

Agent X as the cause of Postweaning Multisystemic Wasting Syndrome of pigs

The case for and against

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Debating the case for and against an unknown is somewhat daunting. What can be discussed is that the current pathogenesis for Postweaning Multisystemic Wasting Syndrome does not fit the clinical observations.

Introduction – hypothesis

The initial case of PMWS in 1991 in Canada was the eventual recognition of PCVII infection in the pig; not the European form of PMWS. This was picked up by veterinarians, largely in North America to form the basis of PCVII lesions in individual pigs and groups of pigs and was called PMWS. Meanwhile, a new condition with extremely high morbidity and mortality was recognised in France in 1994. This condition, was also referred to as PMWS. This PMWS has progressively spread worldwide, moving across Europe over an 8 year period. The condition jumped into Asia in 1990-2000 where it has spread reaching New Zealand. In 2004, the condition crossed the Atlantic to enter the North American industry and throughout 2005 and 2007 has spread West and South where it will eventually affect all of the North American Industry. South America has also started to report European PMWS in 2006. Australia remains free of European PMWS.

The cause of PMWS is not yet recognised. PCVII has been demonstrated to be globally ubiquitous and causes characteristic histological changes. PMWS potentiates the effect of resident secondary pathogens for example *Haemophilus parasuis* and PRRSv, it also potentiates the effects of PCVII. Thus weaner/grower PCVII lesions occur in cases of PMWS.

There are four clinical entities sharing the name PMWS – the initial Canadian experience, the European and subsequent Asian experience, the North American pre-2004 clinical picture and the North American post-2005 clinical picture. Each of these will be briefly examined in turn.

• Initial case report from 1991

Postweaning multisystemic wasting syndrome was coined in 1996 by Harding and Clark (1997) to describe a scenario occurring in Western Canada with an increase in mortality of 10% characterised with wasting and jaundice in 5-6 week old weaned pigs. The condition appeared to have originated on a single Saskatchewan herd in 1991. Similar clinical and histological findings were then seen in several high health herds in Western Canada (Clark, 1997 and Harding, 1997). They noted the similarities to another similar condition reported since 1994 in France, albeit the French condition was much more severe. This Western Canadian condition died out on the initial farm over a period of 3 years. Surrounding farms and other farms throughout North America reported similar problems, the issue effectively became part of the background disease scene, with PRRSv dominating the North American industry until 2005/6.

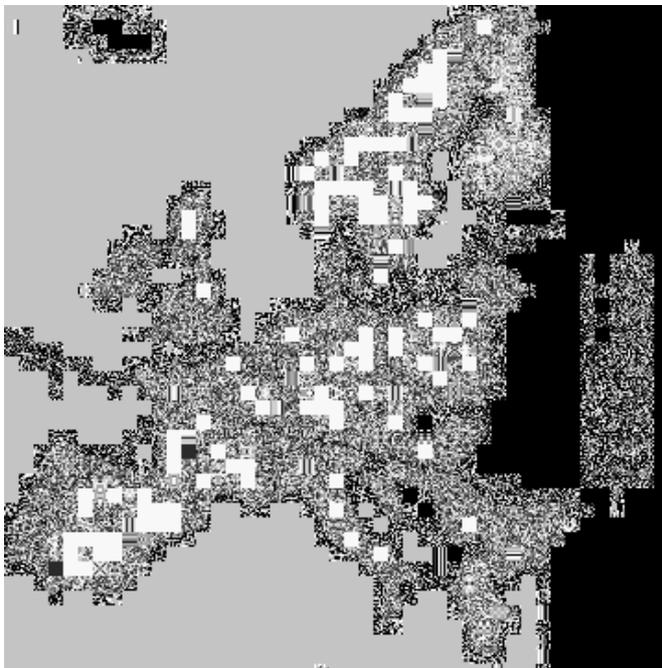
• Events in Northern Europe 1994 to today

In 1994 a condition was described in Brittany France with a significant rise in post-weaning mortality; this condition was described as Postweaning Multisystemic Wasting Syndrome. For the purpose of this paper this condition will be referred to as PMWSEu. This condition has subsequently spread around Europe. The clinical signs of PMWSEu cases seen by the author

