Vaccination strategies for the control of circoviral diseases in pigs: PMWS and PCV2-associated PRDC

S. Beseme[3], A. Brun[3], M. Bublot[3], C. Charreyre[1], N. Dupre[2], JB. Herin[3],

F. Joisel[3], B. Lapostolle[3], and A. Vaganay[3] (2006)

[1]Merial Limited, Duluth, GA, USA, [2]Veterinary Consultant, Athens, GA, USA, [3]Merial SAS, Lyon, France

Introduction

Post-weaning multisystemic wasting syndrome (PMWS) was first described in high health herds in 1996 in Canada (Clark, 1997 (1); Harding and Clark, 1997 (2)) and is now considered to be an important emerging disease syndrome in the pig industry. It was quickly associated with a newly discovered virus, Porcine Circovirus type 2 (PCV2) (Ellis et al., 1998 (3)).

Since then, PCV2 has been increasingly isolated from pigs affected with various other clinical manifestations as PRDC (Porcine Respiratory Disease Complex) (Allan and Ellis, 2000 (4); Harms et al., 2002 (5); Kim et al., 2003 (6)), reproductive failures (Josephson and Charbonneau, 2001 (7); Ladekjaer-Mikkelsen et al., 2001 (8); Kim et al., 2004 (9); O'Connor et al., 2001 (10); West et al., 1999 (11)), PDNS (Porcine Dermatitis and Nephropathy Syndrome) (Allan and Ellis, 2000 (4); Gresham et al., 2001 (12); Meehan et al., 2001 (13); Thomson et al., 2001 (14); Ramos-Vara et al., 1997 (15)), and liver disease, necrotizing lymphadenitis, granulomatous enteritis or possibly exudative epidermitis (Chae, 2005 (16)).

This article will review available data from naturally acquired and experimentally induced diseases to evaluate the involvement of PCV2 in various pathologies. In particular we will examine to what extend co-infections are necessary for the full expression of PCV2-associated diseases. We will also assess the efficacy of the vaccination with CIRCOVAC®* included in more general vaccination regimens, in order to prevent or minimize these syndromes.

*CIRCOVAC® is a registered trademark of Merial in the United States, Japan and elsewhere.

1. Descriptions of PCV2-associated pathologies and syndromes

1.1. Post-weaning Multi-systemic Wasting Syndrome (PMWS)

PMWS is now well associated with PCV2 and has become a major economic concern in all pig-producing areas worldwide. In Asia, Europe or North America, PMWS occurs in both endemic and epidemic forms (Allan and Ellis, 2000 (4); Ellis, 2004 (17) and Segales and Domingo, 2002 (18)). The presence of PMWS in Asia has been well documented (Kawashima et al 2003 (19)).

PMWS is characterized by progressive growth retardation and wasting, enlargement of lymph nodes (especially the more easily visible inguinal lymph nodes), dyspnoea, diarrhoea and jaundice in pigs from about 6 to 12 weeks of age. Individual diagnosis is based on these clinical signs, associated with characteristic histopathological lesions in lymphoid tissues (lymphocyte depletion together with histiocytic infiltration and/or inclusion bodies and/or giant cells), and detection of PCV2 in moderate to massive quantity within these lesions.The herd diagnosis is based on increase in mortality and wasting post weaning compared with the historical level in the herd associated with individual diagnosis established on necropsies of at least 5 pigs. (European Consortium definition - Project No 513928 Sixth Framework Programme - http:// www.pcvd.org).

PCV2 is consistently isolated from PMWS field cases but the virus is found very often in association with other known pathogenic viral or bacterial agents as described in Asia in table I (Jeong et al., 2003 (20)).

In a US field case control study conducted to assess the epidemiological association between PMWS and a

Table I: Pathogens mixed-infection detected with PCV2

Associated Pathogens	No. of positive pigs / No. of pigs examined	Percentage
PRRSV, P. multocida, B. bronchiseptica	1/52	1.9
PRRSV, P. multocida	1/52	1.9
SIV, P. multocida	1/52	1.9
PRRSV	23/52	44.2
Pseudorabies virus	4/52	7.7
PEDV	3/52	5.8
PRCV	1/52	1.9
P. multocida	6/52	11.5
A. pleuropneumoniae	2/52	3.8
Total	42/52	80.8

list of known viruses (PCV2, Porcine Respiratory and Reproductive Syndrome virus (PRRSV), porcine parvovirus (PPV), porcine enterovirus types 1-3, Influenza viruses (SIV), porcine respiratory coronavirus, transmissible gastroenteritis virus, porcine endogenous retrovirus, porcine lymphotropic herpesvirus type 1 and bovine viral diarrhea virus) the strongest association was found between PMWS and PCV2. The risk of contracting PMWS was much higher if the animal was concurrently infected with PCV2 and PRRSV, suggesting that the development of PMWS could be enhanced by cofactors (Pogranichniy et al., 2002 (24)).

PMWS has been reproduced in experimental pig models by both inoculation of PCV2 alone and in association with other agents. It has been possible to induce PMWS with PCV2 alone in various experiments. However co-infections with both PCV2 and PPV, or with PCV2 and PRRS , or with PCV2 and *Mycoplasma hyopneumoniae* (*M. hyo*) generally induced more cases of PMWS. Those experimental co-infections consistently led to more severe clinical signs and histopathological lesions, as well as increased PCV2 viral load (Allan et al., 2000 (47); DeJong et al., 2003 (48); Harms et al., 2001 (49)).

1.2. PCV2 and Porcine Respiratory Disease Complex (PRDC)

Porcine respiratory disease complex is a threat in growing and finishing pigs from 16 to 22 weeks of age. It is characterized by slow growth, decreased feed efficiency, lethargy, anorexia, fever, cough, and dyspnoea (Halbur, 1998 (50); Thacker, 2001 (51) and Harms et al., 2002 (52)).

According to field data, pneumonia in pigs with PRDC is due to a combination of both viral and bacterial agents, such as PRRSV, PCV2, SIV, *M. hyo*, *Actinobacillus pleuropneumoniae* (*APP*), and *Pasteurella multocida* (Halbur, 1998 (50); Thacker, 2001 (51)). For instance, a large retrospective study of 105 PRDC cases in Korea in 2003 (Kim et al., 2003 (6)), found 85 cases positive for PCV2, 66 positive for PRRSV, 60 positive for PPV, and 14 positive for SIV with a majority of co-infections. PCV2 and *Pasteurella multocida* was found in 38 cases, followed by PCV2 and *M. hyo* in 33 cases. A similar picture was described in the US (Harms et al. 2002 (5)). There is a marked increase in mortality when single and multiple concurrent bacterial infections occur (Done, 2002 (53); Harms et al., 2002 (5); Kim et al., 2003 (6); Thacker, 2001 (51)).

A particular case of pneumonia has been described as proliferative necrotizing pneumonia (PNP) a term coined to describe the specific histological features of a sub-acute to chronic pneumonia in swine. Originally, this lesion was associated with SIV and then PRRSV infection (Harms et al. 2002 (52); Morin et al., 1990 (54); Rossow, 1998 (55); Larochelle et al., 1999 (56)). But the consistent identification of PCV2 demonstrated by in situ hybridization and immunohistochemistry in PNP cases has led to the suggestion that PCV2 could also be an important contributor to this syndrome. (Ellis et al., 1999 (57); Harms et al., 2002 (5)

Because the clinical signs of PRDC are variable and its etiology can be multi-factorial, the presence of

PCV2 DNA or antigen in lung tissues, together with a bronchointerstitial pneumonia including peribronchial and peribronchiolar fibrosis are used as the main criteria for the diagnosis of PCV2-associated PRDC.

In the laboratory, experimental evidence indicate that PCV2 and PRRS viruses can act synergistically and together induce more severe respiratory signs and pulmonary lesions (Allan et al., 2000 (58)). Although PCV2 might not increase the severity of PRRS lesions, PRRSV certainly potentiates the action of PCV2 (Allan et al., 2000 (58)). The bronchointerstitial pneumonia produced by co-infection of PCV2 and PRRSV is compatible with the typical lesions seen in field cases of PRDC (Drolet et al., 2003 (59)).

As well experimental co-infection studies with PCV2 and *M. hyo* demonstrated that *M. hyo* can raise the amount and prolong the presence of PCV2 antigen, increase the incidence of PMWS in pigs, increase the severity of PCV2-associated lymphoid lesions, and also the intensity of PCV2-associated lung lesions. A synergetic effect of respiratory associated symptoms can be clearly seen as 1/9 of *M. hyo* infected animals and 2/8 of PCV2 infected animals had necrotizing bronchiolitis while 7/9 of the dually infected animals were presenting this symptom (Opriessnig et al., 2004 (46)).

1.3. PCV2 in other syndromes and diseases

PCV2 has also been associated mainly in field studies with reproductive failures alone or associated with enteritis, with diarrheas and granulomatous enteritis, with liver disease, with exudative epidermitis, with neurological signs and with Porcine Dermatitis and Nephropathy Syndrome (PDNS). The particular role of PCV2 and/or the other pathogens involved in these syndromes will have to be explored in the future.

2. The pathogenic mechanisms of disease in PCV2 infections and possibility of enhancement by co-infections

Different mechanisms have been proposed to describe the pathogenicity of PCV2 infections and ex-

plain the links with different associated diseases (Segales et al., 2004 (60)).

It was first proposed that initial PCV2 replication was probably taking place in macrophages and antigen-presenting cells of lymphoid tissues such as tonsils and regional lymph nodes (Clark, 1997 (61); Rosell et al., 1999 (62)), or alternatively in Peyer's patches (Rosell et al., 1999 (62); Royer et al., 2001 (63)), because the virus is found consistently in those tissues and in those cells. After infection and replication in resident mucosal macrophages and other antigen-presenting cells, PCV2 could be transported intracellularly or migrate freely in lymph and/or blood. The normal traffic of PCV2 infected cells to many tissues would contribute to the spread of viral infection to numerous organs (Rosell et al., 1999 (62)).

However, while this scheme was indeed confirmed as a general picture for the dissemination of the virus, it has been demonstrated that PCV2 does not usually replicate in macrophages and antigen-presenting cells (Vincent et al., 2005 (64)). In fact cells of the macrophage lineage do phagocytize and store huge amounts of PCV2 for very long time which explains why the virus can be found in those cells. In vitro tests demonstrate a rapid uptake of the virus and persistence of antigen and infectious virus for prolonged periods of time in dendritic cells. PCV2 survives there in infectious form by avoiding the cellular degradative machinery and replication in dendritic cells will be at best extremely limited (Mc Cullough et al., 2003 (65)).

When parenchymal cells are eventually infected in the lungs, liver, kidneys, heart and other organs the transition to a full blown PMWS occurs. At this stage PCV2 can actively replicate in endothelial or epithelial cells and tremendous amount of virus can be detected in the organs. This would support the idea that the tissue and cellular tropism of PCV2 expand as PMWS develops (Krakowka et al., 2003 (66)), but how such a shift takes place is still unclear although we know it is linked to immune stimulation.

On the other hand, it has been demonstrated recently that PCV2 does have a profound impact on some categories of dendritic cells and can impair

their functions to an extent that stops immune defenses and leads to immune pathologies and anergy. At this point, any secondary pathogen will have an open access to the pig system (Mc Cullough et al., 2003 (65)).

We will now review the direct effect of PCV2 on the immune system and possible synergistic effect with various triggers and secondary pathogens.

2.1. PCV2 infection produces immune suppression

The signs of immune suppression in PCV2 infections range from the cellular and microscopical level to the clinical level.

PMWS is characterized by widespread granulomatous inflammation, multinucleated giant cells, and variable numbers of intracytoplasmic basophilic viral inclusion bodies within infiltrating histiocytes and macrophages. In fact the hallmark histologic lesion of PMWS is multifocal to diffuse mixed angiocentric granulomatous inflammation. This unusual lesion is unlike what is ordinarily associated with a viral infection and is sufficiently characteristic to be considered diagnostic for PMWS. Histiocytic infiltration is also one of the initial events during PCV2 infection, and coincides with macroscopic lymphadenopathy. More chronic cases tend to show less severe lymphocyte depletion with less pronounced histiocytic/multinucleate giant cell infiltration (Krakowka et al., 2003 (66); Allan et al., 1999 (32); Choi and Chae, 1999 (67); Choi et al., 2000 (68); Ellis et al., 1999 (57); Kennedy et al., 2000 (33); Kim et al., 2002 (69); Krakowka et al., 2000 (27); Clark, 1997 (61); Rosell et al., 1999 (62); Quintana et al., 2001 (70)).

