



BREEDING-HERD VACCINATION

REACHING NEW HIGHS FOR
PCV2 PROTECTION
IN SWINE

LITERATURE REVIEW



REACHING NEW HIGHS FOR **PCV2** PROTECTION IN SWINE



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L I T E R A T U R E R E V I E W



Although vaccinating for porcine circovirus type 2 (PCV2) and associated diseases has become standard practice in commercial swine herds, the disease still remains an economic threat to most production systems.

Research indicates that if properly managed, vaccinating the breeding herd will help achieve higher levels of control — without worrying about vaccination interfering with maternally derived antibodies in baby pigs.¹

Furthermore, our market research indicates that swine veterinarians throughout the world are routinely vaccinating breeding herds for PCV2 to provide additional protection against this ubiquitous virus. For example:

- In the US, **one-third of the veterinarians surveyed** said they were already vaccinating sows at least once a year — usually with one dose — but 23% opted for two doses or more.²
- More significantly, **20% of the US veterinarians** told us they expected to increase frequency of sow vaccination, and another 25% said they would do the same in gilts. It is clear that there is a growing interest in expanding PCV2 vaccination.³

AN INDUSTRY FIRST

My veterinary colleagues and I recently collaborated on this report with the hope of helping the pork industry achieve a higher level of PCV2 control through ongoing management and vaccination protocols that will consistently produce low-incidence piglet populations from breeding farms.

Our research team has also been busy, conducting additional safety studies using our two PCV2 vaccines in pregnant and lactating sows. As a result of their efforts, Foster[®] Gold PCV MH and Foster[®] Gold PCV are now **the only PCV2 vaccines with a USDA-approved claim for “safe for use in pregnant sows and gilts.”***

For more information, please contact your local Zoetis technical services veterinarian.

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* As of March 2022. Always check the vaccine's label for specific indications.

¹ Poulsen Nautrup B, Van Vlaenderen I, Mah CK, Angulo J. Do high levels of maternally derived antibodies interfere with the vaccination of piglets against porcine circovirus type 2? A literature review and data analysis. *Vaccines*. 2021 Aug 19;9(8):923. doi: 10.3390/vaccines9080923.

² Result Report: Americas PCV/MH Tracker Wave 1. 2020 July. Zoetis Market Research.

³ Ibid.



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1

Introduction: A higher level of PCV2 control is possible

PCV2 remains almost universally present in production systems even though vaccination has become standard commercial practice. It may be possible to achieve higher levels of PCV2 control with ongoing management and vaccination protocols to produce low-incidence pig populations.

Porcine circovirus type 2 (PCV2) is usually described as ubiquitous in modern swine production. PCV2-free herds are rare and generally atypical in location and/or management practices.

Piglet vaccination is standard commercial procedure and is generally successful in preventing PCV2-associated disease and sub-clinical depression of growth. Vaccination of breeding animals is also common, both to reduce possible adverse effects of PCV2 on reproduction and to further enhance control in growing pigs.

Despite these practices, however, the virus remains almost universally present in production systems, with low levels of PCV2 viremia a common finding in successfully vaccinated pigs on well-managed farms.

Nevertheless, the incidence of PCV2 has fallen markedly since the initial epidemic, as shown by the comparison of the 2006 and 2012 National Animal Health Monitoring System surveys (Dvorak et al. 2016). The authors attributed the decline to vaccination and speculated that it might eventually lead to PCV2 elimination from the US herd.

ELIMINATION IMPRACTICAL

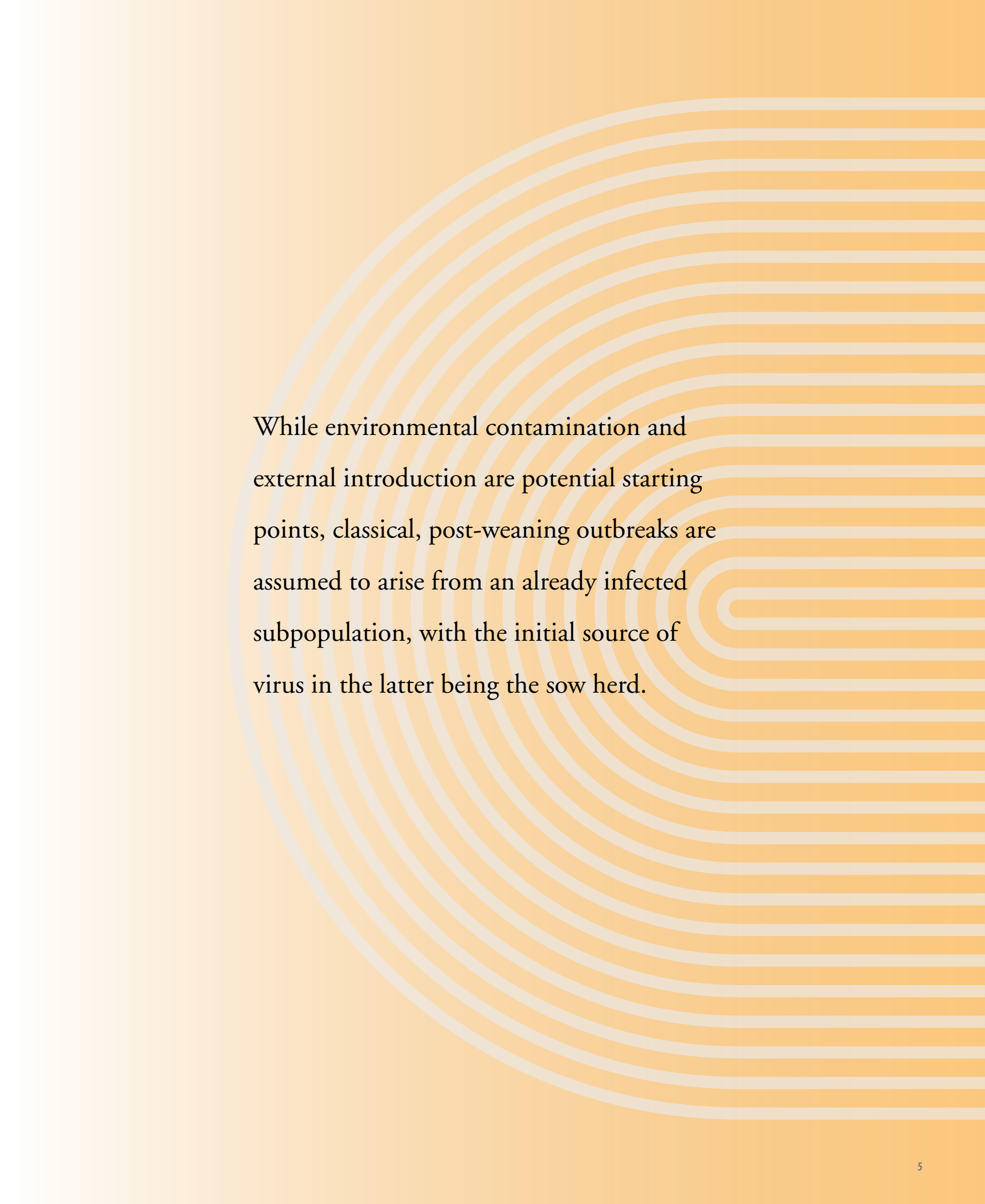
Although PCV2 elimination is considered impractical with current vaccines (Afghah et al. 2017), it remains true that some sites and pig flows can at times appear PCV2 negative, showing that a very high level of control is possible.

In modern, multi-site production systems, pigs are reared after weaning as isolated groups of similar age, with easy spread of pathogens within the group but limited opportunity for external introduction. PCV2 is a contagious virus with most transmission assumed to be by oronasal exposure among pigs in close contact with each other.