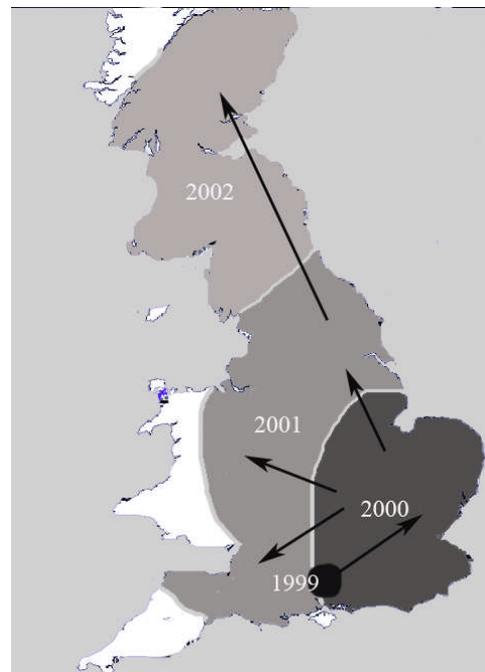
are extremely similar throughout Europe and Asia. Subtle differences are due to secondary pathogens where their clinical signs are superimposed on the underlying PMWSEu clinical case.

The spread around the UK was followed with particular personal interest as the condition started as a point source in 1999 in the south of England (possibly from Germany) and moved to the pig dense area of East Anglia with the movement of breeding stock. The condition spread slowly but persistently, spreading West and North throughout England despite a Classical Swine Fever outbreak. The FMD outbreak in 2001 slowed the spread of PMWSEu into Scotland, but after the movement restrictions were lifted in 2002, Scotland inevitably became positive. The condition is now spread throughout Great Britain. There are still isolated pockets of farms and breeding pyramids that are PMWSEu free.

As Northern European countries export pigs around the world particularly to Asia, the condition PMWSEu followed these animals, spreading rapidly and explosively through individual countries in Asia.



Spread of PMWSEu throughout Europe from 1994 to 2005



Spread around UK (Carr personal observations)

Broad clinical signs of PMWSEu in Europe

In the absence of a clear causal agent, there are four aspects that lead to an accurate diagnosis:

Clinical signs exhibited by the group of pigs

The **pathological signs** exhibited by the group of pigs

The **herd history** over 3 months

The epidemiological **history of the infected area**.

Clinical signs exhibited by the group of pigs with PMWSEu

The course of the condition can make definitive diagnosis difficult, initially. The major clinical signs are variable, depending largely on the secondary pathogens present on the unit. However, these are the prime clinical signs:

- The nursery pigs do well until 15 kg. Several producers actually comment that the pigs have never looked better.

- As the condition starts, many producers note that 60-70 kg pigs start developing an 'ileitis' which does not respond to treatment – either by vaccination or antimicrobial therapy.
- A couple of pigs 30 kg or more develop Porcine Dermatitis and Nephropathy Syndrome (PDNS). This is often dramatic with several pigs in a pen being affected. Note that sporadic (rare) PDNS should be considered normal.
- Increasing numbers of growing pigs 15-80 kg suddenly lose their body condition. The pigs lose weight rapidly, some within 4 days. The condition appears in a few pigs each day; these either die or are moved into the hospital pens. Males tend to be more affected than females and there is generally a litter effect.
- One characteristic of PMWSEu is that some pigs in the pen look normal whereas others are extremely emaciated.
- There is an increase in respiratory diseases in pigs less than 30 kg or an increase in digestive diseases in pigs older than 30 kg – this largely depends on the prevalent conditions on the farm
- The farm experiences a general increase in severity and frequency of secondary pathogens and their clinical signs. Diseases which have not been seen for several years reappear.
- There are no clinical signs in the adults and reproductive performance, litter size and pre-weaning mortality stays the same. Some farmers have reported an increase in coughing in the farrowing house.