PCV2 antigen was also found present in more advanced necrotic lesions, suggesting that PCV2 antigen can be associated with necrotizing lymphadenitis (Kim and Chae, 2005 (71)).

In field or experimental studies, peripheral blood mononuclear cells counts and histopathological evaluations also revealed lymphocyte depletion in different lymphoid organs and a change in the proportions of the different lymphocyte subsets. As the level of PCV2 in lymphoid tissues increases, so does the depletion in both B- and T-cell-dependent areas of these tissues. (Darwich et al., 2002 (72); Nielsen et al., 2003. (73)).

Apoptosis has been proposed to account for loss of B and T lymphocytes in PMWS-affected pigs which could account for disruption in cytokine signaling (Shibahara et al., 2000 (74)) but this mechanism has not been definitively demonstrated in all studies (Krakowka et al., 2003 (66)).

The damage to the immune system of PCV2-infected and PMWS-affected pigs can then naturally lead to impaired immune responses and opportunistic infections are a final evidence of the immune suppression caused by PCV2 infection. For instance, a low prevalence (approximately 5%) of pulmonary infection with *Pneumocystis carinii* was documented in the early cases of PMWS in Western Canada (Ellis et al., 1998 (75)). Another example is the inability of PMWS pigs to produce or sustain neutralizing antibody responses (Charreyre et al., 2000 (76); Meerts et al., 2006 (77)).

2.2 Triggering factors leading from PCV2 infection to more severe clinical diseases

Experimentally PMWS has been obtained more consistently when PCV2-infected piglets are also immune stimulated by injections of an antigen emulsified in an oil-based macrophage-targeted adjuvant. In fact activation of the immune system is the pivotal event that can induce the shift to PCV2 infected towards full blown disease (Allan et al., 1999 (78); Allan et al., 2000 (58); Choi and Chae, 2000 (79); Ellis et al., 1999 (80); Kennedy et al., 2000 (33); Kim et al., 2003 (81); Krakowka et al., 2000 (27); Krakowka et al., 2001 (82)).

Studies demonstrated that vaccination with bacterins commonly used in the USA (*APP* and *M. hyo* bacterins) enhanced PCV2 replication and the severity of clinical signs and lesions found in PMWS. Early vaccination, antigen-rich single shot regimens, oily adjuvants, high PCV2 prevalence in the environment, and low maternal antibody status may lead to increased incidence and severity of PMWS. (Opriessnig et al. 2003 (83); Hoogland et al. 2006 (84)).

As described earlier, PMWS has also been obtained more consistently experimentally in co-infec-

tion models, with PCV2 and PPV, PCV2 and PRRSV, or PCV2 and *M. hyo*.

In one of those experimental studies, pigs infected with PPV appeared to display elevated interleukine 10 responses that could activate B cells therefore favoring immune stimulation and PCV2 uptake. Detection of IL10 was prolonged in dually infected pigs (Hasslung and al., 2005 (38)).

Based on the replicative cycle of PCV2 which, much like PPV, requires or makes use of actively replicating cells (Meehan et al., 1998 (85)), factors that induce the replication of potential target cells would favor PCV2 replication and, by extension, viral load and disease. Therefore, co-infecting agents like PPV that can cause death of various cells and lead to regeneration of damaged tissue may indirectly enhance the replication of PCV-2. Cytokines and other growth factors that affect cell division may also indirectly up-regulate the replication of PCV2.

PRRSV targets and kills specifically pulmonary alveolar macrophages (PAMs), a cell population that can phagocytize and store high amounts of potentially pathogenic PCV2 virus for long periods of time as we described earlier. Destruction of those cells could lead to PCV2 release in large amounts in the lung. Because PRRSV infection is rather persistent in pigs, bursts of PCV2 release could also occur repeatedly over time in chronically dually infected pigs.

Infection with *M. hyo* induces the production of pro-inflammatory cytokines that will produce inflammation. Therefore it is logical to observe that *M. Hyo* infection will induce a bronchiolitis that is enhancing PCV2 respiratory pathogenesis, then raise the amount and prolong the presence of PCV2-antigen, and increase the incidence of PMWS in pigs (Opriessnig et al, 2004 (46)). Interestingly it has been shown recently in vitro that PCV2 infected PAMs are functionally altered and will not be able to control very effectively secondary pathogens like *M. hyo* (Chang et al., 2006 (86)). Another interesting fact is the possibility for Gram-negative bacterial components as LPS to induce PCV2 multiplication in PAMs where it was dormant before.

M. hyo infection will also direct the immune response away from a TH1 type, in which the macrophages would be activated to destroy it, towards a less effective TH2 response, (Thacker, 2001 (87)), thus inducing more immune stimulation that could favor PCV2 uptake.

Other pathogens like SIV and *APP* cause acute inflammation of the lungs (Thacker et al., 2006 (88)), and they could as well up-regulate and favor PCV2 multiplication.

All those possibilities will interact with each other of course in even more complex fashion in field situations when all pathogens can be present together.

3. The influence of virus variation

PCV2 isolates from different clinical disease manifestations and different geographical locations have been sequenced and are all highly homologous with more than 90-96% nucleotide identity between isolates. (Allan et al., 1998 (89); Ellis et al., 1998 (75); Fenaux et al., 2000 (90) ; Hamel et al., 2000 (91); Mankertz et al., 2000 (92); Meehan et al., 1998 (93)). PCV2 differs significantly from the non virulent PCV1 (roughly 62% homology) suggesting that PCV2 isolates are all members of a single pathogenic virus genotype (Hamel et al., 1998 (94); Tischer et al., 1974 (95); Tischer et al., 1986 (96); Meehan et al., 1998 (93)).

A number of studies have found minor differences in the respective PCV2 genomes (Choi et al., 2002 (97); Farnham et al., 2003 (98); Meehan et al., 2001 (13); O'Connor et al., 2001 (10)) but at this time it remains unclear what significance these minor differences may have. Sequence analysis of ORF1 and ORF2 genes has revealed that the extent of nucleotide variation is logically greater for the ORF2 than ORF1 (Fenaux et al., 2000 (90); Hamel et al., 2000 (91); Mankertz et al., 2000 (92)). The alterations in ORF2, which encodes for the major structural capsid protein (Nawagitgul et al., 2000 (99)) may suggest a link between capsid protein variation and pathogenicity of PCV2. Modification of the major viral capsid may alter determinants involved in tissue tropism or virus-host interactions. One study has suggested that the minor variation in the ORF2 of PCV2 may account for differences in tropism with respect to the host organism

(Mankertz et al., 2000 (92)). Two other studies have suggested that PCV2 isolated from reproductive failure and PDNS may be phenotypically or genetically different from PCV2 associated with PMWS (Meehan et al., 2001 (13); O'Connor et al., 2001 (10)). However comparison of various PCV2-isolates side by side in challenge experiments demonstrated no or limited differences (Hasslung et al, 2005 (38); Halbur and Opriessnig, 2006 (100)).

Because other host factors such as age, health status, route of infection, co-infections or other stressors can markedly influence the pathogenicity and clinical manifestations of PCV2 infections, it will be difficult to assess isolate variability in field situations. Furthermore, all of the characterized isolates of PCV2 associated with PMWS are antigenically similar to each other using monoclonal and polyclonal antibodies (Allan et al., 1999 (101)).

4. Circovaccination of the pig herd

A vaccination scheme for PCV2-associated diseases that targeted gilts and sows and the passive transfer of high levels of maternally derived antibodies to PCV2 in colostrum and milk has been proposed (Charreyre et al. 2004 (102)) based on the following information:

- PCV2 is very stable, hardy and abundant in the environment and eradication unlikely in most farms
- In PMWS-affected farms higher levels of PCV2 virus are found in the nurseries and post-weaning phases than in later stages of the pig life (Sibila et al. 2005 (103), Lopez-Soria et al., 2005 (104) Rose et al., 2004 (105))
- Maternal antibodies to PCV2 were demonstrated to be protective against PCV2 infection and development of PMWS (Charreyre et al., 2002 (106); Thomas et al., 2005 (107))
- Abortion and premature farrowing were obtained in sows inoculated with PCV2 three weeks before farrowing, thus emphasizing the need to protect the breeder herd in the gestational phase (Park et al., 2005 (108)).

However, vaccination of the breeder herd and passive transfer of PCV2 antibodies will only protect the

piglets against PCV2 infection for a limited period of time while maternal antibody decline. This is reflected in field conditions, where active seroconversion is reported from 5 to 15 weeks of age (Cotrell, 1999 (109); Larochelle et al., 2003 (110); Segales and Morvan, 2004 (111)).

Several studies by different groups have demonstrated that active antibodies are also protective against PMWS (Blanchard et al., 2004 (112); Pogranichniy et al., 2004 (113); Fenaux et al., 2004 (114)). Therefore a well-controlled natural infection with PCV2 will induce a natural protection against associated diseases.

4.1. Description of two laboratory efficacy studies

The objective of the first study was to demonstrate the efficacy of an inactivated oil adjuvanted PCV2 vaccine (CIRCOVAC) in a PCV2 controlled environment. Specific serological responses in vaccinated gilts and protection of their piglets after PCV2 experimental challenge at 3-4 weeks of age were evaluated. The objective of the second study was to demonstrate the efficacy of this vaccine in piglets born to vaccinated gilts in the field and brought back into a PCV2 controlled environment. Protection of the piglets after PCV2 experimental challenge at about 4 weeks of age was evaluated.

Other studies demonstrated that the vaccine presented a good safety of use in pregnant animals (Reynaud et al., 2004 (115 and 116)).

In the first study, specific pathogen free gilts, specifically seronegative for PCV2 antibodies by ELISA were allocated to two groups. One group of 11 gilts was vaccinated at minimal antigen content via the intramuscular route 5 and 2 weeks pre-breeding and 2 weeks before farrowing. Another group of 12 gilts was not vaccinated. All the gilts were inseminated artificially at 10 months of age and 8 gilts became pregnant. Therefore a first group of 22 piglets born to 4 vaccinated gilts and a second group of 22 piglets born to 4 control gilts were challenged intra-nasally with PCV2 at 3 to 4 weeks of age.

PCV2 antibodies were measured at regular intervals in the blood of the gilts and piglets throughout

Table III: Experimental inoculations with PCV2 alone or in combination to obtain PMWS

Type pigs/ Reference	Age and challenge	Clinical outcome (no.affected/no. inoculated)
CDCD piglets		
Ellis et al., 1999 (26)	3 days PCV2 (Stoon)	Normal (0/6)
Krakowka et al., 2000 (27)	1 day PCV2 (Stoon)	Normal (0/3))
	PCV2 + PCV1	Normal (0/4)
	PCV2 + PPV	Wasting (4/4)
Pogranichniy et al., 2000(28)	8 wks PCV2 (ISU 98-15237)	Normal (0/5)
Krakowka et al., 2001(29)	1 day PCV2 (OSU3)	Normal (0/3)
	PCV2 + immunostimulation	Wasting (24/24)
Bolin et al., 2001 (30)	20-25 d PCV2 (688)	Wasting (6/23)
Harms et al., 2001 (31)	3 wks PCV2 (35358)	Wasting (5/19)
	PCV2 (35358) + PRRSV	Wasting (17/17)
Conventional, colostrum-deprived piglets		
Allan et al., 1999 (32)	1 day PCV2 (Stoon)	Wasting (1/4)
	PCV2 (Stoon) + PPV(Kresse)	Wasting (5/5)
Kennedy et al., 2000 (33)	1 day PCV2 (Stoon)	Wasting (1/4)
	PCV2 (Stoon) + PPV(Kresse)	Wasting (5/5)
Allan et al., 2000 (34)	1 day PCV2 (Stoon)	Normal (0/5)
	PCV2 (Stoon) + PPV(Kresse)	Normal (0/13)
Allan et al., 2000 (35)	1 day PCV2 (48285)	Normal (0/3)
	PCV2 (48285) + PRRSV	Normal (0/5)
Allan et al., 2002 (36)	3 days PCV2 (SPCV2)	Wasting (1/4)
	PCV2 (SPCV2) + PPV	Wasting (5/9)
Kim et al., 2003 (37)	28 days controls	Normal (0/8)
	PCV2 (Korea2) + PPV	Wasting (24/24)
Hasslung et al., 2005 (38)	3 days PCV2 + PPV	Normal (0/7)
	PCV2 1010 + PPV	Wasting (1/10)
	PCV2 (Sweden) + PPV (swe)	Wasting (2/7)
	PCV2 (Sweden) + PPV (den)	Wasting (3/8)
Conventional SPF		
Magar et al., 2000 (39)	3-4 wks PCV2 (LHVA-V53)	Normal (0/11)
Larochelle et al., 2000 (40)	7 mos PCV2 (LHVA-V53)	Normal (0/4)
Ladekjaer-Mikkelsen , 2002(41)	3 wks PCV2 (OSU3)	Wasting (3/5)
	PCV2 + immunostimulation)	Wasting (1/5)
Fenaux et al., 2002 (42)	4 wks Cloned PCV2 40895	Normal (0/10)
Conventional		
Balasch et al., 1999 (43)	8 wks PCV2	Normal (0/8)
Albina et al., 2001 (44)	5-9 wks PCV2	Wasting (4/55)
Rovira et al., 2002 (45)	31-40 d PCV2	Normal (0/7)
	PCV2 + PRRSV(lot/91)	Wasting (1/5)
Opriessnig et al., 2004 (46)	4-6 wks Myco hyo (4 w old)	No PMWS (0/17)
	PCV2 (6 w old)	No PMWS (0/17)
	Myco hyo + PCV2 (6 w old)	Wasting (4/17)

CDCD, Caesarean-derived, colostrum deprived; SPF, specific pathogen-free; IN, intranasal;
ON, oronasal; IT, intratracheal; IM, intramuscular; SQ, subcutaneous;

the study. After challenge, clinical signs were monitored for four weeks. PCV2 viral load in serum and in faecal swabs was also estimated by quantitative PCR (Q-PCR). A complete necropsy assessment was carried out on all 44 piglets at slaughter and mesenteric lymph nodes were collected for PCV2 immunochemistry (IHC).

