Comparison of productivity losses between swine breeding herds adopting killed or attenuated PRRS virus vaccination protocols following PRRS outbreaks

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Abstract

Porcine reproductive and respiratory syndrome virus (PRRSv) has been endemic for more than 30 years in most pig producing countries across the globe, and is still one of the most economically important pathogens affecting swine. The use of modified live vaccines (MLV) on breeding herds has been reported by several investigators and is a common practice in the industry for the control of PRRSv. There is limited published information on efficacy of killed virus (KV) vaccines as part of PRRS control programs in breeding herds. Thus, the objective of this study was to describe productivity losses in breeding herds following PRRS outbreak that used KV vaccination protocol compared to those using MLV vaccination protocol. A retrospective observational study was conducted to describe the production impact between two exposure groups i.e. KV vaccine-boostered group (27 herd-outbreaks from 19 herds) and MLV vaccine-treated group (51 herd-outbreaks from 50 herds). A survey was used to record key demographic information including herd size (number of breeding sows in the inventory), location of gilt acclimation site (offsite or onsite), PRRS status prior to described outbreak (stable or unstable), frequency of weaning events per week (1 and 2 or 3+), PRRSv RFLP type, United States geographic region, and PRRS vaccination protocol of breeding sows (KV vaccine, or MLV vaccine). The productivity losses were calculated using ‘time to baseline production’ (TTBP), and ‘total loss per thousand sows’ (TL/1000 sows). Statistical analyses were performed with SAS version 9.4. There was no difference in TTBP between exposure groups (P 0.4242), but the herd-outbreaks in the KV vaccine-boostered group had a lower median total loss of 697 per 1000 sows compared to the MLV vaccine -treated group (P 0.0021). This study provided information about changes in productivity of commercial breeding herds following PRRS outbreak, using KV vaccination protocol as part of PRRS management strategy when compared to those using MLV vaccination protocol.

Key words: PRRSv; killed virus vaccine; Modified-live virus vaccine; Time to baseline production; Total loss; Swine

1. Introduction

Porcine reproductive and respiratory syndrome virus (PRRSv) has been endemic for more than 30 years in the global swine industry and continues to cause important economic losses. The production losses in the breeding and growing-pig herds resulted in 9.93 million fewer pigs per year, or approximately 1.09 billion fewer kilograms of pork (as measured by carcass weight), marketed per year in the United States (Holtkamp et al., 2013). Production losses due to PRRSv vary widely among herds including death of piglets during pre and post-weaning age, late-term abortion, increase in dead and mummified fetuses, weak-born piglets and early farrowing. (Christianson et al., 1994). It has been proposed that measuring the change in the number of piglets produced is a way to measure of PRRSv infection in the breeding herds (Linhares et al., 2014). This method is referred to as a throughout analysis, and captures most of the production losses:- breeding herds which have piglet production as the ultimate goal. Thus, it is important to use standardized approaches to measure the production losses of the disease when assessing the efficacy of exposure options in affected herds. In that regard, the terms *time to baseline production* (TTBP) and *total loss per thousand sows* attributed to PRRS outbreak (TL/1000 sows) were developed to measure production losses due to PRRS in breeding herds (Linhares et al., 2014).

Different strategies have been described to manage PRRSv infection in breeding herds without depopulation (Corzo et al., 2010). From those, herd vaccination is commonly adopted as part of control and/or elimination protocols (Batista et al., 2003; Dee et al., 1996). Both modified live virus (MLV) PRRSv and killed PRRSv vaccines vaccines are used to control the disease. In the US swine industry, there are many reports of using PRRSv MLV vaccines (Cano et al., 2007; Linhares et al., 2017). However, the currently available commercial vaccines are not capable of fully preventing PRRS infection, shedding, or transmission (Diaz et al., 2006; Zuckermann et al., 2007; Martelli et al., 2009; Darwich et al., 2010; Murtaugh et al., 2011; Geldhof et al., 2012).