The R_0 , or basic reproduction number, is an indicator of the contagiousness and transmissibility of an infectious disease and has been calculated for PCV2 in pigs within a pen as 8.9 while the R_0 for between pens is 1.2 (Andraud et al. 2008). The figures are not based on extensive work, and this report includes alternatives based on different assumptions and mathematical models. The important point is that they are sufficient to ensure virus circulation within a barn.

PCV2 EPIDEMIOLOGY

The traditional view of PCV2 epidemiology is that, in the absence of active immunization, the virus will spread through a group of growing pigs once the population-level protection from maternal immunity declines to a point that will permit it. While environmental contamination and external introduction are potential starting points, classical, post-weaning outbreaks are assumed to arise from an already infected subpopulation, with the initial source of virus in the latter being the sow herd.

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2

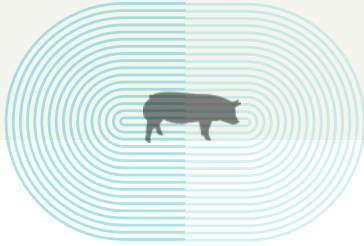
PCV2 infection results from virus exposure and the ability to resist infection

Animal-to-animal virus transmission and the ability to resist infection are main factors that affect incidence of PCV2 infection in weaned pigs, along with residual environmental contamination and introduction from fomites. Beyond reducing viral transmission and contamination, stimulating protection through maternally derived, specific immunity is an important factor in limiting PCV2 incidence in young pigs.

The level of PCV2 infection in a group of weaned pigs will depend on both virus exposure (think breeding-herd vertical transmission) and the pigs' ability to resist infection if exposure occurs. Both aspects have subcomponents.

Table 1. Factors influencing the incidence of PCV2 infection in piglets

| EXPOSURE | RESISTANCE |
|--|--|
| Vertical transmission → <i>in utero</i> /colostrum/sow contact | Innate → genetic susceptibility, general health |
| Horizontal transmission → pig-to-pig in shared environment | Passive immunity → quality and quantity of colostrum |
| Environmental contamination → residual infectious virus | Active/acquired immunity → vaccination or exposure |
| New introduction → brought in via staff/fomites | |



2.1 Exposure of piglets to PCV2

Vertical transmission from sow to piglets, including *in utero* and from colostrum and milk, is well proven by experimental studies (Park et al. 2005; Ha et al. 2009; Madson et al. 2009; Ha et al. 2008; Gerber et al. 2011; Shen et al. 2010; Dvorak et al. 2013; O'Neill et al. 2012; Baker et al. 2011; Tully et al. 2014; Vennekotter et al. 2019; López-Lorenzo 2019; Patterson et al. 2011a; Patterson et al. 2011c).

Differences in sampling technique and assay methodology almost certainly account for some of the differences between the studies cited, but it does seem that a high incidence of vertical transmission is now unusual. It can occur where the PCV2 status of the sow herd is unstable, but it is no longer typical

However, this does not necessarily mean that the sow herd is no longer the primary source of infection for growing-pig populations on average farms. A low level of vertical transmission may still be sufficient to seed an eventual outbreak in unprotected animals, although perhaps taking longer to develop. Most growing-pig populations are protected by vaccination, but testing usually indicates that the virus is present at a low level.

STABLE VIRUS

Although animal-to-animal transmission — vertical or horizontal — is assumed to be the most common route of

continued

Six interesting observations about PCV2

- 1 Studies demonstrate the potential for pre- and peri-natal transmission; they provide no indication of importance in commercial conditions.
- 2 In commercial herds, studies have produced widely different estimates of the extent of *in utero* vertical transmission, with large between-herd differences and a general reduction over time.
- 3 It is important to note that cases of no viremic piglets born are possible when sows are serologically negative (Shen et al. 2010).
- 4 Another report states that there was no statistically significant effect of sow viremia on piglet viremia, but qualitatively piglets from viremic sows showed a wide range of viremia levels, whereas those from non-viremic sows were usually low or undetectable (Dvorak et al. 2013).
- 5 North American studies from the first decade of this millennium recorded very high levels of pre-natal transmission. In the most recent decade (2010s), a lower prevalence compared to earlier surveys was noted, and it was suggested that widespread vaccination of pigs in general might be reducing the prevalence of the virus (O'Neill et al. 2012). This was speculation based on only two farms, but work done since has shown a similar pattern (Baker et al. 2011; Tully et al. 2014; Vennekotter et al. 2019).
- 6 However, a complete contrast to the earlier US vertical-transmission results is also provided by two European studies that showed very low prevalence of PCV2 in 20 German and four Dutch sow farms (Eddicks et al. 2016; Dieste-Pérez et al. 2018).

PCV2 infection results from virus exposure and the ability to resist infection

PCV2 transmission, the virus is very stable and easily isolated from farm environments. Dvorak et al. (2013) found high levels in empty farrowing rooms, although infectivity was not confirmed. Concentrations were decreased but not eliminated by cleaning and disinfection.

López-Lorenzo et al. (2019), working in Spain, also found widespread contamination including in farm areas remote from the animals, probably linked to the high levels found in samples from farm workers, especially their boots.

In experimental work looking at the efficacy of disinfection protocols in model trailers artificially contaminated with PCV2-containing feces (Patterson et al. 2011a), piglets exposed to unwashed, untreated trailers became infected, while those exposed to the cleaned and disinfected trailers did not, although PCV2 DNA was still detected by polymerase chain reaction (PCR).

DIFFICULT TO QUANTIFY

Given these facts, it is logical to think that infection from residual environmental contamination, or introduction on fomites, must be a significant risk to a naïve population, but it is difficult to quantify.

A PCV2 outbreak in a closed, PCV2-free, specific-pathogen-free herd supplying pigs to Iowa State University was considered likely to have arisen from contaminated equipment or people (Patterson et al. 2011c), but this is the only clear example of such transmission found. There are other reports of virus recrudescence after a period of negative samples (Feng et al. 2014; Martelli et al. 2016), but the source has not been identified.

As will be discussed later, PCV2 causes persistent infection with intermittent shedding even in the presence of an apparently normal immune response, including circulating neutralizing antibodies. This makes it difficult to eliminate undetected pig infection as the cause of a herd breakdown.

PCV2 transmission from pig to pig (oronasal) and from dam to piglet (via colostrum and milk) are common. Given the stability of the virus, residual environmental contamination and introduction on fomites should also be considered risk factors.

2.2 Resistance of piglets to PCV2

Whether pathogen exposure results in infection — and whether it's the duration and severity of any infection if one occurs — depends on a piglet's resistance. For completeness, non-specific factors such as general health and genetic susceptibility should be kept in mind (breed differences have been shown for PCV2 by Lopez-Soria et al. (2011) and others), but in the context of this booklet and PCV2 incidence in piglets at weaning, it is the protection provided by maternally derived, specific immunity that is important.

There is no doubt that colostral immunity, usually measured as antibody but potentially also including transferred cells, will protect piglets from PCV2 infection. Relatively early work by McKeown et al. (2005) showed that this was titer dependent, although a specific cut-off was not identified.

The principle is also well illustrated by the fact that PCV2 vaccine-efficacy studies cannot be conducted in piglets

with maternally derived antibodies (MDA) until levels in non-vaccinated controls have declined to the point where a challenge can be successfully administered.

EARLY WORK IN SOWS

One of the first PCV2 vaccines on the market targeted sows and aimed to extend the period of passive protection in piglets by increasing colostral antibody. Opriessnig et al. (2010a) demonstrated protection in piglets challenged at 8 weeks of age from vaccinated sows.

