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Fostera® PRRS Vaccine as an Aid in Preventing Reproductive Disease in Gestating Females

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Porcine reproductive and respiratory syndrome virus (PRRSV) is universally recognized as a major threat to profitable pork production. In an economic assessment study,[1] researchers estimated that PRRS costs the US pork industry $664 million annually ($1.8 million/day) in production-related losses, and the cumulative impact of PRRSV totals more than $1 billion per year when other disease-control expenses are included.

As the name implies, PRRS has two pathological presentations: causing *reproductive disease* in gestating gilts and sows, and causing *respiratory disease* in growing pigs (pneumonia, poor performance, immunosuppression). Exposure of pregnant swine to field strains of PRRSV can devastate the productivity of a breeding herd. Gestating dams may abort their litters or suffer high rates of stillborns and mummies, and the viability of live-born piglets may be jeopardized.

Notably, nearly half of the direct economic damages caused by PRRS is sustained in *breeding herds* (estimated at $302 million/year, equating to $52.19 per breeding female or $2.36 per pig weaned).[1] Most of the economic impact is due to $300 million in reduced revenues resulting from 8.3 million fewer weaned pigs.[1]

Nearly half of the direct economic damages caused by PRRS are sustained in breeding herds ($302 million/year).[1]

This serious economic damage caused by PRRSV in breeding herds has prompted much industry interest in the use of modified-live (MLV) PRRSV vaccines in gilts and sows. For instance, one recent research study found that breeding herds vaccinated with a MLV vaccine as part of a PRRSV control program recovered production sooner and suffered less total loss than herds that employed a live-resident virus inoculation approach.[2] Thus, when selecting a PRRSV vaccine, it is important to consider if a vaccine can help prevent the detrimental reproductive impacts of PRRS (e.g., aborted litters, dead/low-viable piglets, etc.) when used in gilts and sows in addition to offering respiratory protection when used for growing pigs.

Fostera® PRRS

Fostera PRRS, from Zoetis, is the first and only PRRSV vaccine that helps:

1) ***prevent reproductive disease*** due to PRRSV in gestating females ***with a duration of immunity of at least 19 weeks,*** and

2) ***prevent respiratory disease*** associated with PRRSV with a ***duration of immunity of at least 26 weeks.***

Fostera PRRS is the outcome of breakthrough research by Zoetis scientists who discovered a key cellular receptor protein for the PRRS virus, thus allowing for creation of unique cell lines for the growth and attenuation of PRRS vaccine virus.

Fostera® PRRS is now licensed as an aid in preventing reproductive disease due to PRRS virus in gilts and sows.

Respiratory Disease —
Fostera PRRS is licensed for the vaccination of healthy, susceptible swine 1 day of age or older in PRRS virus-positive herds as an ***aid in preventing respiratory disease*** caused by PRRS virus. A 26-week duration of immunity has been demonstrated against respiratory disease. Fostera PRRS is administered as a single 2-mL intramuscular (IM) dose, after aseptic rehydration of the freeze-dried vaccine with sterile diluent provided.

Fostera PRRS is the first and only PRRSV vaccine with a claim for administration as early as 1 day of age. Fostera PRRS helps optimize performance by helping minimize the adverse affects of a subsequent PRRSV challenge, thereby allowing growing pigs to help maximize post-challenge weight gain.[3]

Now also a claim for Reproductive Disease —
Recent on-going research has yielded yet another distinction for Fostera PRRS as clinical efficacy in helping prevent the adverse reproductive impacts of PRRS has demonstrated. As a result, the USDA has now licensed Fostera PRRS (single 2-mL IM dose) with the following additional indication:

