

Influence of Weaning Vaccine Selection on Pre- Breeding Vaccine Options

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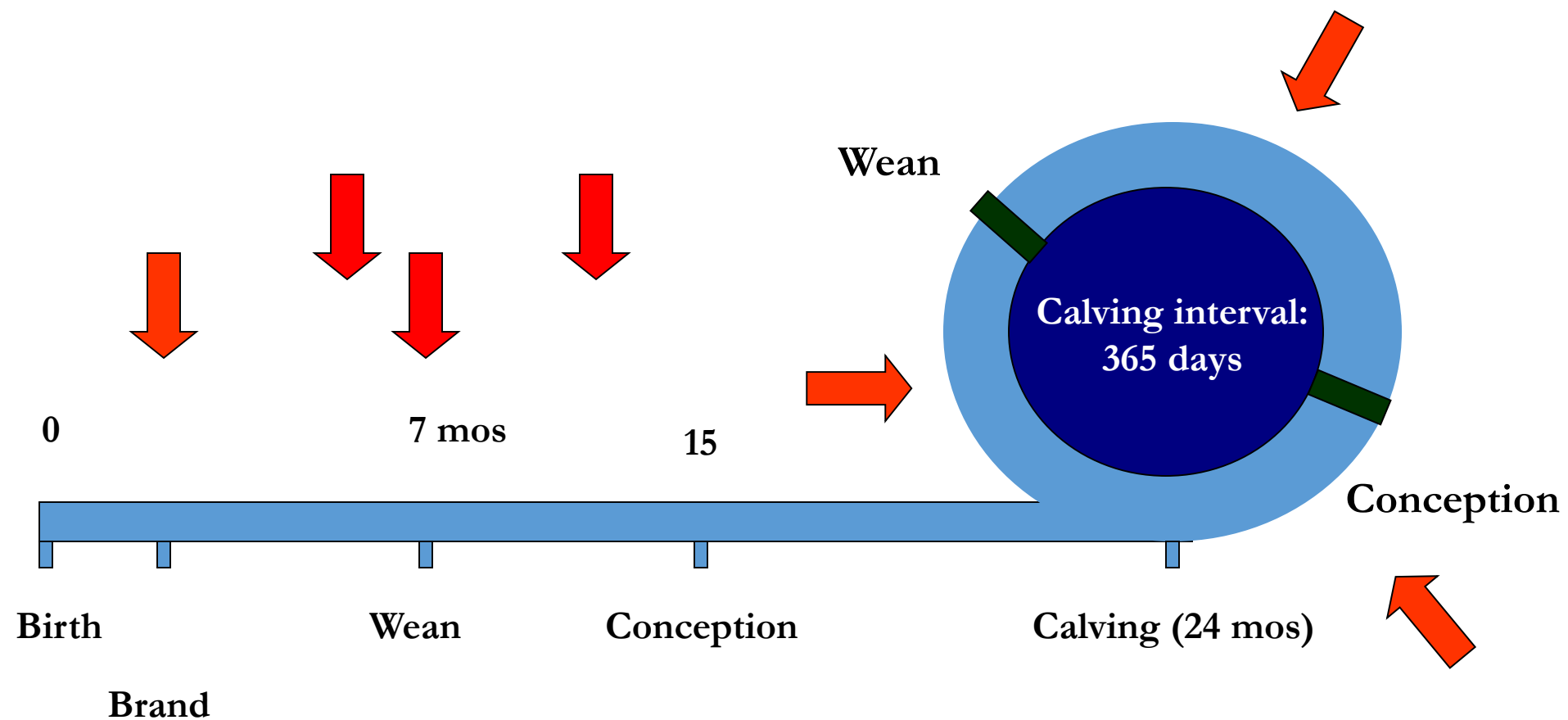


So how do we develop a vaccination program?

- Develop protocol based upon needs of the operation
 - Disease concerns
 - Marketing plan
- Take advantage of opportunity workings and optimize response



Timing of Vaccination



What diseases am I trying to prevent...?

Vaccination
≠
Immunization
≠
Prevention of Infection

Infection ≠ Disease



Vaccination Failures

- Vaccine was not stored properly
- Vaccine was expired
- Vaccine was not administered according to directions
 - Big one!!
- Vaccine was mixed with another vaccine in same syringe



Immunization Failures

- Too many vaccines given at the same time
- Animal was not ready to respond to the vaccine
 - Young
 - Poor nutrition
 - Recent parturition





Precautions:

“This product has been shown to be efficacious in **healthy** animals. A protective immune response may not be elicited if animals are **incubating an infectious disease**, are **malnourished** or **parasitized**, are **stressed** due to shipment or environmental conditions, are otherwise **immunocompromised**, or the vaccine is not administered in accordance with label directions”





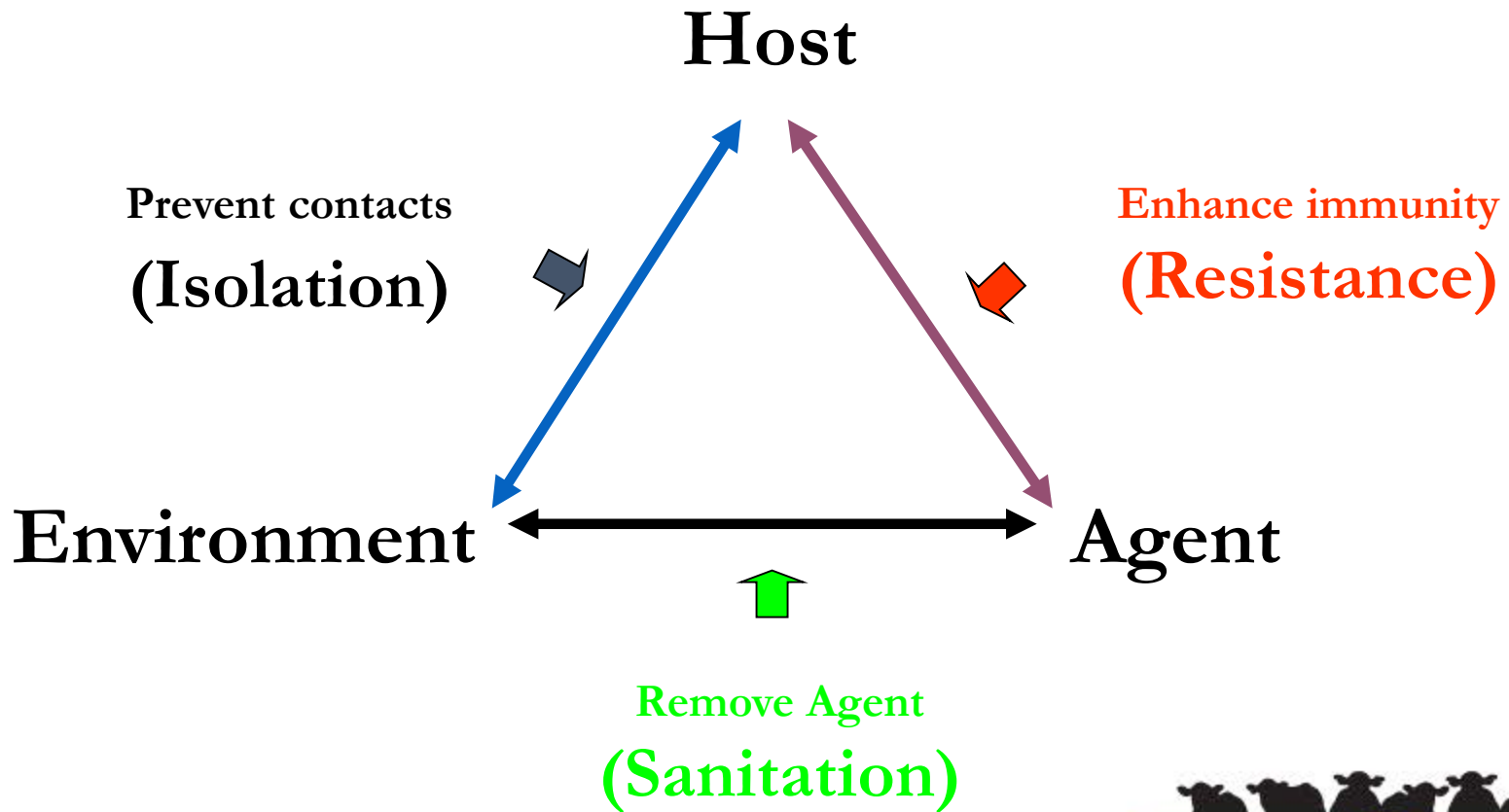
Protection from Disease Failures

- Vaccination is just one part of a herd health program
- Vaccines will reduce severity of clinical disease but do not prevent infection
- Problem is caused by something other than the microbe in the vaccine



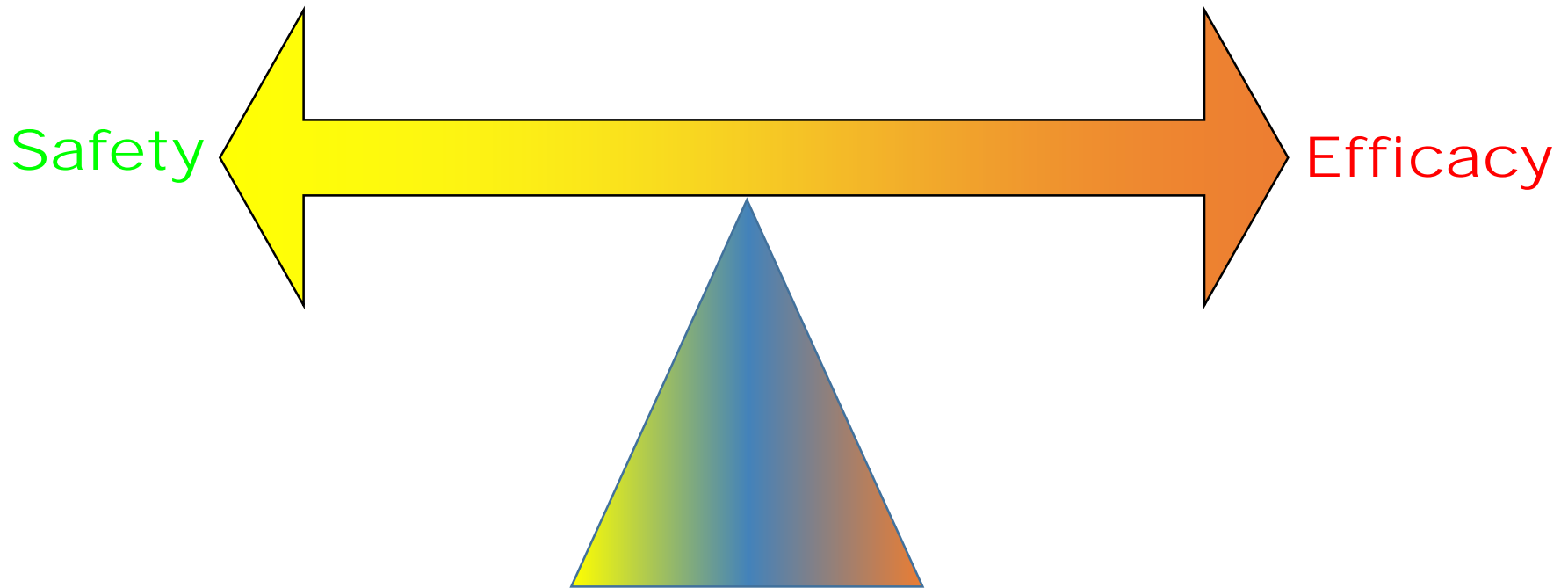
Managing risk factors

I-R-S



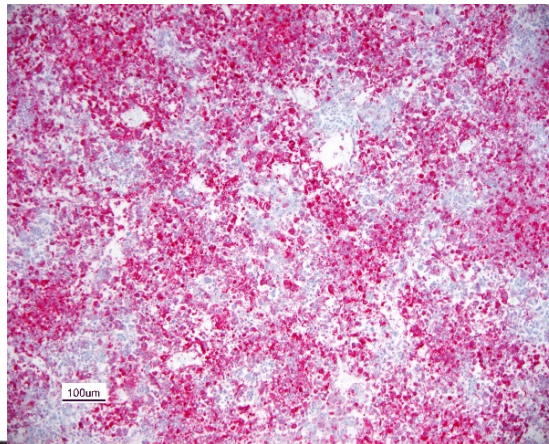
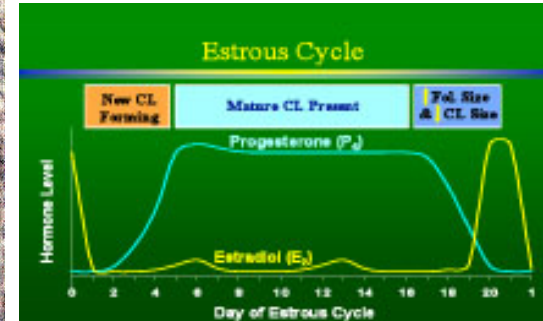
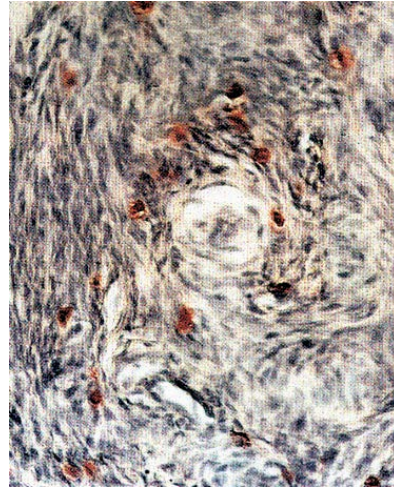
BVDV and BoHV-1 Vaccines