Killed PRRSv vaccines have been considered safe and helped PRRSv-infected pigs to increase virus-specific antibody responses (Bassaganya-Riera et al., 2004; Kim et al., 2011). Use of KV vaccines in a respiratory model could reduce levels of viremia but was not consistent (Zuckermann et al., 2007; Nilubol D et al., 2004). Similarly, in reproductive model KV vaccination improved the percentage of pigs weaned but could not improve overall reproductive performance (Scortti et al., 2007). Repeated administration of KV PRRSv has demonstrated a boostering of anti-PRRSv immunity of individual pigs under controlled condition (Nilubol D et al., 2004; Zuckermann et al., 2007) and have also showed reduction in median TTBP and TL/1000 sows (Rawal et al., 2018).

KV PRRS vaccines have been proposed as a valuable tool to boost the protective immune response and demonstrated shorter median TTBP and lower loss of weaned pigs when previously immunized with a replicating PRRSv such as live wild-type PRRSv, and/or with MLV PRRSv vaccines (Baker et al., 1999; Bassaganya-Riera et al., 2004; Rawal et al., 2019). However, there is limited data available from field-based studies on the efficacy of KV vaccines, and/or its comparative efficacy to MLV vaccines. Thus, the objective of this study was to describe productivity losses from breeding herds using a KV vaccination protocol, as compared to those using a MLV vaccination protocol in response to a PRRSv outbreak.

2. Materials and methods

2.1. Study design

A retrospective observational study was conducted, following breeding herd-outbreaks of PRRSv. Data on herd-outbreak was collected on survey filled by the respective herd veterinarian. To best of our knowledge, there is not a widely accepted definition of PRRSv outbreak in the swine industry. Thus, different vets use slightly different criteria to establish cut off points. Thus, for the purpose of this study the definition of PRRSv outbreak was “according to the herd veterinarian judgement”, and further validated by having significant production damages (i.e. spikes in aborts and/or pre-weaning mortality).

There were 78 herd-outbreaks eligible for this study. The herd-outbreaks were divided into two exposure groups i.e. KV vaccine-boostered group, and MLV vaccine-treated group (Fig 1). The herd-outbreaks in the KV vaccine-boostered group were vaccinated with MJPRRS® (Phibro Animal health corporation) and those in MLV vaccine-treated group were vaccinated with either Ingelvac® PRRS ATP (Boehringer Ingelheim Vetmedica Inc., St. Joseph, MO) vaccine, Ingelvac® PRRS MLV (Boehringer Ingelheim Vetmedica Inc., St. Joseph, MO) vaccine, or Fostera® PRRSv vaccine (Zoetis, Parsippany, NJ, USA). The vaccines were administrated intramuscularly to pigs. In the KV vaccine-boostered group there were 27 herd-outbreaks from 19 herds. The MLV vaccine-treated group had 51 herd-outbreaks from 50 herds.