The farm now has full blown PMWSEu

The occurrence of the disease occurred in many farms whether they had excellent or poor stockmanship. Breed type was not protective, although subsequent breeding with some lines of, (but not all), Canadian Hampshire and Pietrain's have proven somewhat protective in expression of clinical signs.

Pathological findings within the group of animals

PMWSEu is a disease of the lymphoid tissues with secondary lesions in the other major organs. Note PMWSEu cannot be diagnosed on postmortem findings only as these findings can be recognised on many farms without the clinical signs of PMWSEu.

Gross pathological findings which are commonly associated with PMWSEu but not seen in PMWSAm:

- PDNS becomes common in herds with PMWSEu, particularly in the early stage of the condition. Interesting the role of PCVII is controversial in cases of PDNS.
- Cardiac changes: Pericardial effusion often with a rounding of the heart – enlarged right ventricle – this may be the cause of the fluid around the heart and other organs. This is only seen on euthanased pigs immediately postmortemed.
- Colonic oedema in large amounts spreading around the colon and large intestine. This is also discussed in Clark's original paper (1997).

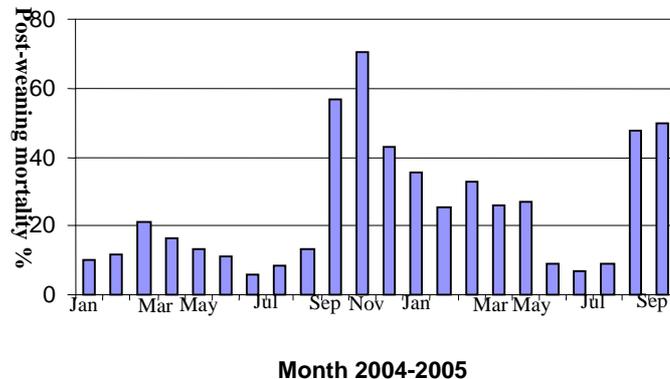
Histological examination of the enlarged lymph nodes reveal a characteristic lesion characteristic of PCVII infection.

Herd history over a 2 month period

PMWS is a disease that affects group after group. A single or even a couple of groups with wasting is not PMWS. Such pigs have occurred for as long as pigs have been farmed.

To give some indication of the severity of PMWS on a farm, the graph below indicates the post-weaning mortality numbers for a single farm.

Post-weaning mortality with PMWSEu by month



This case has been selected because it emphasizes the severity of PMWSEu on a farm's production and also illustrates the continual vulnerability of the farm if management falters as illustrated by the rise in late 2005

The epidemiological history of the infected area

Locality - The disease/syndrome spreads to closed units with high biosecurity within 2km.

Pig to pig movement - Pig to Pig movement is the premier source of infection. The movement of semen and gilts (or boars) from an infected farm has resulted in a spread of the clinical signs of PMWSEu.

Movement of unclean buildings/equipment – wooden weaner shelters were purchased from a clinically affected unit and moved to an isolated clean unit. The clean unit demonstrated clinical signs within 2 months.

Repopulation into a poorly cleaned farm - which was depopulated because of severe clinical signs. The unit was not thoroughly cleaned with clear evidence of faeces remained in the pens.

Other causes of wasting and high mortality in pigs in Europe

There are numerous other causes of wasting and high mortality in the pig. Of particular note is the condition –ill thrift syndrome (Carr and Done, 1994) which is associated with post-weaning starvation. It is very important that clinicians ensure that the “wasting” is present in 2-3 week weaned pigs (15kg plus) and not only in weaners who have failed to thrive post-weaning.

Once the cases of PMWSEu became more common, misdiagnosis through poor herd history and reliance on laboratory reports also became common. The histological findings even being reported in suckling piglets on farms without high post-weaning mortality.

PMWSEu negative herds in Europe and Asia

Several closed breeding pyramids in the UK, Ireland and South Korea have remained free of PMWSEu. All of these farms or pyramids are PCVII positive and have been pre 2000. By maintaining strict genetic biosecurity the farms have remained free of PMWSEu, excluding one farm within 2km of a confirmed case. These farms have supplied similarly PMWSEu negative herds and these herds have stayed negative until they broke genetic biosecurity.

