigs, examination of current vaccine strategies, and reduction of infectious pressures from other agents. Depopulation and restocking of affected farms has resulted in some measure of success for reducing clinical disease.

## Conclusions

PCV-2 is not a new virus, but a newly discovered virus; retrospective studies have shown that PCV-2-associated diseases have been sporadically present in pig populations for over 15 years. In the last 5 years, veritable epidemics of PCV-2-associated PMWS have occurred throughout the world, especially in Europe, resulting in substantial losses to the pig industry. In addition, PCV-2 has been associated with other disease syndromes, notably PDNS, which have apparently increased in prevalence in some countries in the last few years. Control of this infection and its associated disease syndromes will benefit from the pivotal work performed at the WCVM, and should bring long-lasting economic benefits to Canadians.

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