

Porcine Respiratory and Reproductive Syndrome Virus Vaccinology: A Review for Commercial Vaccines

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ABSTRACT

Porcine Reproductive and Respiratory Syndrome (PRRS) since its appearance in Europe in the early 1990's has resulted in tremendous economic losses. Under field conditions vaccination is one of the most efficient strategies for the prevention and control of PRRS. The aim of this study is to perform the PRRSV vaccinology regarding current status of commercial vaccines in Europe. There are two types of PRRSV commercial available vaccines in Europe: Killed Virus (KV) or inactivated vaccines and Modified-Live Virus (MLV) or attenuated vaccines. EU KV commercial vaccines provide limited efficacy due to the weak stimulation of the immune system and no effective induction of neutralizing antibodies. However, KV vaccines can induce a strong Cell Mediated Immune (CMI) response. On the other hand, commercial EU MLV vaccines provide effective strain-specific protection, only partial protection against genetically heterologous PRRSV and elicit relatively late humoral and CMI responses which lead to delayed protection. In Europe, the KV vaccination prove to reduce the negative effects of PRRSV in breeding herds, improving their reproductive performance, e.g., increase of farrowing rate and number of live or weaned pigs, reduction of premature farrowing rate, abortion rate and number of mummified and stillborn piglets. The use of commercial MLV vaccines in PRRSV-infected breeding herds leads to improvement of: (a) reproductive performance e.g., reduction of the abortion and return to oestrus rate and increase of the farrowing rate and number of weaners, (b) the viraemic status, morbidity and mortality rate of piglets and (c) the growth performance of vaccinated pigs. In conclusion, nowadays the use of MLV or KV vaccines in Europe is the most economical tool to control the economic losses of PRRSV infection. However, the development of more efficacious PRRSV vaccines is the significant future goal for PRRSV vaccinology.

Key words: Vaccine, Inactivated, Killed Virus (KV), Cell Mediated Immune (CMI), Porcine Reproductive and Respiratory Syndrome (PRRS), Modified-Live Virus (MLV)

1. INTRODUCTION

Porcine Reproductive and Respiratory Syndrome (PRRS) since its first report in the late 1980s in Western Europe (Wensvoort *et al.*, 1991) and North America (Keffaber, 1989) has caused a significant economic impact on the global swine industry (Neumann *et al.*, 2005). The aetiological agent of PRRS is an RNA virus (PRRSV) of the order Nidovirales, family Arteriviridae, genus Arterivirus. PRRSV strains are divided into two genotypes, the Type I or European (EU) type and Type II

or North American (NA) type. Type I, with the prototype Lelystad Virus (LV), has a predominant spread on Europe, while Type II with the prototype ATCC VR2332, represents strains isolated on the American continent, as well as in Asia (Wensvoort *et al.*, 1991; Meulenber *et al.*, 1993; Murtaugh *et al.*, 1995; Nelsen *et al.*, 1999; Mateu *et al.*, 2006). According to the recent reports for PRRSV classification, Type I is divided into 3 subtypes: a pan European subtype 1 and East European subtypes 2 (Stadejek *et al.*, 2002; 2006; 2008; Toplak *et al.*, 2012). Among them, the subtype 1

was further divided into 12 different clades (Stadejek *et al.*, 2008; Shi *et al.*, 2010a). For Type II, 9 well-defined lineages have been described (Shi *et al.*, 2010a; 2010b). Both NA (Kapur *et al.*, 1996; Goldberg *et al.*, 2000; Key *et al.*, 2001) and EU (Indik *et al.*, 2000; Oleksiewicz *et al.*, 2000; Forsberg *et al.*, 2002) genotype strains are antigenically and genetically highly distinguishable. Nowadays, a coexistence of the two genotypes has been reported in Europe, North America and Asia, complicating the diagnosis, prevention and control of disease (Dewey *et al.*, 2000; Ropp *et al.*, 2004; Fang *et al.*, 2007; Balka *et al.*, 2008; Amonsin *et al.*, 2009).