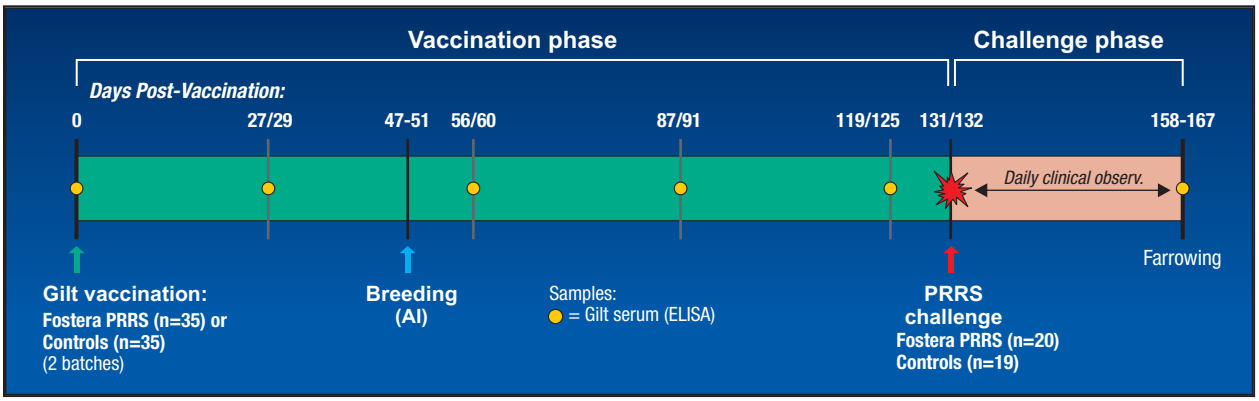
- *For vaccination of healthy, susceptible swine in PRRS virus-positive herds as an **aid in preventing reproductive disease** caused by PRRS virus. **A 19-week duration of immunity** against reproductive disease has been demonstrated in swine vaccinated prebreeding. Safety of this product has been demonstrated when sows or gilts are vaccinated prior to breeding or at any stage of pregnancy. Protection against reproductive disease, however, was demonstrated when animals were vaccinated 6 weeks prior to breeding. Consult your veterinarian for appropriate use and timing of vaccination.*

The addition of this unique reproductive indication to the Fostera PRRS label represents yet another innovative attribute that further differentiates Fostera PRRS from other PRRSV vaccines. A summary of efficacy and safety research supporting the ability of Fostera PRRS vaccine to help prevent reproductive disease follows.

Challenge Study – Experiment Design

A clinical research study evaluated the immunogenicity of Fostera PRRS in gilts vaccinated approximately 6 weeks pre-breeding and then challenged with PRRSV in the third trimester (about 85 days of gestation; the stage of pregnancy that is most sensitive to PRRSV),[4] thus simulating a 'worst-case' scenario in regards to the stage in which PRRS impact is greatest on a sow farm. The study involved 70 healthy, cross-bred, breeding-age gilts (approximately 6 months of age) sourced from a Minnesota producer and shipped to an in-state research facility (2 batches of gilts, 40 in June and 30 in November). No

Figure 1. Study design and timeline.



animals had a history of PRRS disease or vaccination, and all were confirmed serologically negative for PRRSV (IDEXX ELISA S/P < 0.4).

Gilts were randomly allotted to 2 treatment groups upon arrival at the study site, with each treatment group housed in separate rooms (air spaces). After an acclimation period of 3 to 10 days, animals in each treatment group received the following injections on study day 0 (vaccination phase, Figure 1):

- Control (placebo, 2 mL IM left neck, n=35);
- Fostera PRRS (2 mL IM left neck, n=35).

Animals were monitored for any abnormal local and systemic adverse events within 1 hour post-vaccination (none observed).

Gilts were synchronized by oral administration of altrenogest for 14 consecutive days prior to breeding (artificial insemination) on days 47 to 51. Ultrasound pregnancy checks performed at days 88 or 92 confirmed 39 pregnancies:

- Control, n=19;
- Fostera PRRS, n=20.

The challenge phase of the study began at approximately 85 days of gestation (day 131-132) when all pregnant gilts were commingled and re-housed in individual crates in a BSL2 facility. Each gilt received a PRRSV NADC20 isolate administered intranasally (3 mL/nostril) and IM (2 mL right neck). Gilts were observed daily for signs of clinical PRRS until farrowing on study days 158 to 167.