Vaccines for Reproductive Disease

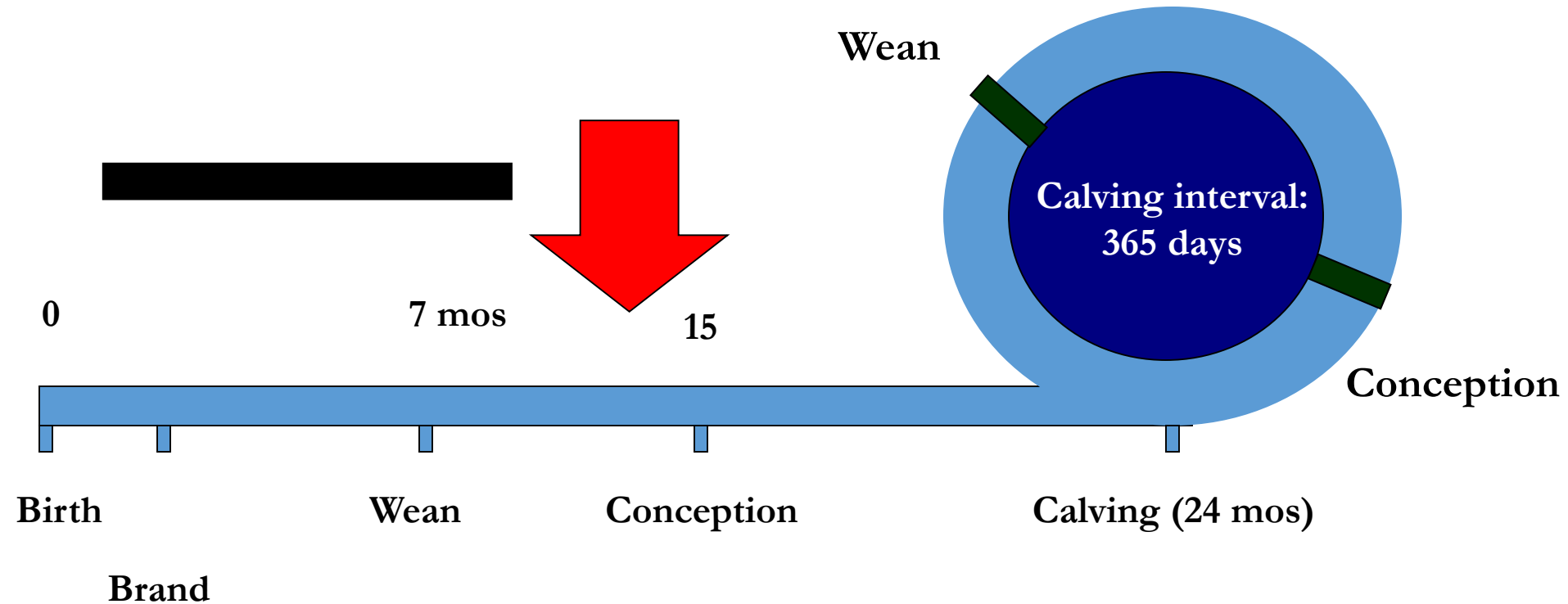


Safety concerns associated with multivalent MLV vaccine

- BVDV:
 - Abortion
 - Infertility
- BoHV-1
 - Abortion
 - Infertility



Timing of Initial Vaccination and Revaccination with Modified-live Viral Vaccines is Critically Important



Reproductive Safety of Vaccination with Vista 5 L5 SQ Near Breeding Time as Determined by the Effect on Conception Rates*

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CLINICAL RELEVANCE

Replacement heifers ($N = 799$; 10 to 13 months of age) were vaccinated with Vista 5 L5 SQ (Intervet; a reconstituted vaccine–bacterin product containing modified-

live • **Control Group** ($n = 399$): Revaccinated with Vista 5 L5 SQ 40 ± 5 days before breeding

• **Test Group** ($n = 400$): Revaccinated with Vista 5 L5 SQ 3 days before peak breeding day

rates will not differ between heifers vaccinated with Vista 5 L5 SQ 3 days before breeding and those vaccinated approximately 40 days before breeding.

Reproductive Safety of Vaccination with Vista 5 L5 SQ Near Breeding Time as Determined by the Effect on Conception Rates*

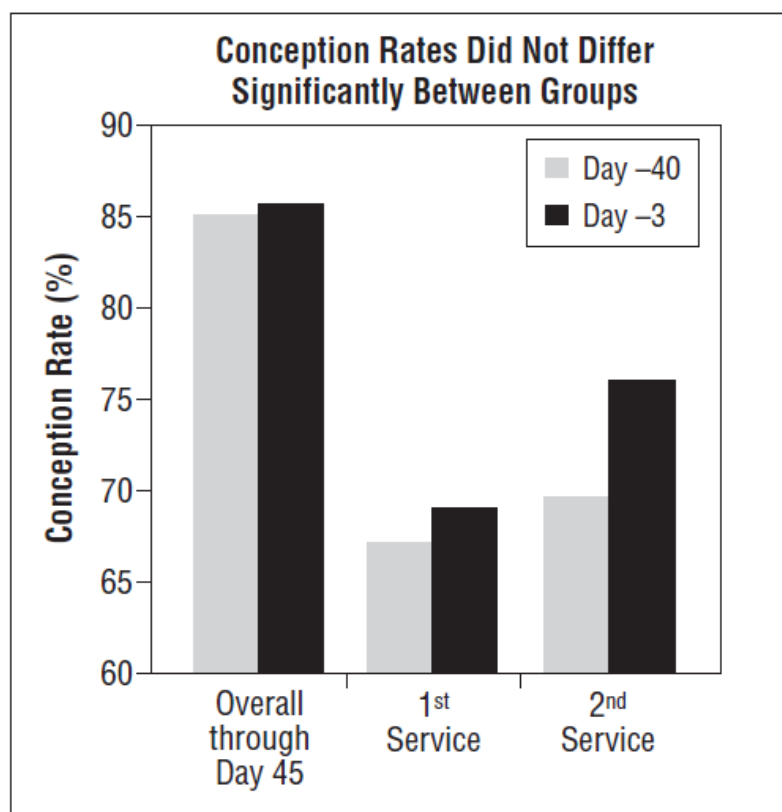


Figure 1. Conception rates for beef replacement heifers vaccinated either 40 or 3 days before breeding.

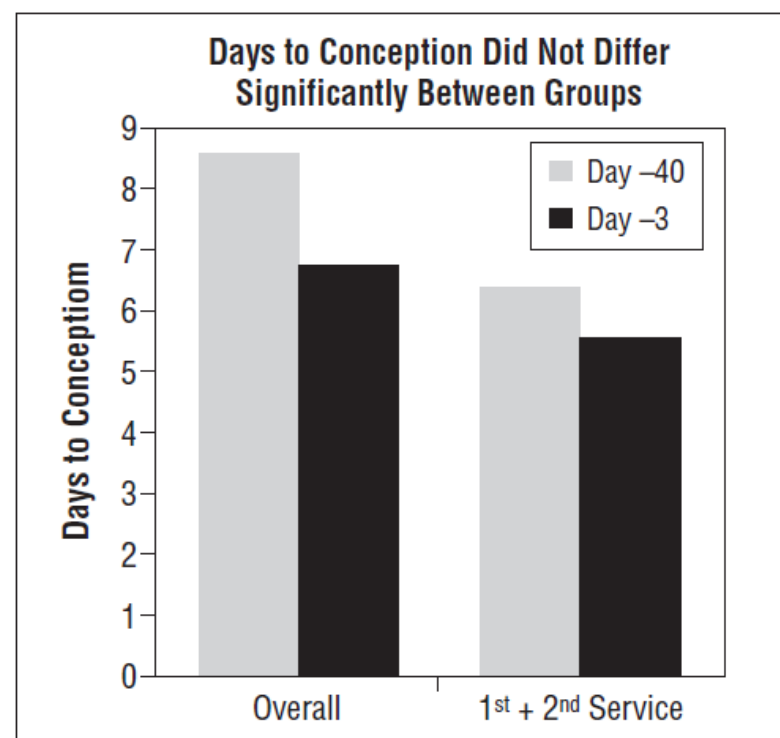
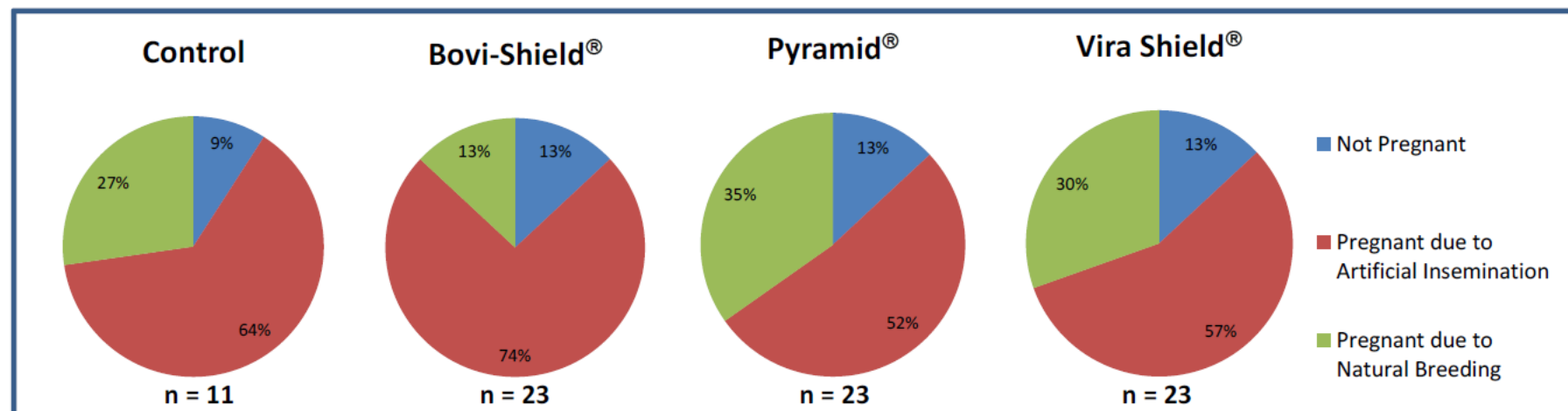


Figure 2. Days to conception for beef replacement heifers vaccinated either 40 or 3 days before breeding.

Figure 1. A graphical representation of data in Table 1 indicating lack of significant differences in pregnancy rates and fetal ages in heifers receiving the designated vaccines at weaning (d0), four weeks post-weaning (d28), one-year of age (d168), and four weeks later (d196) with the final revaccination administered 23 days prior to timed artificial insemination.



Not significantly different ($p = 0.468$; Fisher Exact Probability Test).

ⁱ Rodning SP, Marley MSD, Zhang Y, Eason AB, Nunley CL, Walz PH, Riddell KP, Galik PK, Brodersen BW, Givens MD. Efficacy of vaccination in preventing the birth of calves persistently infected with bovine viral diarrhea virus. Theriogenology, 2010; 73(8):1009-17. Supported by a grant from the Alabama Agricultural Experiment Station.

The effects of vaccination on serum hormone concentrations and conception rates in synchronized naïve beef heifers

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Conception

Estradiol

Progesterone

Estrous cycle

- MLV BVDV & BHV-1
- Bovishield
- Off-label “Consistent with good vaccination practices, it is recommended that heifers receive at least 2 doses with the second dose administered approximately 30 days prebreeding”
- Vaccine safety ?

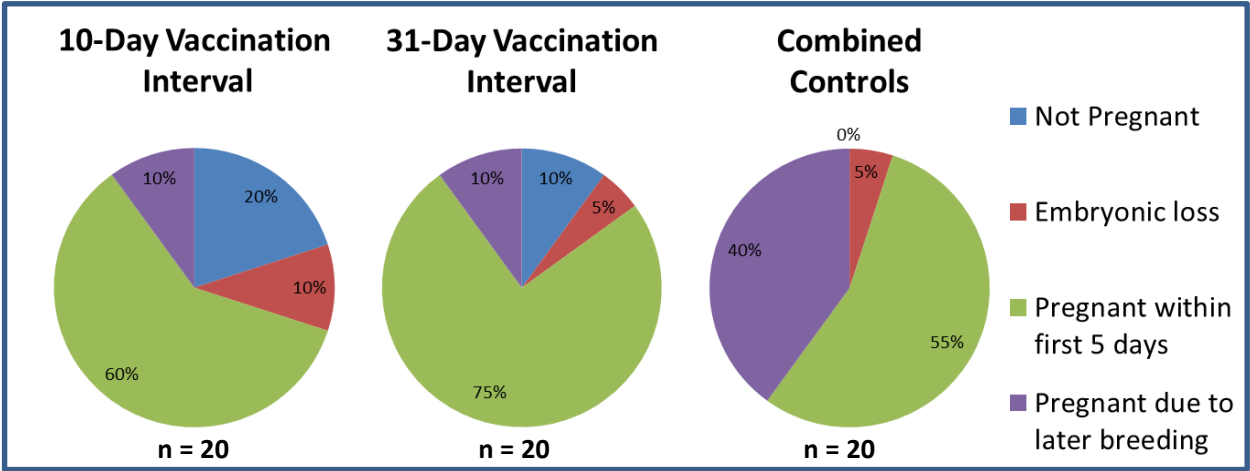
ABSTRACT

Crossbred beef heifers (N = 59) were vaccinated at the time of synchronization/breeding with either a commercially available bovine herpesvirus type 1 modified live virus (MLV) (one dose) or inactivated virus vaccine (one or two doses). The estrus cycle was synchronized at vaccination and heifers were artificially inseminated 8 days (one dose) or 36 days (two dose) after initial vaccination. Pregnancy rates were greater for control heifers (90%; $P = 0.02$) and heifers given the inactivated virus vaccine (one dose: 86%; $P = 0.08$; or two: 90%; $P < 0.01$) than those given the MLV vaccine (48%). No control heifers experienced an abnormal estrous cycle, whereas only two (two dose; 2/21) and one (one dose; 1/7) heifers in the inactive virus groups had abnormal estrous cycles and were similar to control ($P > 0.10$). Heifers given the MLV vaccine had a greater ($P = 0.02$) percentage of abnormal estrous cycles (38%; 8/21) compared with the control and inactivated groups. Of the heifers with an abnormal estrous cycle, 100% of heifers given the inactivated vaccine (one or two dose) conceived at their return estrus, whereas only 38% of heifers given the MLV vaccine conceived at their return estrus ($P > 0.10$). During the synchronization period, concentrations of estrogen were greater ($P < 0.01$) in the control and the two-dose inactivated group compared with the MLV group. After AI, progesterone concentrations were greater ($P < 0.01$) in control heifers compared with the inactivated and MLV groups, but were similar ($P \geq 0.18$) between the inactivated and MLV groups. Therefore, naïve heifers vaccinated with the inactivated vaccine were less likely to have an abnormal estrous cycle and had significantly higher pregnancy rates compared with heifers vaccinated with the MLV vaccine. In summary, vaccination of naïve heifers with an MLV vaccine at the start of a fixed-time AI protocol had a negative effect on pregnancy success.

