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GUIDELINES FOR CLINICAL PRACTICE

Porcine reproductive and respiratory syndrome virus vaccines: Immunogenicity, efficacy and safety aspects

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Abstract

Porcine reproductive and respiratory syndrome virus (PRRSV) infection is the leading cause of economic casualty in swine industry worldwide. The virus can cause reproductive failure, respiratory disease, and growth retardation in the pigs. This review deals with current status of commercial PRRS vaccines presently used to control PRRS. The review focuses on the immunogenicity, protective efficacy and safety aspects of the vaccines. Commercial PRRS modified-live virus (MLV) vaccine elicits delayed humoral and cell-mediated immune responses following vaccination. The vaccine confers late but effective protection against genetically homologous PRRSV, and partial protection against genetically heterologous virus. The MLV vaccine is of concern for its safety as the vaccine virus can revert to virulence and cause diseases. PRRS killed virus (KV) vaccine, on the other hand, is safe but confers limited protection against either homologous or heterologous virus. The KV vaccine yet helps reduce disease severity when administered to the PRRSV-infected pigs. Although efforts have been made to improve the immunogenicity, efficacy and safety of PRRS vaccines, a better vaccine is still needed in order to protect against PRRSV.

Key words: Porcine reproductive and respiratory syndrome virus; Vaccine

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INTRODUCTION

Porcine reproductive and respiratory syndrome virus (PRRSV) causes severe economic loss in swine production industry worldwide[1]. The virus has brought about severe PRRS outbreaks in many countries in Southeast Asia including Thailand, leading to an unusually high mortality of pigs of all ages[2]. The virus also has recently devastated pig industry in China, causing losses of more than 30% of pig populations[3].

PRRSV belongs to the *Arteriviridae* family. The virus possesses enveloped positive-sense, single-stranded RNA genome of approximately 15 kb in size and with nine open-reading frames (ORF)[4]. The up-to-date information of PRRSV ORF is summarized in Table 1. PRRSV can be classified into two genotypes, the North American (NA) and the European (EU). Both genotypes of PRRSV share an approximately 60% nucleotide sequence

homology to each other[4]. Within each genotype, the virus isolates can exhibit up to 20% variability of nucleotide sequences, making them a variety of heterogeneous clusters or subpopulations[5].

PRRSV of either genotype causes reproductive failures in breeding age swine, which are characterized by mummification, stillbirth, late-term abortion and delayed return to estrus[4]. The virus also causes respiratory disorders in growing pigs, which can be subclinical or fatal depending on the virulence of the virus[4]. PRRSV-infected pigs usually suffer from poor growth performance and are highly susceptible to co- or secondary bacterial and other viral infections[4].

The measures used currently to control PRRS include management (e.g. whole herd depopulation/repopulation and herd closure), bio-security, test and removal, and vaccination[6]. Vaccination is used generally for the purpose of reduction of clinical losses, but not of prevention of virus infection. The vaccination strategy costs lowest to the pig producers and is feasible to all sizes of pig producers (i.e. small, medium and large), compared with other PRRS control strategies. There are two types of PRRS vaccines that are commercially available. One is a modified-live virus (MLV) vaccine and the other is a killed virus (KV) vaccine. PRRS MLV vaccine is well recognized for its protective efficacy against PRRSV that are genetically homologous to the vaccine virus. It is of concern, however, for its immunogenicity, cross protective efficacy and safety. PRRS KV vaccine, on the other hand, is well known for its safety, but it only confers limited protection.

This article aims to summarize the current status of commercial PRRS vaccines with respect to their immunogenicity, efficacy and safety. The article also discusses current efforts to develop an ideal PRRS vaccine.

MLV VACCINE

General information

PRRS MLV vaccine is licensed for use in several countries worldwide (http://www.cfsph.iastate.edu/Vaccines/disease_list.php?disease=porcine-reproductive-respiratory-syndrome&lang=en). The MLV vaccines licensed for use in the US are derived from the NA PRRSV, which include Ingelvac® PRRS MLV and ReproCyc® PRRS-PLE (both from VR-2332; Boehringer Ingelheim), and Ingelvac® PRRS ATP (from JA-142; Boehringer Ingelheim). The MLV vaccines licensed for use in the EU countries are, likewise, derived only from the EU PRRSV, which comprise Porcilis PRRS® (from DV; Merck), Amervac-PRRS® (from VP046; Hipra), and Pyrsvac-183® (from All-183; Syva). The MLV vaccines licensed for use in other countries may not be restricted to either virus genotype and may be available for both PRRSV genotypes. Details of the commercial PRRS MLV vaccines are summarized in Table 2.