PRRSV causes reproductive failure in breeding herd and respiratory disease in growing/finishing pigs (Zimmerman *et al.*, 2006). While the severity of the disease can be variable depending on the particular strain of PRRSV that infects the herd, all strains are capable of causing reproductive failure in the breeding herd e.g., increased premature farrowing and late term abortion rate, poor farrowing rate, mummified fetuses and stillborn piglets as well as respiratory disease, characterized by elevated mortality and decreased growth performance in piglets and growing/finishing pigs (Chung *et al.*, 1997; Cho and Dee, 2006).

Vaccination belongs to the most predominant strategies for the prevention and control of economic losses caused by PRRSV. The purpose of this present study is to perform the PRRSV vaccinology regarding current status of commercial PRRS vaccines in European market.

1.1. PRRSV Vaccinology in Europe

The vaccination is considered a crucial measure for the prevention and control of PRRS infection. It is also the most economic strategy for all sizes of pig farms i.e., small, medium and large) compared with other control strategies. There are two types of PRRSV commercial available vaccines in Europe: Killed Virus (KV) or inactivated vaccines and Modified-Live Virus (MLV) or attenuated vaccines.

1.2. KV (Inactivated) Vaccines

Inactivated PRRSV vaccines are used for the immunization of breeding herd. Information about vaccination schedule of available commercial inactivated PRRSV vaccines in Europe are summarized in **Table 1**.

Their main advantage is safety, as the vaccine virus cannot transmit to other pigs and cannot revert to virulence. Field studies reported that the KV vaccines did not induce reproductive failure in vaccinated sows and gilts (Plana-Duran *et al.*, 1997; Joisel *et al.*, 2001;

Papatsiros *et al.*, 2006). However, their efficacy has been frequently questioned. The capacity of KV vaccines induce a protective immunity against challenge with wild-type virus has been questioned. Kim *et al.* (2011) reported that the KV vaccination did not elicit detectable Virus-Nutralizing (VN) antibodies and provide weak memory responses with sequential challenge (Kim *et al.*, 2011). It also barely elicits strong Cell Mediated Immune (CMI) response as determined by lymphocyte proliferation and IFN γ production in recall response (Bassaganya-Riera *et al.*, 2004; Piras *et al.*, 2005). The KV vaccination of PRRSV-positive pigs results in an increase of VN antibodies and CMI responses, 2 weeks after the revaccination, providing significant protection (Kim *et al.*, 2011; Bassaganya-Riera *et al.*, 2004). Studies with commercial KV vaccines indicated that the vaccination did not induce VN antibodies and did not sufficiently protect against viremia or prevent from the clinical signs of PRRS (Nilubol *et al.*, 2004; Scorti *et al.*, 2007; Zuckermann *et al.*, 2007). However, the long term use of a commercial KV vaccine under field conditions resulted in a remarkable improvement of reproductive performance in breeding herd, without VN antibodies induction (Papatsiros *et al.*, 2006). On the contrary, studies with experimental KV vaccines reported induction of VN antibodies and decrease of the viremia duration (Misinzo *et al.*, 2006; Vanhee *et al.*, 2009).

The first KV vaccine in European market was Cyblue® (Lab. Ford Dodge). Studies with this vaccine had shown conflicting results about its efficacy, such as beneficial effects on reproductive performance of vaccinated sows (Plana-Duran *et al.*, 1997) or weakness to prevent viremia nor to avoid transplacental infection in vaccinated gilts exposed to PRRSV at the time of conception (Prieto *et al.*, 1997) or no effect on reproductive performance of vaccinated females in comparison to unvaccinated ones (Scorti *et al.*, 2007). However, nowadays, there are four commercial available KV vaccines in Europe (**Table 1**). Field studies with some of these nowadays commercial available KV vaccines reported that the vaccination has beneficial effects on reproductive performance and litter characteristics of vaccinated sows in PRRSV-infected farms, where PRRSV circulate among breeding animals (**Table 2**). In particular, the KV vaccination proved to reduce the negative effects of the PRRSV on the breeding herd with persistent PRRSV infection and high seroprevalence, improving their reproductive performance, e.g., increase of farrowing rate, number of live or weaned pigs and reduction of premature farrowing rate, abortion rate and number mummified and

stillborn piglets (Joisel *et al.*, 2001; Papatsiros *et al.*, 2006; Papatsiros, 2012a). The beneficial effects of vaccination with KV vaccines can reduce the culling rate due to reproductive failure, resulting in a significant improvement of longevity and number of non-productive days in the vaccinated breeding herd (Papatsiros, 2012a). However, the KV vaccination in naive animals, fails to prevent reproductive losses and congenital infection in foetuses (Scortti *et al.*, 2007).