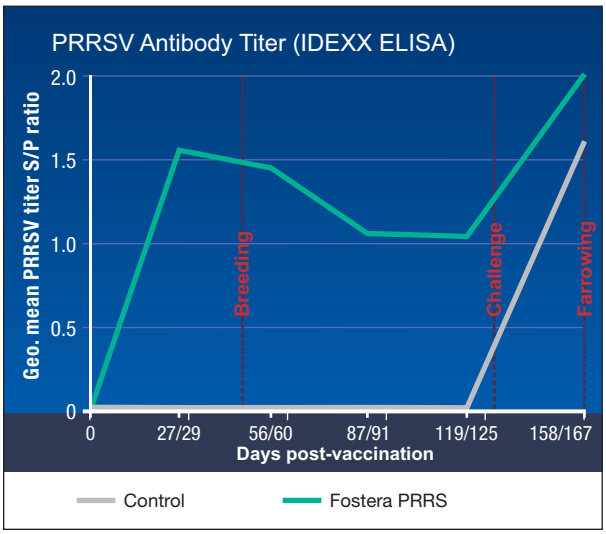
Data collected during the study included gilt PRRSV serology, gilt PRRS morbidity, and litter productivity parameters. The clinical parameters most relevant to reproductive disease efficacy included live-born piglets vs dead-born piglets (mummies or stillborn) or low-viability piglets (< 1 kg, non-ambulatory); and litter viability (100% loss of a litter via abortion or all non-viable). Additional clinical parameters that were assessed included post-challenge clinical signs of PRRSV in gilts (general condition, inappetence, depression, respiratory distress, etc.) and gilt PRRSV serology (serum samples collected prior to vaccination, at approximately 30-day intervals pre-challenge, and at farrowing were evaluated for anti-PRRSV antibody by IDEXX ELISA).

Data were statistically analyzed by appropriate standard methods using each pig as an experimental unit. Statistical significance was recognized at $P \leq 0.05$. The study was conducted in accordance with the Zoetis Institutional Animal Care and Use Committee.

Challenge Study – Results

Serology results summarized in Figure 2 revealed that gilts vaccinated with Fostera PRRS generated higher PRRSV antibody titers on all sample days compared to control animals. All but 1 gilt in the Fostera PRRS group had seroconverted by day 27/29, and all were seropositive at the time of

Figure 2. Mean serological responses of treatment groups.



Fostera® PRRS

Fostera® PRRS helps deliver more live pigs by helping prevent the reproductive form of the disease caused by PRRSV.

Table 1 – Litter viability outcomes.

Parameter	Control	Fostera PRRS
No. gilts	19	20
Litters removed	2 (11%)	0
Litters aborted	5 (26%)	3 (15%)
Litters farrowed	12 (63%)	17 (85%)
- Viable* litters	1 (5.3%)[a]	17 (85%)[b]

*Non-viable litters include aborted or farrowed with no viable piglets.
[ab] $P = 0.0047$

Table 2 – Piglet viability outcomes.

Parameter	Control	Fostera PRRS
Total piglets born	244	251
Live	9 (3.7%)	155 (61.8%)
- Viable	4 (1.6%)	134 (53.4%)
- Low viability*	5 (2.1%)	21 (8.4%)
Dead	235 (96.3%)	96 (38.2%)
- Stillborn	80 (32.8%)	60 (23.9%)
- Mummies	155 (63.5%)	36 (14.3%)