Table 3. Pregnancy rates and mean day of conception within breeding season resulting from treatments A (10-day interval between vaccination and breeding submission), B (31-day interval between vaccination and breeding submission), C (10-day control), and D (31-day control).

Group	Embryonic loss detected prior to study end date	Pregnant at study end date	Pregnant at study end date from first 5 days of breeding season	Mean day of conception within breeding season
Group A	2/20 (10%)	14/20 (70%)	12/20 (60%)	4.2
Group B	1/20 (10%)	17/20 (85%)	15/20 (75%)	3.1
Group C	1/10 (10%)	9/10 (90%)	6/10 (60%)	5.3
Group D	0/10 (0%)	10/10 (100%)	5/10 (50%)	6.3
P-value	p = 0.720	p = 0.177	p = 0.556	p = 0.459

Figure 7. Embryonic loss rates during the study and pregnancy rates at end of study due to first five days of the breeding season associated with estrus synchronization and due to later breeding detected in treatments A (10-day interval between revaccination with Express® FP 5-VL5 and breeding submission), B (31-day interval between revaccination with Express® FP 5-VL5 and breeding submission), C (10-day control), and D (31-day control; according to a priori plans, data from control groups were combined as no significant differences were detected among control groups).



Take Home Points

- Safety of MLV on estrus cycles
 - Risky if too close and not previously immunized
 - Follow label directions to ensure safety and efficacy
 - Administer 30 days prior to breeding
 - Even if not stated on label, good idea to not administer **45** days prior to breeding
- *Duration between vaccination and initiation of estrus synchronization??*



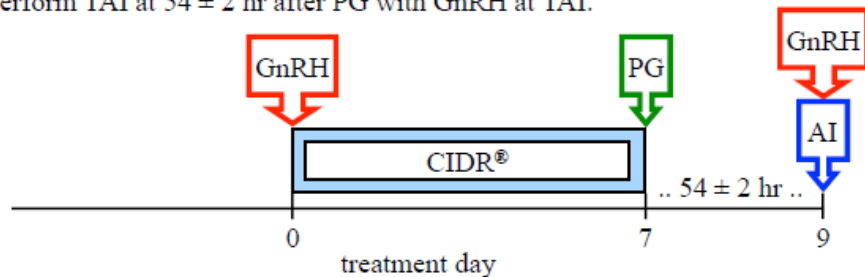
Beef Heifer Estrus Synchronization

FIXED-TIME AI (TAI)*

Short-term Protocols

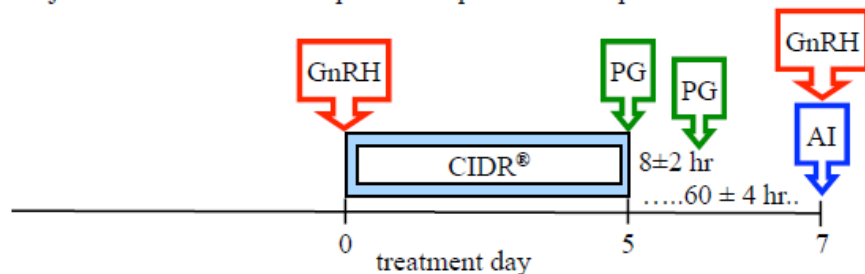
7-day CO-Synch + CIDR®

Perform TAI at 54 ± 2 hr after PG with GnRH at TAI.



5-day CO-Synch + CIDR®

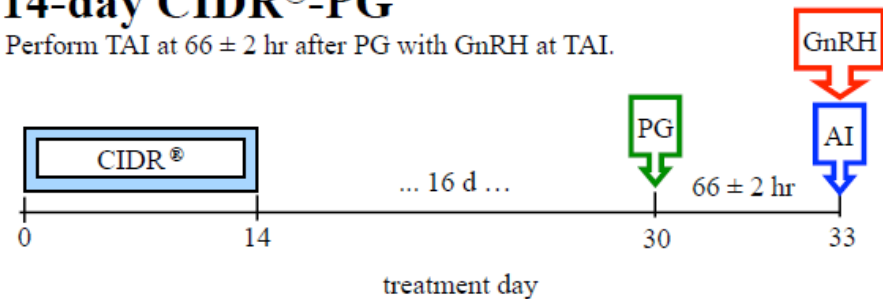
Perform TAI at 60 ± 4 hr after CIDR removal with GnRH at TAI.
Two injections of PG 8 ± 2 hr apart are required for this protocol.



Long-term Protocols

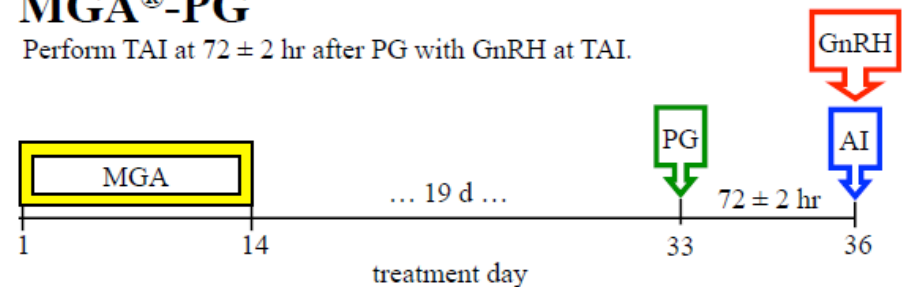
14-day CIDR®-PG

Perform TAI at 66 ± 2 hr after PG with GnRH at TAI.



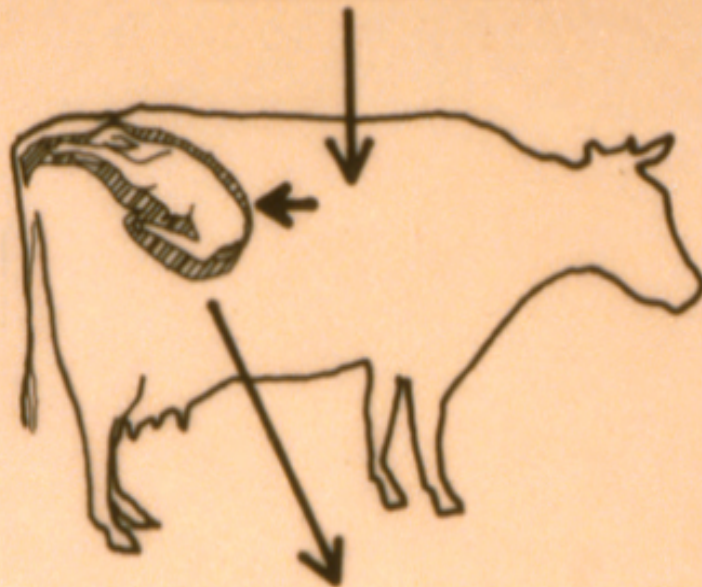
MGA®-PG

Perform TAI at 72 ± 2 hr after PG with GnRH at TAI.



* The times listed for “Fixed-time AI” should be considered as the approximate average time of insemination. This should be based on the number of heifers to inseminate, labor, and facilities.

BVDV



Abortion, Fetal Resorption,
Mummification

Congenital Malformations

Birth of weak, undersize calves

Persistently infected calves

Normal calves

Efficacy of viral reproductive vaccines BVD virus

Efficacy of bovine viral diarrhea virus vaccination to prevent reproductive disease: A meta-analysis



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journal homepage: www.theriojournal.com



Table 1

Meta-analysis results for the effect of bovine viral diarrhea virus vaccination on fetal infection showing the risk ratio, 95% confidence interval, and associated P value.

Factor	Risk ratio	Lower	Upper	P value
Overall	0.152	0.103	0.224	<0.001
Cattle studies	0.135	0.091	0.203	<0.001
Field challenge	Insufficient data			
MLV vaccine	0.117	0.074	0.184	<0.001
Inactivated vaccine	0.236	0.131	0.426	<0.001
Heterologous challenge	0.542	0.290	1.014	0.055
Homologous challenge	0.158	0.084	0.296	<0.001
Polyvalent vaccine	0.097	0.056	0.168	<0.001
Monovalent vaccine	0.177	0.096	0.328	<0.001

Abbreviation: MLV, modified live.

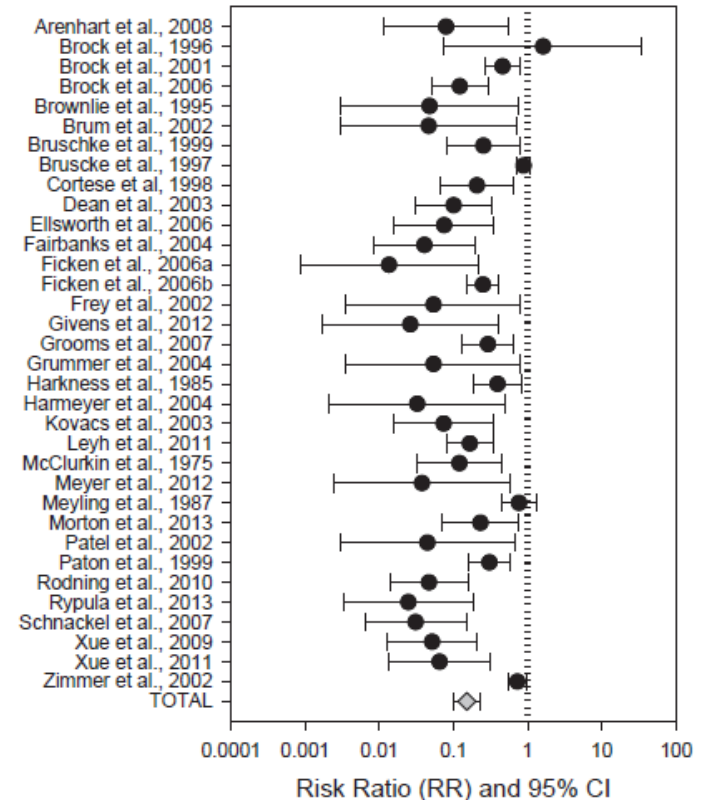


Fig. 1. Forest plot of the meta-analysis of the effect of bovine viral diarrhea virus vaccination on fetal infection. The study names included in the analysis are shown on the left ([2–9,11–27,28–30,32,33,35,37–39] of Appendix A) with their corresponding effect size and 95% confidence interval (CI). The overall effect is shown at the bottom, represented by the shaded diamond. The dotted vertical line represents a risk ratio (RR) of 1, indicating no significant difference between vaccinates and controls.