Before challenge, vaccinated gilts had high, stable and homogeneous PCV2 antibody levels while the control gilts and their piglets remained seronegative. Vaccination induced a seroconversion immediately after the first injection and this was further boosted by the third injection before farrowing. An efficient transmission and persistence of maternal antibodies following colostrum intake was demonstrated by the measurement of high and homogeneous antibody titres to PCV2 in serum from piglets born to vaccinated gilts.

After challenge, a strong seroconversion was observed in piglets born to non-vaccinated gilts while the level of antibodies in piglets born to vaccinated gilts continued to decrease.

Although no classical PMWS cases was recorded in this experiment, clinical signs and growth impairment were observed after PCV2 challenge and the clinical scores were significantly higher in piglets born to non-vaccinated gilts (p = 0.015).

At necropsy, the lesion scores were significantly lower in piglets born to vaccinated gilts than in piglets born to non-vaccinated gilts (p<0.00001) Additionally, the amount of PCV2 DNA in the serum of piglets the amount of PCV2 DNA in rectal swabs and the viral load in mesenteric lymph nodes were also significantly lower in piglets born from vaccinated gilts (p = 0.00002).

The inactivated vaccine proved to be highly immunogenic as shown by the high and stable antibodies titres obtained in vaccinated gilts. Vaccination induced a significant protection after virulent PCV2 challenge in piglets born to vaccinated gilts. The results demonstrated that vaccination with CIRCOVAC was beneficial in improving the piglet health and performances after PCV2 challenge in a highly controlled environment.

Sows enrolled in a field efficacy trial in a PMWS affected farm were selected as source of piglets for the second study.

A first group of 12 piglets was born on the farm to 8 non-vaccinated sows. The second group of 10 piglets was born on the farm to 7 sows that had been vaccinated once with CIRCOVAC at minimal antigen content via the intramuscular route 2 weeks before farrowing. A third group of 11 SPF piglets was added to the study to monitor challenge. Piglets from the farm were brought into the challenge facility at about 3 days of age at a convenient date depending on the herd management calendar. Therefore the 3 groups of piglets were subsequently submitted to intra-nasal PCV2 challenge on the same day but at somewhat different ages: group 1 from control sows were 32 days of age, group 2 from vaccinated sows were 25 days of age and SPF pigs were 47 days of age.

Throughout the study, PCV2 antibodies in blood were evaluated in samples from the farm sows and from the piglets and PCV2 virus in faeces was evaluated in serial samples from the piglets. The follow-up after challenge lasted four weeks. Clinical signs were monitored and a complete necropsy evaluation was carried out at the end. Mediastinal lymph nodes were collected to evaluate PCV2 viral load by immunochemistry (IHC).

Two weeks before farrowing, at the time of vaccination, all sows were seropositive and had similar PCV2 antibody titers. Two weeks after farrowing the level of PCV2 antibody in the vaccinated sows had increased significantly (p < 0.005) and the levels of PCV2 antibody in piglets from vaccinated sows were higher than the levels in piglets from non-vaccinated sows up to challenge (p = 0.01).

During these first 3 to 5 weeks of age it appeared that fewer piglets born from vaccinated sows excreted less PCV2 in faeces than piglets born from non-vaccinated sows. This was correlated with a higher level of maternal antibodies.

In this experiment, PCV2 challenge did not induce severe clinical signs in any group. The challenge was nonetheless validated because of the elevated clinical score in the SPF group, of the strong seroconversion

to PCV2 in this group, and of the PCV2 excretion in faeces of all challenged piglets.

Piglets born from non-vaccinated sows exhibited a rise in PCV2 antibody levels after challenge, while PCV2 serum antibodies continued to decay in piglets born to vaccinated sows. The absence of a booster effect in that group after challenge can be linked to the good protection conferred by maternal antibodies against subsequent PCV2 infections.

At necropsy, the piglets born from vaccinated sows displayed significant reduced lesion scores than the piglets born from non-vaccinated and/or SPF sows (p = 0.0001). No gross lesion was noted in the mesenteric lymph nodes of piglets born from vaccinated sows, while 70 to 80% of the piglets in the two other groups had high to very high lesion scores (p = 0.00043).

Those results demonstrated that the sow vaccination with CIRCOVAC in field conditions was beneficial in reducing the natural PCV2 circulation and shedding in the first weeks of the piglet life, but also in improving the piglet health and performances after an additional experimental PCV2 challenge.

4.2. MERIAL field efficacy studies in France and Germany

Under field trial authorisation, a field efficacy study has been on-going in three PMWS-affected farms in France for more than 18 months. Two farms were organized with 7 groups of about 35 sows farrowing every three weeks, and the third farm had 22 groups of about 12 sows farrowing every week.

Groups 1 and 2 out of 7 or groups 1, 3, 5, 7, 9 and 11 out of 22 were kept as control groups. The remaining groups were vaccinated over time with one injection of the minimal dose of CIRCOVAC vaccine 3 weeks before each farrowing time. The replacement gilts were obtained from outside sources and vaccinated twice in quarantine before introduction in the herds throughout the experiment. Therefore up to 70% of the animals were vaccinated over time.

Besides serological follow-up of the breeder herd, all piglets born from groups 1 to 4 and groups 1 to 12 in two successive gestations were followed up until

slaughter at market time for signs of PCV2 disease. A global comparison of all piglets born from vaccinated and from controls during an entire year was finally done.

When the experiment started, all dams on the 3 farms studied were seropositive with about 12% of them being highly seropositive. Following vaccination 56% of vaccinated sows were deemed highly seropositive versus only 7% in the non-vaccinated groups. Concurrently to the rise in PCV2 antibody level in the breeder herds in the 3 farms following vaccination , PMWS cases decreased quickly from more than 5% when the farms were selected to 1.12% in pigs from non-vaccinated sows (n = 4,183 piglets) and 0.67% in pigs from vaccinated sows (n = 10,462 piglets) in about 18 months.

These results were confirmed in very large numbers of animals, under temporary licenses for CIRCOVAC, in Germany and in France. During these trials, about 366,895 sows have been vaccinated. Adverse reactions have been very limited (1 local reaction per 4,300 doses, 1 abortion per 44,000 doses).

Some results of the German survey are presented as example. They contain the results obtained for 13,992 vaccinated sows from all geographical areas of Germany. The effects of vaccination with CIRCOVAC were mainly analyzed through the following parameters: mortality rates in suckling piglets, in weaners and in finishers, as well as medications or drugs use for prevention or cure in the farms.

Mortality results are shown in table IV. Because of some late implementations of the vaccination in part of the farms, the full effect of vaccination had not yet taken place in the herds when the analysis was done. However, the reduction of mortality was significant in the three age groups, with a decrease of 5.3% in the nursery stage and 3% in the fattening units. These improvements represented a tremendous economical benefit for the farms.

In summary, positive results have been observed with a great reduction of losses and number of wasted pigs, more homogeneous growth rates, and reduction in the use of antibiotic treatments. Global mortality rates between weaning and the end of fat-

Table IV: mortality rates in German survey (Results before and during vaccination are significantly different in all groups, p<0.05)

		% mean losses	STD	Number of farms
Suckling piglets	Before V	14.5	5.1	33
	During V	12.0	4.1	34
Piglets in flatdecks	Before V	8.4	7.6	34
	During V	3.1	2.4	31
Fattening pigs	Before V	5.8	3.4	23
	During V	2.8	1.5	18

tening decreased by at least 50% in the vast majority of the farms.

Conclusion

It is now confirmed from laboratory and field trials that vaccination against PCV2 infection can provide protection against the development of PMWS signs.

Vaccination of the piglet is efficacious in controlled laboratory conditions as long as maternal antibody levels are not too high. Vaccination of the breeder herd including pregnant animals is safe and was found efficacious in controlled laboratory conditions. This result has been confirmed in field conditions in very large numbers of gilts and sows with a commercial vaccine under temporary license that promoted an economically relevant level of protection against clinical PMWS.

Although the efficacy of PCV2 vaccines in the protection against the development of other PCV2-associated diseases and syndromes still needs to be evaluated, it is remarkable that field vaccination of breeder herds against PCV2 did reduce total losses significantly, up to the end of the pig life. This improvement could be related to the deleterious, acute and chronic immune suppression that unchecked PCV2 infections can cause throughout the pig life, opening the door to other pathogens.

References

1- Clark, E.G., 1997. Post-weaning wasting syndrome. Proceedings of the American Association of Swine Practitioners 28, pp. 499-501.

2- Harding, J.C. and Clark, E.G., 1997. Recognizing and diagnosing postweaning multisystemic wasting syndrome (PMWS). Swine Health and Production 5, pp. 201-203.

3 - Ellis et al., 1998. J. Ellis, L. Hassard, E. Clark, J.C.S. Harding, G.M. Allan, P. Willson, J. Strokappe, K. Martin, F. McNeilly, B.M. Meehan, D. Todd and D.M. Haines, Isolation of circovirus from lesions of pigs with postweaning multisystemic wasting syndrome. Can. Vet. J. 39 (1998), pp. 44-51.

4- Allan, G.M. and Ellis, J.A., 2000. Porcine circoviruses: a review. Journal of Veterinary Diagnostic Investigation 12, pp. 3-14.

5- Harms, P.A., Halbur, P.G. and Sorden, S.D., 2002. Three cases of porcine respiratory disease complex associated with porcine circovirus type 2 infection. Journal of Swine Health and Production 10, pp. 27-30.

6- Kim, J., Chung, H.-K. and Chae, C., 2003. Association of porcine circovirus 2 with porcine respiratory disease complex. The Veterinary Journal 166, pp. 251-256

7- Josephson, G. and Charbonneau, G., 2001. Case report of reproductive problems in a new startup operation. Journal of Swine Health and Production 9, pp. 258-259.

8- Ladekjaer-Mikkelsen, A.-S., Nielsen, J., Storgaard, T., Botner, A., Allan, G. and McNeilly, F., 2001. Transplacental infections with PCV-2 associated with reproductive failure in a gilt. Veterinary Record 148, pp. 759-760.

9- Kim, J., Jung, K., Chae, C., 2004. Prevalence and detection of porcine circovirus 2 in aborted fetuses and stillborn piglets. Veterinary Record, in press

10- O'Connor, B., Grauvreau, H., West, K., Bogdan, J., Ayroud, M., Clark, E.G., Konoby, C., Allan, G. and Ellis, J.A., 2001. Multiple porcine circovirus 2-associated abortion and reproductive failure in a multisite

swine production unit. Canadian Veterinary Journal 42, pp. 551-553.

11- West, K.H., Bystrom, J.M., Wojnarowicz, C., Shantz, N., Jacobson, M., Allan, G.M., Haines, D.M., Clark, E.G., Krakowka, S., McNeilly, F., Konoby, C., Martin, K. and Ellis, J.A., 1999. Myocarditis and abortion associated with intrauterine infection of sows with porcine circovirus 2. Journal of Veterinary Diagnostic Investigation 11, pp. 530-532.

12- Gresham, A., Allan, G., McNeilly, F. and Kennedy, S., 2001. Links between post-weaning multisystemic wasting syndrome and porcine dermatitis nephropathy syndrome. The Pig Journal 47, pp. 155-159.