Passive immunity can provide resistance to infection, provided piglets ingest sufficient colostrum of adequate quality. A generally high level of MDA will thus limit animal-to-animal spread pre-weaning. It will not, however, eliminate infections that are already present (Seo et al. 2014), and piglets infected *in utero* will remain a potential source of virus as the group ages.

It's important for veterinarians to remember that high levels of MDA may reflect active infection in the sow herd, which may itself be associated with a higher proportion of piglets being born viremic.

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3

Dynamics of PCV2 infection and immunity in individual animals

Persistent infections can occur with many pathogens, but reappearance has been linked to waning immunity or antigenic shifts. With PCV2, it is possible for circulating virus and neutralizing antibodies to co-exist in individual pigs. Vaccine-induced immunity may provide greater protection against subsequent viral challenges than existing immunity.

Control of infection at the herd level must consider the behavior of the virus in individuals. Despite decades of work, there are still many unknowns about PCV2, but two key points are the **persistence of infection** and the **incompleteness of some aspects of immune protection**.

In growing pigs, long persistence has been reported by many, from 69 days after experimental infection and confirmed by bioassay to 209 days (Patterson et al. 2011d) following natural exposure (Patterson et al. 2011b).

Previously infected pigs can also test negative for viremia for up to 7 weeks before returning to positivity (Opriessnig et al. 2010b). These same pigs were also tested by pen-based oral fluids and remained consistently positive up to the end of monitoring 98 days post-infection, despite concurrent presence of antibody (Prickett et al. 2011). Sample types matter!

PERSISTENT INFECTIONS

Persistence of infection in sows is less well studied, but sows infected at 56 days of gestation had PCV2 DNA in their colostrum after farrowing, including animals that had been vaccinated pre-challenge and that had mounted an immune response (Madson et al. 2009).

The paper by Dvorak et al. (2013) has already been mentioned as finding a high level of sow infection and vertical transmission, despite the presence of immunity. The overall results led the authors to suggest that PCV2 infection was lifelong, and this could indeed be true, at least in some animals. The fact that viremia (or at least detection of viremia) becomes intermittent makes it practically impossible to confirm elimination of infection and explains why viremic piglets can be born to apparently non-viremic sows.

The persistence of infection is linked to the fact that immunity to PCV2 is not sterilizing. Antibody, including neutralizing antibody, does not always prevent infection nor does it eliminate existing infection. The following quote from Dvorak et al. (2018) summarizes a point made by several authors: "The simultaneous presence of circulating antibody, neutralizing activity and PCV2 virus is perplexing and has not been satisfactorily answered."

Persistent infections can occur with many pathogens, but reappearance is often linked to waning immunity or some sort of antigenic shift. With PCV2, it seems to be possible for circulating virus and neutralizing antibody to co-exist, which is unusual but not unique. The same has been reported for chick anemia virus (Brentano et al. 2005), which is also a circovirus. Note that this does not mean that neutralizing antibody is not useful. It has been clearly linked to protection from clinical disease and reduces viremia even if it does not eliminate it (Fort et al. 2007).

Understanding PCV2 epidemiology and immunology

The following key points are relevant to the subsequent discussion on opportunities for PCV2 control and elimination:

- 1 **Vertical transmission** from sow to piglet, either *in utero* or after birth, can be very common but has become markedly less so in the past 10 years, with a high incidence now being unusual.
- 2 **Horizontal transmission** is usually among pigs in close contact. Given the stability of the virus, residual environmental contamination and introduction on fomites could also be risks, and the latter has been reported, but the significance cannot be quantified.
- 3 **PCV2 causes long-lasting infection.** An effective immune response protects from disease but, in the timeframes studied (up to 209 days), does not result in viral clearance. Viremia and shedding may, however, become intermittent.

SUCCESSIVE CHALLENGES

The fact that some of the pigs described in Opriessnig et al. (2010b) were re-challenged has already been mentioned. Following identification of PCV2a/PCV2b co-infected pigs in field surveys, an attempt was made to produce such animals by successive challenges.

One group was inoculated with PCV2a at 11 weeks of age, PCV2b at 16 weeks, PCV2a again at 21 weeks, and PCV2b again at 26 weeks. Low levels of PCV2b DNA were found in serum samples from two of six pigs at the final sampling at 31 weeks of age but not in any previous samples.

One possible explanation is that the immune response generated by the initial infection, while not able to clear that infection, was more successful in preventing a second infection by a new strain.

MORE-COMPLEX EXPERIMENTS

The above theory is consistent with the results of a much more complex experiment conducted by Seo et al. (2014)

where piglets naturally infected with PCV2a or PCV2b were challenged with PCV2b or PCV2a, so allowing differentiation of the original infecting strain from the subsequent challenge strain in later samples. Some groups were also vaccinated prior to challenge using either a PCV2a-based or PCV2b-based vaccine (SLCD adjuvanted Foster Gold PCV and an experimental vaccine, respectively).

Both vaccines produced neutralizing antibody and cell-mediated immune (CMI) responses, despite the presence of moderate MDA. Neither, however, resulted in clearance of existing infections — homologous or heterologous — but both reduced colonization by a subsequent challenge strain, compared to non-vaccinated but already viremic controls.

Vaccine-induced immunity therefore provided greater protection against the latter than existing immunity, which could have been maternally derived or actively stimulated by the initial infection (the study did not differentiate).

4

Opportunities for PCV2 elimination

To fully prevent vertical transmission, a sow herd would need to remain free of PCV2, requiring a way to identify carrier sows or the use of differentiating vaccines. Non-pig sources, including contaminated farm environments and fomite introductions, also limit the ability to eliminate PCV2.

4.1 Theoretical considerations

Piglet resistance to infection is important, but the fact that colostrum intake and quality are variable and that passive immunity to PCV2 is not sterilizing even if present mean total prevention of exposure is a requirement if PCV2-free piglets are to be reliably produced from a sow farm.

One major unknown is the true duration of infection and the risk that long-term carriers pose to others, including their offspring. The early epidemiology work would suggest that many, or even all, sows infected early in life remain carriers capable of producing viremic piglets. Unfortunately, carrier sows were also not reliably identified using available tests, probably due to viremia being intermittent, at least at a detectable level.

PREVENTING TRANSMISSION

To fully prevent vertical transmission, a sow herd would have to be kept free of PCV2, which would require a way

to identify carrier sows. Based on the literature reviewed, it seems likely that seronegative sows can be reasonably assumed to be virus free, although this is not proven, and obviously very recent infection cannot be excluded. Even if confirmed, however, this has limitations as a practical means of identification. Sows might be positive from vaccination rather than infection, and avoiding vaccination, even when young, could create an undesirably vulnerable population.

A DIVA vaccine — differentiating infected from vaccinated animals — would allow the differentiation of sows only positive through vaccination from those that had been infected, whether also vaccinated or not. Dvorak et al. (2016) attempted to do this in their survey work by testing for antibodies to PCV2 replicase (only expected from the presence of replicating virus) as well as to the more usual capsid protein. This is a possible approach, but the procedure is not well validated.

The second major unknown is the risk of exposure from non-pig sources, either a contaminated farm environment or external introduction. Overall, a theoretical consideration of the available background information points out areas of vulnerability but does not give a clear answer on the feasibility of elimination.