BVDV Vaccination: Fetal Infection

MLV

KV

**MLV and
KV**

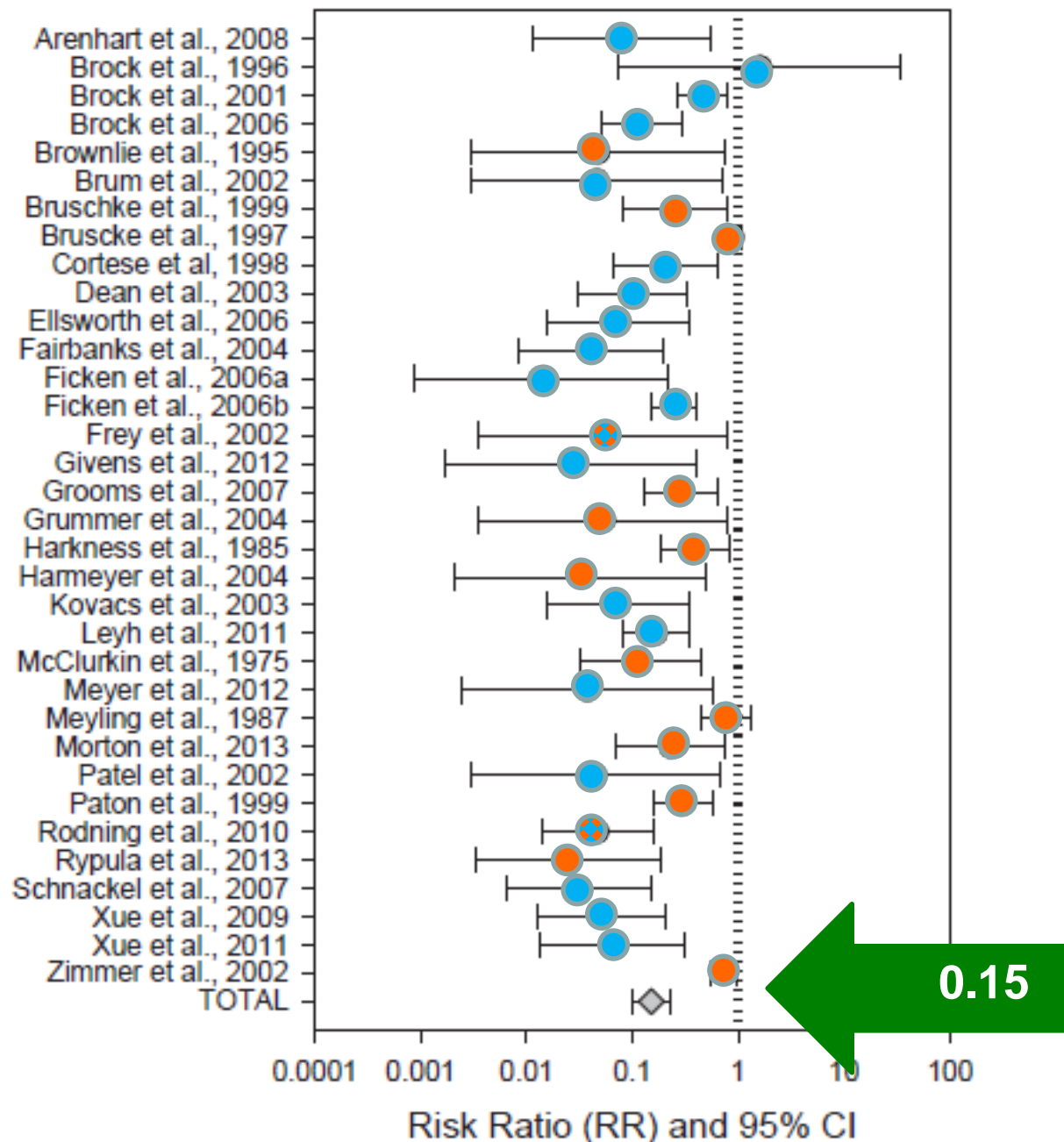


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Abbreviation: MLV, modified live.



Prevention of abortion in cattle following vaccination against bovine herpesvirus 1: A meta-analysis

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Department of Pathobiology, 127 Sugg Laboratory, College of Veterinary Medicine, Auburn University, AL 36849-5516, USA





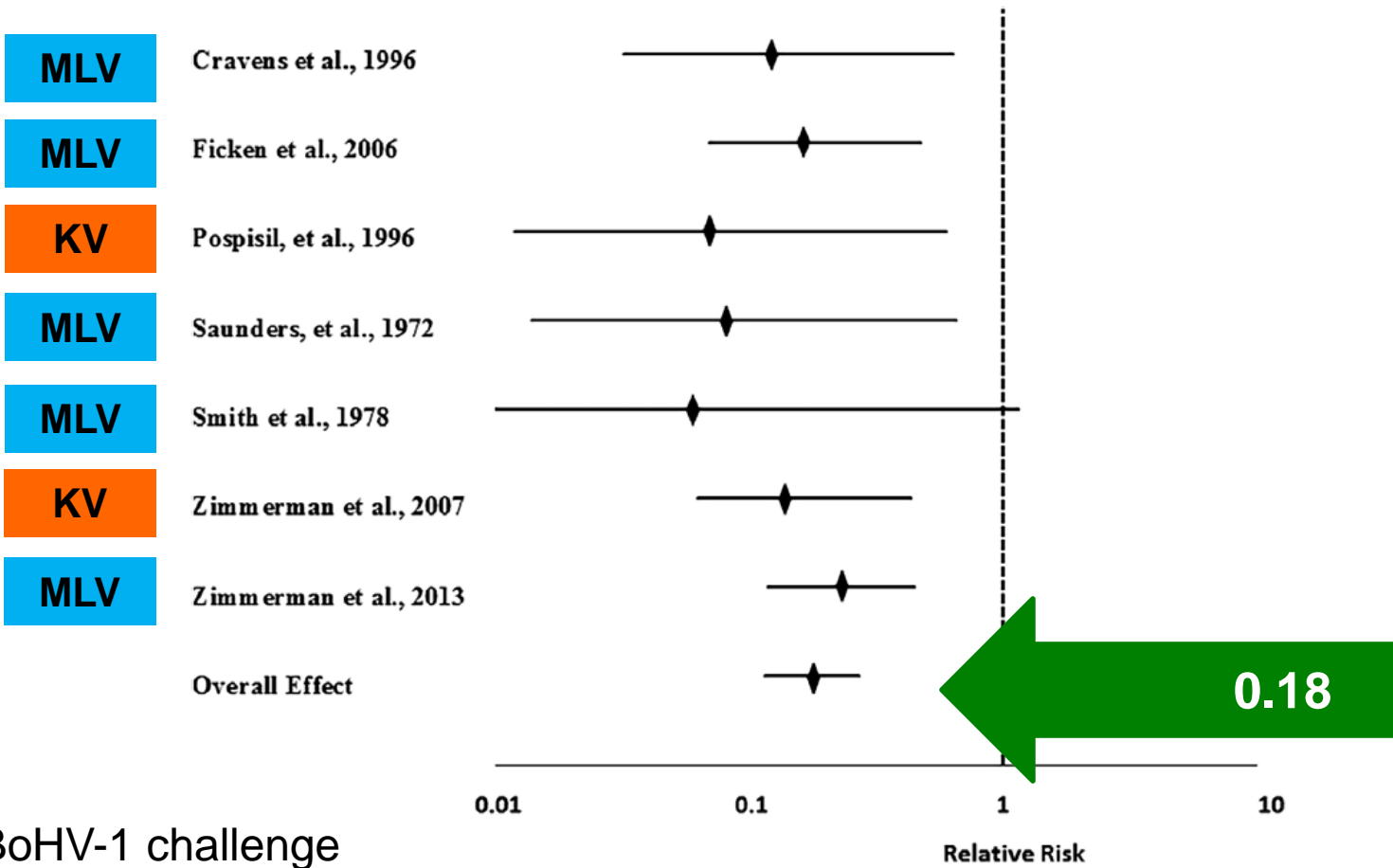
ELSEVIER

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journal homepage: www.elsevier.com/locate/prevetmed





Intentional BoHV-1 challenge

Fig. 5. Forest plot of the meta-analysis of the effect of vaccination on abortion following intentional BoHV-1 challenge. The study names included in the analysis are shown on the left with their corresponding effect size (shaded diamond) and 95% confidence interval (CI) with the overall effect (0.18; 0.12–0.27) shown at the bottom.

Summary Recommendation From Studies Evaluating Protection of the Fetus

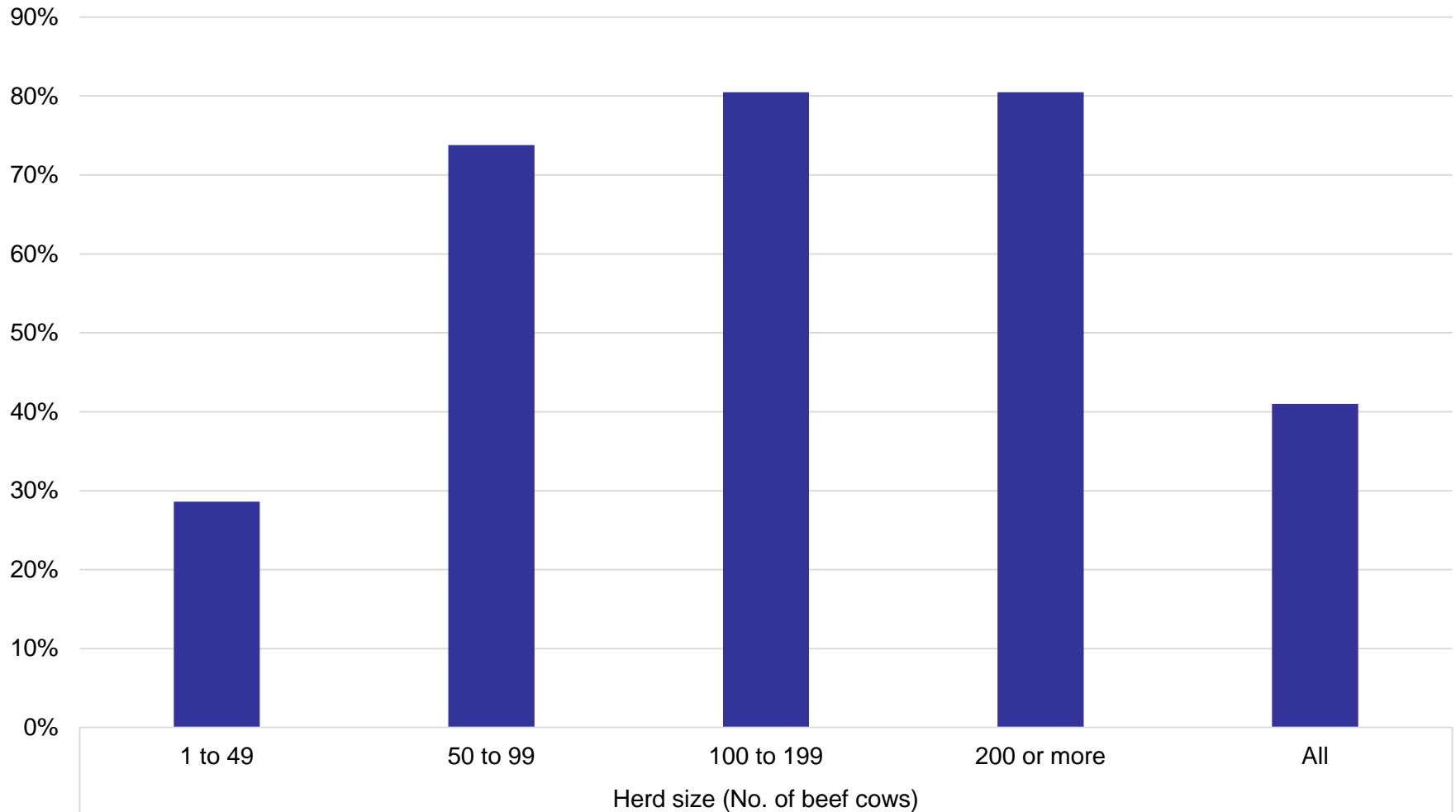
Vaccination provides the best protection when the best products are administered at the best times

Vaccination of developing heifers to prevent reproductive losses:

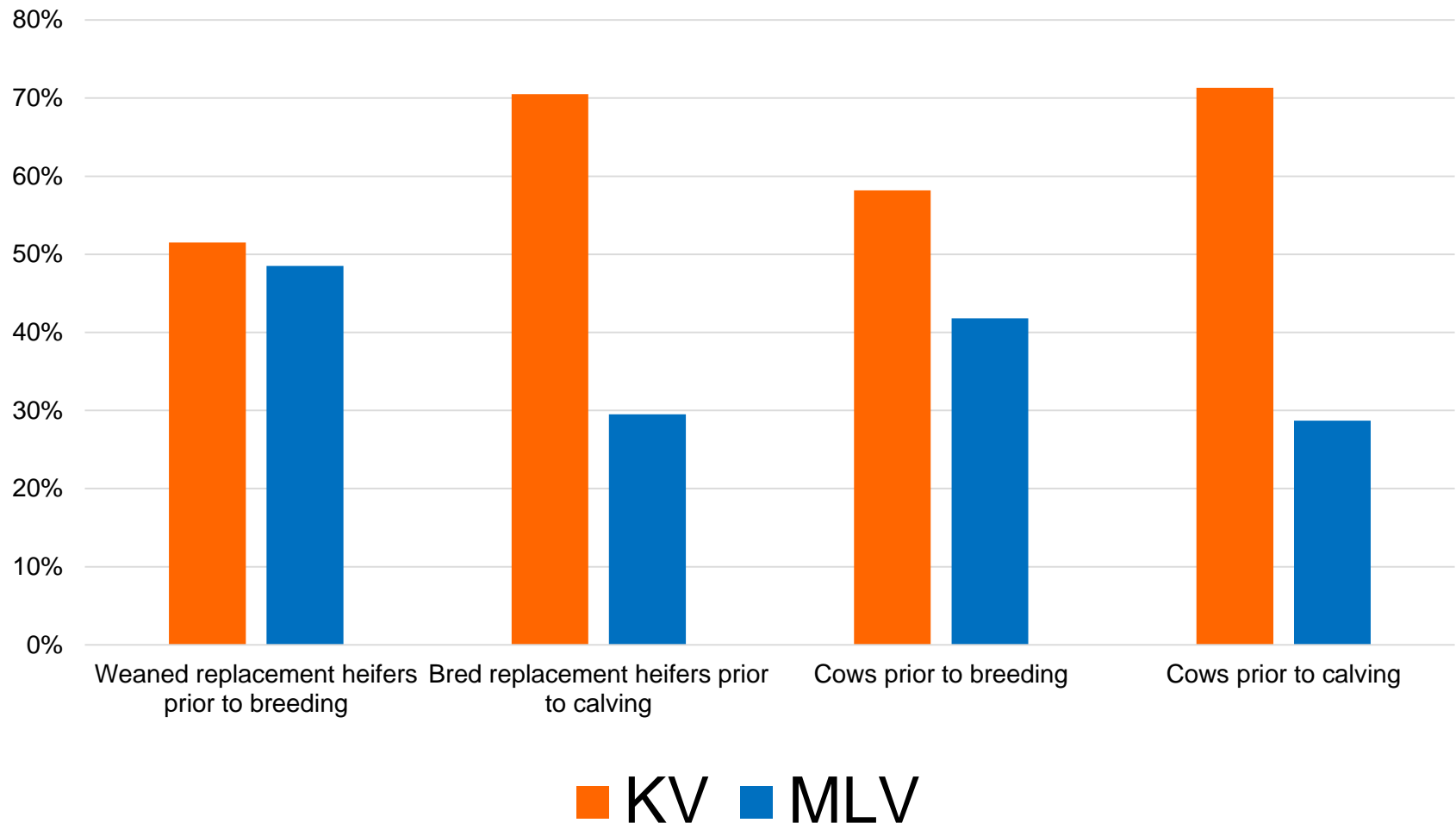
<div>Least Reliable</div> <div>↑ ↓</div> <div>Most Reliable</div>	1	Vaccination of heifers <u>prior to breeding</u> with a <u>single dose</u> of <u>killed virus</u> . NOT RECOMMENDED
	2	Vaccination of heifers with <u>two doses</u> of <u>killed virus</u> with the second dose at least 30 days before initial breeding.
	3	Vaccination of heifers with a <u>single dose</u> of <u>modified-live virus</u> at least 30 days before initial breeding.
	4	Vaccination of heifers with <u>two doses</u> of <u>modified-live virus</u> with the second dose at least 30 days before initial breeding.