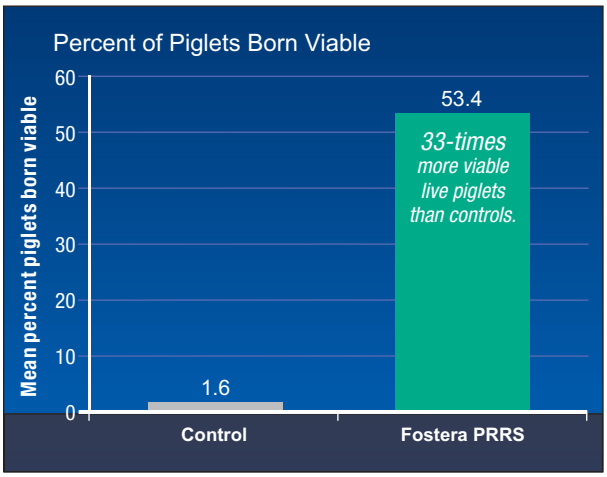
*Piglets weighing less than 1 kg at birth or non-ambulatory piglets.

challenge. In contrast, all control gilts remained seronegative until challenge. All gilts in both groups were seropositive at farrowing, with animals in the Fostera PRRS group demonstrating an anamnestic response to PRRSV challenge.

Litter outcomes for the study (Table 1) indicated that gilts vaccinated with Fostera PRRS farrowed substantially more litters (fewer abortions and removals) than non-vaccinated controls. Furthermore, only 1 of 19 litters (5.3%) farrowed by control gilts included viable piglets, but 17 of 20 litters (85%) farrowed by vaccinated gilts included viable piglets ($P = 0.0047$). In addition to demonstrating Fostera PRRS efficacy, these outcomes also provide evidence that the PRRSV challenge was successful and severe.

Piglet viability results are summarized in Table 2 and Figure 3. Notably, 33-times more viable piglets were born from gilts vaccinated with Fostera PRRS (134 piglets) vs control gilts (4 piglets). The virulent challenge infection clearly exerted severe impacts on piglet production for both groups, but Fostera PRRS helped preserve the viability of piglets produced by vaccinated gilts.

Figure 3. Piglets born live and viable.



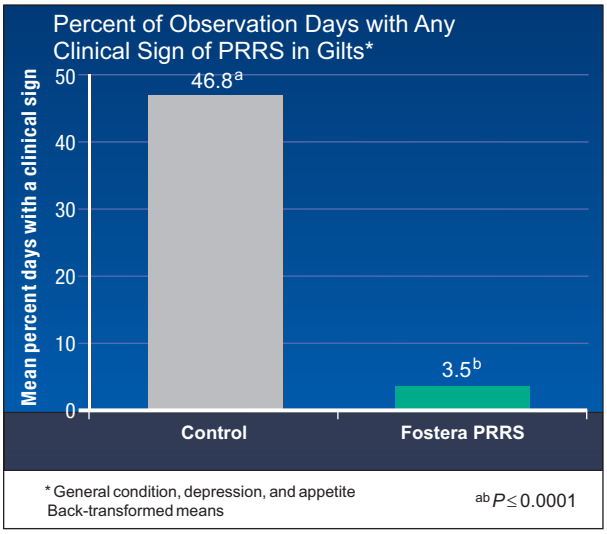
Fostera® PRRS helped reduce the incidence and duration of clinical signs of PRRS in gilts.

Table 3 – Percent of gilts exhibiting any clinical sign of PRRS.

Parameter	Control	Fostera PRRS
Poor condition (%)	42.1	5.0
Depression (%)	100.0	45.0
Respiratory distress (%)	21.1	0.0
Cough (%)	5.3	0.0
Inappetence (%)	100.0	40.0
Other (%)*	26.3	0.0
Death (%)	15.8	0.0

*Vomiting, abortion, failure to stand

Figure 4. Clinical signs of PRRS in gilts.



Other study criteria concerned the incidence of PRRS clinical signs in gilts (Table 3). Depression and inappetence were the primary abnormal clinical signs observed in gilts after challenge. The incidence of clinical signs was much lower for Fostera PRRS vaccinates compared to non-vaccinated controls. The duration of clinical signs was also much shorter in the Fostera PRRS group (Figure 4). The mean percent of observations days with any clinical sign of PRRS was reduced from 46.8% for controls to 3.5% for the Fostera PRRS group ($P \leq 0.0001$). Thus, Fostera PRRS reduced the percent of gilt sick days by 92.5% vs controls.