The use of inactivated PRRSV vaccine should be administered on a regular basis for obtaining the maximum beneficial effect, as it has been observed that the higher the degree of immunization of sows, the better the improvement of their health status and reproductive performance (Papatsiros, 2012b). In a field study with long term use of a commercial vaccine indicated that while the increase of the number of booster vaccinations improved respectively several performance parameters, no further improvement of the level of immunity as measured by IPMA were noticed (Papatsiros *et al.*, 2006). In general, the KV vaccination is proposed to be applied on a regular basis in breeding herd of endemic PRRSV-infected farms, in order to obtain a stabilization of their

immunity, preventing the losses due to annually PRRS outbreaks (Papatsiros, 2012b).

Except of the vaccination of females, the vaccination of boars with KV vaccines is considered to be safe. Field study with long term use of commercial KV vaccine shown that the vaccination is absolutely safe and no negative effects on semen quality were noticed (Papatsiros *et al.*, 2011).

1.3. Modified (or Attenuated) Live Vaccines (MLV)

Commercial MLV vaccines elicit relatively weak humoral and CMI responses. PRRSV-specific antibodies appear approximately 2 weeks and peak around 4 weeks after vaccination, which have no neutralizing activity and they do confer some clinical protection (Darwich *et al.*, 2010). PRRSV-specific VN antibodies appear approximately 4 weeks after vaccination and have relatively low titers throughout the course of immunization (Darwich *et al.*, 2010). PRRSV-specific CMI response appears approximately 2-4 weeks after vaccination as determined by lymphocyte blastogenesis and interferon γ (IFN γ) production in recall reaction (Meier *et al.*, 2003; Bassaganya-Riera *et al.*, 2004).

Table 1. Commercial available PRRSV vaccines in Europe

Current name	Type	Virus strain	Manufacturer	Vaccination schedule
PROGRESSIS®	Inactivated	P120 KV strain > 2.5 log ₁₀ IF units	Merial animal health Ltd	Primary vaccination (gilts and sows): twice (im), 3-4 wk interval at least 3 wk prior to mating Revaccination (booster) one dose (im) at 60-70d of each gestation
INGELVAC® PRRS KV	Inactivated	P120 KV strain > 2.5 log ₁₀ IF units	Boehringer Ingelheim Ltd	Breeding stock Primary vaccination (gilts and sows): twice im, 3-4 wk interval, at least 3 wk prior to mating Revaccination (booster): one injection im at 60-70d of each gestation
SUIVAC® PRRS-Ine	Inactivated	VD-E1 KV strain (10 ^{4.8} up to 10 ^{6.3} CCID ₅₀ prior to inactivation) VD-E2 KV strain (10 ^{3.8} up to 10 ^{5.3} CCID ₅₀ prior to inactivation) VD-A1 KV strain (10 ^{4.8} up to 10 ^{6.3} CCID ₅₀ prior to inactivation)	Dyntec spol. sr.o.	Breeding stock Primary vaccination (gilts and sows): twice (im), 3-4 wk interval, at least 3 wk prior to mating Piglets three doses (im) at 3-4 wk
SUIPRAVAC® PRRS	Inactivated	5710 KV strain	HIPRA	Breeding stock Primary vaccination: entering the farm / Sows (pregnancy or lactation): Twice (im), at 3-4 wk interval Revaccination (booster)
AMERVAC® PRRS	MLV	Live strain VP046 BIS $\geq 10^{3.5}$ TCID ₅₀	HIPRA	Piglets: one dose (im) at age of 4-5 wk
PYRSVAC-183®	MLV	Live strain ALL-183 $\geq 10^{5.0}$ TCID ₅₀	SYVA laboratories	Piglets: one dose (im) over
PORCILIS® PRRS	MLV	Live strain DV 10 ^{4.0} TCID ₅₀ -10 ^{6.3} TCID ₅₀	MSD animal health	Breeding stock Primary vaccination: one Revaccination (booster) 6 d of lactation or at random Piglets one dose (im or id), from vaccinated at least 2-4 wk

The frequency of PRRSV-specific T cells producing IFN γ increases gradually with age, reaching a peak at approximately 32 weeks of vaccination (Meier *et al.*, 2003). Studies indicated that MLV-vaccinated pigs could not develop systemic anamnestic antibody and CMI responses after the challenge with homologous strains to the MLV vaccine virus, while they could develop anamnestic immune responses to the genetically heterologous strains (Martelli *et al.*, 2007; 2009). However, the aforementioned findings are yet unknown, but it did not seem to affect the protective efficacy of the MLV vaccine (Martelli *et al.*, 2007; 2009).