4.2 Practical experience

The possibility of PCV2 elimination can also be assessed empirically, by looking at practical experience. For use in research trials, Opriessnig et al. (2004) obtained PCV2-negative piglets from six PCV2-positive herds by segregated early weaning (10 to 12 days of age) of piglets

The early epidemiology work would suggest that many, or even all, sows infected early in life remain carriers capable of producing viremic piglets.

from sows that were either seronegative (S:P ratio < 0.2) or of relatively low titer, which were generally a minority of those tested. The sow-selection procedure probably excluded most persistently infected animals, but the apparently high success of the approach still seems surprising given other epidemiological data.

Patterson et al. (2011c) attempted to derive negative gilts from a farm that had recently broken with PCV2 (already mentioned as the example of likely fomite transmission) by off-site isolation of female piglets that tested negative at 13 days of age, but this proved unsuccessful with 100% of the 15 animals eventually being found to be positive. In this case, however, it is likely that the piglets came from infected sows and were carrying the virus despite the negative test.

A PCV2-free herd was eventually re-established on the original site by depopulation, an extremely rigorous cleaning and disinfection protocol and repopulation with naïve animals from another herd 63 days later. The farm was small with only 38 breeding animals, so while the decontamination procedure was apparently successful, it cannot be seen as a practical model for larger, more-commercial units. It may have been more than required, but there is no evidence to confirm this.

ERADICATION ATTEMPTS

Feng et al. (2014) attempted to eradicate PCV2 from a 390-sow, two-site Spanish farm (breeding plus nursery with separate, continuous-flow finishing) using intensive vaccination. Prior to the start of the study, sows had been routinely vaccinated pre-farrowing and piglets half-dosed.

There was no history of porcine circovirus associated disease (PCVAD), but PCV2 was clearly present with both virus-positive pigs and rising titers evident in samples from finishers.

During the 12-month elimination program, all gilts, sows and boars were blanket vaccinated every 4 months. Piglets were vaccinated at 4 and 7 weeks of age with a full dose on each occasion. Blood samples for PCV2 PCR and serology were taken monthly from 15 sows and 90 piglets (15 at each of 4, 8, 12, 16, 20 and sometimes 24 weeks of age), but not all were analyzed.

Over the full study — which comprised the 2 months prior to the vaccination campaign, the 12 months of intensive vaccination, and the 6 months following the campaign during which PCV2 vaccination was stopped — nine groups of piglets were tracked longitudinally with monthly samples, and cross-sectional surveys were done on seven occasions.

All sow samples were PCR negative throughout the study, but positive samples were obtained from growing pigs both before and during the early stages of the vaccination campaign. In the latter half of the vaccination phase, all samples from all ages were PCR negative, and rising titers in finishers were not observed, implying possible virus elimination.

continued

Opportunities for PCV2 elimination

POSITIVE SAMPLES FOUND

Following the end of vaccination, however, positive samples were again found, together with evidence of recent seroconversion in finishers, indicating PCV2 circulation. No new animals had been introduced to the farm, and the authors considered failure to completely clear the virus the most likely explanation for the recrudescence. They did not comment on whether this might be persistence within animals or the farm environment.

As part of a field study on MDA interference, Martelli et al. (2016) also used a sow and piglet vaccination regimen over a prolonged period. Starting as gilts, sows were vaccinated every cycle at time of mating. Piglets were vaccinated at either 4, 6 or 8 weeks of age. Elimination was not the objective, but the following is a quote from the paper: "In an almost one year and a half period of observation in the field conditions of this study, PCV2 infection was undetectable for a certain period of time (two replicates) and suddenly re-appeared without any evident or expected reason."

4.3 Conclusion on PCV2 elimination

Unfortunately, the available information does not allow a firm conclusion about the possibility of PCV2 elimination. It seems that the prevalence in a herd can be driven to low

levels relatively easily — happening almost naturally if there is consistent application of an effective vaccination program and obvious risks, such as those posed by incoming gilts, are well managed.

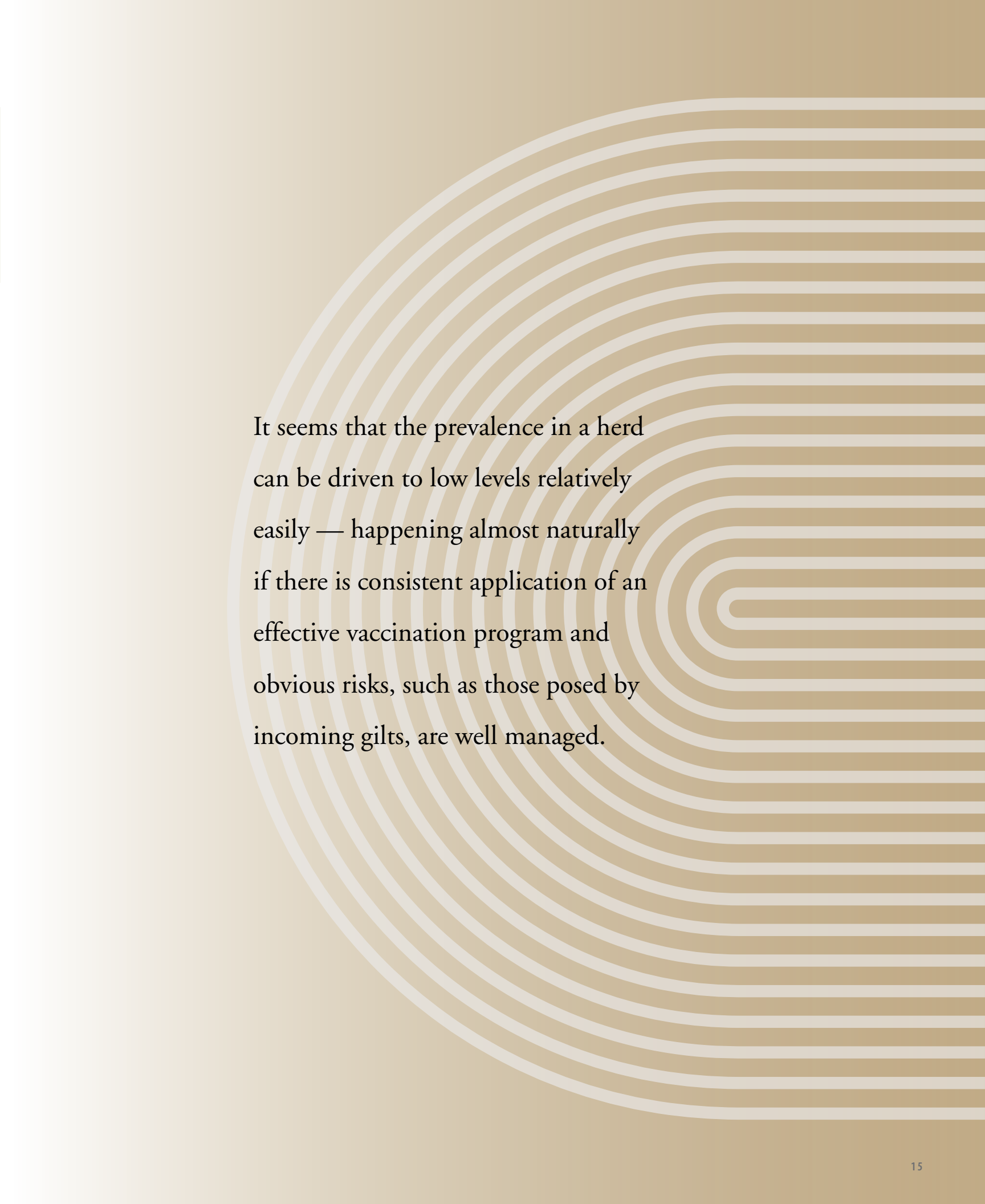
Nevertheless, elimination is a step beyond this and requires stamping out the very low level of infection that still seems to occur. Whether the ultimate source for this is maintenance within the population, environmental contamination or external introduction is not clear, and it may be that all three are possible.