Safety Study – Experiment Design

A clinical safety study involved 1200 gilts and sows (parities 0 to 9) that were enrolled at 2 separate commercial production sites (PRRSV seropositive/stable) in North Carolina (n=600) and Iowa (n=600).[5] The study protocol was reviewed and approved by the Zoetis Kalamazoo Ethical Review Board, and a Zoetis Animal Welfare Risk Assessment was completed for each site prior to initiation of the study. Healthy breeding-age females at each site were selected to populate 4 gestational classes (n=150/class):

- pre-breeding;
- first trimester (days 1-40 of gestation);
- second trimester (days 41-75 of gestation);
- third trimester (days 76-110 of gestation).

Within each of these gestational classes, animals were assigned to 2 treatment groups (approximately 2:1 ratio) using a randomized complete block design with blocking based on crate/pen location. On study day 0, each gilt or

Fostera® PRRS

sow received a single 2-mL IM injection in the right neck with either:

- Saline or sterile water (control, n=50);
- Fostera PRRS (n=100).

As a result, the overall study (2 sites) involved the following animal allotments:

	Control	Fostera PRRS
Pre-breeding	n=100	n=200
First trimester	n=100	n=200
Second trimester	n=100	n=200
Third trimester	n=100	n=200

All gilt/sows were observed for adverse reactions within 1 hour, 6 hours, and 1 day post-vaccination, and clinical observations were conducted at approximately weekly intervals starting on day 7 until study conclusion on day 21. All injection sites were observed and palpated on days 1 and 7 for adverse reactions, with any reactions reevaluated weekly until resolution. Animals were also observed daily for any clinical disease or adverse events requiring treatment. All cases were determined whether to be related to vaccine or saline administration, and any sows/gilts that died were necropsied and a diagnosis determined when possible.

Reproductive data collected during the study included farrowing outcomes (e.g., number of gilts/sows farrowed, aborted, not bred, not pregnant, culled/died) and litter details (e.g., number of normal live-born piglets, low-viability piglets, stillborns, and mummies; 'low-viability' defined as < 1 kg, non-ambulatory, unable to suckle). The general health of piglets was assessed daily for 1 week. When a sow or gilt aborted, tissues were collected and submitted to a diagnostic laboratory to identify cause when possible. All personnel performing clinical observations, injection site reaction measurements, or data collections were blinded to treatment group assignments.

The non-vaccinated control group provided baseline information regarding the current herd health conditions at each site. Thus, the incidence and severity of health events in the Fostera PRRS group were compared to those occurring in the control group. Data were evaluated by appropriate methods using crate/pen as the experimental unit.

Safety Study – Results

A total of 28 and 46 gilts/sows were removed from the NC and IA sites, respectively, prior to study completion for various reasons including not pregnant, death or euthanasia, culling for various health reasons, or deviation from the protocol. No confounding disease factors were detected at the NC site, but an outbreak of porcine epidemic diarrhea virus (PEDv) was experienced at the IA site which heavily impacted piglets born to sows vaccinated in the second-trimester gestational phase (most litters euthanized at birth). Some litters were also impacted by a Delta Corona virus outbreak in the pre-breeding gestational class (piglets or occasionally entire litters euthanized when scours observed). However, Fostera PRRS vaccine safety and reproductive data from the IA site were still considered valid.

Only very low rates of abnormal post-vaccination reactions (anorexia, depression) were observed on day 0 (0.25% and 0.88% for controls and vaccinates, respectively). No observations of diarrhea or dyspnea were recorded. Similarly, few gilts/sows (2.3% controls, 1.0% vaccinates) showed abnormal clinical signs (lameness, abortion, prolapse, anorexia, depression) at days 7, 14, or 21. Thus, no clinically significant differences were detected between treatment groups and gestational classes in either the types or numbers of abnormal health observations recorded.