Immunogenicity

Commercial PRRS MLV vaccine of either NA or EU genotype elicits relatively weak humoral and cell-mediated immune (CMI) responses. PRRSV-specific antibodies appear approximately 2 wk, and peak around 4 wk after vaccination[7]. Majority of the antibodies are against viral nucleocapsid (N) proteins which have no neutralizing activity[7]. These antibodies do confer some clinical protection, but their protective mechanism is yet unknown[7].

PRRSV-specific neutralizing antibodies appear approximately 4 wk after vaccination, and have relatively low titers (approximately 2^3-2^5) throughout the course of immunization[7]. The reason for poor neutralizing titers is not exactly known but is proposedly attributed to the presence of decoy neutralizing epitopes and the heavy glycosylation of the major and minor neutralizing epitopes[8-10].

PRRSV-specific CMI response appears approximately 2-4 wk after vaccination as determined by lymphocyte blastogenesis and interferon γ (IFNγ) production in recall reaction[11,12]. Majority of T cell subsets responsive to PRRSV are $CD4^+CD8^{lo}$ and $CD4^-CD8^+$[11-13], which are identified as porcine memory T helper cells and cytotoxic T cells, respectively[14,15]. The frequency of PRRSV-specific T cells producing IFNγ increases gradually with age, reaching a peak at approximately 32 wk of vaccination[11]. This is extremely delayed compared with T cell response to pseudorabies virus (PRV) MLV vaccine, which appears within 1 wk of vaccination and peaks approximately at 4 wk after vaccination[11]. The reason for delayed and weak CMI response to PRRSV is not thoroughly known, but is reported to be attributed, at least in part, to virus-mediated suppression of type I IFN and other pro-inflammatory cytokines, e.g. interleukin-1 (IL-1), IL-12, and tumor-necrosis factor α (TNFα)[16]. The poor CMI response might be also attributed to the virus capacity to up-regulate anti-inflammatory cytokine production, i.e. IL-10 and transforming-growth factor β, in infected cells, and to induce regulatory T cell response[17-19].

Following a challenge exposure to virulent PRRSV, MLV-vaccinated pigs do not develop systemic anamnestic antibody and CMI responses to the challenge viruses that are genetically homologous to the vaccine virus, but do develop anamnestic immune responses to the genetically heterologous viruses[12,20,21]. This absence of anamnestic antibody and CMI responses is observed also following repeated immunizations with PRRS MLV vaccine[12]. The reason for the absence of anamnestic immune responses to homologous virus, and the presence of anamnestic responses to heterologous virus is yet unknown. These phenomena, however, seem not to affect the protective efficacy of the MLV vaccine[12,20,21].

Protective efficacy

PRRS MLV vaccine effectively protects pigs from PRRSV-mediated reproductive and respiratory diseases. The vaccine helps protect gilts from viremia and helps reduce numbers of pre- and post-natal death and congenitally infected piglets[22]. Piglets born to vaccinated gilts had higher body weight and survival rate at weaning than those born to non-vaccinated control gilts[23]. The MLV vaccine, when

Table 1 Porcine reproductive and respiratory syndrome virus genome and relevant information