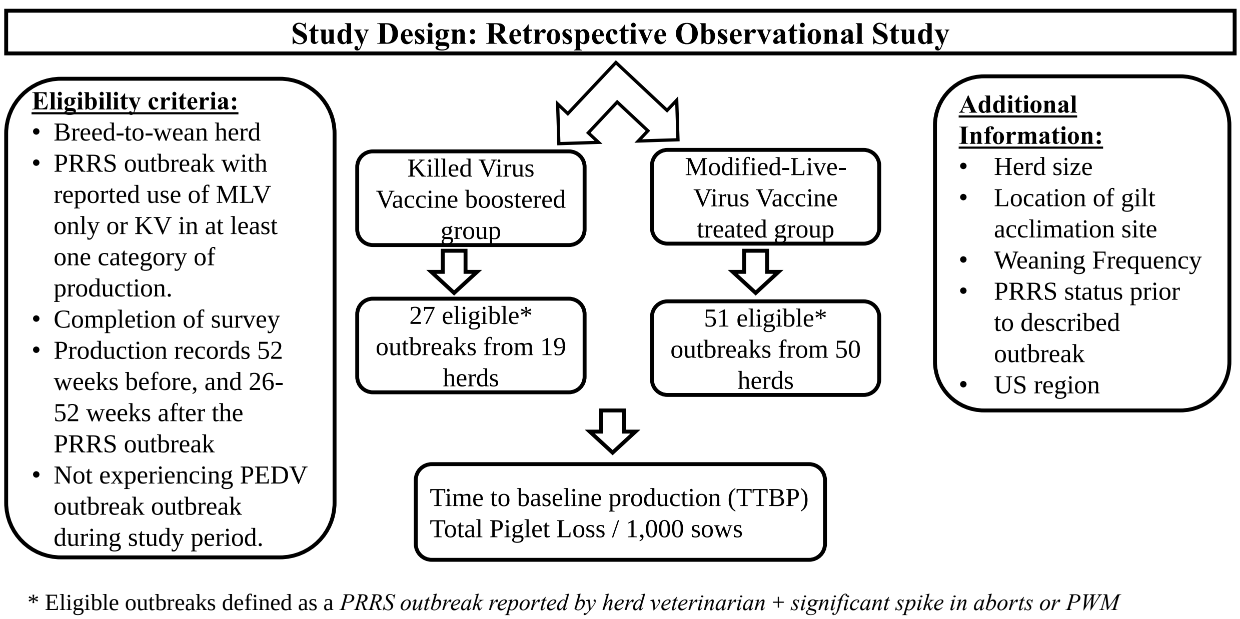

Fig 1. Study design.

2.2. Source population and eligibility criteria

Breed-to-wean herds in the United States were conveniently selected based on an eligibility criteria: (a) diagnostic documentation of a PRRS outbreak; (b) use of PRRSv MLV vaccine, and/or use of PRRSv KV vaccines in the breeding herd; (c) available open reading frame (ORF)-5 sequence from the PRRS outbreak; (d) producer agreement to share weekly production records for 52 weeks before, and up to 52 weeks after the PRRS outbreak; (e) willingness of producer to share information on herd demographics, and use of immunologic solutions (exposure to PRRSv live, attenuated or, killed) in the herd, confirmed by completing a survey; (f) not experiencing a porcine epidemic diarrhea virus (PEDv) outbreak during the study period.

2.3. Data collection

Data collection occurred between June 1, 2017 to March 31, 2018. Veterinarians and producers were contacted to participate in the study by completing a survey via phone calls, email and visits. The survey contained key herd demographic information including herd size (number of breeding sows in the inventory), location of gilt acclimation site (offsite or on site), United States region (midwest or southeast), PRRS status prior to described outbreak (stable or unstable), frequency of weaning events per week (1 and 2 or 3+), and PRRS vaccination protocol of breeding sows (KV vaccine or MLV vaccine).

2.4. Sample size calculation

Assuming a standard deviation of 6 weeks in TTBP (Linhares et al., 2014), 18 herd-outbreaks per exposure group were required to detect a minimum difference of 4 weeks between exposure groups at alpha level of 0.05 and power of 80%.

2.5. Exposure groups, and key co-variates of interest

There were two exposure groups: (i) the KV vaccine-boostered group consisted of herd-outbreaks that implemented whole-herd immunization with KV vaccine after previous exposure to a replicating PRRSv, including MLV vaccine, live PRRSv inoculation, or feedback materials (tissues, serum or fecal materials). The (ii) PRRS MLV vaccine-treated group consisted of herd-outbreaks that reported use of a commercial PRRSv MLV vaccine, with or without combination with live virus inoculation or feedback materials. The herd-outbreaks in the MLV vaccine-treated group did not report the use of any KV vaccine.

The PRRSv restriction fragment length polymorphism (RFLP) type for each herd-outbreak was reported in the survey by the attending herd veterinarians. The PRRS status prior to described outbreak was classified for each outbreak as stable (positive stable or negative) or unstable (positive unstable) based on American Association of Swine Veterinarians (AASV) classification of herds (Holtkamp et al., 2011). Briefly, PRRS stable herds consisted of those without evidence of PRRSv RNA detection in suckling piglets by RT-PCR testing, and PRRS unstable herds consisted of those with diagnostic evidence of PRRSv viremia in the suckling pig population.