13- Meehan, B.M., McNeilly, F., McNair, I., Walker, I., Ellis, J.A., Krakowka, S. and Allan, G.M., 2001. Isolation and characterization of porcine circovirus 2 from cases of sow abortion and porcine dermatitis and nephropathy syndrome. Archives of Virology 146, pp. 835-842.

14- Thomson, J., Henderson, L., Meikle, C. and MacIntyre, N., 2001. Porcine dermatitis and nephropathy syndrome. Veterinary Record 148, pp. 282-283.

15- Ramos-Vara, J.A., Duran, O., Render, J.A. and Craft, D., 1997. Porcine dermatitis and nephropathy syndrome in the USA. Veterinary Record 141, pp. 479-480

16- Chae C. 2005. A review of PCV2 associated syndromes and diseases. The Veterinary Journal 169 pp. 326-336

17- Ellis J., Clark E., Haines D., West K., Krakowka S., Kennedy S., Allan G.M. 2004. Porcine circovirus-2 and concurrent infections in the field. Veterinary Microbiology 98 pp. 159-163

18- Segales, J. and Domingo, M., 2002. Postweaning multisystemic wasting syndrome (PMWS) in pigs. A review. Veterinary Quarterly 24, pp. 109-124.

19- Kawashima K., Hiroshi Tsunemitsu H and Katsuda K. , 2003, Epidemiological Situation of PMWS in Asia Environmental Hygiene Section, Shichinohe Research Unit, National Institute of Animal Health (NIAH), Aomori, JAPAN in Merial White book on PCV2 2003 p49

20- Jeong S.Y, BongKyun P. 2003, PCV2 and PCV2 Disease Diagnosis in Asia Department of Veterinary Medicine, Virology Lab, College of Veterinary Medicine, Seoul National University, Seoul, Korea in Merial White book on PCV2 2003 p41

21- Ellis J. A., Bratanich A., Clark E.G., Allan G. M., Meehan B., Haines D.M., Harding J., West K.H., Krakowka S., Konoby C., Hassard L., Martin K., McNeilly F.: (2000) Coinfection by porcine circoviruses and porcine parvovirus in pigs with naturally acquired post-weaning multisystemic wasting syndrome. J Vet Diagn Invest 12: 21-27.

22- Kim J. H., Chung H. K., Jung T., Cho W. S., Choi C., Chae C.: (2002) Post-weaning multisystemic wasting syndrome of pigs in Korea: prevalence, microscopic lesions and coexisting microorganisms. J Vet Med Sci 64(1): 57-62.

23- Sato K., Shibahara T., Ishikawa Y., Kondo H., Kubo M., Kadota K.: (2000) Evidence of porcine circovirus infection in pigs with wasting disease syndrome from 1985 to 1999 in Hokkaido, Japan. J Vet Med Sci 62(6): 627-633.

24- Pogranichniy R. M., Yoon, K.J., Harms P.A., Sorden S. D., Daniels M. 2002. Case-control study on the association of PCV2 and other swine viral pathogens with PMWS. J. Vet. Diagn. Invest. 14 (6) pp. 449-456

25- Allan G. 2004 Porcine Circovirus Diseases Research:a Personal Retrospective Department of Agriculture for Northern Ireland, Veterinary Sciences Division, Belfast, Northern Ireland, United Kingdom in Merial White book on PCV2 2004 p15

26- Ellis, J., Krakowka, S., Lairmore, M., Haines, D., Bratanich, A., Clark, E., Allan, G.,Konoby, C., Hassard, L., Meehan, B., Martin, K., Harding, J., Kennedy, S. and McNeilly,F.: (1999) Reproduction of lesions of post-weaning multisystemic wasting syndrome ingnotobiotic piglets. J Vet Diag Invest. 11: 3-14.

27- Krakowka, S., Ellis, J.A., Meehan, B., Kennedy, S., McNeilly, F. and Allan, G.: (2000) Viralwasting syndrome of swine: experimental reproduction of post-weaning multisystemicwasting syndrome in gnotobiotic swine by co-infection with porcine circovirus 2 andporcine parvovirus.Vet Pathol. 37: 254-263.

28- Pogranichniy, R.M., Yoon, K.J., Harms, P.A., Swenson, S.L., Zimmerman, J.J. andSorden, S.D.: (2000) Characterization of immune response of young pigs to porcinecircovirus type 2 infection.Vir Immunol. 13: 143-153.

29- Krakowka, S., Ellis, J.A., McNeilly, F., Ringler, S., Rings, D.M. and Allan, G.: (2001)Activation of the immune system is the pivotal event in the production of wasting diseasein pigs infected with porcine circovirus-2 (PCV2).Vet Pathol 38: 31-42.

30- Bolin, S.R., Stoffregen, W.C., Nayar, G.P. and Hamel, A.L.: (2001) Post-weaningmultisystemic wasting syndrome induced after experimental inoculation of cesarean-derived,colostrum-deprived piglets with type 2 porcine circovirus. J Vet Diag Invest. 13: 185-194.

31- Harms, P.A., Sorden, S.D., Halbur, P.G., Bolin, S.R., Lager, K.M., Morozov, I. and Paul, P.S., 2001. Experimental reproduction of severe disease in CD/CD pigs concurrently infected with type 2 porcine circovirus and porcine reproductive and respiratory syndrome virus. Veterinary Pathology 38, pp. 528-539.

32- Allan, G.M., Kennedy, S., McNeilly, F., Foster, J.C., Ellis, J.A., Krakowka, S.J., Meehan, B.M.and Adair, B.M.: (1999) Experimental reproduction of severe wasting disease by co-infectionof pigs with porcine circovirus and porcine parvovirus. J Comp Pathol. 121: 1-11.

33- Kennedy, S., Moffett, D., McNeilly, F., Meehan, B., Ellis, J., Krakowka, S. and Allan,G.M.: (2000) Reproduction of lesions of post-weaning multisystemic wasting syndrome byinfection of conventional pigs with porcine circovirus type 2 alone or in combination withporcine parvovirus. J Comp Pathol. 122: 9-24.

34- Allan, G.M., McNeilly, E., Kennedy, S., Meehan, B., Moffett, D., Malone, F., Ellis, J. and Krakowka, S.: (2000) PCV2-associated PDNS in Northern Ireland in 1990. Porcine dermatitis and nephropathy syndrome.Vet Rec 146:711-712.

35- Allan G., McNeilly F., Ellis J. et al., 2000, Experimental infection of colostrum deprived piglets with porcine circovirus 2 (PCV2) and porcine reproductive and respiratory syndrome virus (PRRSV) potentiates PCV2 replication, Arch Virol, 145: 2421-2429

36- Allan, G.M., McNeilly, F., Meehan, B., Kennedy, S., Johnston, D., Ellis, J., Krakowka, S.,Fossum, C., Wattrang, E. and Wallgren, P.: (2002) Reproduction of PMWS with a 1993 Swedish isolate of PCV2.Vet Rec 150: 255-256.

37- Kim J., Choi C. and Chae C. 2003. Pathogenesis of PMWS reproduced by coinfection with Korean isolates of PCV2 and PPV. J. Comp. Path. 128 pp. 52-59

38- Hasslung F. Wallgren P., Ladekjar-Hansen A., Botner A., Nielsen J., Wattrang E., Allan G., McNeilly F., Ellis J. and Timmusk S. 2005 .Experimental reproduction of postweaning multisystemic wasting syndrome (PMWS) in pigs in Sweden and Denmark with a Swedish isolate of porcine circovirus type 2 Vet Microb (106) pp. 49-60

39- Magar, R., Muller, P. and Larochelle, R.: (2000) Retrospective serological survey ofantibodies to porcine circovirus type 1 and type 2. Can J Vet Res 64: 184-186.

40- Larochelle, R., Bielanski, A., Muller, P., Magar, R.: (2000) PCR detection and evidence ofshedding of porcine circovirus type 2 in boar semen. J Clin Microbiol 38(12):4629-4632.

41- Ladekjaer-Mikkelsen, A.S., Nielsen, J., Stadejek, T., Storgaard, T., Krakowka, S., Ellis,J., McNeilly, F., Allan, G., Botner, A.: (2002) Reproduction of postweaning multisystemicwasting syndrome (PMWS) in immunostimulated and non-immunostimulated 3-week-oldpiglets experimentally infected with porcine circovirus type 2 (PCV2).Vet Microbiol 89(2-3):97-114.

42- Fenaux, M., Halbur, P.G., Haqshenas, G., Royer, R., Thomas, P., Nawagitgul, P., Gill,M., Toth, T.E., Meng, X.J.: (2002) Cloned genomic DNA of type 2 porcine circovirus isinfectious when injected directly into the liver and lymph nodes of pigs: characterization ofclinical disease, virus distribution, and pathologic lesions. J Vir 76(2):541-551.

43- Balasch, M., Segales, J., Rosell, C., Domingo, M., Mankertz, A., Urniza, A. and Plana-Duran, J.: (1999) Experimental inoculation of conventional pigs with

tissue homogenatesfrom pigs with post-weaning multisystemic wasting syndrome. J Comp Pathol 121:139-148.

44- Albina, E., Truong, C., Hutet, E., Blanchard, P., Cariolet, R., L'Hospitalier, R., Mahe, D.,Allee, C., Morvan, H., Amenna, N., Le Dimna, M., Madec, F. and Jestin, A.: (2001) Anexperimental model for post-weaning multisystemic wasting syndrome (PMWS) in growingpiglets. J Comp Pathol 125: 292-303.

45- Rovira A., Balasch M., Segales J. et al., 2002, Experimental inoculation of conventional pigs with porcine reproductive and respiratory syndrome virus and porcine circovirus 2, J Virol, 76:3232-3239

46- Opriessnig T., Thacker E.L., Yu S., Fenaux M., Meng X.J.,and Halbur P.G., 2004, Experimental reproduction of postweaning multisystemic wasting syndrome in pigs by dual infection with Mycoplasma hyopneumoniae and porcine circovirus type 2, Vet Pathol. 41(6):624-40

47- Allan G., McNeilly F., Ellis J. et al., 2000, Experimental infection of colostrum deprived piglets with porcine circovirus 2 (PCV2) and porcine reproductive and respiratory syndrome virus (PRRSV) potentiates PCV2 replication, Arch Virol, 145: 2421-2429

48- deJong M., Elbers A.R.W., Wellenberg G. and Stokehofe-Zurwieden N., 2003, Interactions among PRRS and other respiratory diseases: the interaction of PRRS and PCV2 on PMWS and PDNS, XXXVI Semana Nacional del Ganado Porcino - Symposium Internacional de Porcinocultura, 15th-18th September 2003 (SEPOR) Murcia, Spain, 85-96

49- Harms P., Sorden S., Halbur P., Bolin S.R., Lager K.M., Morozov I. and Paul P.S., 2001. Experimental reproduction of severe disease in CD/CD pigs concurrently infected with type 2 porcine circovirus and porcine reproductive and respiratory syndrome virus, Vet Pathol, 38:528-539

50- Halbur, P.G., 1998. Porcine respiratory disease. Proceedings of the International Pig Veterinary Society Congress 15, pp. 1-10

51- Thacker E., 2001, Mycoplasma diagnosis and immunity, Proceedings, American Association of Swine Veterinarians 32nd annual, 467-469

52- Harms P.A., Halbur P.G. and Sorden S.D., 2002, Three cases of porcine respiratory disease complex associated with porcine circovirus type 2 infection, J Swine Health Prod. 10: 27-30

53- Done, J.T. and Harding, J.D.J., 1967. Kongenitaler tremor der schweine (zitterkrankheit der ferkel): veranderungen und ursachen. Deutsche Tierarztliche Wochenschrift 74, pp. 333-334.

54- Morin et al., 1990. M. Morin, C. Girard, Y. ElAzhary, R. Fajardo, R. Drolet and A. Lagace, Severe proliferative and necrotizing pneumonia in pigs: a newly recognized disease. Can. Vet. J. 31 (1990), pp. 837-839.

55- Rossow, 1998. K.D. Rossow, Porcine reproductive and respiratory syndrome. Vet. Pathol. 35 (1998), pp. 1-20.

56 - Larochelle et al., 1999. R. Larochelle, M. Morin, M. Antaya and R. Magar, Identification and incidence of porcine circovirus in routine field cases in Quebec as determined by PCR. Vet. Rec. 145 (1999), pp. 140-142.

57- Ellis, J., Krakowka, S., Allan, G., Clark, E. and Kennedy, S., 1999. The clinical scope of porcine reproductive and respiratory syndrome virus has expanded since 1987; an alternative perspective. Veterinary Pathology 36, pp. 262-265.