The vaccination schedule of available commercial MLV vaccines in Europe is summarized in **Table 1**. MLV vaccines are used for the prevention and control of PRRS infection both in breeding stock and young piglets, as is shown in **Table 2**. Studies with the use of commercial MLV vaccines in PRRSV-infected breeding

herds reported beneficial effects on their health and performance, reducing the abortion and return to estrus rate and increasing farrowing rate and number of weaners (Alexopoulos *et al.*, 2005; Pejsak and Markowska-Daniel, 2006). In addition, MLV vaccination of gilts protect them from viremia and reduce numbers of pre- and post-natal death and congenitally infected piglets (Scotti *et al.*, 2006), while born piglets from vaccinated gilts can have higher body weight and survival rate at weaning than those derived from non-vaccinated gilts (Rowland, 2010). Recent evidences based on personal experience and field observations in endemic PRRSV-infected farms suffering by significant reproductive failure, the MLV vaccination of breeding stock can improve; (a) the reproductive performance, (b) the viraemic status of piglets, (c) the morbidity and mortality of piglets, (d) the growth performance of piglets (Papatsiros, 2012b).

Table 2. Literature data about the trials with commercial available PRRSV vaccines in Europe

Type	Vaccination schedule	Results
Inactivated	Gilts/sows: primary vaccination (im), twice at 3-4 wk apart, except those being 1 wk prior to 2 wk post-service (the skipped Booster vaccination: 55 - 60 d of gestation	Improvement of reproductive performance and litter characteristics (e.g., reduction of premature farrowing and abortion rate, increase of farrowing rate, increase of live born and weaned piglets and decrease of stillborn, mummified, weak and splay-legged piglets per litter) The higher the degree immunization of a sow, the better the improvement of her reproductive parameters Reduction of culling rate due to reproductive failure
Inactivated	Gilts (180 d of age): (im), twice at 3 wk i	No detectable specific IFN- γ response or protective immunity
Inactivated	Piglets: (im) at weaning age	Induction of a strong CMI response (significant specific IFN γ + T-cell response soon after vaccination)
Inactivated	Piglets: (im) at mean age of 24 days	No induction of specific IFN- γ response 60 d after vaccination
MLV	Piglets: (im), twice, 21 and 42 d of age	Elicited modest titre of neutralizing antibodies Protection against homologous strain Reduction of post-challenge viremia and completely blocking of PRRSV dissemination to peripheral tissues
MLV	Gilts: 90 d of gestation (intranasal)	No clinical symptoms of general or reproductive performance Vaccine strains can replicate in gilts and cross the placental barrier No detrimental effects on the litters and congenitally infected pigs Lack of transmission to non-infected piglets during lactation
MLV	Gilts: 90 d of gestation (intranasal)	No clinical symptoms of general or reproductive performance Vaccine strains can replicate in gilts and cross the placental barrier No detrimental effects on the litters and congenitally infected pigs Lack of transmission to non-infected piglets during lactation
MLV	Gilts (5,5 months of age): (im), twice at 3 wk apart	Establishing of protective immunity
MLV	Sows: (im) every 6 months	Protection is not based on humoral but rather on CMI
MLV	Piglets: (im) at 40 d of age	Protection up to 108 d of age The high levels of sequence divergence between the vaccine and Polish field strains may reduce vaccine efficacy
MLV	Piglets: (im or id) at 5 wk of age	No effect of clinical protection by the route of administration Partial clinical protection to a heterologous field strain Efficient CMI response Id route induce efficiently protection against a heterologous strain
MLV	Piglets: (im or id) at 3 wk of age	Partial cross-protection against closely related virulent strain
MLV	Piglets: (im) at 4 wk of age	Genetic diversity among European PRRSV field isolates may affect the efficacy of the current European-type vaccines
MLV	Gilts: (im) at 180 d of age Sows: (im) at 10 d post-partum	Improvement of health status and reproductive performance of gilts/sows and their litters (e.g., reduction of premature farrowing rate and the number of dead and mummified born piglets, increase of farrowing rate and the number of piglets born alive or weaned per litter)
MLV	Piglets: (im) at 5 wk of age	Reduction of grower's mortality Improvement of average daily gain and feed conversion ratio