NO REPORTS OF SUCCESS

In the end, it is probably significant that there are no reports of successful, long-term PCV2 elimination in commercial farms. Anecdotally those that stopped vaccination in apparently PCV2-free herds usually saw the virus appear after a relatively short period, similar to the experience of Feng et al. (2014).

This is not to say that elimination is impossible, and it may be that relatively simple additional procedures would be sufficient, but these have not been identified. Without better background knowledge, it is impossible to design a protocol that promises a high chance of success, and as vaccination is effective in controlling losses, there is little motivation to proceed.

MDA INTERFERENCE
PCV2 ELIMINATION?
CONSISTENCY

The background of the slide features a series of concentric circles on the left side, which transition into a series of horizontal stripes on the right side. The colors are in shades of beige and light brown.

It seems that the prevalence in a herd can be driven to low levels relatively easily — happening almost naturally if there is consistent application of an effective vaccination program and obvious risks, such as those posed by incoming gilts, are well managed.

5

Consistent production of PCV2-negative piglets

The consistent production of PCV2-negative pigs, which can be actively immunized against future viral challenges, requires PCV2-negative sows. However, maintaining a low-prevalence sow herd requires limiting virus introduction and limiting virus spread if introductions occur. Maintaining protective immunity in the sow herd through vaccination will not only positively affect the sows but also their offspring.

As mentioned previously, even if elimination is not achieved, farms can reach a state where PCV2 prevalence is extremely low. Without actual elimination, maintaining such status requires on-going control measures, and absolute absence of PCV2 in weaned piglets cannot be guaranteed, but consistent production of (almost) PCV2-negative batches seems to be possible.

If such piglets are then actively immunized to protect from future challenge, there should be no opportunity for PCV2 to have a negative impact on production, thus achieving a higher level of control.

NEGATIVE SOWS ARE KEY

The main requirement to produce negative piglets from a sow farm is negative sows. The main requirements for maintaining a low-prevalence sow herd are limiting virus introduction and limiting virus spread if (when) introductions occur. While there may be other routes of infection, the highest risk for new virus is likely to be replacement gilts. The major influence on spread will be immunity, which in a largely negative herd will reflect vaccination.

In principle, replacement gilts should be free of PCV2 and have high immunity, so that they represent neither a source of virus nor a pool of vulnerable animals to multiply virus already present. As discussed already, guaranteeing freedom may be difficult, but the chances should be maximized if the gilts come from a low-prevalence source and are vaccinated early before infection is acquired.

Maintaining protective immunity in the sow herd is potentially more complicated. Sow vaccination will not only affect the sow but also the piglets, perhaps requiring changes to the vaccination protocol for the latter. It is, therefore, discussed in detail in the next section.

The main requirement to produce negative piglets from a sow farm is negative sows. The main requirements for maintaining a low-prevalence sow herd are limiting virus introduction and limiting virus spread if (when) introductions occur.

Vaccination of sows

High levels of vaccine-induced immunity in sows should prevent, or reduce, losses from PCV2-associated reproductive disease, as well as extend the duration of passive immunity provided to newborn piglets through colostrum and reduce vertical transmission from sows to piglets.

6.1 Protection against PCV2-RD

PCV2 infection in sows has been linked to abortion and stillbirths, with presence of lesions and PCV2 in fetal tissues. Infection earlier in pregnancy has been associated with return to estrus, probably following embryonic death due to virus infection of the embryo (Segales et al. 2019).

A high level of vaccine-induced immunity would be expected to prevent (or at least reduce) such losses, but no vaccine has a licensed claim relating to PCV2 reproductive disease (PCV2-RD), there is no proven challenge model, and evidence of a benefit from field use is mixed.

Two papers have reported challenge experiments after sow vaccination. While both showed reduction in sow viremia compared to non-vaccinated controls neither showed an advantage in reproductive parameters (Madson et al. 2009; Hemann et al. 2014). Both studies were small, and the results probably reflect the limitations of the experimental designs.

Three recent publications described field trials prospectively designed to look at the impact of vaccination on reproductive performance in breeding herds with confirmed

continued

Three possible benefits of sow vaccination

1

Protection of sows from PCV2-related reproductive disease (PCV2-RD)

2

Protection of piglets through provision of maternal immunity

3

Protection of piglets through reduction in exposure to virus from the sow herd.

Although these are closely linked, and in real life it may be impossible to separate the effects of the last two, they will first be discussed separately.

6

Vaccination of sows

presence of PCV2 but no specific diagnosis of PCV2-RD. Oliver-Ferrando et al. (2018) compared 94 vaccinated sows with 97 non-vaccinated sows and showed a statistically significant improvement in liveborn per litter (15.42 versus 14.16) and piglet vitality index⁴ in the second cycle, partly due to numerical (non-significant) reductions in stillbirths and mummies.

MIMICKING SOW-HERD VACCINATION

The same research group recently published a second paper (Pleguezuelos et al. 2021), vaccinating different groups of sows at different stages (pre-mating, mid-gestation, late gestation) in order to mimic the effect of a blanket sow-herd vaccination.

Comparing the combined vaccinated groups to non-vaccinated sows, there was a significant improvement in mean birthweight (1.64 kg versus 1.58 kg), with the difference still being significant at weaning. There were also numerical improvements in total born (14.1 versus 13.6) and liveborn (13.4 versus 12.9) per litter.

In contrast, Cybulski et al. (2020) found no reproductive benefit from sow PCV2 vaccination (538 sows in three experimental groups) conducted on a 3,200-sow farm, with one of the vaccinated groups showing the highest numerical incidences of stillborn, mummified and weak piglets.

Rather than differences in vaccine efficacy, the results of the above studies probably reflect between-farm differences in the reproductive impact of PCV2. The debate around the significance of PCV2-RD is still fluid.

It seems reasonable to assume that vaccination will prevent PCV2-RD losses if they are occurring, but most farms do

not have a significant PCV2-RD problem. However, there may be unrecognized, on-going reproductive losses in breeding farms that are unstable for PCV2, over and above those from more obvious outbreaks that are investigated and diagnosed.

6.2 Protection of piglets through provision of MDA

Sow vaccination, not surprisingly, will increase MDA, which, in turn, should extend the duration of passive protection provided.

Overall, any PCV2 sow-vaccination program is likely to have some effect on the level of maternal antibody transferred to piglets. At the population level, it should both increase the duration and reduce the variability of the MDA protection provided.

The effect will be maximized if the vaccine is given a few weeks before farrowing and if the vaccine chosen has an adjuvant that promotes an adequate serological and CMI response. The potential complication of increased MDA is possible interference with the active immunization of piglets.

It is clear that at least the serological response to vaccination can be inhibited, but the evidence shows that protective immunity may still be induced. A 2022 literature search to understand if high levels of MDA interfere with vaccination of piglets against PCV2 concluded that vaccination of piglets is effective with respect to production parameters and viremia even in the presence of high MDA, with an age of 3 weeks at vaccination being most beneficial (Poulsen Nautrup et al. 2021).

continued

⁴ The piglet vitality index is a four-point scoring scheme developed in Europe to assess the strength and vigor of a piglet. It is similar to the APGAR score used in human medicine (Schodl et al. 2019).

What we know about MDA (in a general sense)

Interference from maternally derived antibodies (MDA) appears to be possible with all types of vaccine, and it predominantly affects the serological response. Priming for an anamnestic antibody response and generation of cell-mediated immunity (CMI) may both still occur in conditions where antibody formation is inhibited, although higher levels of MDA may also suppress priming.