Numerous PMWSEu positive herds have been repopulated from these PMWSEu negative sources following a detailed depopulation. The depopulation has been successful if strict biosecurity was maintained. The prevalence and incidence of PCVII pre depopulation and post-repopulation is the same.

- **Events in North America pre October 2004**

The condition described by Harding and Clark (1997), raised a great deal of interest. Increasingly similar cases were reported, largely based on pathological findings of “unusual” histological changes in lymphoid tissues. These changes were summarized by Sorden (2000) to provide North American practitioners with a working diagnosis of PMWS – which for the purpose of this paper will be referred to as PMWS*Am*.

Diagnosis of PMWS*Am* requires that a pig/group of pigs exhibit all of the following:

Clinical signs: Wasting/weight loss/ill thrift/failure to thrive, with or without other signs;

Histological lesions: Depletion of lymphoid tissues +/- lymphohistiocytic to granulomatous inflammation in any organ (typically lungs and/or lymphoid tissues, and less often liver, kidney, pancreas, intestine);

PCVII infection: Preferably via demonstration of PCVII antigen by immunohistochemistry (IHC) or genome associated with characteristic lesions by in-situ hybridisation.

This definition does not describe the clinical picture of PMWS*Eu* as seen in Europe. There is no requirement for any specific age group or significantly raised post-weaning mortality. Cases of PMWS*Am* were farm specific. Where PMWS*Am* was diagnosed, the condition tended to occur in older pigs – late grower early finisher 60-80kg. While wasting was seen in cases diagnosed as PMWS*Am*, after 5 years of working extensively throughout North America and the Mid West in particular, the author never reached a clinical diagnosis of PMWS*Eu*, despite local veterinarians and laboratory diagnostician’s diagnosis of “PMWS”. In all the cases of PMWS*Am* relatively simple management changes resulted in the resolution of the post-weaning mortality or wasting syndrome. While the diagnosis of PMWS*Am* was common at Iowa State University Diagnostic laboratory, these findings were not repeated at surrounding laboratories and even within ISU the results were contradictory. Cases of PMWS*Am* were confidently diagnosed on individual wasted animals on farms with no history of persistent herd mortality.

- **North American – October 2004 to today**

An explosive PMWS*Eu* clinical problem started in Quebec and Ontario at the end of 2004 and rapidly spread throughout the pig farms in both provinces. It is probable that once PMWS*Eu* was introduced and gained entrance into the common AI studs (with all breeding companies present) the disease was then rapidly disseminated throughout Eastern Canada. There have been some notable exemptions including closed family farms – for example Mennonite community pig farmers not using AI and only purchasing from their own family breeding companies. These farms have become islands of PMWS*Eu* freedom – a very similar picture to genetically biosecure farms in the UK and Korea. Weaned pigs from Canada were moved into the USA and a clinical picture of PMWS*Eu* was immediately recognized with mortality rates of 50% in the moved pigs. Subsequently, the disease has become more common in the Northern USA states and North Carolina, particularly when the major Canadian export state of Manitoba, which supplies the USA with pigs, became progressively infected in 2006.

The role of type 2 porcine circovirus

It has been demonstrated that Porcine Circovirus II, through the use of a DNA clone (Fenaux *et al.*, 2002) can reproduce the gross and microscopic lymphoid lesions of PMWS (Sorden definition). This was obtained by the use of a North American PCVII isolate (pre 2004). Similar work in France demonstrated the same results (Grasland *et al.*, 2005) using a European PCVII isolate.

PCVII is ubiquitous throughout the world and exists in all of the global pig industries. There are potential pockets of PCVII free pigs in isolated island communities – possibly Ossabaw Island Pigs, Georgia USA (Carr personal observations) and Auckland Island Pigs – New Zealand (Jaros *et al.*, 2006).

