How long does it take for breeding herds to produce PRRSv-negative piglets? (TTNP study)

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Acknowledgments

• Participating producers and veterinarians

• Boehringer Ingelheim Vetmedica and U of MN Swine Disease Eradication Center (SDEC) for funding
Objective

To compare time to reach TTNP* between herd exposure methods using LVI or MLV.

(*) based on AASV’s PRRS herd classification (category II-b)
The study groups are PRRSv-infected herds exposed to one of the following treatments:

A. Live-virus inoculation (LVI)

B. Modified-live virus (MLV) vaccines

Statistical analysis:

- Descriptive statistics
- Kaplan-Meier & Cox proportional hazards regression
Monitoring

- Herds were monitored for PRRSv by serum PCR
- Monthly testing of at least 30 piglets, starting at 12 weeks post intervention
- Herds were considered as producing negative pigs when 4 consecutive negative PCRs were obtained.
Baseline demographic characteristics of all enrolled herds*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>LVI</th>
<th>MLV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number enrolled</td>
<td>41</td>
<td>20</td>
</tr>
<tr>
<td>Prior PRRSv-infection (y/n)</td>
<td>20 (49%)</td>
<td>13 (65%)</td>
</tr>
<tr>
<td>RFLP strain 1-4-4</td>
<td>15 (38%)</td>
<td>12 (60%)</td>
</tr>
<tr>
<td>Herd size (Mean ± SE)</td>
<td>3,499± 303\textsuperscript{a}</td>
<td>2,471 ± 250\textsuperscript{b}</td>
</tr>
<tr>
<td>Days from PRRSv-detection to intervention (Mean ± SE)</td>
<td>28 ± 3</td>
<td>39 ± 9</td>
</tr>
</tbody>
</table>

* There were no significant differences between groups at alpha level of 0.05 for prior infection and RFLP 1-4-4 (Fisher’s exact, p-values 0.2813 and 0.1102 respectively), and for days from PRRSv-detection to intervention, (t-test, p-value 0.2526). For herd size, LVI herds were significantly larger than MLVs (t-test p-value 0.0324).

80% power to detect a difference of TTNP between treatment groups assuming hazard ratio of at least 2.3.
“200 days” was not enough to achieve TTNP for ~half of the herds:

Linhares, Cano, Torremorell & Morrison
- Great variability of TTNP
- Intermittent pattern of PRRSv-detection by PCR
Treatment: LVI vs MLV

50% survival and 95% CI:
LVI: 26.3 (22.57, 29.57)
MLV: 33.0 (32.00, 41.00)

(p-value 0.0171)
50% survival and 95% CI:
Prior_infection: 26.00 (20.71, 30.57)
No prior infect: 32.57 (26.28, 38.00)

\(p\)-value 0.0066
RFLP pattern, herd size and “days from PRRSv detection to intervention” were not good predictors of TTNP.
Proportional hazards regression (multivariate analysis)

The following covariates were removed from the model after backward elimination procedure, as they were not statistically significant in the multivariate model:

• “Days from PRRSv-infection to treatment”,
• “RFLP pattern”,
• “Herd size”.

Type 3 Tests

<table>
<thead>
<tr>
<th>Effect</th>
<th>DF</th>
<th>Chi-Square</th>
<th>Pr &gt; ChiSq</th>
</tr>
</thead>
<tbody>
<tr>
<td>trt</td>
<td>1</td>
<td>9.9084</td>
<td>0.0016</td>
</tr>
<tr>
<td>prior_inf</td>
<td>1</td>
<td>5.9704</td>
<td>0.0145</td>
</tr>
</tbody>
</table>

Analysis of Maximum Likelihood Estimates

<table>
<thead>
<tr>
<th>Parameter</th>
<th>DF</th>
<th>Parameter Estimate</th>
<th>Standard Error</th>
<th>Chi-Square</th>
<th>Pr &gt; ChiSq</th>
<th>Hazard Ratio</th>
<th>95% Hazard Ratio Confidence Limits</th>
</tr>
</thead>
<tbody>
<tr>
<td>trt LVI</td>
<td>1</td>
<td>1.94932</td>
<td>0.61927</td>
<td>9.9084</td>
<td>0.0016</td>
<td>7.024</td>
<td>2.087</td>
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<tr>
<td>prior_inf yes</td>
<td>1</td>
<td>1.00227</td>
<td>0.41019</td>
<td>5.9704</td>
<td>0.0145</td>
<td>2.724</td>
<td>1.219</td>
</tr>
</tbody>
</table>
Summary

• PRRSv monitoring must be done repeatedly over time:
  • 17 farms had at least 1 month of PCR-neg results followed by PCR-pos results
  • 4 farms (MLV) had at least 2 consecutive months of PCR-neg results followed by PCR-positive results (>99% ORF 5 homology)
  • 3 farms (2 LVI, 1 MLV) likely had new virus introduction (based on sequence, time and history)

• Wide range of TTNP (12 – 43 weeks). Median time ~ 210 days.