58- Allan, G.M., McNeilly, F., Ellis, J., Krakowka, S., Meehan, B., McNair, I., Walker, I. and Kennedy, S., 2000. Experimental infection of colostrum deprived piglets with porcine circovirus 2 (PCV2) and porcine reproductive and respiratory syndrome virus (PRRSV) potentiate PCV2 replication. Archives of Virology 145, pp. 2421-2429.

59- Drolet, R., Larochelle, R., Morin, M., Delisle, B. and Magar, R., 2003. Detection rates of porcine reproductive and respiratory syndrome virus, porcine circovirus type 2, and swine influenza virus in porcine proliferative and necrotizing pneumonia. Veterinary Pathology 40, pp. 143-148.

60- Segales J., Rosell C. and Domingo M. 2004. Pathological findings associated with naturally acquired PCV2 associated disease. Vet. Microb. 98 pp. 137-149

61- Clark, 1997. E. Clark, Post-weaning multisystemic

wasting syndrome. Proc. Am. Assoc. Swine Pract. 28 (1997), pp. 499-501.

62- Rosell et al., 1999. C. Rosell, J. Segales, J. Plana-Duran, M. Balasch, G.M. Rodriguez-Arrioja, S. Kennedy, G.M. Allan, F. McNeilly, K.S. Latimer and M. Domingo, Pathological, immunohistochemical, and in situ hybridization studies of natural cases of post-weaning multisystemic wasting syndrome (PMWS) in pigs. J. Comp. Pathol. 120 (1999), pp. 59-78.

63- Royer et al., 2001. R.L. Royer, P. Nawagitgul, P.G. Halbur and P.S. Paul, Susceptibility of porcine circovirus type 2 to commercial and laboratory disinfectants. Swine Health Prod. 9 (2001), pp. 281-284.

64- Vincent I.E., Summerfield A., Steiner E., Guzylack-Piriou L., Mc Cullough K.C.: (2005) Porcine Circovirus Type 2 blocks immune activation of natural interferon producing cells. Intern. Conf on Animal Circoviruses and Associated Diseases, Europ. Society for Vet Virol.

65- McCullough K. ;Vincent I., Summerfield A., Nielsen J., Krakowka S., Ellis J. , Nauwynck H., Charreyre C., McNeilly F. and M. Allan, G. 2003 The Immunology of PCV2 Infections and PMWS in Merial White Book p 25

66- Krakowka S., Rings M. Ellis, J., Allan G., McNeilly F., Meehan B., McCulloug, K. , Botner A. , Nauwynck H. and Charreyre C. 2003. The Pathogenesis of PCV2 Infection and PMWS in Merial White Book p 9

67- Choi, C. and Chae, C., 1999. In-situ hybridization for the detection of porcine circovirus in pigs with postweaning multisystemic wasting syndrome. Journal of Comparative Pathology 121, pp. 265-270.

68- Choi, C., Chae, C. and Clark, E.G., 2000. Porcine postweaning multisystemic wasting syndrome in Korean pig: detection of porcine circovirus 2 infection by immunohistochemistry and polymerase chain reaction. Journal of Veterinary Diagnostic Investigation 12, pp. 151-153.

69- Kim, J., Chung, H.-K., Jung, T., Cho, W.-S., Choi, C. and Chae, C., 2002. Postweaning multisystemic wasting syndrome of pigs in Korea: prevalence, microscopic lesions and coexisting microorganisms.

Journal of Veterinary Medical Science 64, pp. 57-62.

70- Quintana et al., 2001. J. Quintana, J. Segales, C. Rosell, M. Calsamiglia, G.M. Rodriguez-Arrioja, F. Chianini, J.M. Folch, J. Maldonado, M. Canal, J. Plana-Duran and M. Domingo, Clinical and pathological observations of pigs with postweaning multisystemic wasting syndrome. Vet. Rec. 149 (2001), pp. 357-361.

71- Kim J., Chae C. 2005. Necrotizing lymphadenitis associated with porcine circovirus type 2 in pigs. The Veterinary Record 156 pp. 177-178

72- Darwich L. , Segales J., Domingo M., and Mateu E. 2002. Changes in CD4+, CD8+, CD4+ CD8+, and Immunoglobulin M-Positive Peripheral Blood Mononuclear Cells of Postweaning Multisystemic Wasting Syndrome-Affected Pigs and Age-Matched Uninfected Wasted and Healthy Pigs Correlate with Lesions and Porcine Circovirus Type 2 Load in Lymphoid Tissues .Clin. Diagn. Lab. Immunol. 2002 9: pp. 236-242.

73- Nielsen J., Vincent I., Botner A., Ladekjar-Mikkelsen A., Allan G., Summerfield A. and McCullough K. 2003 Association of lymphopenia with porcine circovirus type 2 induced postweaning multisystemic wasting syndrome (PMWS) Vet immuno immunopath (92) pp.97-111

74- Shibahara, T., Sato, K., Ishikawa, Y. and Kadota, K., 2000. Porcine circovirus induces B cell depletion in pigs with wasting disease syndrome. Journal of Veterinary Medical Science 62, pp. 1125-1131.

75- Ellis, J., Hassard, L., Clark, E., Harding, J., Allan, G., Willson, P., Strokappe, J., Martin, K., McNeilly, F., Meehan, B., Todd, D. and Haines, D., 1998. Isolation of circovirus from lesions of pigs with postweaning multisystemic wasting syndrome. Canadian Veterinary Journal 39, pp. 44-51.

76- Charreyre C., Boeuf L., Reynaud G.: (2000) Natural decrease of anti PCV2 maternal antibodies in conventional piglets. Proceedings of the 16th IPVS, Melbourne, Australia

77- Meerts P., Misinzo G., Lefebvre D., Nielsen J., Botner A., Kristensen C.S. and Nauwynck H.J., 2006, Correlation between the presence of neutralizing antibodies against porcine circovirus 2 (PCV2) and

protection against replication of the virus and development of PCV2-associated disease, BMC Veterinary Research, 2:6 (doi:10.1186/1746-6148-2-6)

78- Allan, G.M., Kennedy, S., McNeilly, F., Foster, J.C., Ellis, J.A., Krakowka, S.J., Meehan, B.M. and Adair, B.M., 1999. Experimental reproduction of severe wasting disease by co-infection of pigs with porcine circovirus and porcine parvovirus. Journal of Comparative Pathology 121, pp. 1-11.

79- Choi, C. and Chae, C., 2000. Distribution of porcine parvovirus in porcine circovirus 2-infected pigs with postweaning multisystemic wasting syndrome as shown by in-situ hybridization. Journal of Comparative Pathology 123, pp. 302-305.

80- Ellis, J., Krakowka, S., Lairmore, M., Haines, D., Bratanich, A., Clark, E., Allan, G., Konoby, C., Hassard, L., Meehan, B., Martin, K., Harding, J., Kennedy, S. and McNeilly, F., 1999. Reproduction of lesions of postweaning multisystemic wasting syndrome in gnotobiotic piglets. Journal of Veterinary Diagnostic Investigation 11, pp. 3-14.

81- Kim, J., Choi, C. and Chae, C., 2003. Pathogenesis of postweaning multisystemic wasting syndrome reproduced by co-infection with Korean isolates of porcine circovirus 2 and porcine parvovirus. Journal of Comparative Pathology 128, pp. 52-59.

82- Krakowka, S., Ellis, J.A., McNeilly, F., Ringler, S., Rings, D.M. and Allan, G., 2001. Activation of the immune system is the pivotal event in the production of wasting disease in pigs infected with porcine circovirus-2 (PCV-2). Veterinary Pathology 38, pp. 31-42

83- Opriessnig T., YU S., Gallup J.M., Evans R.B., Fenaux M., Pallares F., Thacker E.L., Brockus C.W., Ackermann M.R., Thomas P., Meng X. J., Halbur P.G.: (2003) Effect of vaccination with selective bacterins on conventional pigs infected with type 2 porcine Circovirus. Vet. Pathol. 40:521-529.

84- Hoogland M.J., Opriessnig T., and Halbur P. G., 2006, Effects of adjuvants on porcine circovirus type-2-associated lesions. Journal of swine health and production 14: 133-139

85- Meehan et al., 1998. B.M. Meehan, F. McNeilly, D. Todd et al., Characterization of novel circovirus DNA's associated with wasting disease syndromes in pigs. J. Gen. Virol. 79 (1998), pp. 2171-2179.

86- Chang H-W., Jeng C-R., Lin T-L., Liu J. J., Chiou M-T., Tsai Y-C., Chia M-Y., Jan T-R., and Pang V. F., 2006, Immunopathological effects of porcine circovirus type 2 (PCV2) on swine alveolar macrophages by in vitro inoculation, Vet Immunol and Immunopathol., 110: 207-219

87- Thacker E., 2001, Mycoplasma diagnosis and immunity, Proceedings, American Association of Swine Veterinarians 32nd annual meeting, 467-469

88- Thacker E. 2006. Lung inflammatory responses Vet. Res. (37) pp. 469-486

89- Allan, G.M., Meehan, B., Todd, D., Kennedy, S., McNeilly, F., Ellis, J., Clark, E.G., Harding, J., Espuna, E., Botner, A. and Charreyre, C., 1998. Novel porcine circoviruses from pigs with wasting disease syndromes. Veterinary Record 142, pp. 467-468.

90- Fenaux, M., Halbur, P.G., Gill, M., Toth, T.E. and Meng, X.-J., 2000. Genetic characterization of type 2 porcine circovirus (PCV-2) from pigs with postweaning multisystemic wasting syndrome in different geographic regions of North America and development of a differential PCR-restriction fragment length polymorphism assay to detect and differentiate between infections with PCV-1 and PCV-2. Journal of Clinical Microbiology 38, pp. 2494-2503.

91- Hamel, A.L., Lin, L.L., Sachvie, C., Grudeski, E. and Nayar, G.P.S., 2000. PCR detection and characterization of type-2 porcine circovirus. Canadian Journal of Veterinary Research 64, pp. 44-52.

92- Mankertz, A., Domingo, M., Folch, J.M., LeCann, P., Jestin, A., Segales, J., Chmielewicz, B., Plana-Duran, J. and Soike, D., 2000. Characterisation of PCV-2 isolates from Spain, Germany and France. Virus Research 66, pp. 65-77.

93- Hamel et al., 1998. A.L. Hamel, L.L. Lin and G.P.S. Nayar, Nucleotide sequence of porcine circovirus associated with postweaning multisystemic wasting syndrome in pigs. J. Virol. 72 (1998), pp. 5262-526

94- Hamel, A.L., Lin, L.L. and Nayar, G.P.S., 1998. Nucleotide sequence of porcine circovirus associated with postweaning multisystemic wasting syn-

drome in pigs. Journal of Virology 72, pp. 5262-5267.

95- Tischer, I., Rasch, R. and Tochtermann, G., 1974. Characterization of papovavirus- and picornavirus-like particles in permanent pig kidney cell lines. Zentralblatt fur Bakteriologie, Parasitenkund, Infecktionskrankheiten und Hygiene - Erste Abteilung Originale - Reihe A: Medizinische Mikrobiologie und Parasitologie 226, pp. 153-167.

96- Tischer, I., Mields, W., Wolff, D., Vagt, M. and Greim, W., 1986. Studies on epidemiology and pathogenicity of porcine circovirus. Archives of Virology 91, pp. 271-276

97- Choi, C., Kim, J., Kang, I.J. and Chae, C., 2002. Concurrent outbreak of PMWS and PDNS in a herd of pigs in Korea. Veterinary Record 151, pp. 484-485.

98- Farnham, M.W., Choi, Y.K., Goyal, S.M. and Joo, H.S., 2003. Isolation and characterization of porcine circovirus type-2 from sera of stillborn fetuses. Canadian Journal of Veterinary Research 67, pp. 108-113.

99- Nawagitgul, P., Morozov, I., Bolin, S.R., Harms, P.A., Sorden, S.D. and Paul, P.S., 2000. Open reading frame 2 of porcine circovirus type 2 encodes a major capsid protein. Journal of General Virology 81, pp. 2281-2287.

100- Halbur P., and Opriessnig T., 2006, Proceedings of the AASV seminar on PCV2/PMWS, pp 31 -38

101- Allan, G.M., McNeilly, F., Meehan, B.M., Kennedy, S., Mackie, D.P., Ellis, J.A., Clark, E.G., Espuna, E., Saubi, N., Riera, P., Botner, A. and Charreyre, C.E., 1999. Isolation and characterization of circoviruses from pigs with wasting syndromes in Spain, Denmark and Northern Ireland. Veterinary Microbiology 66, pp. 115-123.