CMI development appears to be normal even in the presence of MDA, although occasional failures have been reported, predominantly with live vaccines.

Several mechanisms have been suggested for this, and it is possible that more than one may be involved, depending on the type of vaccine. It is likely that the way the immune system manages the transition from passive to active protection is a highly evolved process, and that the selective suppression of antibody formation, but not other aspects of the immune response, is optimal for survival under natural conditions, where the value of immune protection must be balanced against the metabolic cost of producing it.

VACCINE TRIALS

At the individual level, most animals in vaccine trials can be classified as serological responders or non-responders, implying a switch effect at a certain MDA threshold. Although not well supported by published data, it appears likely that variation among individuals for a given disease and a given vaccine, and assuming a reliable assay, will normally be low enough to estimate a threshold that can be applied at the population level. Unfortunately, however, the result will be disease and vaccine specific.

Antigen/antibody ratio is important, and increasing antigen mass can meaningfully raise the threshold at which interference occurs. There are examples of doubling being successful in field use, but no general rules to predict quantitative impact can be identified, which would likely be highly dependent on circumstances.

BROADER DEFINITION OF MDA

Nearly all research in this area refers to MDA, but the broader definition of maternally derived interference includes cells, cytokines, complement proteins and corticosteroids, all of which are also transferred to neonates. Some antigen-specific, vaccine-interference effect from the first cannot be ruled out but has not been identified. The others could well influence vaccine responses in the first weeks or days of life but probably in a non-specific way.

Any effects on protection will depend on the pathogen and the relative importance of antibody-mediated and cell-mediated immunity.

SEROLOGICAL RESPONSE:**Impact of MDA on immune responses to PCV2 vaccination**

Multiple authors have shown that MDA can inhibit serological responses to PCV2 vaccination (Opriessnig et al. 2008; Feng et al. 2016; Martelli et al. 2016; Fort et al. 2009). However, vaccination can still induce memory and priming for an anamnestic antibody response in conditions where initial production is inhibited by MDA.

Having said that, the study by Opriessnig et al. (2008) did find an increase in titer within 1 week of an experimental challenge in MDA-positive pigs that showed no evidence of a post-vaccination response, although one was seen in MDA-negative pigs. There seems no reason to doubt the fact that B-cell memory for PCV2 can be induced in the presence of MDA interference, and the assumption does not seem to be challenged, even though it is not well-proven in the literature.

Although it is assumed that priming can occur under conditions of high MDA, it is still believed that very high levels of MDA might inhibit it, probably because researchers have observed instances where this seems to have occurred. Again, however, although probably correct, no specific study or analysis could be found that conclusively proves the point or identifies a possible threshold.

6.3 Protection of piglets through reduction in PCV2 exposure from the sow herd

The importance of vertical transmission, particularly *in utero* and peri-natal, was already discussed. Piglets may become infected before they ingest colostrum, and such infections are not cleared, or not necessarily cleared, by subsequent colostrum intake or active immunization. Although much less common than it was, a high level of vertical transmission may still be found in specific herds, and even a low level may be significant as a source of virus in batches of weaned pigs.

A review by Lehman et al. (2020) suggested that unstable sow herds with high vertical transmission were a common cause of apparent vaccine failure in growing pigs, with piglets already viremic at the time of vaccination. They also commented that in their experience testing of young pigs for viremia did not reliably identify infected animals.

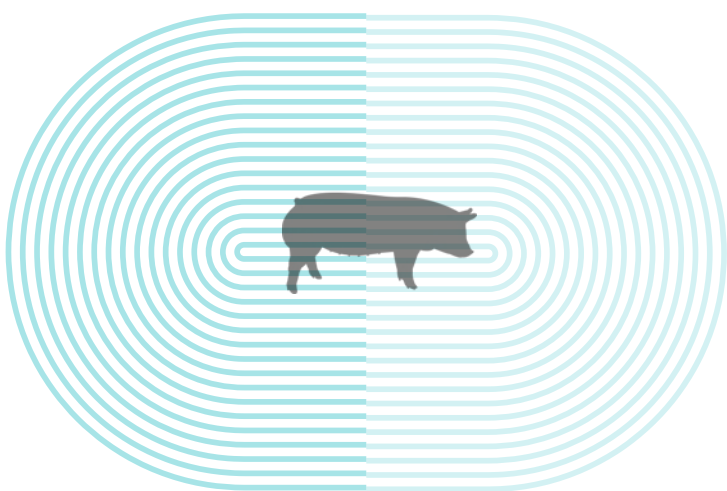
UNSTABLE SOW HERD

In an unstable sow herd, vaccination could theoretically do two things: It could protect uninfected sows or gilts from becoming infected, and it could reduce vertical transmission from already infected animals to their piglets.

As discussed already, vaccination against PCV2 will not eliminate an existing infection. Dvorak et al. (2013) found high proportions of viremic sows and piglets in both vaccinated and non-vaccinated herds, as did Gerber et al. (2012) in a much smaller study, but at that time it was likely that many sows had become persistently infected much earlier in life.

Dvorak et al. (2013) also found no correlation between vaccination and the level of sow viremia, which might have influenced transmissibility, but Gerber et al. (2011), comparing naturally infected sows from vaccinated and non-vaccinated herds, did find that vaccination was associated with significant reductions in both the proportion of sows shedding virus into colostrum and milk and the viral load present.

O'Neill et al. (2012), in two, within-herd comparisons of vaccinated and non-vaccinated sows, found that vaccination reduced the proportion of positive piglets from 30.2% to 15.4% ($P < 0.001$) in the one herd with an appreciable incidence. The reduction in vertical transmission found by O'Neill et al. (2012) could have resulted from either or both of the theoretical mechanisms described above, and the same applies to similar anecdotal reports. Overall, it does appear that sow vaccination will reduce sow-to-piglet transmission, although not to zero, and the success rate may depend on the proportion of the herd already infected.



CMI RESPONSE:

Impact of MDA on immune responses to PCV2 vaccination

It is well-established that CMI can play an important role in protection against PCV2, including viral clearance (Fort et al. 2009), and that both the capsid and replicase proteins are targets (Fort et al. 2010), which is an important consideration for vaccines that can (subunit) or are most likely to (inactivated) only stimulate immunity against the former.

Many of the available vaccines have been shown to induce CMI (Oh et al. 2014; Jeong et al. 2018; Koinig et al. 2015; Fort et al. 2009; Martelli et al. 2011).

Key points to remember about MDA interference include:

- 1 MDA can interfere with serological response to PCV2 vaccination.
- 2 Establishment of “immunological memory” is less sensitive to MDA interference than primary Ab response.
- 3 CMI is equally important for PCV2 protection. CMI develops even in the presence of high MDA.
- 4 PCV2 vaccine appears to be efficacious in conditions of high MDA, including those where a serologic response wasn't seen.

7

Intensive vaccination/hyperimmunization

Intensive vaccination through repeated vaccinations against PCV2 may raise immunity to exceptional levels, but feedback mechanisms may limit beneficial effects at an individual level. At the herd level, repeated doses may move the group toward a tighter distribution around a higher mean antibody titer with fewer vulnerable, low responders.

A final strategy worthy of mentioning is “hyperimmunization” or “intensive vaccination.” The terms are often interchangeable, but to give more precise definitions, intensive vaccination simply describes the administration of multiple doses of vaccine, more than the number normally used, whereas hyperimmunization more specifically refers to an enhanced immune response, usually at the individual level.