ORF	Product	Function	Role in immunity/protection	Ref.
1a	Nsp1α	Papain-like cysteine protease	Potential IFN and TNFα antagonist	[66-68]
	Nsp1β	Papain-like cysteine protease	Potential IFN and TNFα antagonist	[66,68,69]
	Nsp2	Cysteine protease	Potential IFN antagonist	[70]
	Nsp3	Transmembrane protein	NA	[70]
	Nsp4	Serine protease	NA	[70]
	Nsp5	Transmembrane protein	NA	[70]
	Nsp6	NA	NA	[70]
	Nsp7α	NA	Potential antigen for serological determination of persistence infection	[70]
	Nsp7β	NA	Potential antigen for serological determination of persistence infection	[70]
	Nsp8	NA	NA	[70]
1b	Nsp9	RNA-dependent RNA polymerase	NA	[70]
	Nsp10	Helicase	NA	[70]
	Nsp11	Endoribonuclease	Potential IFN antagonist	[70,71]
	Nsp12	NA	NA	[70]
2a	GP2	Minor envelope protein; interacts with CD163	Minor neutralizing epitope	[72]
2b	E protein	Minor envelope protein; possibly form oligomeric ion channel	NA	[72]
3	GP3	Minor envelope protein	Minor neutralizing epitope	[72]
4	GP4	Minor envelope protein; interacts with CD163	Minor neutralizing epitope	[72]
5	GP5	Major envelope protein; interacts with sialoadhesin	Major neutralizing epitope	[72]
6	M protein	Major envelope protein; interacts with heparan sulfate	T cell epitope; minor neutralizing epitope	[72]
7	N protein	Nucleocapsid	Non-neutralizing epitope	[72]

Nsp: Non-structural protein; GP: Glycoprotein; NA: No data available; ORF: Open-reading frames.

Table 2 Recommendation and vaccination schedule of commercial PRRS modified-live virus vaccines

Vaccine[1]	Pigs[2]	Route	Dose (mL)	Program
Ingelvac® PRRS MLV	Gilt/Sow	im	2	At any stage of production[3]
	Piglet/Nursery/Growing	im	2	At any stage of production[3]
ReproCyc® PRRS-PLE	Gilt/Sow	im	5	Primary: 4-6 wk prior to breeding Booster: prior to subsequent breeding
Ingelvac® PRRS ATP	Nursery/Growing	im	2	At 3-18 wk of age
Porcilis PRRS®	Gilt/Sow	im/id	2/0.2	Primary: 2-4 wk prior to breeding Booster: 2-4 wk prior to subsequent breeding/or every 4 mo
	Piglet/Nursery/Growing	im/id	2/0.2	At 2 wk of age or older
Amervac-PRRS®	Nursery/Growing	im	2	At 4 wk of age or older
Pyrsvac-183®	Gilt/Sow	im	2	Primary: 2-4 wk prior to breeding Booster: 3-4 wk prior to subsequent breeding
	Piglet/Nursery/Growing	im	2	At 2-3 wk of age or older

[1]Not recommended for use in porcine reproductive and respiratory syndrome virus-negative farms; [2]Not recommended for use in boars due to negative impact on semen quality[73]; [3]Recommended to revaccinate every 3-4 mo for whole herd vaccination program. im: Intramuscularly; id: Intradermally.

used in PRRSV-infected sows, effectively helps reduce abortion and return to estrus rate, and increase farrowing rate and number of weaning pigs[24,25].

In growing pigs, immunization with PRRS MLV vaccine associates with reduced viremia, respiratory signs, and improved growth performance[13,26,27]. The MLV vaccine, when vaccinated during acute PRRS outbreak or in endemically PRRSV-infected pigs, helps reduce virus shedding and respiratory disease, and improve growth performance[26-28].

Despite good protection, several concerns have been raised with respect to the MLV vaccine efficacy. First, PRRS MLV vaccine confers relatively delayed protection, which is usually detectable around 3-4 wk after vaccination[29]. Second, vaccine protection is rather virus genotype-specific and, to the most extent, strain-specific. Protection conferred by EU PRRS MLV vaccine is seen only after EU, but not NA PRRSV challenge[20,22]. Likewise, protection by NA PRRS MLV vaccine is seen after NA, and to some extent, EU PRRSV challenge[13,29]. And third, immunization with PRRS MLV vaccine might interfere with the protective efficacy of other swine vaccines, e.g. *Mycoplasma hyopneumoniae* bacterin. The MLV vaccine, when administered with certain schedule of the bacterin, might lower the bacterin efficacy[30,31].