102- Charreyre C., Andreoni C., Beseme S., Brun A., Juillard V., and Reynaud, G. 2004. Vaccination concepts in controlling PCV2-associated diseases, in "PCV2 diseases: from research back to the field again", MERIAL, Hamburg, Germany, 95-107.

103- Sibila M., Calsamiglia M., Segales J., Blanchard P., Badiella L., Le Dimma M., Jestin A., Domingo M. : (2004) Use of polymerase chain reaction assay and an ELISA to monitor porcine circovirus infection in pigs from farms with and without post-weaning

multisytemic wasting syndrome. AJVR 65 :88-92

104- Lopez-Soria S., Segales J., Nofrarias M., Sibila M., Espinal A., Ramirez H., Minguez A., Serrano J., Marin O., Joisel F. , and Charreyre C. 2005. PCV2 infection dynamics in two farms: relationship with PMWS expression, mortality and weight, submitted

105- Rose N., Abherve-Gueguen A., Le Diguerher G., Eveno E., Jolly J.P., Blanchard P., Oger A., Jestin A., Madec F. : (2004) Effet de la genetique Pietrain sur l'expression clinique de la maladie de l'amaigrissement du porcelet (MAP). JRP 36 :339-344.

106- Charreyre C., Beseme S., B?uf-Tedeschi L., Bublot M., Reyaud G.: (2002) Protection against PCV2 experimental challenge in 3-week-old piglets by maternal antibodies. Proceedings of the 17th IPVS, Ames, Iowa, USA

107- Thomas P., Opriessnig T., McKeown N., Meng X.J., and Halbur P. 2005. Effect of PCV2 passive antibody levels on immunization with chimeric PCV1-2 vaccine and challenge with wild-type PCV2, Proceedings of the American Association of Swine Veterinarians, 23-25.

108- Park JS., Kim J., Ha Y., Jung K., Choi C., Lim JK., Kim SH., and Chae C. 2005. Birth abnormalities in pregnant sows infected intranasally with porcine circovirus 2. Journal of Comparative Pathology 132: 139-144.

109- Cotrell, T. 1999. Epidemiology of post-weaning multisystemic wasting syndrome and pathogenic strains of porcine circovirus in Southern Ontario, MS Thesis, University of Guelph, ON, Canada.

110- Larochelle, R., Magar, R., and Dallaire, S. 2003. Comparative serologic and virologic study of commercial swine herds with and without postweaning multisystemic wasting syndrome, Canadian Journal of Veterinary Research - Revue Canadienne de Recherche Veterinaire 67(2):114-120.

111- Segales J. and Morvan H. 2004. PMWS: how to define the "herd case"? in "PCV2 diseases: from research back to the field again", MERIAL, Hamburg, Germany, 65-78.

112- Blanchard, P., Mahe, D., Cariolet, R., Keranflec'h, A., Baudouard, MA., Albina, E., and Jestin, A. 2004.

Protection contre la maladie d'amaigrissement du porcelet (MAP) par vaccins a ADN et proteines recombinantes, Journees Recherche Porcine 36:345-352.

113- Pogranichniy, R., Yoon, KJ., Yaeger, M., Vaughn, E., Stammer, R., and Roof, M. 2004. Efficacy of experimental inactivated PCV2 vaccines for preventing PMWS in CDCD pigs, AASV Proceedings, Des Moines, Iowa, USA, 443-444.

114- Fenaux M., Opriessnig T., Halbur P., Elvinger F., and Meng XJ. 2004. A chimeric porcine circovirus (PCV) with the immunogenic capsid gene of the pathogenic PCV type 2 (PCV2) cloned into the genomic backbone of the non pathogenic PCV1 induces protective immunity against PCV2 infection in pigs, Journal of Virology, 78: 6297-6303

115- Reynaud, G., Beseme, Brun A., Charreyre, C., Desgouilles S., Jeannin P., and Rehbein S. 2004. Safety of a high dose of an inactivated adjuvanted PCV2 vaccine in conventional gilts. Proceedings of the 18th IPVS, Hamburg, Germany, 709.

116- Reynaud, G., Brun A., Charreyre, C., Desgouilles S., and Jeannin P. 2004. Safety of a repeated dose of an inactivated adjuvanted PCV2 vaccine in conventional pregnant gilts and sows. Proceedings of the 18th IPVS, Hamburg, Germany, 710.

117- Meehan, B.M., McNeilly, F., Todd, D., Kennedy, S., Jewhurst, V.A., Ellis, J.A., Hassard, L.E., Clark, E.G., Haines, D.M. and Allan, G.M., 1998. Characterization of novel circovirus DNAs associated with wasting syndromes in pigs. Journal of General Virology 79, pp. 2171-2179.

ワクチネーションによるブタサーコウイルス関連症
（PMWS および PCV2 が関与する PRDC）のコントロール

始めに

　離乳後多臓器性発育不良症候群（PMWS）は、1996年、カナダの衛生レベルの高い農場で最初に報告され、現在、養豚産業での重要な新興性疾患となっている。（Clark, 1997 (1); Harding and Clark, 1997 (2)）最初の報告後すぐに、PMWS には新たに見つかったブタサーコウイルス 2 型（PCV2）が関与することが明らかとなった。（Ellis et al., 1998 (3)）PCV2 は、その後 PMWS に留まらず、他の様々な疾患；PRDC（豚呼吸器複合感染症、Porcine Respiratory Disease Complex）、（Allan and Ellis, 2000 (4); Harms et al., 2002 (5); Kim et al., 2003 (6)）異常産、（Josephson and Charbonneau, 2001 (7); Ladekjaer-Mikkelsen et al., 2001 (8); Kim et al., 2004 (9); O'Connor et al., 2001 (10); West et al., 1999 (11)）PDNS、（豚皮膚炎腎症症候群、Porcine Dermatitis and Nephropathy Syndrome）（Allan and Ellis, 2000 (4); Gresham et al., 2001 (12); Meehan et al., 2001 (13); Thomson et al., 2001 (14); Ramos-Vara et al., 1997 (15)）肝炎、壊死性リンパ節炎および肉芽腫性腸炎の症例から分離され、また、おそらく滲出性皮膚炎との関連（Chae, 2005 (16)）も推察されている。

　ここでは、様々な病理学的機序における PCV2 の関与を検討するために野外感染豚ならびに実験感染豚からの現在までのデータをレビューする。とりわけ、いかにして共感染因子が PCV2 関連症の発症に関わり合っているかを述べたい。また、PCV2 関連症を防御あるいは軽減化するために、その一般的な投薬計画を含めて CIRCOVAC®* の有効性について評価したい。
*CIRCOVAC®は米国、日本および各国でのメリアル社の登録商標。

1．PCV2 関連病変ならびに症候群の解説
1.1　離乳後多臓器性発育不良症候群（PMWS）

　PMWS は PCV2 感染が強く関わり、世界中の豚養豚地帯において主要な生産性阻害要因となっている。アジア、ヨーロッパおよび北アメリカにおいて PMWS は常在疾病（endemic form）あるいは流行病（epidemic form）として発生している。（Allan and Ellis, 2000 (4); Ellis, 2004 (17) and Segales and Domingo, 2002 (18)）アジアにおける PMWS の発生についてはまとまった記述がある。（Kawashima et al 2003 (19)）

　PMWS の特徴的な臨床所見は、約 6 ～12週齢の豚の進行性の発育遅延および削痩、リンパ節の腫脹（特にそけいリンパ節は認めやすい外貌所見）、呼吸困難、下痢および黄疸である。PMWS の個体診断は、上記の臨床症状に加えて、特徴的なリンパ組織における組織学的病変（組織球浸潤、封入体形成および巨細胞浸潤を伴うリンパ球減少、これらの病変は単独でも同時にも認められる）ならびに病変内における中程度から多量の PCV2 の検出に基づく。群診断は、少なくとも 5 頭の解剖検査に基づく個体診断を合わせた、平時と比べた事故率と発育不良豚の上昇から判断する。（European Consortium definition - Project No 513928 Sixth Framework Programme - http:// www.pcvd.org ）.

　PCV2 は PMWS の野外症例から必ず検出されるが、表 1 のアジアでの報告のように他の病原ウイルスもしくは病原細菌と同時に検出されることが多い。（Jeong et al., 2003 (20)）

　米国での症例対照研究において、PMWS と既知のウイルス（PCV2、PRRS ウイルス、ブタパルボウイルス（PPV）、ブタエンテロウイルス 1 － 3 型、ブタインフルエンザウイルス、ブタ呼吸器コロナウイルス、TGE ウイルス、ブタ内因性レトロウイルス、ブタリンパ球向性ヘルペスウイルス 1 型および BVD ウイルス）の疫学的な関連性の強さを検討したところ、PCV2 と PMWS との関連性が最も強かった。PMWS に罹患するリスクは、PCV2 と PRRS ウイルスが同時に感染した場合に上昇し、PMWS 発症にはコーファクターによる増悪化が必要であることが推測された。（Pogranichniy et al., 2002 (24)）

　PMWS は PCV2 単独接種ならびに他の感染因子による関与の両方の実験的再現モデルが報告されている。いくつかの実験感染では PCV2 単独接種により PMWS を誘発することは可能であった。しかしながら、PCV2 と PPV、PCV2 と PRRS ウイルス、あるいは PCV2 と Mycoplasma hyopneumoniae（M.hyo）の混合感染が多くの実験で PMWS の発症頻度を上昇させた。これらの実験感染に共通して、混合感染はより重篤な臨床症状ならびに組織学的病変形成を誘発し、また PCV2 量を上昇させた。（Allan et al., 2000 (47); DeJong et al., 2003 (48); Harms et al., 2001 (49)）.

1.2　PCV2 と豚呼吸器複合感染症（PRDC）

　豚呼吸器複合感染症は、16週から22週齢の育成から肥育期に発生する疾病で、発育遅延、飼料効率の低下、元気消沈、食欲不振、発熱、咳および呼吸困難を特徴とする。（Halbur, 1998 (50); Thacker, 2001 (51) and Harms et al., 2002 (52)）野外調査結果から、PRDC 罹患豚の肺炎は、ウイルスと細菌；例えば PRRS ウイルス、PCV 2、ブタインフルエンザウイルス（SIV）、*M.hyo, Actinobacillus pleuropneumoniae*（*APP*）および *Pasteurella multocida* の混合感染に起因する。（Halbur, 1998 (50); Thacker, 2001 (51)）一例をあげると、2003年韓国での PRDC 105 症例の後ろ向き調査では、（Kim et al., 2003 (6)）85症例が PCV2 陽性、66症例が PRRS ウイルス陽性、60症例が PPV 陽性、14症例が SIV 陽性であり、これらの症例の多くが混合感染であった。PCV2 と *Pasteurella multocida* の混合感染症例が38症例、次いで PCV2 と *M.hyo* が33症例であった。類似の調査結果は、米国でも報告されている。（Harms et al. 2002 (5)）PRDC では、もし１種類あるいは複数種の２次的な細菌感染が起これば、死亡率は急上昇する。（Done, 2002 (53); Harms et al., 2002 (5); Kim et al., 2003 (6); Thacker, 2001 (51)）

　肺炎の特殊な症例は増殖性壊死性肺炎（proliferative necrotizing pneumonia (PNP)）で、特徴的な組織病変を示す亜急性から慢性肺炎として名付けられた。元来 PNP は SIV 感染、次いで PRRS ウイルス感染と関連すると報告された。（Harms et al. 2002 (52); Morin et al., 1990 (54); Rossow, 1998 (55); Larochelle et al., 1999 (56)）*In situ* hybridization あるいは免疫組織化学的染色法による PNP 症例での一貫した PCV2 の検出から、PCV2 は PNP の重要な因子であると推測されている。（Ellis et al., 1999 (57); Harms et al., 2002 (5)）PRDC の臨床症状は様々で、その原因は複数にまたがると考えられるが、上記手法による肺組織での PCV2 DNA や抗原検出は、気管支周囲あるいは細気管支周囲の線維化を伴う気管支間質性肺炎とともに、PCV2 が関連する PRDC の主要な診断指標として用いられている。

　実験室レベルでは、PCV2 と PRRS ウイルスは相乗してより重篤な呼吸器症状と肺病変を現すことが証明されている。（Allan et al., 2000 (58)）PCV2 は PRRS ウイルスの病変は重篤化しないが、PRRS ウイルスは PCV2 感染を増強するのは確かなようである。（Allan et al., 2000 (58)）PCV2 と PRRS ウイルスの混合感染に