The latter may not capture herd-level benefits from intensive vaccination, such as greater homogeneity, and need not be linked to vaccination: It describes the presence of abnormally high levels of antibody, and in the human medical literature is often linked to undesirable effects ranging from autoimmune disorders to excessive reactions to insect bites.

CLASSIC EXAMPLE

A classic example of deliberately induced hyperimmunization is the production of snake antivenoms in horses:

Animals are repeatedly administered small doses, sometimes with adjuvants, to stimulate high antibody titers, which are then harvested and processed for potential use in people (World Health Organization 2017).

Whether repeated vaccinations against PCV2 will raise immunity to exceptional levels is unknown. There are feedback mechanisms that eventually limit antibody production (e.g., FcγRIIB-receptor-mediated signaling, see Niewiesk (2014)), and long-term studies where sows have received repeated vaccinations have shown antibody titers plateauing (Martelli et al. 2015) or even declining (Feng et al. 2014), although the latter may be due to a change in commercial vaccine used.

IMPACT OF INTENSIVE VACCINATION

Fortunately, the impact of intensive vaccination at the herd level is easier to consider. Individuals in a group will always show a range of vaccine responses, with many of those at the lower end due to temporary factors that may not affect a subsequent dose.

Individuals may reach a plateau, but theoretically at least, repeated doses should still move the group toward a tighter distribution around a higher mean, with progressively fewer vulnerable, low responders. This is the usual objective of intensive vaccination, for example, as practiced for porcine reproductive and respiratory syndrome management.

The principle holds true for PCV2, and in the previously mentioned paper by Martelli et al. (2015), the initial vaccination raised the mean antibody titer and reduced the coefficient of variation compared to non-vaccinates. Subsequent doses, however, gave little further improvement,

which is probably not surprising as a law of diminishing returns would be expected.

Although the principle is clear, a review of the published literature does not give clear guidelines on when to do what. In describing an approach to problem herds, Lehman et al. (2020) recommend starting with two blanket vaccinations of the sow herd 4 weeks apart and then maintaining immunity with vaccinations every cycle, or once or twice a year on a blanket basis.

Cessation of detectable shedding and resolution of downstream problems were said to usually occur after 3 to 5 months. This, however, was in the context of problem solving rather than elimination. Whether a longer period of more intensive vaccination would achieve more is unknown.

Fortunately, the impact of intensive vaccination at the herd level is easier to consider. Individuals in a group will always show a range of vaccine responses, with many of those at the lower end due to temporary factors that may not affect a subsequent dose.



Overall assessment of sow vaccination

In principle, sow vaccination should reduce vertical transmission while extending passive immunity until piglets can develop active immunity from their own vaccination.

Control of PCV2-RD stands on its own as a potential benefit of sow vaccination. It may be the primary justification if a sudden PCV2-RD problem is diagnosed (in which case the timing of introduction may well coincide with the natural resolution of the problem), but the impression is that it is more often perceived as a secondary reason where the primary motivation is improved control in growing pigs.

Sow vaccination on its own is rare, and most producers, mainly in Europe, eventually found that it failed to adequately protect pigs in finishing. There are many reports, however, of combining both sow and piglet vaccination as an approach to overall PCV2 control.

Pejsak et al. (2010) found that sow plus piglet vaccination in a PCVAD-affected farm gave superior production results, as measured in average daily gain (ADG), than either on its own, but the comparisons were across batches and could have been influenced by many other factors.

MORE TRIALS

A much better, prospectively designed field trial was conducted by Fraile et al. (2012), where 476 piglets were divided into four well-balanced treatment groups, with piglets from vaccinated (V) and non-vaccinated (NV) sows being either V or NV themselves, with the final groups designated V-V, V-NV, NV-V and NV-NV, respectively, with the first designation referring to the sow.

Sows were vaccinated pre-mating and piglets at 4 weeks of age with the same vaccine. The V-V group had a significantly lower incidence of PCV2 viremia at 12 weeks of age compared to all other groups, although at later time points it was not statistically different from the NV-V group. It also had the highest overall ADG, although only significantly different from NV-NV, and again the NV-V group did well, suggesting that piglet vaccination was the most important component, at least on this farm. A further analysis of the same trial data (Fraile et al. 2015) tends to confirm this.

In contrast, the study by Opriessnig et al. (2010a), with experimental challenge at 8 weeks of age, included groups comprising vaccinated piglets from vaccinated sows. There was no apparent advantage from the combined regimen, but this was probably to be expected in a study where the pigs were kept PCV2 negative early in life.

NO HEAD-TO-HEAD COMPARISONS

Although no other head-to-head, within-herd comparisons could be found, sow and piglet vaccination is quite common in some countries, and in two recent herd surveys (Lin et al. 2020; Wozniak et al. 2019), conducted in Taiwan and Poland, respectively, significantly higher levels of PCV2 control (lower

Sow vaccination on its own is rare, and most producers, mainly in Europe, eventually found that it failed to adequately protect pigs in finishing. There are many reports, however, of combining both sow and piglet vaccination as an approach to overall PCV2 control.

viremia) were associated with sow and piglet vaccination rather than piglet only, but some farms had good control with piglet only, and the results do not allow any conclusion about cause and effect.

In Taiwan, some farms were vaccinating pre-farrow and others as a blanket vaccination twice a year. All farms in the survey used the same PCV2 vaccine in growing pigs at somewhere between 2 and 4 weeks of age, with no apparent delay if also using sow vaccination. In contrast, Wozniak et al. (2019) reported that most farms vaccinating sows delayed piglet vaccination to 6 weeks, and from anecdotal reports this seems to be common practice.

NO CLEAR ANSWER

As with many aspects of PCV2 control, there is still no clear answer on how much sow vaccination aids control in piglets. In principle, it should reduce vertical transmission and, through provision of MDA, early-life horizontal transmission, resulting in fewer piglets being infected before they can develop active immunity from a piglet vaccine. Already-acquired infections will not be cleared by vaccination, but vaccination may still reduce any ill effects that they cause.

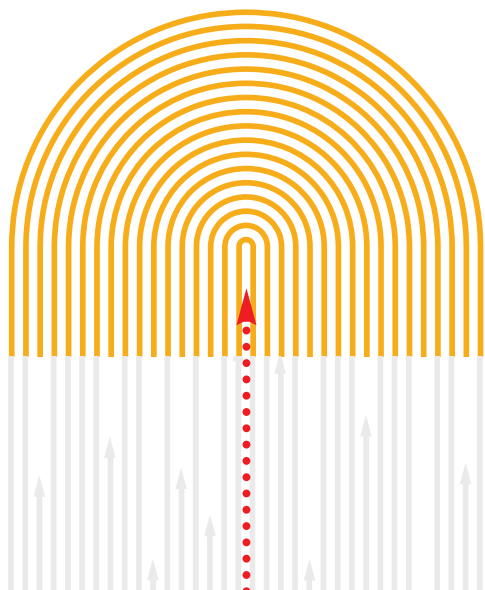
In the early days of PCV2 vaccination, the vaccines were judged as spectacularly successful, even though many piglets were presumably viremic when vaccinated. Having said this, however, reducing the incidence will still represent a higher level of control, which in principle is a good thing, and sow vaccination should provide direct benefits if actual losses from PCV2 are occurring in the early post-weaning period, which is perhaps most likely if there are both infected and low-MDA piglets in the population.

PRAGMATIC APPROACH

Taking a pragmatic approach, finding evidence of a low level of PCV2 infection in pre-wean piglets, perhaps in routinely monitored samples such as processing fluids, is probably normal and not a cause for concern.