Vaccination Practices in the U.S.

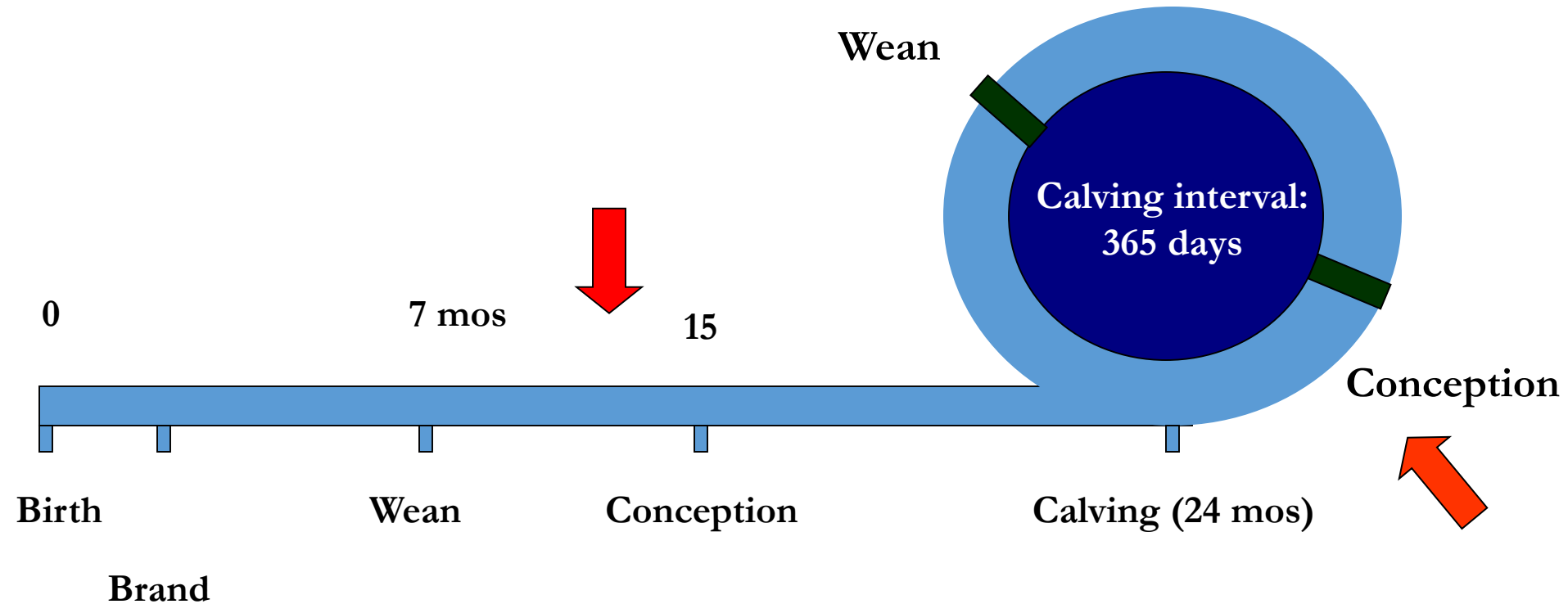
Percentage of beef cattle operations that vaccinated against BVD in 2007



Percent Beef Battle Operations That Vaccinated Against BVD in 2007 by Class of Cattle



Timing of Vaccination

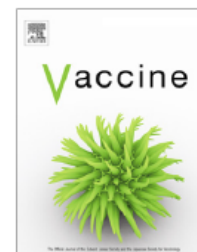




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Vaccine

journal homepage: www.elsevier.com/locate/vaccine



Evaluation of reproductive protection against bovine viral diarrhea virus and bovine herpesvirus-1 afforded by annual revaccination with modified-live viral or combination modified-live/killed viral vaccines after primary vaccination with modified-live viral vaccine



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^b College of Agriculture, Auburn University, Auburn, AL 36849, USA

^c School of Veterinary Medicine and Biomedical Sciences, University of Nebraska, Lincoln, NE 68683, USA

^d Zoetis, INC., Florham Park, NJ 07932, USA

^e Great Plains Veterinary Educational Center, School of Veterinary Medicine and Biomedical Sciences, University of Nebraska, Clay Center, NE 68933, USA

<http://www.sciencedirect.com/science/article/pii/S0264410X17300099>

Open Access: [Vaccine](#)



Vaccination provides the best protection when the best products are administered at the best times

Annual revaccination of cows to prevent reproductive losses:

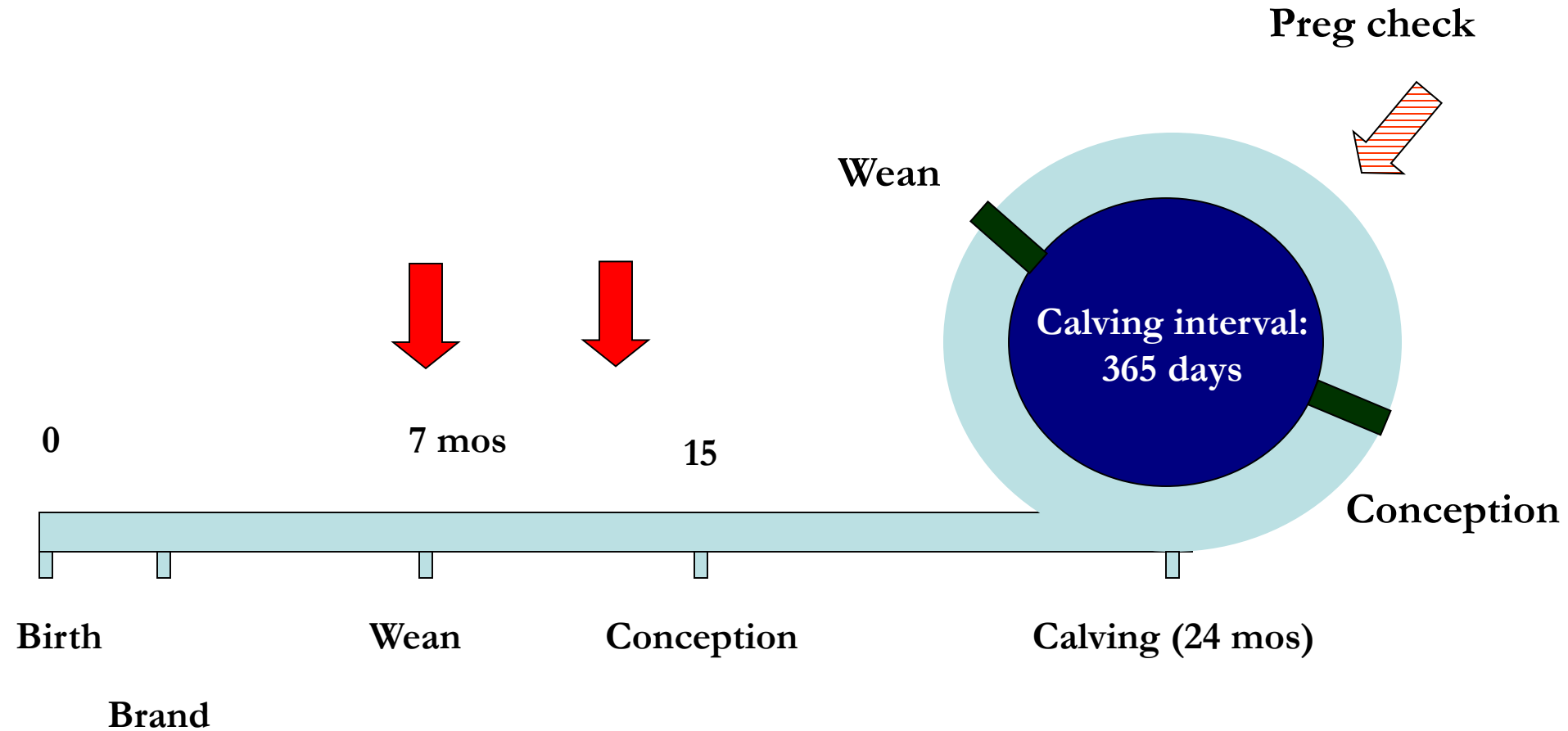
	Protocol #	Revaccination with a single dose of:		Timing		After initial vaccination of heifers with:		Doses	
		Modified-live	Killed	Prior to breeding	Post-breeding*	Modified-live	Killed	1 dose	2 doses
<div> <div>Least Reliable</div> <div>↑</div> <div>↓</div> <div>Most Reliable</div> </div>	Ø	1	None				✓	✓	
	Ø	2		✓	Either		✓	✓	
	Ø	3	None				✓		✓
		4	None			✓		✓	
		5	None			✓			✓
		6		✓	✓		✓		✓
		7		✓			✓		✓
		8		✓	✓	✓		✓	
	§	9	✓		✓	✓		✓	
		10		✓	✓	✓			✓
	§	11	✓		✓	✓			✓
		12	✓		✓	✓		✓	
		13	✓		✓	✓			✓

*Post-breeding vaccination is less protective for the early fetus than vaccination prior to breeding.

Ø = Not recommended.

§ = Follow specific label directions.