im: intramuscularly; id: intradermal; wk: week; d: day; CMI: Cell-Mediated Immune

According to several studies, the use MLV commercial vaccines has beneficial effects on clinical disease occurrence and severity, the duration of viremia and virus shedding (Stadejek *et al.*, 2005; Alvarez *et al.*, 2006; Scortti *et al.*, 2006; Martelli *et al.*, 2007; Kimman *et al.*, 2009). MLV vaccination can induce VN antibodies and protect against viremia, virus replication in lungs and virus induced respiratory and reproductive disorders (Labarque *et al.*, 2003; Scortti *et al.*, 2007; Zuckermann *et al.*, 2007). In particular, the use of MLV commercial vaccines in piglets results in reduction of viremia, severity of respiratory clinical signs and improvement of their growth performance (Cano *et al.*, 2007a; 2007b; Kritas *et al.*, 2007). In co-infected farms by both PRRSV and PCV2, the MLV vaccination of piglets (at roughly 5 weeks old) improves their growth performance in vaccinated pigs (Kritas *et al.*, 2007).

On the other hand, some studies have raised concerns about the efficacy of MLV vaccines. The protective immune response induced by current commercial MLV vaccines is influenced by genetic diversity, as these vaccines do not always sufficiently protect (or only partially) against re-infection and transplacental infections caused by heterologous PRRSV strains (Stadejek *et al.*, 2005; Scortti *et al.*, 2006; Prieto *et al.*, 2008; Kimman *et al.*, 2009). However, a recently study reported that vaccination of piglets at 5 weeks of age with a commercial MLV vaccine induced a partial clinical protection, associated with an efficient CMI response, when the above vaccinated pigs were exposed to a heterologous field strain (Martelli *et al.*, 2009). It is possible that farmers using an MLV vaccine for the first time may experience a decrease in the herd productivity. Studies with MLV vaccinations in breeding stock reported outbreaks of acute PRRS-like clinical signs, associated with increased late term abortions, increased numbers of stillborns and mummified piglets, as well as decreased numbers of live born and weaned piglets (Botner *et al.*, 1997; Dewey *et al.*, 1999). Moreover, Zuckermann *et al.* (2007) reported delayed protection after MLV vaccination.

However, the use of MLV vaccines is remaining questionable. The major concern of MLV vaccines is the safety and mainly the possibility of the reversion of the vaccine virus to virulence due to genetic mutations of the vaccine virus and/or recombination with field virulent PRRSV strains (Murtaugh *et al.*, 2010). Experimental and field studies reported that MLV strains can cause viremia, revert to virulence and spread transplacentally and horizontally not only within the vaccinated herds

(transmission and detection in non-vaccinated pigs), but also to neighbouring non-vaccinated herds (Botner *et al.*, 1997; Beilage *et al.*, 2009; Kimman *et al.*, 2009). The revert-to-virulent MLV vaccine can potentially cross placenta during late terms of gestation, causing increased number of mummified and stillborn piglets (Rowland, 2010). Piglets born to these MLV-infected sows can become carriers of PRRSV, shedding the MLV vaccine virus to other naive pigs (Rowland, 2010). Moreover, MLV vaccine can cause clinical respiratory signs and affect negative the growth performance of vaccinated piglets (Rowland, 2010). These vaccinated piglets can develop viremia, transmitting the MLV vaccine virus to other naive animals for a period of at least 4 weeks (Thanawongnuwech and Suradhat, 2010). Hence, it is possible that farmers using an MLV vaccine for the first time may experience decreased herd productivity, characterized for example by increased late term abortions or increased numbers of stillborns and mummified piglets (Botner *et al.*, 1997; Dewey *et al.*, 1999). An additional concern according to recently studies is that the MLV vaccination might interfere with the protective has efficacy of *Mycoplasma hyopneumoniae* vaccines (Thacker *et al.*, 2000; Drexler *et al.*, 2010; Roitha *et al.*, 2011).