2.6. Outcome variables

The exposure groups were compared using *time to baseline production* (TTBP) and *total loss per thousand sows* (TL/1000 sows) as previously established (Linhares et al., 2014). TTBP was defined as time in weeks to recover the level of 'weaned pigs per week' that the herd had prior to the PRRSv outbreak. The TTBP calculation was done using the exponentially weighted moving average (EWMA) control chart method (Montgomery, 2012), which is a type of statistical process control. The parameter of EWMA control chart were measured based on intention of operating with a low false alarm rate and used weight (λ) of 0.40 and a multiple of sigma (σ) of 3 for control limits (Krieter et al., 2009).

The “TL/1000 sows” was measured by reporting the number of pigs not weaned per 1,000 sows between the time of PRRS detection and herd reaching baseline production (TTBP). The calculation was done by adding the sum number of pigs weaned below the expected value from the time of reporting PRRSv outbreak to TTBP status achievement.

2.7. Statistical analyses

Herds were censored if dropped from this study between enrollment and reaching TTBP, or at 52 weeks if not reaching TTBP by then. The outcomes (TTBP and TL/1000 sows) were calculated for each herd-outbreak. Descriptive analysis was done to report demographic characteristics of herd-outbreak(s) using t-test for continuous variables and chi-square for frequencies of categorical variables between exposure groups.

Survival analyses were used to compare TTBP between exposure groups. More specifically, Kaplan-Meier log-rank test was used for univariate analysis, and Cox proportional hazards regression was used on the multivariate analysis. To adjust the analysis for the effect of other potentially confounding factors, the effect of the co-variates on the outcome variables was investigated. Factors associated with the outcomes (TTBP or TL/1000 sows) at $P < 0.200$ in the univariate analysis were entered in the multivariate model, and non-significant factors ($P > 0.05$) were removed by backward-selection procedure. The vaccine exposure factor (main effect) was forced into all multivariate models. Major model assumptions including proportional hazards for Cox regression, normality for residuals for GLM, and linear relationship for numerical predictors were tested. All statistical analyses were performed with SAS 9.4 software (SAS Institute Inc., Cary, North Carolina).

3. Results

The study included 78 eligible herd-outbreaks (Table 1).

Table 1 - Baseline demographic characteristics of the eligible outbreaks enrolled in the study.

Characteristics	Exposure groups	
	KV vaccine -boostered	MLV vaccine-treated
Number of outbreaks	27	51
Herd size (mean ± SE)	2918 ± 1198[a]	2531 ± 1129[a]
Weaning frequency	1 and 2/week: 10 (37%)[a]	1 and 2/week: 40 (78%)[b]
	3+/week: 17 (63%)[a]	3+/week: 11 (22%)[b]
Gilt acclimation site	Offsite: 11 (41%)[a]	Offsite: 38 (75%)[b]
	Onsite: 16 (59%)[a]	Onsite: 13 (25%)[b]
Prior PRRS status	Unstable: 3 (11%)[a]	Unstable: 10 (20%)[a]
	Stable: 24 (89%)[a]	Stable: 41 (80%)[a]
US Region	Midwest: 27 (100%)[a]	Midwest: 13 (26%)[b]
	Southeast: 0 (0%)[a]	Southeast: 38 (74%)[b]

Different superscripts indicate statistical significance at P<0.05 between groups on T-test or Chi-square.

3.1. TTBP

All the herd-outbreaks reached TTBP by 30 weeks as shown in figure 2.