• TTNP was significantly shorter in
  • LVI farms and
  • farms with prior PRRSv-infection.
Limitations

• Results might be biased due to:
  – Monitoring duration may have missed some infected herds
  – Existence of unknown confounder variables
  – Allocation of treatment (LVI or MLV) was not at random. Some factors such as frequency of PRRSv infection, density of pig farms and pig flow could influence the decision of veterinarians to decide between treatments.
Deciding between whole-herd exposure methods
Quantifying production losses in PRRSv control & elimination projects

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Outcomes

• Comparison between LVI and MLV farms:
  – Median time to reach production levels at baseline (TTBP) \textit{SPC tool (EWMA chart, \( \lambda 0.4, 3.0 \sigma \))}
  – Magnitude of the production loss as reflected by number of pigs weaned/1,000 sows

• Correlation of TTNP, TTBP & Production loss
Time to baseline production (TTBP): EWMA chart, back to “in control” level

Exponentially Weighted Moving Average Chart for TW

- Status
  - Inf_Int
  - LCH
  - TTNP

3σ Limits
- For n=1
- UCL=1957.5
- $\bar{x}=1764.2$
- LCL=1570.8

Total pigs weaned

Subgroup Sizes: n=1
Weight = 0.4
Subgroup Mean

TTBP (24 weeks)

Quantifying the production losses: AUC to sum “pigs not weaned”

Status
Inf_Int  LCH  TTNP

Δ pigs A
3,754.8 pigs
Below expected

Δ pigs B
15,229 pigs
Below expected

TTBP

3σ Limits For n=1
UCL=2150.8
\bar{x}=1764.2
LCL=1377.5
Distribution of total production loss

Distribution of AUC_LCH_TTBP_1Ksows

- Mean: 2377.264
- Std Deviation: 2227.125
- Maximum: 9561.172
- Minimum: 0.003127
- Lower Quartile: 616.805
- Median: 2004.084
- Upper Quartile: 3464.656
Pigs not weaned / 1,000 sows: from PRRSv detection to LCH

Wilcoxon p-value 0.0119
Pigs not weaned / 1,000 sows: from LCH to TTBP

Wilcoxon p-value 0.1323
Removing outliers

Wilcoxon p-value 0.0171
Correlation TTBP & Magnitude = 0.87
Correlation TTNP & TTBP = 0.43
MLV reached TTBP sooner:

Log-rank p-value 0.1799

Removing 3 outliers

Log-rank 0.0140
TTBP: no diff between single vs multiple doses

Product-Limit Failure Curves
With Number of Subjects at Risk

Log-rank p-value 0.8571
Herds w/ prior infection reached TTBP sooner

Log-rank p-value <0.0001
TTBP across systems...

Log-rank p-value 0.0097

Log-rank p-value 0.0017
Multivariate analysis:
System, Prior_infection and # doses

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<tbody>
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<td>treatment</td>
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<td>0.0136</td>
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<tr>
<td>prior_inf</td>
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<td>5.1157</td>
<td>0.0237</td>
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<tr>
<td>system</td>
<td>3</td>
<td>3.9231</td>
<td>0.0153</td>
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<tr>
<td>multiple_doses</td>
<td>1</td>
<td>4.1686</td>
<td>0.0412</td>
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<td>trt*multiple_doses</td>
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<td>5.7676</td>
<td>0.0163</td>
</tr>
<tr>
<td>prior_inf*multiple_d</td>
<td>1</td>
<td>10.5330</td>
<td>0.0012</td>
</tr>
</tbody>
</table>
Interaction prior_infection and # doses (p-value 0.0012)

Herds with prior infection reached TTBP sooner when they were exposed multiple times.
Interaction treatment and # doses (p-value 0.0163)

LVI herds with single doses reached TTBP sooner than LVI herds with multiple doses.

MLV herds with multiple doses reached TTBP sooner than MLV herds with single dose.
Limitations

• “Baseline” in TTBP was defined as productivity levels of 21 weeks prior to PRRSv-detection.
  – Assumption that those levels were the farm’s standard
  – Herds with non-stable reference periods or herds with specific problems such as “went through a fire” were removed.
  – 21-weeks production levels predicted 52-week levels (data not shown)

• We did not investigate the possible effect of other infectious agents.
  – Assumed that PRRSv was the primary cause of production losses compared to reference period.
General summary

• Time to negative
  – PRRSv monitoring must be done repeatedly over time
  – Median TTNP was ~ 210 days, ranging from ~ 90-300 days
  – TTNP was shorter in LVI farms and farms with prior PRRSv-infection

• Production analysis
  – In general, TTNP was poorly correlated with TTBP
  – TTBP was highly correlated with total production loss
  – Farms with MLV had a less severe PRRSv impact at the moment of whole-herd exposure (compared to LVI)
  – MLV farms recovered quicker and had a less severe PRRSv-impact compared to LVI farms
  – Farms with “prior infection” achieved TTBP sooner and had ↓ impact
  – TTNP, TTBP and total production loss varied among vet clinics
Thank you!

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