As PCVII is ubiquitous and can result in the hallmark lesions of PMWS on its own, it would be expected that these ‘hallmark’ lesions would be common in the normal pig population as they are reasonable easy to reproduce. The need to use cofactors to create Porcine Circovirus Associated Diseases (PCVAD) only replicate the real world where Parvovirus, Porcine Reproductive and Respiratory Syndrome virus (PRRSv) or *Mycoplasma hyopneumoniae* are extremely common/normal in any group of weaned/growing/finishing pig. Interestingly however, examination of numerous lymph nodes from PMWSEu negative pigs by IHC has not revealed PCVII presence or the lesions.

Individual Pigs

The hallmark lesions of PMWS have been found in individual pigs in North America associated with wasting, often with an ileitis like condition. These animals present at 60 kg with multiple enlarged lymph nodes. The subsequent pathology presents with all of the hallmark lesions of PMWS (Sorden 2000). These animals were not diagnosed as Porcine Circovirus Associated Disease (PCVAD) enteritis.

Groups of pigs on a farm

Individual groups of pigs can present with wasting and a higher than normal post-weaning mortality. Such conditions are not uncommon on pig farms and are generally related to repeated substandard management practices.

Postmortem examination reveals the multiple lymph node enlargement. There may be a range of other postmortem findings often associated with the degree of secondary pathogens present. However, PDNS, rounding of the heart and colonic oedema are not characteristic. Histological findings of the lymph node enlargement may reveal the characteristic lesions of PCVII (Sorden 2000).

Definition of PMWS by Sorden 2000.

The definition offered by Sorden 2000, described the local North American clinical form of PCVII infection, not European PMWSEu. Therefore, this case definition cannot be used as a basis of worldwide diagnosis of PMWS.

Differences in PCVII – a novel more virulent form?

Despite extensive investigation genetic differences between PCVII isolates from diseased and non-diseased pigs and areas demonstrate no specific differences. Currently North America is looking at the possibility of PCVIIb as a more virulent strain, but the evidence is not as yet convincing and also does not explain the pre2004 PMWSAm position. The “virulent” PCVII 321 RFLP is found on PMWSEu positive and PMWSEu negative farms in Eastern Canada. If there

is evidence of a virulent PCVII the previous US investigations only then describe the normal non-PMWSEu situation – it does not describe PMWSEu.

It is interesting that the current highly successful vaccines using PCVII against PMWSEu originate from North American pre2004 PCVII isolates – not the virulent “European like” PCVIIIB.

PCVII is also associated with a variety of other none PMWSEu conditions:

PCVII associated abortions/SMEDI – myocarditis of aborted fetuses - no reproductive effects seen in PMWSEu cases

PCVII enteritis – in enteritis cases – not a characteristic finding in PMWSEu cases

PCVII necrotizing pneumonia – not a characteristic findings in PMWSEu cases

Congenital tremor All – now generally believed to be unlikely to be even associated with PCVII – no increase in congenital tremor seen in PMWSEu cases

PDNS and PCVII but this is controversial. PDNS very rare with PCVII, common in acute PMWSEu cases – one of the founding clinical signs.

These other type 2 porcine Circovirus associated diseases (PCVAD) are not consistent in cases of PMWSEu. If PMWSEu was primarily associated with PCVII it would be expected that the full range of PCVII clinical entities would occur. For example PRRSv causes the full range of described reproductive and respiratory clinical signs, particularly in the acute forms, albeit in a variety of severities dependent on genetic type. Only after time are the clinical signs subdued.

PCVII Naïve pigs exposed to PMWSEu and PCVII

When pigs naturally naïve to PCVII (Jaros *et al.*, 2006) were exposed to groups of pigs with PMWSEu (and PCVII) and PCVII alone (no PMWSEu) – only the group exposed to PMWSEu became classically clinically sick. The group exposed to PCVII alone did not develop PMWSEu. In a similar paper from Denmark, PMWS negative pigs were exposed to potentially PMWS positive pigs at weaning (4-5 weeks). The PMWS negative pigs developed PMWS. The PMWS negative pigs which were not exposed to PMWS did not develop the condition. The presence of PCVII in PMWS negative pigs was not discussed (Kristensen *et al.*; 2006)

Depopulation and repopulation

There have now been a number of examples where depopulation followed by repopulation with pigs negative to PMWSEu have eliminated clinical PMWSEu. The prevalence of PCVII pre depopulation and post-repopulation was not altered. Several commercial attempts to eliminate PCVII by segregated early weaning have failed, although this technique can be used experimentally to produce small numbers of PCVII naïve animals.