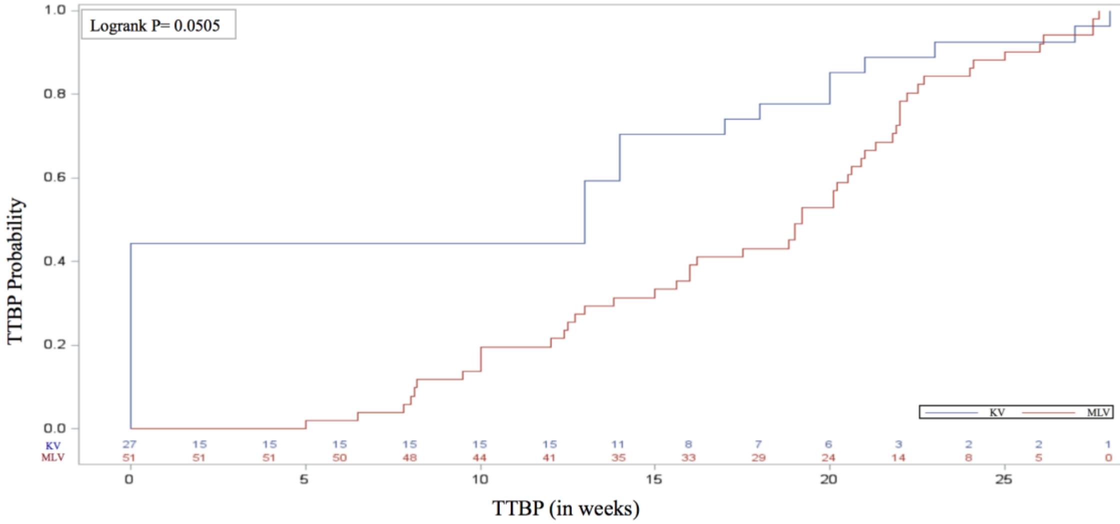

Fig 2. EVMA control chart illustrating time-to-baseline production (TTBP). Y-axis describing TTBP probability from 0-100%; X-axis describing TTBP in weeks from 0-30 weeks. The blue line representing killed virus (KV) vaccine boostered group and red line representing modified live virus (MLV) vaccine treated group. Pairwise log rank test between two groups not statistically significant (P= 0.0505).

The median TTBP of the herd-outbreaks in the KV vaccine-boostered group was 13 weeks with an interquartile range (25th to 75th percentile) of 0-18 weeks. The median TTBP of the herd-outbreaks in MLV vaccine-treated group was 19 weeks with an interquartile range of 13-22 weeks. The difference between the two exposure groups was not statistically significant in the univariate (P 0.0505) as well as in the multivariate analysis (P 0.4242).

Univariate analysis

The KV vaccine-boostered group had a trend of shorter TTBP compared to MLV vaccine-treated group by 6 weeks (P 0.0505) as shown in Table 2.

Table 2 - Comparison of TTBP and TL/1000 sows

Results	Exposure groups		P-value
	KV vaccine-boostered	MLV vaccine-treated	
Median TTBP (in weeks) (25th and 75th percentile)	13^{a} (0, 18)	19^{a} (13, 22)	0.0505
Median TL/1000 sows (25th and 75th percentile)	231^{a} (0, 1897)	1845^{b} (1154, 2964)	0.0003

Different superscripts indicate statistical significance at P<0.05 between groups on log rank and Wilcoxon test for TTBP and TL/1000 sows, respectively

The univariate analysis of co-variates revealed that there was a shorter TTBP when herd-outbreaks: had a weaning event 3+ per week (P< 0.0001), herd size ≤ 8000 (P< 0.0001), onsite gilt acclimation site (P< 0.0001), herd-outbreaks from midwest region (P< 0.0001), and unstable PRRS status prior to an outbreak (P< 0.0001) were significant, independent of the exposure (sow exposure).

Multivariate analysis

The final TTBP multivariate model, included frequency of weaning events per week (P 0.0122). After adjusting for frequency of weaning events per week, there was no difference in TTBP between exposure groups (P 0.4242).

3.2. Total loss outcome

The median TL/1000 sows of the herd-outbreaks in the KV vaccine-boostered group was 231 pigs with an interquartile range (25th to 75th percentile) of 0-1897 pigs. The median TL/1000 sows of the herd-outbreaks in MLV vaccine-treated group was 1845 pigs with an interquartile range of 1154-2964 pigs. The difference between the two exposure groups was statistically significant in both the univariate and multivariate analysis at (P 0.0003) as shown in figure 3 and (P 0.0021).