よって形成される気管支間質性肺炎は、PRDC の野外典型病変と類似する。（Drolet et al., 2003 (59)）同様に、PCV2 と *M. hyo* のの混合感染試験では *M. hyo* が PCV2 抗原量の増加とその存在期間の延長、PMWS の発生率の増加、PCV2 感染によるリンパ組織病変の重篤化と PCV2 感染による肺病変の重篤化をもたらした。両微生物による呼吸器疾患の相乗効果は明らかで、*M.hyo* 単独感染で 1/9、PCV2 単独感染で 2/8 頭の豚が壊死性細気管支炎が認められたのに対し、混合感染させた 7/9 頭に壊死性細気管支炎が認められた。（Opriessnig et al., 2004 (46)）

1.3　PCV2 が関連する他の症候群と病気

　野外症例として、PCV2 は単独で異常産との関連が報告されており、その他、腸炎、下痢と肉芽腫性腸炎、肝疾患、滲出性皮膚炎、神経症状あるいは皮膚炎腎症症候群（PDNS）との関連が指摘されている。これらの疾患の PCV2 の役割あるいは混合感染する病原体については、将来、調査の必要があるだろう。

２．PCV2 感染の病理発症メカニズムと混合感染による増悪化作用

　PCV2 感染の病理発生については多様なメカニズムが提起され、それが異なる PCV2 関連疾患に結びつくと説明されている。（Segales et al., 2004 (60)）当初、PCV2 の宿主体内での最初の複製は扁桃や局所リンパ節（Clark, 1997 (61); Rosell et al., 1999 (62)）、あるいはパイエル板（Rosell et al., 1999 (62); Royer et al., 2001 (63)）のようなリンパ組織中のマクロファージや抗原提示細胞で起こると推測された。これらのリンパ組織中や上記の細胞中にウイルスが一貫して見つかることからの推測であった。PCV2 は粘膜局所のマクロファージや抗原提示細胞に感染・複製した後、細胞とともに、ないしは細胞から離れてリンパ流や血流に乗って移動すると考えられた。この多くの組織につながる体内運搬経路に PCV2 感染細胞が乗ることによって、様々な器官にウイルス感染が拡がることが考えられたのである。しかしながら、この考えは PCV2 の全身への主な拡散手段として支持されたものの、PCV2 はマクロファージや抗原提示細胞では通常は複製しないことが明らかにされた。（Vincent et al., 2005 (64)）要するに、単球／マクロファージ系細胞は PCV2 を貪食し、長期間、大量のウイルスを保持することから、これらの細胞で容易にウイルスが検出されると思われ

る。*In vitro* の試験結果から、樹状細胞ではウイルスの急速な取り込みと細胞内で長期間にわたって抗原と感染ウイルスが持続することが明らかにされた。PCV2は細胞内分解機構を避けることによって感染力を保って細胞内に持続し、樹状細胞内での複製はあっても限定されていた。（Mc Cullough et al., 2003 (65)）肺、肝臓、腎臓、心臓や他の臓器における実質細胞が最終的に感染すると PMWS 状態へ推移する。このステージでは、内皮細胞や上皮細胞で活発にウイルスが複製し、爆発的な数のウイルスがこれらの臓器で検出される。組織や細胞への親和性が拡大し、PMWS が発症すると考えられている。（Krakowka et al., 2003 (66)）免疫刺激と関連していると思われるが、いかにしてその変位が起こるかについては、まだわかっていない。一方、PCV2 は樹状細胞に深刻な影響を与え、その機能を傷害して免疫防御を停止させて免疫病やアネルギー（活動停止）へ導く可能性があることが最近、報告された。この事実は、あらゆる 2 次的病原体が豚の生体内に容易に侵入し易くなる説明となる。（Mc Cullough et al., 2003 (65)）次は免疫システムに対する PCV2 の直接作用と様々なトリガーや 2 次的病原体との可能性のある相乗作用についてレビューする。

2.1　PCV2 感染は免疫抑制を導く

　PCV2 感染の免疫抑制の事象は、細胞ならびに顕微鏡レベルから臨床レベルまで幅広く認められる。PMWS の病変は、全身性の肉芽腫性炎症、多核巨細胞の浸潤および浸潤した組織球やマクロファージ内に様々な数で形成される細胞質内好塩基性ウイルス封入体を特徴とする。とりわけ、PMWS の最も特徴的な組織病変は、多発性からびまん性に認められる血管周囲性の肉芽腫性の炎症である。この特異な病変は通常のウイルス感染による病変とは異なっており、PMWS の診断に有用である。組織球浸潤は PCV2 感染初期病変のひとつで、肉眼的にはリンパ節腫脹として認められる。慢性期には重篤なリンパ球減少や明瞭な組織球・多核巨細胞浸潤は認めがたくなる。（Krakowka et al., 2003 (66); Allan et al., 1999 (32); Choi and Chae, 1999 (67); Choi et al., 2000 (68); Ellis et al., 1999 (57); Kennedy et al., 2000 (33); Kim et al., 2002 (69); Krakowka et al., 2000 (27); Clark, 1997 (61); Rosell et al., 1999 (62); Quintana et al., 2001 (70)）．PCV2抗原は進行した壊死病変に多量に認められることから、壊死性リンパ節炎との関連が推測されている（Kim and Chae,

2005 (71)）．野外調査ならびに実験感染での末梢血単核球細胞数ならびに組織病理所見から、様々なリンパ組織においてリンパ球減少やリンパ球サブセットの割合の変化が起こることが示された。リンパ組織における PCV2 量が増加するのに伴い、リンパ組織中のBリンパ球とTリンパ球領域のリンパ球が消失する。（Darwich et al., 2002 (72); Nielsen et al., 2003. (73)）．アポトーシスは PMWS 罹患豚のBならびにT細胞減少の原因となり、それにはサイトカインのシグナル伝達の混乱があると提起されたが、（Shibahara et al., 2000 (74)）このメカニズムは全ての研究で確かめられたわけではない。（Krakowka et al., 2003 (66)）PCV2 感染豚ならびに PMWS 罹患豚では免疫系障害により免疫応答が阻害され、日和見感染症が PCV2 感染によって誘発される最終像となる。例えば、低罹患率（約 5 ％）の *Peumocystis carinii* 感染が西カナダのPMWSの初期の症例で報告されている。（Ellis et al., 1998 (75)）．別の例は、PMWS 罹患豚の中和抗体応答の産生や持続の不全である。（Charreyre et al., 2000 (76); Meerts et al., 2006 (77)）．

2.2　PCV2 感染を重篤化に向かわせるトリガー

　実験的に PCV2 感染豚を油性マクロファージ標的アジュバント乳化抗原で刺激することにより、PMWS の発症が高まる。免疫刺激は PCV2 感染を PMWS 状態に転換させうる極めて重要な因子であることが報告された。（Allan et al., 1999 (78); Allan et al., 2000 (58); Choi and Chae, 2000 (79); Ellis et al., 1999 (80); Kennedy et al., 2000 (33); Kim et al., 2003 (81); Krakowka et al., 2000 (27); Krakowka et al., 2001 (82)）

　米国で通常使用されているバクテリンを用いたワクチネーション（*APP* と *M.hyo* バクテリン）は PCV2 の複製を促し、PMWS の臨床症状と病変を増悪化させることが報告された。若齢期のワクチネーション、抗原量の多いワンショットでの投薬法、オイルアジュバント、環境中の高い PCV2 浸潤および低い移行抗体レベルは PMWS の発生率や増悪化を促す可能性がある。（Opriessnig et al. 2003 (83); Hoogland et al. 2006 (84)）

　前記したように、PMWS は、PCV2 と PPV、PCV2 と PRRS ウイルスおよび PCV2 と *M. hyo* の混合感染モデルで再現されている。ひとつの実験モデルにおいて、PPV 感染豚ではインターロイキン10が上昇することによりB細胞を活性化し、免疫刺激と PCV2 の取り込みを促すことが示唆された。また、インターロイキン10

の検出が混合感染豚では延長していた。（Hasslung and al., 2005 (38)）PPV に類似して、PCV2 もまた活発に分裂している細胞が必要もしくは利用する複製サイクルを有するので、（Meehan et al., 1998 (85)）ウイルスに親和性のある細胞の分裂を誘発する因子は、PCV2 の複製を促し、ひいてはウイルス量の増大と発症につながる。それゆえ、様々な細胞を破壊し傷害された組織の再生を誘発する PPV のような共感染因子は、間接的に PCV2 の複製を増強する可能性がある。サイトカインや他の成長因子もまた、細胞分裂を促すことで、間接的に PCV2 の複製を上昇させうる。

　PRRS ウイルスは肺胞マクロファージ（PAMs）に特異的に感染し破壊する。前述したように単球／マクロファージ系細胞は、PCV2 を貪食し、長期間、細胞内で病原性を保っている多量のウイルスを貯蔵しているため、PAMs の破壊は、肺内に極めて多量の PCV2 を放出することにつながる。PRRS ウイルスの感染は豚体内でかなり長期にわたるため、慢性の混合感染豚では、PCV2 の多量放出も長期にわたって繰り返し起こりうる。

　M. hyo 感染は炎症性サイトカインの産生を誘導する。それゆえ、*M. hyo* は細気管支炎を誘導して PCV2 の呼吸器病原性を亢進することは明白で、PCV2 抗原量の増大と局在の持続を促し、PMWS の発生率を増大させる。（Opriessnig et al, 2004 (46)）興味深いことに、In vitro 試験で PCV2 感染 PAMs は機能的に変化し、*M. hyo* のような 2 次感染病原体を効果的に抑圧できないことが、最近、報告された。（Chang et al., 2006 (86)）さらに LPS のようなグラム陰性細菌の構成要素が不活発であった PAMs 内での PCV2 の複製を誘導する興味ある報告がなされた。また、*M. hyo* 感染はマクロファージを活性化しウイルス破壊が亢進する Th1 反応から、より効果の弱い Th2 反応へシフトさせ、（Thacker, 2001 (87)）PCV2 の取り込みを促進する可能性がある。他の SIV や *APP* は肺の急性炎症を惹起し、（Thacker et al., 2006 (88)）炎症反応が亢進することで PCV2 の複製を促すかも知れない。全ての病原体が関与するような野外の状況では、より複雑に上記のメカニズムが相互作用しているであろう。

３．ウイルス株の差違による影響

　異なる臨床症状を呈する豚や地理的に異なる地域から分離された PCV2 株の塩基配列が比較され、すべての PCV2 株間の相同性は90－96％以上と非常に高いこ

とが明らかとなった。（Allan et al., 1998 (89); Ellis et al., 1998 (75); Fenaux et al., 2000 (90)；Hamel et al., 2000 (91); Mankertz et al., 2000 (92); Meehan et al., 1998 (93)）PCV2 は非病原性の PCV1 との相同性が約 62％であることから、PCV2 は病原性をもつ単一の遺伝子型と推測される。（Hamel et al., 1998 (94); Tischer et al., 1974 (95); Tischer et al., 1986 (96); Meehan et al., 1998 (93)）分離された PCV2 の塩基配列にはマイナーな差違はあるが、（Choi et al., 2002 (97); Farnham et al., 2003 (98); Meehan et al., 2001 (13); O'Connor et al., 2001 (10)）　今のところ、このマイナーな違いにどのような意義があるかは不明である。ORF1 と ORF2 の塩基配列の分析から、塩基配列の変動の大きさは ORF1 に比べ ORF2 で大きいことが明らかとなった。（Fenaux et al., 2000 (90); Hamel et al., 2000 (91); Mankertz et al., 2000 (92)）主要な構造キャプシド蛋白をエンコードする ORF2（Nawagitgul et al., 2000 (99)）の変化は、キャプシド蛋白のバリエーションと PCV2 の病原性とに関わるかも知れない。主要ウイルスキャプシドの修飾によって組織親和性ないしはウイルス－宿主の相互作用に関わる決定要素を変化させる可能性がある。ある報告では、PCV2 の ORF2 のマイナーな変化が宿主親和性の差違につながると推測している。（Mankertz et al., 2000 (92)）別の 2 つの報告では、異常産と PDNS から分離される PCV2 株は表現型や遺伝子型が PMWS から分離される株とは異なる可能性を推察している。（Meehan et al., 2001 (13); O'Connor et al., 2001 (10)）しかしながら、攻撃試験での PCV2 株の同時比較ではこの差違は無いかあっても限定的である。（Hasslung et al, 2005 (38); Halbur and Opriessnig, 2006 (100)）　日齢や健康状態等の宿主因子、感染経路、共感染因子あるいは他のストレス因子は PCV2 感染の病原性と臨床症状発現を大きく左右するので、野外農場における分離株の病原性を検討することは困難である。さらに PMWS に関連する全ての PCV 2 株はモノクロナール抗体やポリクロナール抗体の検討から抗原的に類似している。（Allan et al., 1999 (101)）