Safety

The major concern of PRRS MLV vaccine is reversion to

Table 3 Recommendation and vaccination schedule of commercial PRRS killed virus vaccines

Vaccine	Pigs	Route	Dose (mL)	Program
Progressis®/ Ingelvac® PRRS KV	Gilt	im	2	Primary: twice, 3-4 wk interval, at least 3 wk prior to breeding Booster: 60-70 d of each gestation
	Sow			Primary: twice, 3-4 wk interval, at any stage of production
		im	2	Booster: 60-70 d of each gestation
Suipravac-PRRS	Gilt	im	2	Primary: twice, 3-4 wk interval, when entering the farm Booster: Follow sows' vaccination program
	Sow	im	2	Primary: twice, 3-4 wk interval, during pregnancy or lactation Booster: every 4 mo
Suivac PRRS-INe/ Suivac PRRS-IN	Gilt/Sow	im	2	Primary: three times; 1st at 5-6 mo of age, 2nd at 3-4 wk after 1st, and 3rd at 6-4 wk prior to expected farrowing Booster: twice; 1st at 3-4 wk after the farrowing, and 2nd at 6-4 wk prior to the further expected farrowing
	Boar	im	2	Primary: twice, 4 wk interval, starting at 6 mo of age Booster: every 4-6 mo
	Nursery/Growing	im	2	Three times: 3-4 wk interval, starting at 6-10 wk of age

im: Intramuscularly; KV: Killed virus.

virulence. This is predominantly through genetic mutations of the vaccine virus and/or recombination with field virulent PRRSV[32]. The revert-to-virulent vaccine virus can cause clinical diseases, both reproductive and respiratory, and affect growth performance[23]. The vaccine-like virus can potentially cross placenta during late gestation, and cause mummification and stillbirth[23]. Piglets born to these infected sows can be carriers of PRRSV and can shed the virus to other naive pigs[23]. In addition, the MLV-vaccinated pigs can develop viremia of the vaccine virus at least 4 wk after vaccination, and during this period, the animals can spread the virus to other naïve animals[33].

KV VACCINE

General information

PRRS KV vaccine is licensed for use in EU countries and other parts of the world, but not in the US. In the US, the vaccine appeared once in the market (under the trade name PRRomiSe™; Intervet), but the manufacturer discontinued it in 2005. The PRRS KV vaccines licensed for use in the EU can be derived from both EU and NA PRRSV. These vaccines include Ingelvac® PRRS KV (derived from P120; Boehringer Ingelheim), Suipravac-PRRS (from 5710; Hipra), Progressis® (from proprietary strain; Merial), Suivac PRRS-INe (from VD-E1 and VD-E2; Dyntec), and Suivac PRRS-IN (from VD-E1, VD-E2, and VD-A1; Dyntec). Details of the commercial PRRS KV vaccines are summarized in Table 3.

Immunogenicity

In contrast to PRRS MLV vaccine, vaccination with PRRS KV vaccine does not elicit detectable antibodies as determined by IDEXX ELISA and serum virus neutralization assay[34]. The vaccine also barely elicits CMI response as determined by lymphocyte proliferation and IFNγ production in recall response[12,35].

When PRRS KV vaccine is used in PRRSV-positive pigs, the vaccine helps increase antibody and CMI responses to the infecting virus[12,34]. The enhanced immune responses are detected approximately 2 wk after the second shot of vaccination, and correlate with protection[12,34]. These findings lead to the potential application of PRRS KV vaccine as a therapeutic vaccine in PRRSV-positive farms.

Protective efficacy

PRRS KV vaccine is considered less efficacious than PRRS MLV vaccine. In naïve animals, the vaccine fails to prevent reproductive losses and congenital infection in fetuses[36]. When used off-label in growing pigs and boars, the vaccine fails to reduce viremia, duration and titers of virus shedding in semen, and respiratory signs after virulent PRRSV challenge[29].

The benefit of PRRS KV vaccine is seen more obviously in virus-infected animals. In these cases, the vaccine helps improve reproductive performance, e.g. increased farrowing rate, number of weaned pigs, and health status of piglets born to vaccinated sows[37].

Safety

The PRRS KV vaccine is considered safe. Up to date, there has been no report on the negative impact of PRRS KV vaccine on pig health.