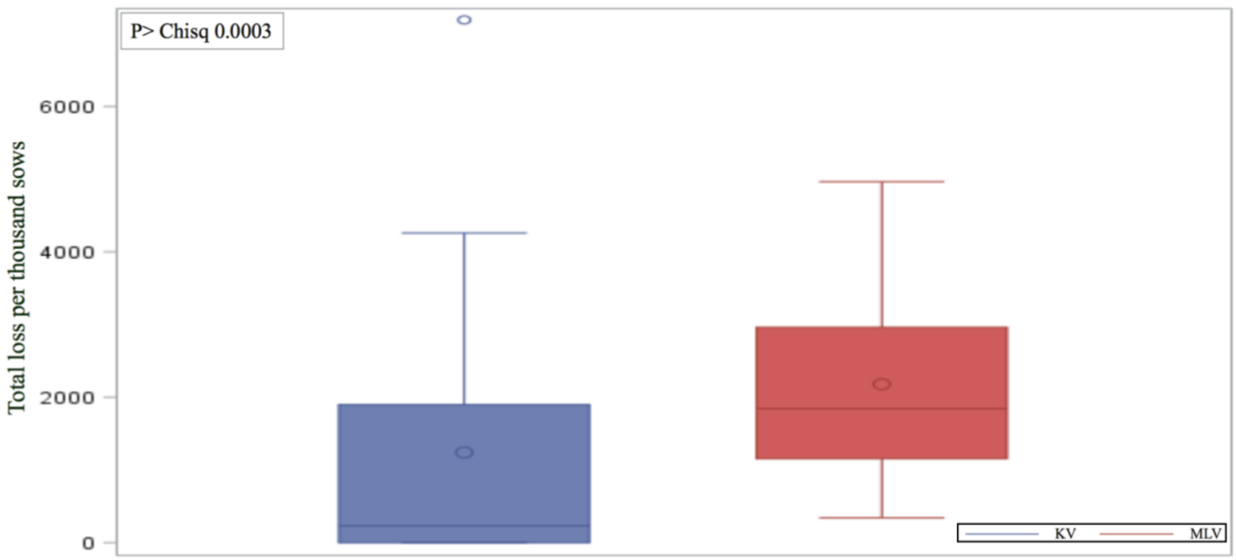

Fig 3. Box plot showing total loss in the weaned pigs per 1000 sows. Y-axis describing number of pigs loss from 0-8000. The blue box representing killed virus (KV) vaccine boostered group and red box representing modified live virus (MLV) vaccine treated group. Wilcoxon test between two groups showing statistical significant difference in TL/1K sows (P= 0.0003).

Univariate analysis

The herd-outbreaks using KV vaccination protocol had significantly fewer losses compared to herd-outbreaks utilizing MLV protocol (P 0.0003) as shown in Table 2. The univariate analysis of co-variates showed that there were fewer TL per thousand sows when herd-outbreaks: had frequency of weaning events 3+ per week (P 0.0003), followed KV vaccination protocol in sows (P 0.0003), herd-outbreaks from mid-west region (P< 0.0001), herd size ≤ 8000 (P< 0.0007, had onsite gilt acclimation site (P< 0.0001), and had an unstable PRRS status prior to the outbreak (P< 0.0001) were significant, independent of the exposure (sow exposure).

Multivariate analysis

The final TL/1000 sows multivariate model included frequency of weaning events 3+ per week (P < 0.0001), PRRS vaccination protocol in sows (P 0.0130) and unstable PRRS status prior (P 0.0411).

Adjusting for weekly weaning frequency and prior PRRS status, the herd-outbreaks in the KV vaccine-boostered group had a median total loss that was 697 pigs per 1000 sows lower compared to the MLV-treated group (P 0.0021). The herd-outbreaks with the frequency of weaning events 3+ per week experienced lower losses, reporting 982 fewer pigs per 1000 sows respectively compared to herd-outbreaks weaning ≤ 2 times per week. The herd-outbreaks with prior PRRS status before an outbreak as unstable had a lower loss by 599 pigs per 1000 sows when compared with herd-outbreaks with stable prior PRRS status.