Transient injection site reactions were minimal and similar rates occurred in all gestational classes

Table 4 – Incidence of injection site reactions (days after vaccination, summary of 2 sites).

Treatment	n	Day 1	Day 7	Day 14	Day 21
Control	400	1.0%	1.3%	0.8%	0.0%
Fostera PRRS	799	2.1%	1.1%	0.5%	0.1%

Fostera® PRRS had no adverse impacts on farrowing rates or piglet viability, regardless of vaccination timing.

Table 5 – Farrowing rates.

	Control		Fostera PRRS	
Gestational class	**n**	**Farrow rate**	**n**	**Farrow rate**
All gilts/sows	397	92.9%	795	93.3%
Pre-breeding	100	82.0%	200	84.0%
1st trimester	100	99.0%	200	96.0%
2nd trimester	99	94.9%	199	95.5%
3rd trimester	98	95.9%	196	98.0%

and treatment groups. Low rates of injection site reactions (swelling, rubbing) were observed on day 1 (1.0% and 2.1% for controls and vaccinates, respectively; Table 4). Most reactions had resolved by day 14, and all but 1 had resolved by day 21 (resolved by day 29).

As shown in Table 5, the overall farrowing rates for gilts/sows were similar between treatment groups (92.9% and 93.3% for controls and vaccinates, respectively). Abortions were noted in all treatment groups and were within the normal range for the breeding herds. Farrowing rates between treatment groups were similar for all gestational classes, suggesting that vaccination with Fostera PRRS had no adverse impact on farrowing regardless of the timing of administration.

Piglet viability results summarized in Table 6 indicate that both treatment groups also generated similar rates of live-born viable piglets, low-viability piglets, stillborns, and mummies. No clinically relevant differences were observed between groups and viability rates were similar for all gestational classes, suggesting that Fostera PRRS had no adverse impact on piglet viability regardless of vaccination timing.

Table 6 – Piglet viability outcomes.

Parameter*	Control	Fostera PRRS
Live/viable (%)	**91.2**	**91.6**
Pre-breeding	90.8	91.5
1st trimester	91.6	90.7
2nd trimester	93.3	93.7
3rd trimester	88.7	90.2
Low-viable (%)	**2.7**	**2.5**
Pre-breeding	2.2	2.2
1st trimester	2.2	2.4
2nd trimester	2.4	1.5
3rd trimester	4.0	4.4
Stillborn (%)	**1.6**	**1.7**
Pre-breeding	2.2	2.1
1st trimester	1.7	2.2
2nd trimester	0.9	1.4
3rd trimester	1.9	1.1
Mummy (%)	**0.5**	**0.6**
Pre-breeding	0.9	0.7
1st trimester	0.5	0.6
2nd trimester	0.3	0.6
3rd trimester	0.4	0.5

*Back-transformed means.

Fostera® PRRS

Fostera® PRRS offers comprehensive herd management of PRRSV by helping protect against both the respiratory and reproductive forms of the disease.

Conclusions

Results of the challenge study confirm that single-dose vaccination of gestating females with Fostera PRRS before breeding helps prevent reproductive disease due to PRRS virus. When Fostera PRRS was administered to gilts approximately 50 days before breeding, the detrimental impacts of virulent PRRSV challenge in the third trimester of pregnancy (about 19 weeks after vaccination) were reduced as evidenced by the farrowing of more viable litters, the birth of more live pigs, and reduced clinical signs of disease in gilts.

In the safety study, the rate of abnormal health events for vaccinates during the 21-day post-vaccination observation period was consistent with herd health observations and not related to administration of Fostera PRRS. Injection site reactions were minimal and occurred in all treatment groups, with most resolved by day 14. No clinically relevant differences in any reproductive parameters were detected during the reproductive portion of the study, regardless of which gestational phase vaccination was performed.

Fostera PRRS offers swine veterinarians and pork producers the opportunity to achieve comprehensive whole-herd management of PRRS by helping protect against *both* the reproductive and respiratory consequences of unmitigated disease.

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