CURRENT EFFORTS ON PRRS VACCINE DEVELOPMENT

Numerous efforts have been made to develop an ideal PRRS vaccine, i.e. vaccine that possesses high immunogenicity, confers broad protection, and is safe[38,39]. These efforts reportedly included use of several adjuvants[40-42], use of mixed strains of PRRSV[43,44], and generation of alternative vaccines, i.e. DNA vaccine[45,46], subunit vaccine[47,48], synthetic peptide vaccine[13], viral vector vaccines using adenovirus[49-51], PRV[52,53], poxvirus[54,55], and

Table 4 Alternative PRRS vaccines

	Encoded ORF/GP	Immunogenicity		Protection		Ref.
		Antibody	CMI	Homologous	Heterologous	
DNA vaccine	ORF1-7	+	+	+	ND	[45,46]
Subunit vaccine	GP5	Poor	Poor	-	ND	[47,48]
Synthetic peptide vaccine	GP5	-	-	ND	-	[13]
Adenovirus vector vaccine	GP3, 4, 5	+	+	ND	ND	[49-51]
PRV vector vaccine	GP5, M	+	+	+	ND	[52,53]
Poxvirus vector vaccine	GP3, 5, M	+	+	+	ND	[54,55]
TGEV vector vaccine	GP5, M	+	ND	+	ND	[56]
Alphavirus-derived replicon	GP5, M	+	+	+	+	[57]
Bacterial vector vaccine	GP5, M	+	-	+	ND	[58]
Insect cell-derived vaccine	ORF3, 5, 7	+	ND	+	ND	[59]
Plant-derived vaccine	GP5	+	+	ND	ND	[60,61]
Gene-deleted MLV (deleted15-mer nsp2 epitope)		+	ND	ND	ND	[65]

+: Success; -: Failure; ND: Not determined.

transmissible gastroenteritis virus[56] as vectors, alphavirus-derived replicon[57], bacterial vector vaccine[58], insect cell-derived vaccine[59], and plant-derived vaccine[60,61] (Table 4). These efforts, however, can achieve at best some, but not all, properties of an ideal PRRS vaccine. In fact, none of these efforts can confer significantly better protection than PRRS MLV vaccine.

Development of mucosal vaccine also has been attempted in order to induce protective mucosal immunity, primarily at the site of PRRSV entry, i.e. respiratory and vaginal[62]. The success of mucosal vaccination concept has been reported in many other virus models, e.g. poliovirus, influenza virus and human immunodeficiency virus[63]. PRRSV glycoprotein 5 and N proteins conjugated with cholera toxin, a potent inducer of mucosal immunity[64], were shown to enhance the antibody response in mucosal surfaces, i.e. intestinal and genital, when the vaccine was administered orally, but the protective efficacy of the vaccine was not evaluated[62]. The vaccine, when administered intramuscularly, however, failed to confer respiratory and viremia protection[13].

There is also an effort to produce a PRRS vaccine that can differentiate infected from vaccinated animals for PRRS eradication[65]. This is accomplished by a deletion of 15-mer of non-structural protein 2 (nsp2) epitope of PRRSV. This gene-deleted vaccine is waiting for evaluation of its protective efficacy in the pigs (Table 4).

FUTURE PROSPECTS

Current major obstacle for development of an ideal PRRS vaccine is the lack of complete knowledge on several aspects of PRRSV, including (1) the virus strategies to suppress and evade host innate and adaptive immune responses; (2) the virus epitope(s) responsible for such immune suppression and evasion; (3) the virus epitope(s) common to both NA and EU PRRSV and can confer broad protection; and (4) the roles of PRRSV non-structural proteins and structural proteins on virus replication, virulence, immunity and protection. Efforts are needed to elucidate all these gap of knowledge. Addressing these questions will be essential to advance our understanding on PRRSV immunology and to provide valuable information for vaccine development.

CONCLUSION

There are two types of commercial PRRS vaccines currently used to control PRRS. PRRS MLV vaccine confers effective genotype/strain-specific protection, but provides only partial protection against genetically heterologous PRRSV. The MLV vaccine elicits relatively late humoral and CMI responses which lead to delayed protection. The vaccine virus has a potential to revert to virulence and cause diseases. PRRS KV vaccine, on the other hand, has poor immunogenicity and poor protective efficacy against either homologous or heterologous PRRSV. The vaccine, however, confers some protection when administered to the PRRSV-infected pigs.

The development of PRRS vaccine is and will be the topic of interest among PRRS researchers for years to come. With efforts from laboratories worldwide, it is possible that we will come up with a better PRRS vaccine.

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