Both KV and MLV commercial EU vaccines are not able to protect completely against PRRSV infection. However, these vaccines have some beneficial effects on prevention and control of PRRS under field conditions, as shown in **Table 2**. According to Dotti *et al.* (2011) distinct patterns of immune response to a field PRRSV strain can be recognized in PRRS-vaccinated and naive pigs, which probably underlies fundamental differences in the development and differentiation of PRRSV specific immune effector cells.

Commercial EU MLV vaccines provide effective genotype/strain-specific protection, only partial protection against genetically heterologous PRRSV and elicit relatively late humoral and CMI responses which lead to delayed protection (Scortti *et al.*, 2006; Prieto *et al.*, 2008; Martelli *et al.*, 2009). However, the MLV vaccine virus has a potential risk to revert to virulence and cause clinical disease (Murtaugh *et al.*, 2010). On the other hand, EU KV vaccines provide limited efficacy due to the weak stimulation of the immune system and no effective induction of VN antibodies, which might play a significant role in protection against either homologous or heterologous PRRSV. However, KV vaccines can induce a strong CMI response, which may associate with protection when are administered to the PRRSV-infected

pigs (Scorti *et al.*, 2007; Zuckermann *et al.*, 2007). In a recent study the effects of PRRSV vaccination, using combination of KV and a MLV vaccine was investigated by Gimeno *et al.* (2010). Initially piglets at six weeks of age were vaccinated with a EU MLV vaccine and three months later revaccinated with a commercial EU KV vaccine (once or twice) or with a EU MLV vaccine. At 6.5 months of age, all pigs were intranasal challenged with a Lelystad-like PRRSV strain. The results of this study indicated no differences in the humoral response but the revaccination with the KV vaccine had equal or better effect than the use of a repeated MLV vaccination in terms of maintaining the PRRSV-specific IFN- γ response. These findings suggest that further studies are needed to carry out in order to evaluate and reclaim the advantages both of MLV and KV available vaccines.

The disadvantage of current commercially PRRSV (inactivated and MLV) vaccines to provide efficient or complete protection against PRRSV infection due to genetic diversity among European PRRSV field isolates and the limited cross-reactivity between strains of commercial vaccines and challenge strains (wild-virus strains) (Labarque *et al.*, 2004). A significant genetically and antigenically diversity are noticed between mainly among EU PRRSV strains, but also different strains are isolated within the same area or the same farm (Labarque *et al.*, 2004; Indik *et al.*, 2000; Shi *et al.*, 2010b; Toplak *et al.*, 2012). This is probably caused by the introduction of a new strain into a single herd due to the introduction of replacement animals or semen rather than by local evolution, because different PRRSV strains are also isolated at the same time. Hence, the high heterogeneity among PRRSV strains is likely to be the main obstacle to effective control of PRRSV infection using current commercial vaccines (MLV and KV), since the immunity induced by one strain may be only partial against a different strain, even within the same genotype (Mateu and Diaz, 2008; Kimman *et al.*, 2009). However, vaccine efficacy may be associated with an efficient CMI and it is not only related with its immunological properties, but also with the characteristics of the challenging strain to trigger an immune response (Martelli *et al.*, 2009). Therefore, the ability of each strain to induce a strong CMI response is more important than the genetic similarity between the vaccine strain and the field strains for inducing clinical protection (Mateu and Diaz, 2008). The complexity of the immune response to PRRSV and the ability of the virus to escape or modulate the host's immune system make it difficult

to develop an effective vaccine for control and eradication of PRRS.

2. CONCLUSION

In vaccinations are remained economical and effective control strategies for PRRS. The current use of MLV or KV vaccines in Europe is managing to moderate the economic losses due to PRRSV outbreaks. However, the major obstacle for the development of an ideal PRRSV vaccine is the lack of complete knowledge on several aspects of pathogenesis and immunity of PRRSV. The development of more efficacious PRRSV vaccines remains an important goal for the swine industry worldwide.

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