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

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

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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.

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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 explain 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 upregulate 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.

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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。

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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ッガーや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ッガー

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。(Charreyre 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）