４．豚農場でのサーコウイルスワクチネーション

　初乳やミルクを介した高いレベルの抗 PCV2 移行抗体付与による繁殖候補豚や母豚への PCV2 関連疾病のワクチネーションは、以下の情報によりその有効性が提起される。（Charreyre et al. 2004 (102)）

● PCV2 は非常に安定しており、農場環境中に多量

に存在するため、多くの農場で撲滅は困難である。

● PMWS 発生農場では、肥育期に比べて哺育期や離乳後の育成期の豚で多量の PCV2 が検出される。（Sibila et al. 2005 (103), Lopez-Soria et al., 2005 (104) Rose et al., 2004 (105)）

● PCV2 に対する移行抗体は PCV2 感染と PMWS 発症に対して防御効果があることがわかった。（Char-reyre et al., 2002 (106); Thomas et al., 2005 (107)）

● 流産と早産が分娩 3 週前の母豚に PCV2 を接種することにより再現された、このため妊娠中の繁殖豚群を防御する必要がある。（Park et al., 2005 (108)）

　しかしながら、繁殖豚群のワクチネーションと PCV2 抗体の受動免疫によっては、移行抗体が低下するので、子豚の PCV2 感染に対する防御効果は限定的な期間に限られている。生後 5 ～ 15 週間に感染抗体の上昇が起こる野外の状況からも受動免疫が限定的であることが推察できる。（Cotrell, 1999 (109); Larochelle et al., 2003 (110); Segales and Morvan, 2004 (111)）異なるグループにより感染抗体は PMWS 発症に対して防御効果があることが報告された。それゆえ、よくコントロールされた PCV2 の自然感染は PCV2 関連疾患に対する自然防御誘導すると考えられる。

4.1　実験室における 2 つの有効性試験

　最初の実験の目的は、PCV2 感染がコントロールされた環境下で不活化オイルアジュバンド PCV2 ワクチン（CIRCOVAC）の有効性を調べることであった。ワクチン接種された繁殖母豚の特異抗体の上昇と生まれた子豚の生後 3 - 4 週間での PCV2 攻撃試験による防御効果が評価された。2 番目の試験の目的は、野外農場でのワクチン接種繁殖母豚から生まれた子豚を実験室に運び、そこで攻撃試験を行うことによりワクチンの有効性を調べることであった。この試験では生後約 4 週齢で PCV2 に攻撃され、その防御効果が評価された。この 2 つの試験以外にワクチンの妊娠豚に対する安全性を証明した。（Reynaud et al., 2004 (115 and 116)）

　最初の試験では、ELISA 検査による PCV2 抗体が陰性の SPF 繁殖母豚が 2 群に分けられた。11頭の繁殖母豚グループには交配 5 および 2 週前、および分娩 2 週前に筋肉内に最小限の抗原がワクチン接種された。別の12頭の繁殖母豚はワクチン非接種群であった。すべての繁殖母豚は10ヶ月齢で人工授精され 8 頭の母豚が妊娠した。それゆえ、第 1 群が 4 頭のワクチン接種

母豚由来の22頭の子豚で、第 2 群が 4 頭のワクチン非接種母豚由来の22頭で、おのおの 3 ～ 4 週齢に PCV2 が鼻腔内接種された。母豚ならびに子豚の血清中の PCV2 抗体は実験期間中、一定間隔で調べられた。攻撃後、臨床症状を 4 週間観察した。血清中ならびに糞中の PCV2 ウイルス量は定量 PCR 法（Q-PCR）で調べられた。全44頭の解剖検査が実施され、腸間膜リンパ節が PCV2 を免疫組織化学的に検出するために採取された。攻撃前、ワクチン接種母豚は高く安定した PCV2 抗体価を保ったが、一方、ワクチン非接種群の母豚ならびにその子豚は抗体陰性であった。最初のワクチン接種後すぐに抗体の陽転が誘導され、分娩前の 3 回目の接種により一層の追加免疫がみられた。初乳による移行抗体の十分な付与と持続は、ワクチン接種母豚から生まれた子豚の血清中 PCV2 抗体の高力価で個体間のばらつきのない抗体価により確認された。攻撃後、顕著な抗体の陽転がワクチン非接種母豚由来の子豚に認められたが、ワクチン接種母豚群由来の子豚は抗体価の減少が続いた。この実験では典型的な PMWS 症例は認められなかったものの、PCV2 攻撃後に臨床症状と発育遅延が観察され、臨床スコアは、ワクチン非接種母豚由来の子豚が顕著に高値であった（p = 0.015）。解剖時、病変スコアはワクチン接種母豚由来の子豚がワクチン非接種母豚由来の子豚に比べて有意に低い値であった（p < 0.00001）。さらに血清中、直腸スワッブおよび腸間膜リンパ節での PCV2 DNA 量はワクチン接種母豚由来の子豚が有意に低い値であった（p = 0.00002）。この不活化ワクチンはワクチン接種された繁殖母豚が高く安定した抗体価を維持したことから、高い免疫原性があることが立証された。このワクチネーションによりワクチン接種母豚由来の子豚は病原性のある PCV2 の攻撃に対して著明な防除効果を示した。この結果から、CIRCOVAC によるワクチネーションは高度にコントロールされた環境下では、PCV2 攻撃後の豚の健康状態の改善に有効性があることが示された。

　2 番目は野外効果試験で、PMWS 発生農場における母豚から生まれた子豚が試験に用いられた。第 1 群をこの農場の 8 頭のワクチン非接種母豚由来の子豚12頭とした。第 2 群をこの農場の分娩 2 週間前に最小限の抗原（CIRCOVAC）が筋肉内に一回接種された 7 頭の母豚由来の子豚10頭とした。攻撃対照として、11頭の SPF 豚が第 3 群として設けられた。この農場から、約 3 日齢の子豚が農場管理スケジュールに沿った日に

実験感染施設に運び込まれた。それゆえ、これら３群の豚は同じ日に PCV2 が鼻腔内接種されたが、いくぶん異なる接種日齢となった。すなわち、攻撃された日齢は、第１群のワクチン非接種対照母豚由来の子豚は32日齢、第２群のワクチン接種母豚由来の子豚は25日齢および第３群の攻撃対照の SPF 豚は47日齢であった。試験期間を通して、連続的に母豚ならびにその子豚の血中 PCV2 抗体価、および子豚の糞中に検出される PCV2 ウイルスが調べられた。攻撃後４週間、臨床症状をモニターし、４週目に解剖検査された。解剖時、縦隔リンパ節が免疫組織化学的検査によるウイルス量測定のために採取された。分娩２週間前、すなわちワクチン接種日には、全ての母豚は類似した抗体価のPCV2 抗体を保有していた。ワクチン接種母豚の分娩後２週後の PCV2 抗体価は有意に上昇し（p＜0.005）、ワクチン接種母豚由来の子豚の PCV2 抗体価はワクチン非接種母豚由来の子豚に比べ、攻撃日まで有意に高値であった（p＝0.01）。３～５週齢の期間、糞中に小量の PCV2 が検出される子豚の数は、ワクチン接種母豚由来の子豚群がワクチン非接種母豚由来の子豚群より少なく、子豚の移行抗体の抗体価の高低と関連していた。実験期間中、重篤な PMWS 症状を示す接種子豚はいずれの群にも認められなかった。しかしながら、SPF 豚群での臨床スコアの上昇と PCV2 抗体の顕著な陽転ならびに全ての接種子豚の糞中への PCV2 の排泄から、この攻撃試験の有効性は認められた。ワクチン非接種母豚由来の子豚は攻撃後 PCV2 抗体価の上昇が認められたが、一方、ワクチン接種母豚由来の子豚では抗体価の減少が続いた。ワクチン接種母豚由来の子豚で攻撃後の PCV2 抗体価の上昇が認められないことは、移行抗体により付加された PCV2 感染に対する防御効果に関連すると推察される。解剖時、ワクチン接種母豚由来の子豚では、ワクチン非接種母豚由来子豚ならびに SPF 豚に比べ、肉眼病変スコアの顕著な減少が認められた（p＝0.0001）。全てのワクチン接種母豚由来の子豚では腸間膜リンパ節に肉眼病変は認められなかったが、一方、他の２群の70－80％の子豚では高～極めて高い病変スコアが認められた（p＝0.00043）。以上の結果により、野外農場での CIRCOVAC による母豚ワクチネーションは農場内の PCV2 の循環や哺育豚のウイルス排泄の抑制に対し有効性があるばかりでなく、PCV2 攻撃後の子豚の健康状態の改善に有効であった。

4.2　メリアルによるフランスとドイツでの野外有効性試験

　野外試用承認のもと、フランスの３つの PMWS 発生農場で18 ヶ月以上にわたる野外有効性試験が継続中である。２農場では、３週ごとに分娩する１群約35頭の母豚が７群、残り１農場では毎週分娩がある１群12母豚の22群が計画された。７群中の１ならびに２群、22群中１、３、５、７、９および11群がワクチン非接種群とした。残りの群には長期間にわたって分娩３週間前に CIRCOVAC の最小用量が１回ワクチン接種された。更新母豚は外部から導入され、試験期間中は導入前の検疫期間に２回ワクチン接種された。この接種により試験期間中にワクチン接種された豚は母豚の70％になった。繁殖豚群の血清学的な追跡調査以外に、第１～４群および１～12群の連続２回の妊娠から生まれた全ての子豚において PCV2 関連疾病の有無が出荷まで調べられた。ワクチン接種ならびにワクチン非接種母豚由来の全ての子豚の全期間に渡る大規模な比較試験が終了した。試験開始時、３つの農場の全ての母豚は PCV2 抗体陽性で、その12％に高い抗体価が認められた。ワクチンネーション後、56％のワクチン接種母豚が高い抗体価を持つと判断されたのに対し、ワクチン非接種母豚では７％のみであった。ワクチネーション後の繁殖豚群での PCV2 抗体価の上昇に伴い、PMWS 症例はこの18 ヶ月の期間に、農場選択時の５％以上の発症率からワクチン非接種母豚由来の子豚（4,183頭）で1.12％、ワクチン接種母豚由来の子豚で（10,462）0.67％と急激に減少した。以上の結果は、ドイツとフランスでの CIRCOVAC の暫定認可下の非常に大規模な試験によっても確認された。試験期間中、366,895頭の母豚がワクチン接種された。副作用報告は非常に限定されていた(4,300ドーズのうち１つの局所反応と44,000ドーズのうち１つの流産例)。ドイツでのいくつかの調査結果を例に挙げる。ドイツ全国にわたった13,992頭のワクチン接種母豚からの結果が含まれている。CIRCOVAC のワクチネーションの有効性は、主に以下のパラメーター；哺乳豚、離乳豚および肥育豚の死亡率ならびに農場での疾病防除に使用された薬剤使用によって解析された。死亡率は表４に記載した。一部の農場でのワクチネーション実施の遅れから、解析時点ではワクチネーション効果の完全な判定はまだである。しかしながら、哺乳豚で5.3％、肥育豚で３％と３つの肥育ステージでの死亡率の減少は顕著であった。これらの改善効果は農場に多大な利益を

もたらしている。結論として、死亡豚と削痩豚の発生数の著明な減少、より均一な発育、および抗生物質使用の減少という肯定的な結果が得られた。離乳から出荷までの全体の死亡率の減少は少なくとも、50%の農場で認められた。

結論

　実験室内ならびに野外試験成績から、PCV2感染に対するワクチネーションはPMWS発症を抑制する効果があることが立証された。子豚へのワクチネーションは移行抗体レベルが高くない限りコントロールされた実験室内レベルでは有効である。妊娠豚を含む繁殖母豚のワクチネーションは安全でコントロールされた実験室内レベルで有効であることが認められた。ワク

チネーションの有効性は、ワクチンが臨床的なPMWSの防除に経済的に適切なレベルであることを確かめる暫定認可のもとでの市販ワクチンを用いた繁殖母豚と妊娠母豚の大規模な野外有効性試験で立証された。他のPCV2関連疾病や症候群に対する防除におけるPCV2ワクチンの有効性に関してはさらに検討する必要があるが、繁殖母豚へのPCV2に対するワクチネーションは、出荷に至るまでの損耗を大幅に軽減することは注目に値する。この改善効果は、他の病原体の易感染化につながる野放しのPCV2感染によってもたらされる長期にわたる有害で、急性ないしは慢性の免疫抑制状態の改善と関連しているのであろう。

（翻訳：川嶌健司　動衛研東北支所）