Timing of Vaccination



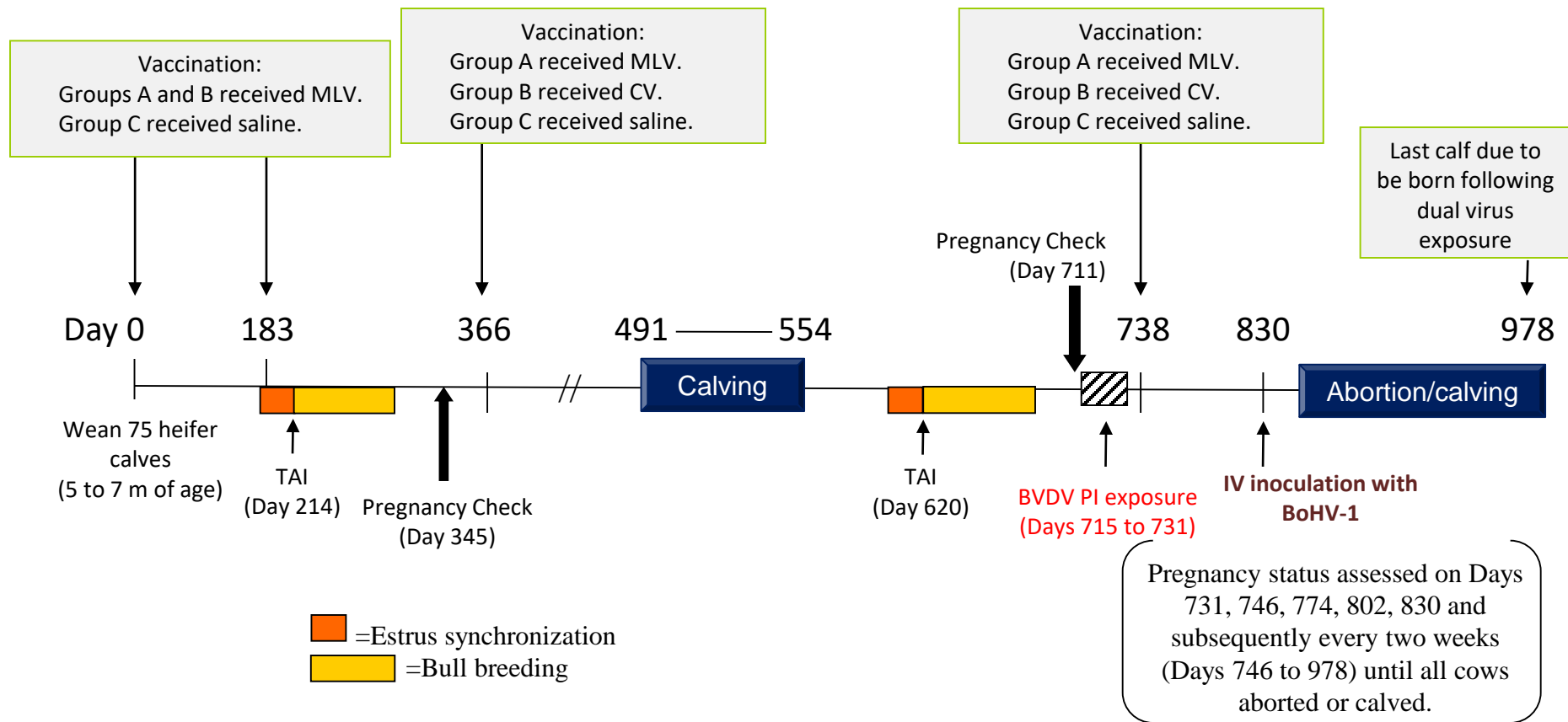


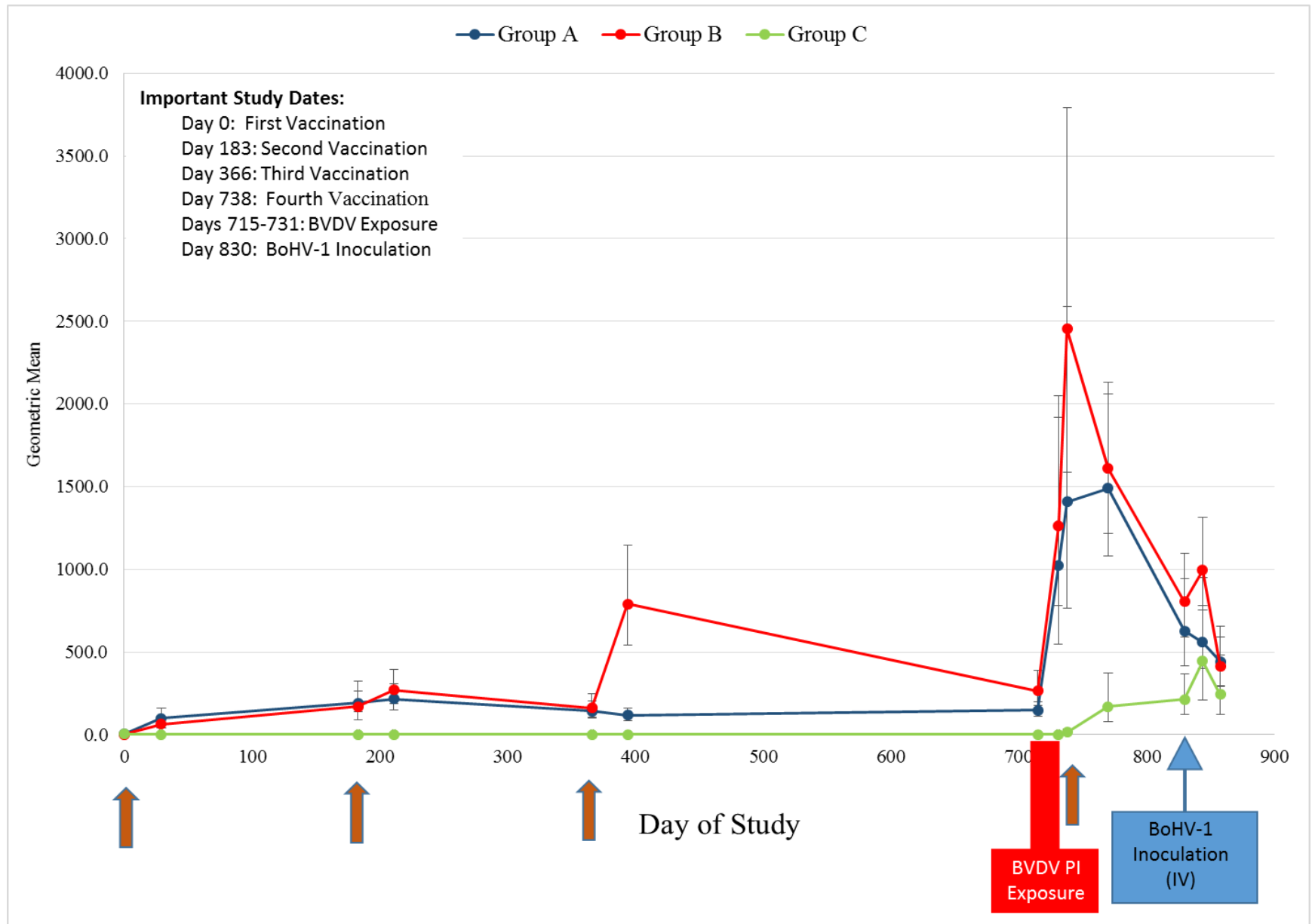
Figure 1. Design of research to assess efficacy of revaccination with multivalent modified-live viral (MLV) or combination viral (CV; temperature-sensitive MLV BoHV-1 and killed BVDV). The study was initiated with 30 heifers in Treatment Group A, 30 heifers in Treatment Group B, and 15 heifers in Treatment Group C. m = months; TAI = timed artificial insemination; BVDV = bovine viral diarrhea virus; PI = persistently infected; IV = intravenous; BoHV-1 = bovine herpesvirus-1.

Vaccine Composition

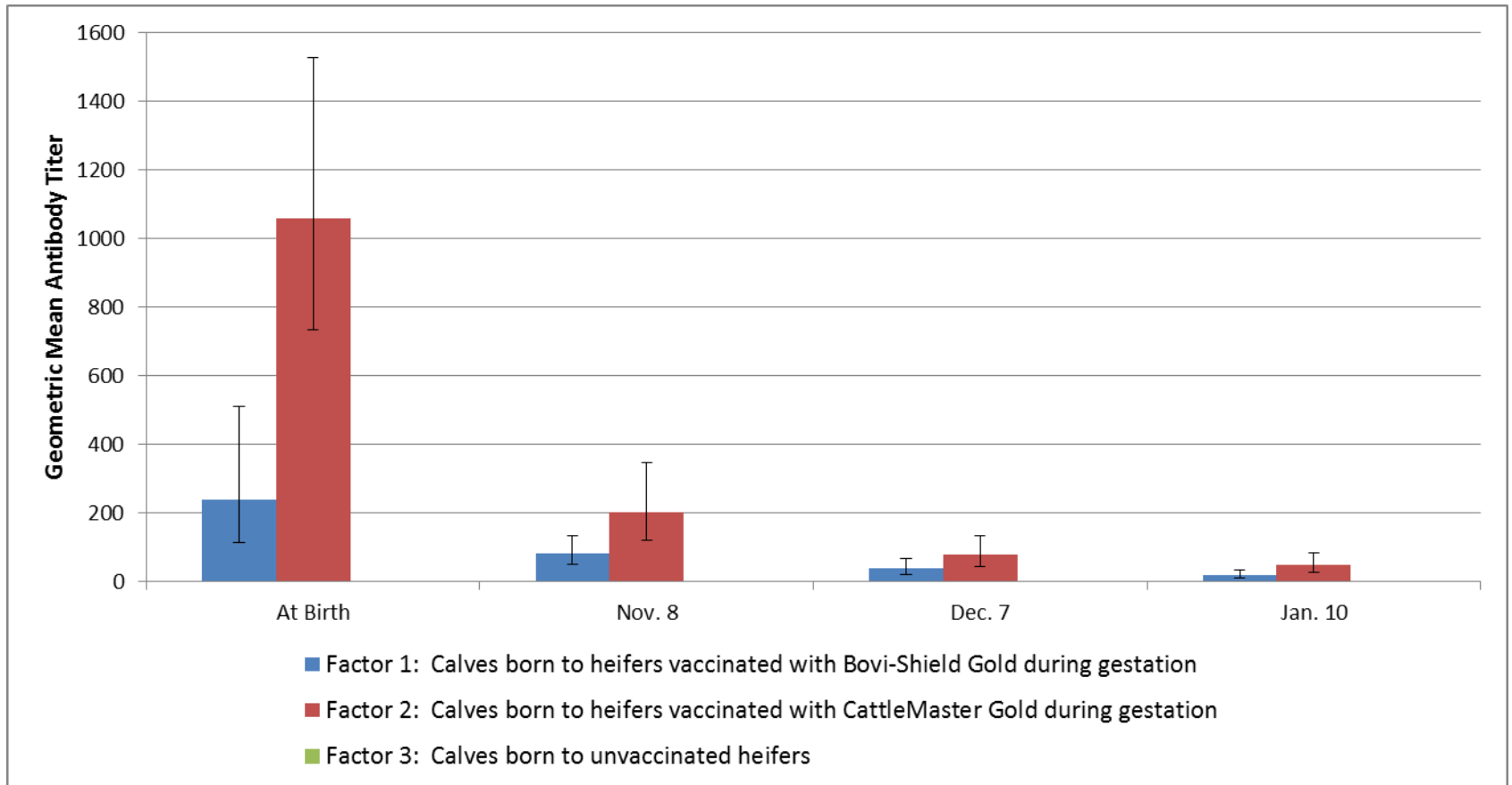
BOVI-SHIELD GOLD FP® 5		CATTLEMASTER GOLD FP® 5
Modified-live	BVD Type 1	Killed
Modified-live	BVD Type 2	Killed
Modified-live	IBR	Temperature-sensitive
Modified-live	PI₃	Temperature-sensitive
Modified-live	BRSV	Modified-live



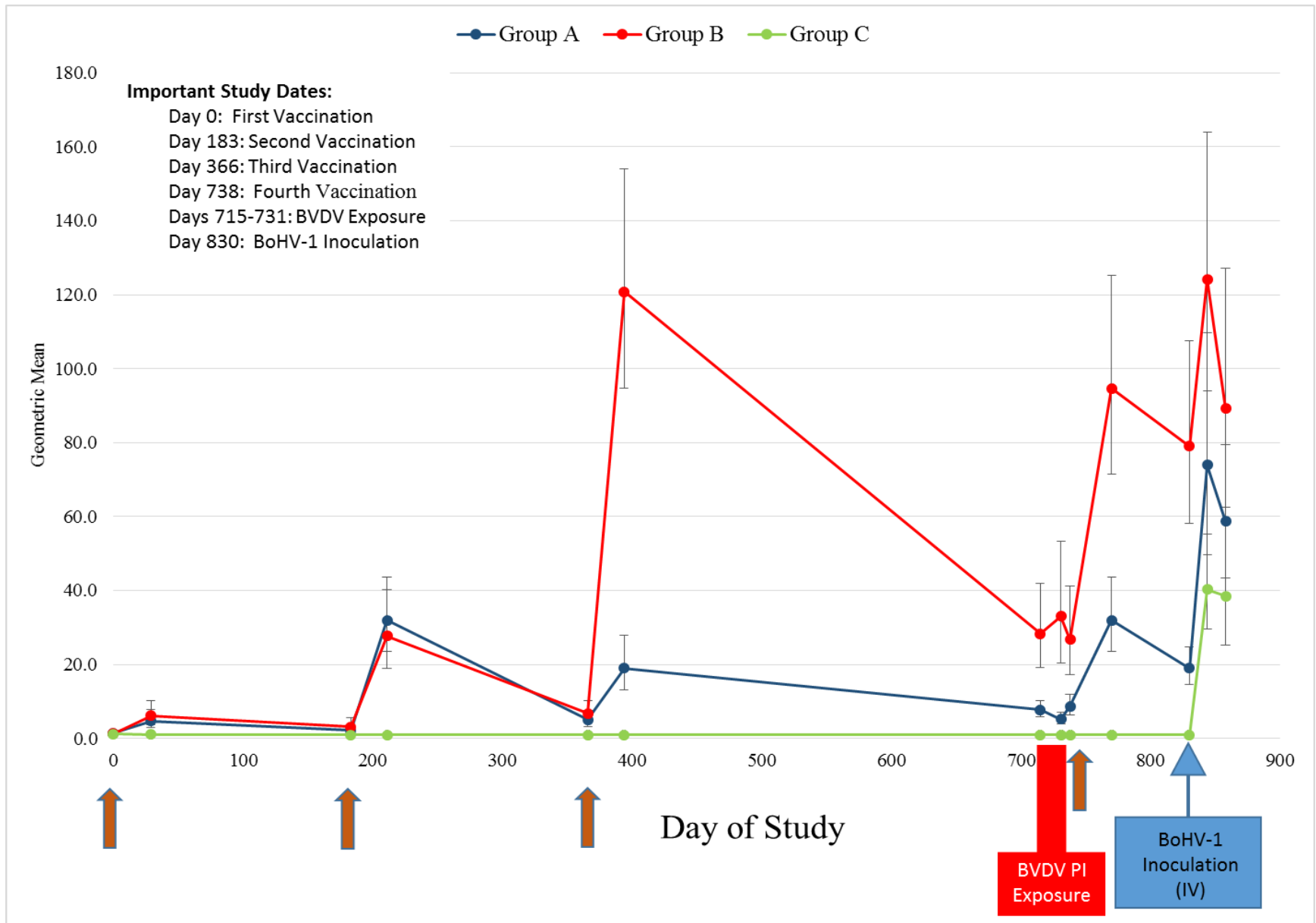
Antibody Titers to Bovine Viral Diarrhea Virus 2 (Strain 125c)



Immunity acquired by booster vaccination with CATTLEMASTER GOLD FP® 5 following priming vaccination with BOVI-SHIELD GOLD FP® 5 prior to breeding is transferred to the nursing calf



Antibody Titers to Bovine Herpesvirus-1 (Colorado Strain)