Table 1

A list of differences* noted between different forms of “PMWS”.

Observation	Clark and Harding PMWS 1991-1997	North American “PMWS” pre 2005	PMWS European and Asian	PCVII On none PMWS farms	Canadian and USA PMWS post 2005
Sudden onset	Variable	Variable – on and off	Yes	Variable	Yes
Mortality	10%	Variable <10%	25-90%	8% (with other agents)	30%
Morbidity	20% Variable	Variable – low numbers	40-60%	10%	50-80%
Good pigs and sick pigs in same group		No-variable	Yes clear	Variable	Yes clear
Good pigs become thin rapidly	Yes	No	Yes	No	Yes
Pigs rapidly – within 4 days – lose enormous body condition and continue to eat	Not stated	No	Yes	No	Yes
Recovered pigs market reasonably normally	Not stated	No	Yes	No	Yes
PDNS	No	No – rare	Yes common	No	Yes common
Enlarged multiple lymph nodes	Yes	No (variable)	Yes	No	Yes
Histological changes described re PCVII	Yes	Yes	Yes	Yes	Yes
Presence of PCVII	Yes	Yes	Yes	Yes	Yes
Massive presence of PCVII	Yes	Yes	Yes	Yes	Yes
Spread lateral between farms	No	No	Yes	No	Yes
Spread by Pigs – AI/genetics	No	No	Yes	Present	Yes
Closed isolated farms can remain clinically negative		No	Yes	No	Yes
Each progressive group becomes sick	Not stated	No	Yes	No	Yes
Clinical signs in the next group of weaners moved to a clean farm	No	No disease seen in pigs	Moved pigs get sick	No disease seen in pigs	Moved pigs get sick
Affects multiple groups at the same time	Variable	Variable	Yes	No	Yes
Resolution with antibiotics	No	Variable	No	Variable	No
Resolution with simple management	Yes	Yes	No	Yes	No
Control with advanced management	Yes	Yes	Yes - difficult	Yes	Yes - difficult
PCVII Vaccine response		Yes	Yes (some)	Yes	Yes
Persistence	No	No	Yes 10 years	No	Yes (24 months+)
Effect of depopulation	Not stated	Variable No to PCVII	Yes – “negative stock”	No to PCVII	Unknown
Age group	5-6 weeks	Variable >60 kg common	15-70 kg	Variable – under 20 kg	>25 < 80kg
Affect on adults and reproduction	No	Suspected	No	No	No

Summary

Table 2
Agent X the cause of PMWS for and against

	Traditional PCVII	PMWS European
Epidemiology		
Ubiquitous	Yes	No
Global	Yes	No
Moves between farms	No	Yes
Moves like a new infection	No	Yes
Present in North America pre 2004	Yes	No
PCVII naive pigs develop PMWS	No	Yes
Age group	All	20-70 kg
Other specific conditions	Yes	PDNS
PDNS	No (v. rare)	Yes (common)
Clinical signs ameliorated by		
Management (basic)	Yes	No
Antibiotics	Variable	No
Genetics	No (mild)	Yes
Pathology		
Lymphoid depletion	Yes	Yes
Histiocytic changes	Yes	Yes
PCVII Antibodies indicative	Yes	No
PCVII concentration indicative	Yes	Variable
Treatment/control		
PCVII protective	No	No
PCVII dead vaccine protective	Yes	Yes
Depopulation control	No	Yes
Biosecurity affects clinical signs	No	Yes

Conclusion

PMWS is a disease syndrome that results from a unique single organism whose action on the immune system releases type 2 porcine Circovirus on the 20-70 kg pig. This organism originated in commercial pigs in Brittany France in 1994 (possibly from the wild pig population) and has spread globally primarily following the movement of commercial pigs.

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