4. Discussion

This was an observational retrospective study characterizing the herd-level outcomes of PRRSv infection on U.S. breeding herds adopting different immunologic solutions on the breeding herd. To the best of our knowledge, this is the first peer reviewed manuscript comparing the change in productivity in the breeding herds adopting KV or MLV vaccination protocols following PRRSv outbreak under field conditions. The metrics used to report the outcomes were time to baseline production (TTBP) and total loss per thousand sows (TL/1000 sows). These metrics together provide applied information for veterinarians and producers to aid in understanding and making informed decision regarding health interventions in breeding herds that become infected with PRRSv (Linhares et al., 2014).

On the univariate analysis, the study reported a TTBP 6 weeks shorter (P 0.0505) for outbreaks in the KV vaccine-boostered group as compared to those in the MLV group. This was nearly statistically significant. However, after adjusting for significant co-variates, there was no difference of TTBP between exposure groups (P 0.4242).

In the final model, after adjusting for weekly weaning frequency and prior PRRS status the herd outbreaks in the KV vaccine-boostered group had a lower median total loss of 697 per 1000 sows compared to the MLV-treated group (P 0.0021).

The advantage observed in the KV vaccine-boostered group may be due to an immunologic boosting effect of killed PRRSv vaccination. As reported by various research groups, repeated administration of a KV vaccine was capable of boosting anti-PRRSv immunity as demonstrated by increase in serum neutralizing antibodies and interferon gamma cells (Zuckermann et al., 2007; Nilubol D et al., 2004). It has been reported that exposure of KV vaccine to sows and gilts, increased the serum neutralizing antibodies which are important immune response for viremia clearance and protective immunity against PRRSv infection (Joo et al., 1999; Osorio et al., 2002).

Another study showed that KV vaccine administered to pigs with previous PRRSv exposure to MLV or natural infection, induced greater serum neutralizing antibody response (Baker et al., 1999). Thus, it is within reason to speculate that higher serum neutralizing antibodies in pigs can potentially lower TL/1000 sows and shorten TTBP. The shorter TTBP and lower

TL/1000 sows in the KV vaccine-boostered group may have been due to other factors such as PRRS virus selection process, and vaccine adjuvant.

This retrospective observational study showed that the herd-outbreaks with frequency of weaning events 3+ per week had a shorter TTBP and lower TL/1000 sows when compared to the herds with the frequency of weaning events 1 and 2 per week which is in agreement with what has been reported in another study (Linhares et al., 2017). This study also found that the herd-outbreaks with an unstable prior PRRS status before an outbreak had a lower TL/1000 sows compared to herd-outbreaks with a stable PRRS status prior to an outbreak which could be due to presence of the underlying immunity against PRRSv in those unstable herds prior to a PRRSv outbreak. As revealed by Murtaugh et al. (2002) previously infected pigs develop immunity to PRRSv faster than pigs infected for the first time.

Some of the limitations of this study are that being retrospective study, it was not possible to compare directly between two exposure group other risk factors may be present that were not addressed; herd immunity level of herd-outbreaks may not have been completely comparable between the two exposure groups; the analysis was done in herd-outbreak(s) rather than herds hence outbreaks from same herds were not independent; and there was no group consisting of no exposure following outbreak, which did not enable assessing the full benefit of the vaccination programs.

5. Conclusions

In the multivariate model, after adjusting for frequency of weaning events per week, there was no difference in TTBP between exposure groups (P 0.4242). However, for TL per 1000 sows after adjusting for weekly weaning frequency and prior PRRS status the herd-outbreaks the KV vaccine-boostered group had a lower median total loss of 525 per 1000 sows compared to the MLV-treated group (P 0.0130). A prospective field study is needed to further clarify the role of KV vaccination protocols on herd-level metrics of PRRS control including time to produce PRRSv-negative pigs at weaning, TTBP and total loss.

6. Acknowledgement

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