Titers of bovine viral diarrhea virus (BVDV) in serum samples and nasal swabs from persistently infected (PI) animals used for BVDV exposure. Titers are expressed as cell culture infectious dose 50% per mL (CCID₅₀/mL)

PI Animal	BVDV genotype	Study Day 715		Study Day 731	
		serum	nasal swab	serum	nasal swab
A	2	3.5×10^4	3.5×10^5	2.0×10^5	2.0×10^6
B	2	2.0×10^4	2.0×10^5	2.0×10^4	3.5×10^5
C	1a	3.5×10^4	3.5×10^5	3.5×10^4	1.11×10^6
D	1b	6.25×10^4	2.0×10^6	3.5×10^5	6.25×10^5
E	1a	6.25×10^3	3.5×10^5	2.0×10^4	6.25×10^5
F	1b	2.0×10^4	2.0×10^5	6.25×10^4	1.11×10^6



Detection of BVDV and BoHV-1 in Fetuses and Calves

a = abortion after BVD exposure but before inoculation with BoHV-1

A = abortion after BVDV exposure and inoculation with BoHV-1

C = live calf

Red =BVDV

Blue = BoHV-1

Black = both viruses



Detection of BVDV in fetuses & calves

Group	% Abortion**	% BVDV Positive**																								
A	3/23 (13%)	2/23 (9%)	a	A	A	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	
B	1/22 (5%)	0/22 (0%)	A	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	
C	11/15 (73%)	14/15 (93%)	a	a	A	A	A	A	A	A	A	A	C	C	C	C										

Detection of BoHV-1 in fetuses & calves

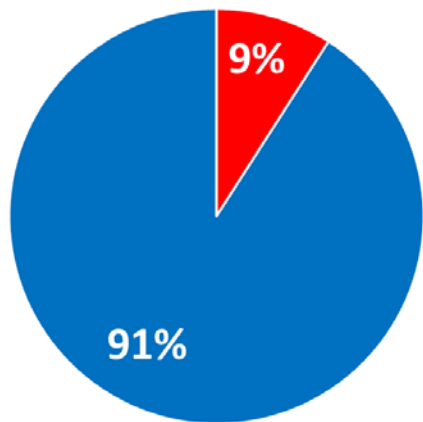
Group	% Abortion**	% BoHV-1 Positive**																								
A	3/23 (13%)	2/23 (9%)	a	A	A	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C		
B	1/22 (5%)	0/22 (0%)	A	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C		
C	11/15 (73%)	8/15 (53%)	a	a	A	A	A	A	A	A	A	C	C	C	C											

Detection of BVDV and/or BoHV-1 in fetuses & calves

Group	% Abortion**	% BVDV and/or BoHV-1																								
A	3/23 (13%)	4/23 (17%)	a	A	A	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	
B	1/22 (5%)	0/22 (0%)	A	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	C	
C	11/15 (73%)	15/15 (100%)	a	a	A	A	A	A	A	A	A	C	C	C	C											

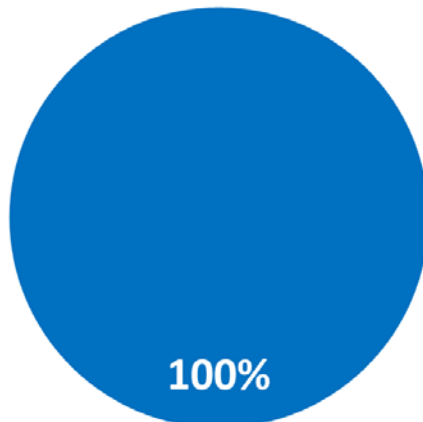
**Significant difference detected among treatment groups for samples cumulatively.

Group A (Two Pre-breeding Bovi-shield
Gold Vac & Bovi-shield Gold Revac)



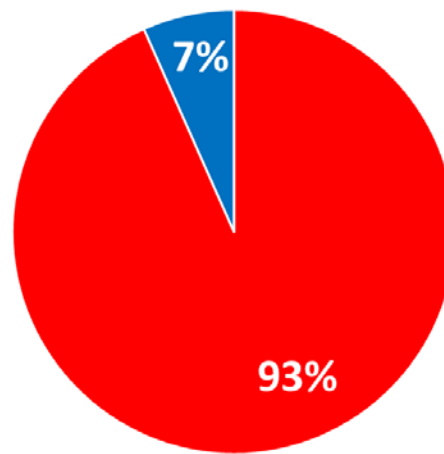
n=22

Group B (Two Pre-breeding Bovi-shield
Gold Vac & CattleMaster Revac)



n=22

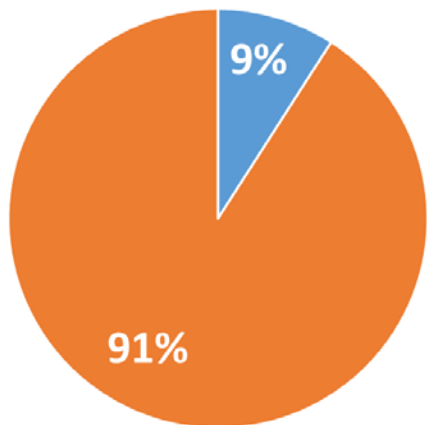
Group C (Unvaccinated Control)



n=13

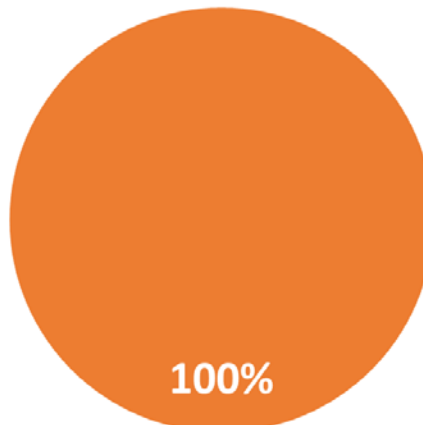
■ BVDV-positive
■ BVDV-negative

Group A (Two Pre-breeding Bovi-shield
Gold Vac & Bovi-shield Gold Revac)



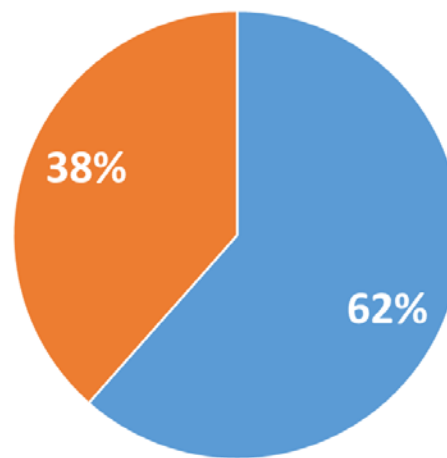
n=22

Group B (Two Pre-breeding Bovi-shield
Gold Vac & CattleMaster Revac)



n=22

Group C (Unvaccinated Control)



n=13

■ BoHV-positive
■ BoHV-negative

Conclusion

This research demonstrates efficacy of administering two pre-breeding doses of MLV vaccine with annual revaccination using a combination vaccine to prevent fetal loss due to exposure to BVDV and BoHV-1.



But are all Killed BVDV vaccines created equal?

Safety concerns associated with MLV vaccines have led some producers to utilize only KV vaccines in prebreeding and annual revaccination herd health programs.

Thus, a comparative assessment of the fetal and abortive protective efficacy resulting from pre-breeding vaccination of cows with different KV vaccines is needed.



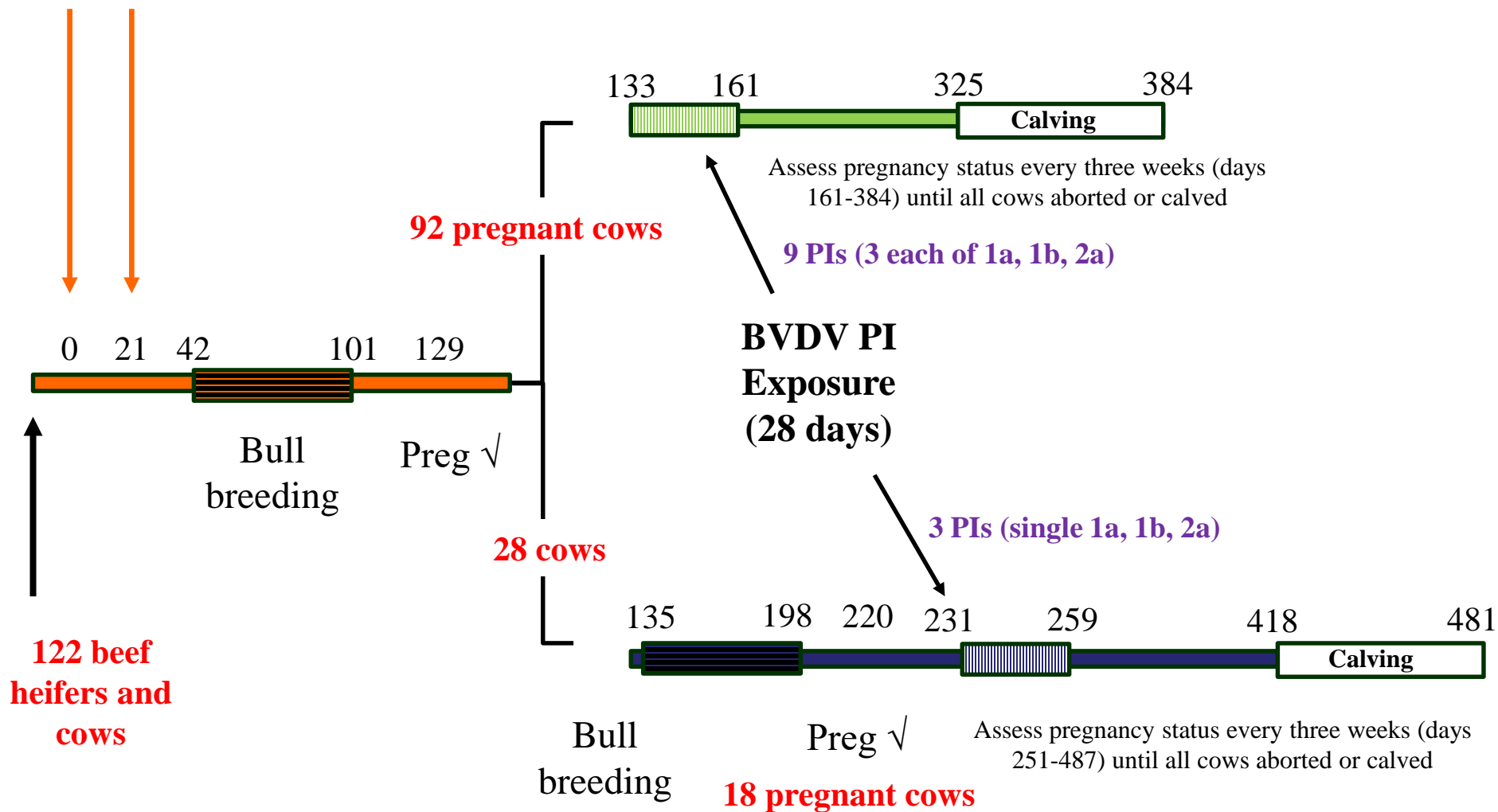
Vaccinate:

Group A: CattleMaster® Gold FP®5; Spirovac®L5

Group B: ViraShield® 6 + L5 HB

Group C: Triangle™ 10 HB

Group D: Control (saline)



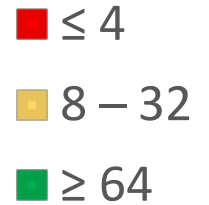
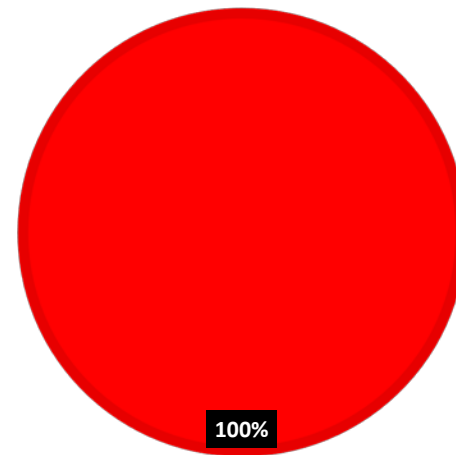
PI Animal	BVDV genotype	Day 133, 4/26/16		Day 161, 5/24/16	
		serum	nasal swab	serum	nasal swab
11	1b	6.25×10^4	6.25×10^4	2.0×10^4	6.25×10^4
12	2	3.51×10^5	2.0×10^5	2.0×10^4	6.25×10^4
18	2	3.51×10^3	2.0×10^5	died: 23May2016	
28	2	4.86×10^3	3.51×10^5	died: 28Apr2016	
32	1a	6.25×10^3	3.51×10^4	3.51×10^3	3.51×10^4
34	1a	6.25×10^3	2.0×10^4	3.51×10^3	6.25×10^4
285	1b	6.25×10^4	3.51×10^4	6.25×10^3	6.25×10^3
407	1a	3.51×10^3	2.0×10^4	3.51×10^2	3.51×10^4
819	1b	2.0×10^3	6.25×10^4	2.0×10^3	2.0×10^4
3/16*	2	6.25×10^4	3.51×10^5	6.25×10^3	6.25×10^4
* 02May2016					

PI Animal	BVDV genotype	Day 231, 8/2/16		Day 259, 8/30/16	
		serum	nasal swab	serum	nasal swab
12	2	6.25×10^3	6.25×10^4	2.0×10^4	6.25×10^4
32	1a	3.51×10^4	3.51×10^4	3.51×10^3	3.51×10^4
285	1b	3.51×10^5	2.0×10^5	6.25×10^4	6.25×10^3