Sow vaccination in such circumstances would provide insurance but probably no immediate return. A high or rising level of infection, however, should be a concern, and in today's environment of generally low incidence, would be justification for instituting sow vaccination, probably on a blanket basis. In problem herds, starting by vaccinating the herd twice with a 4-week gap has been recommended (Lehman et al. 2020).

As already mentioned, MDA interference is not proven but is a concern; there is no hard evidence that it is necessary to delay piglet vaccination, but it is equally not well proven that it is not. Higher MDA should provide protection during the longer pre-vaccination phase, so the downside is inconvenience.



9

Sow vaccination recommendations

Research and field experience have yielded clear goals and specific recommendations for whole-herd vaccination programs for managing PCV2 and associated diseases.

The previous chapters presented the good science and rationale for vaccinating breeding herds for PCV2.

Together with this information and field experience, the US swine technical services team of Zoetis developed the accompanying recommendations for vaccinating gilts, sows and piglets.

Veterinarians should check their PCV2 vaccine's label for usage guidelines and whether the vaccine has been shown to be safe for use in breeding females.

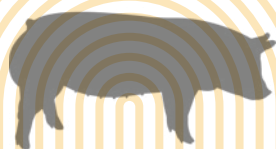
PCV2 VACCINATION:

Three goals in the breeding herd

1 Consistently produce negative or very low-incidence piglet populations from breeding farms.

2 Protect pigs through reduction in PCV2 exposure from the sow herd.

3 Combined sow and pig vaccination is superior.



RECOMMENDATIONS:

IDEAL VACCINATION PROTOCOLS

GILTS

(MINIMUM)



A split-dose vaccination protocol administered at 3 and 6 weeks of age



A full (2 cc) booster dose 2 weeks prior to entry to the breeding herd

SOWS

Routinely vaccinating sows has been shown to limit risks associated with PCV2 viremia. Consider these two options:

1

Ongoing sow vaccination (PREFERRED)

-➤ Regular whole-herd
-➤ Rolling vaccination
 - Administration to sows between weaning and late gestation

2

Vaccination in the face of disease (LESS DESIRABLE)

-➤ Whole-herd vaccination in the face of clinical PCV2 issues downstream

PIGLETS

The gold standard for piglet vaccination is a split-dose protocol at two critical times.*



Weaning



3 weeks later

Important: Single-dose protocols should be implemented only if key risk factors are not a concern — e.g., suspected instability, low individual pig wean age, disease coinfection.

* The optimal choice of the dosing regimen, including age at time of vaccination, will depend on farm circumstances. Each farm/producer should consult with a veterinarian of its choice. Field experience with PCV2 vaccines indicates that waiting until 3 weeks of age to initiate a split-dose regimen may yield a better immune response, even though the vaccine is safe when given at a younger age.



Additional insights from Zoetis swine veterinarians

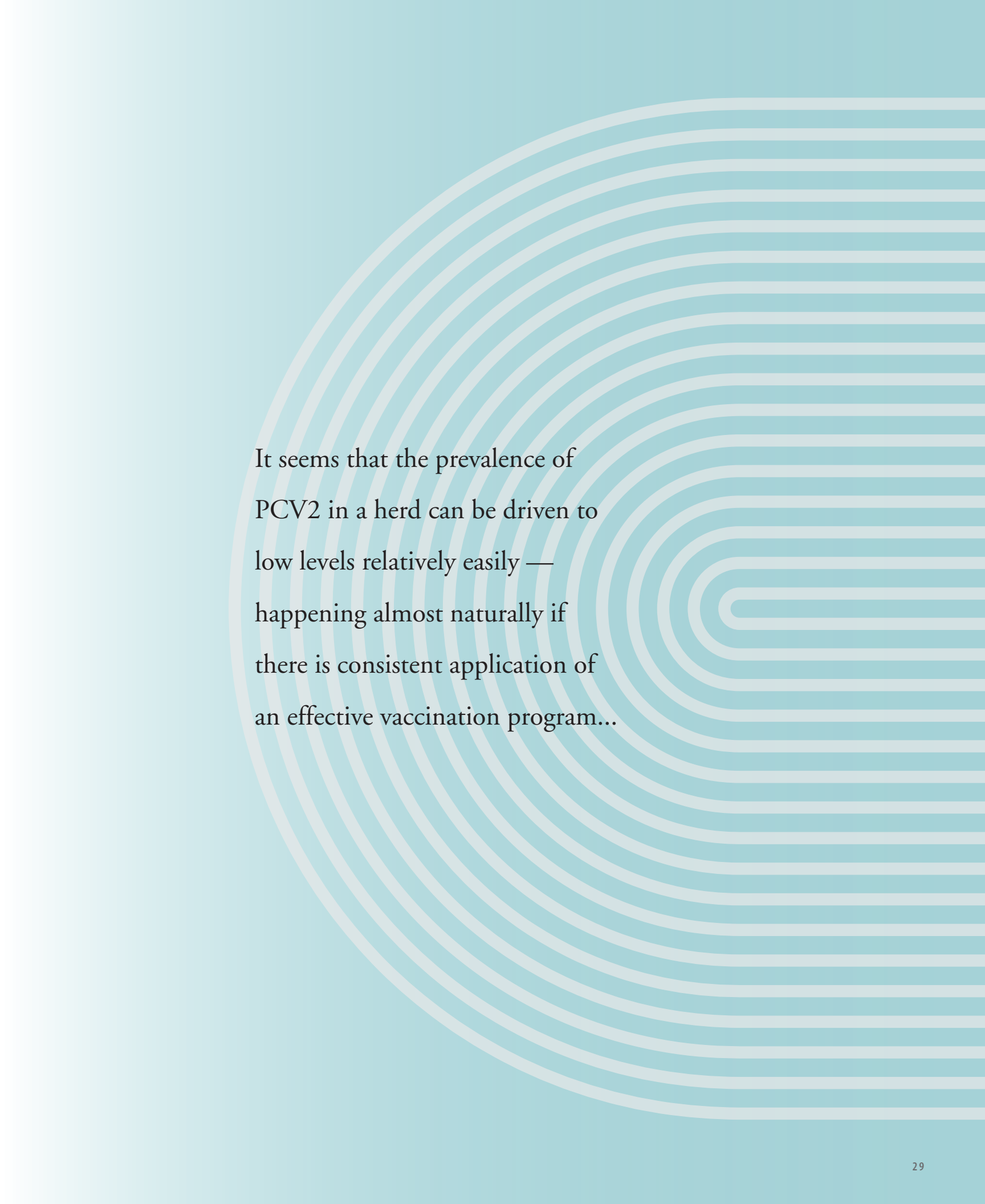
Risk of a non-vaccinated sow herd is much greater than the risk of MDA interference in the growing-pig population. Stated another way, a high level of control at the breeding herd level is possible, with consistent production of negative pigs.

Regular sow-herd vaccination will help achieve this goal, but if gilt management is good — that is, if gilts are free of the virus and immune at introduction — sow vaccination provides insurance.

Field experience suggests that a direct, disease-control impact will be seen only in unstable sow herds with virus circulation — a situation where reproductive performance benefits also might be obtained in sows, depending on the herd.

It seems that the prevalence of PCV2 in a herd can be driven to low levels relatively easily — happening almost naturally if there is consistent application of an effective vaccination program and obvious risks, such as those posed by incoming gilts, are well managed.

Experience suggests that farms that stop vaccination in apparently PCV2-free herds usually often see the virus appear after a relatively short period, similar to the experience of Feng et al. (2014).

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It seems that the prevalence of PCV2 in a herd can be driven to low levels relatively easily — happening almost naturally if there is consistent application of an effective vaccination program...