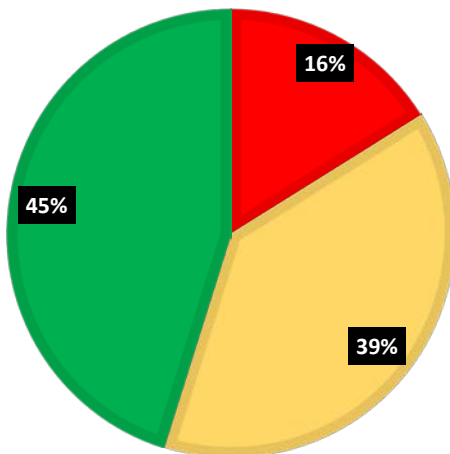


Proportion of study cows
(n=110) with antibody
titers directed against
BVDV 1a (NADL) at the
onset of challenge

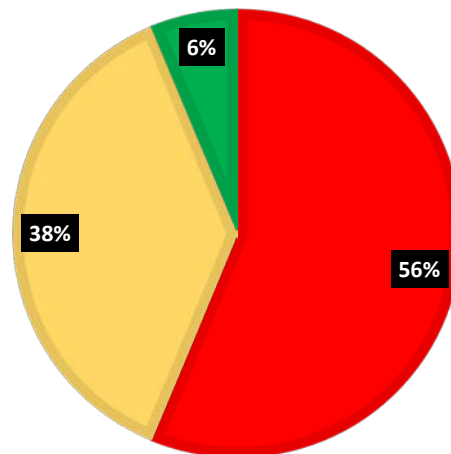
CONTROL (SALINE)



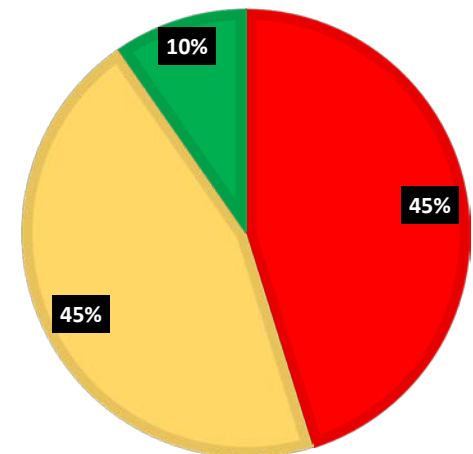
CATTLEMASTER® GOLD FP®5; SPIROVAC®L5



VIRASHIELD® 6 + L5 HB



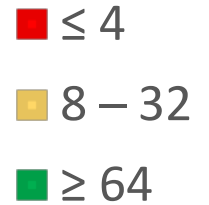
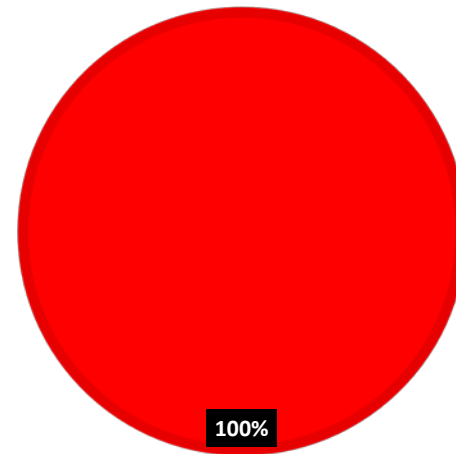
TRIANGLE™ 10 HB



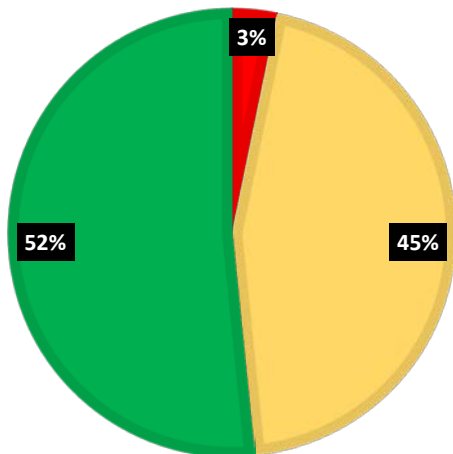


Proportion of study cows
(n=110) with antibody
titers directed against
BVDV 2 (125c) at the
onset of challenge

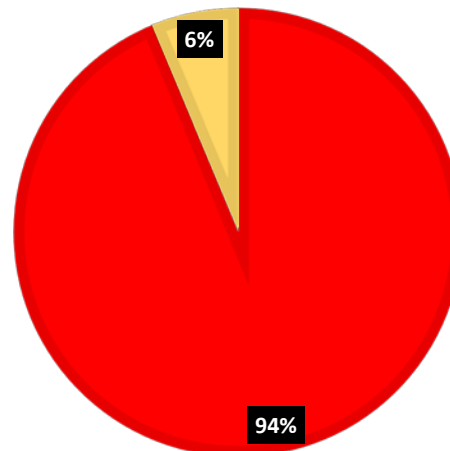
CONTROL (SALINE)



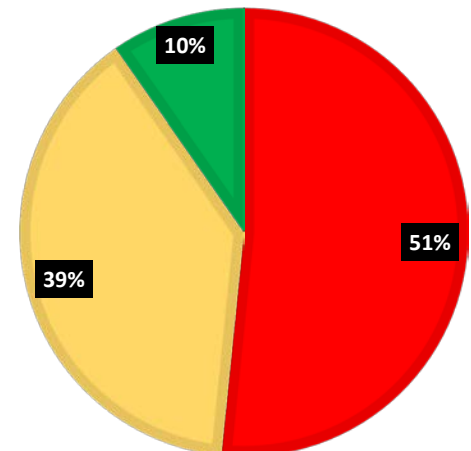
CATTLEMASTER® GOLD FP®5; SPIROVAC®L5



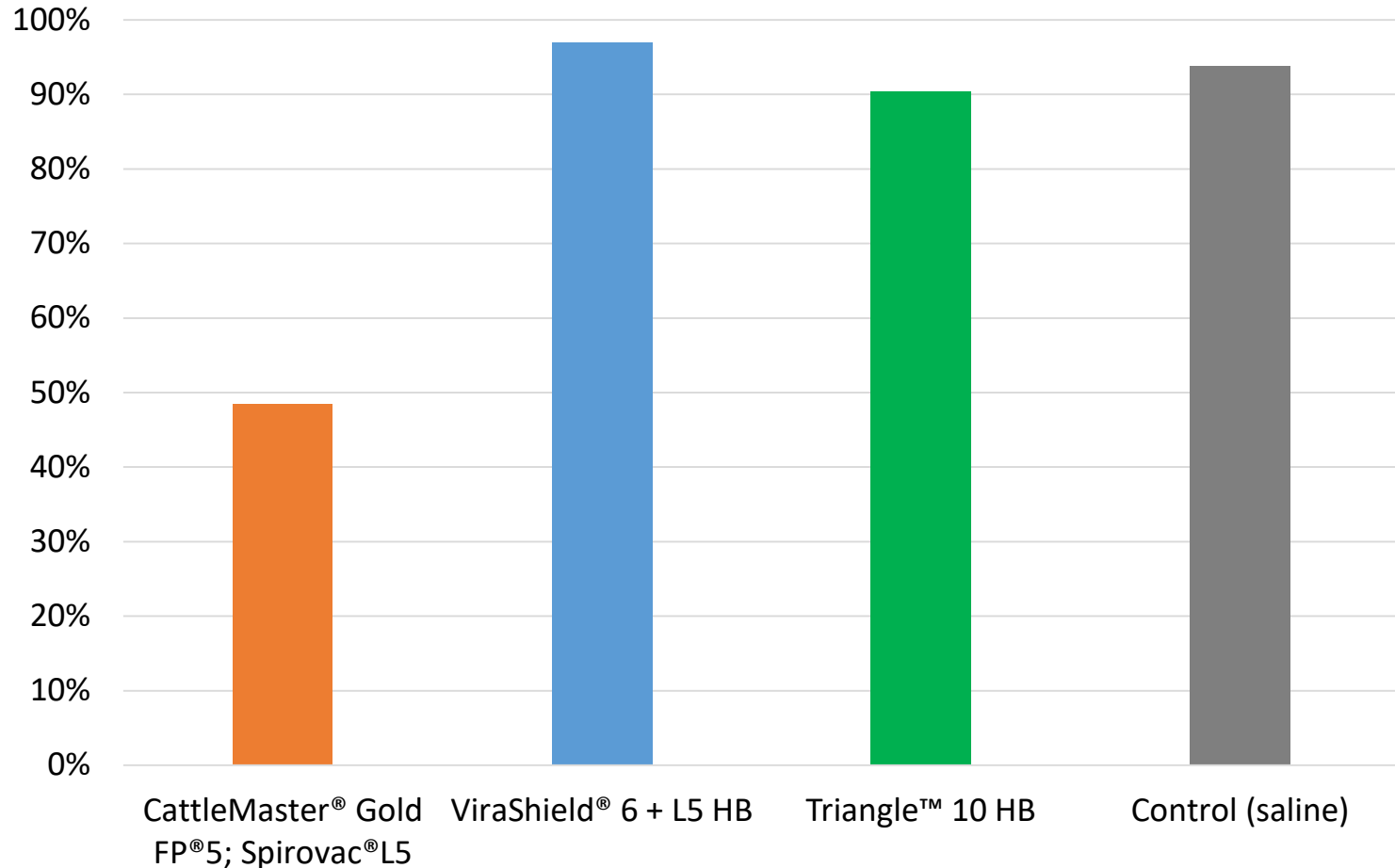
VIRASHIELD® 6 + L5 HB



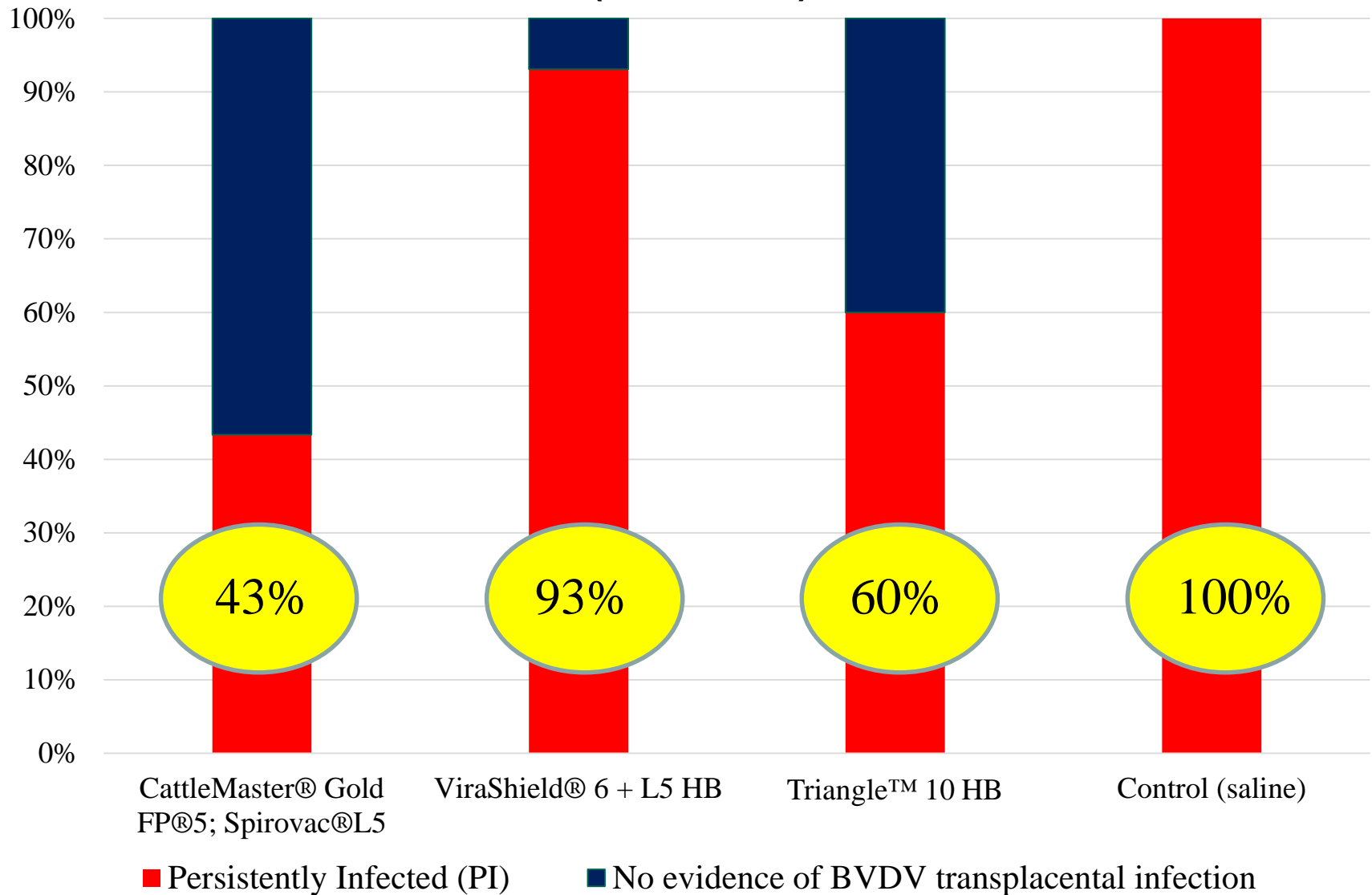
TRIANGLE™ 10 HB



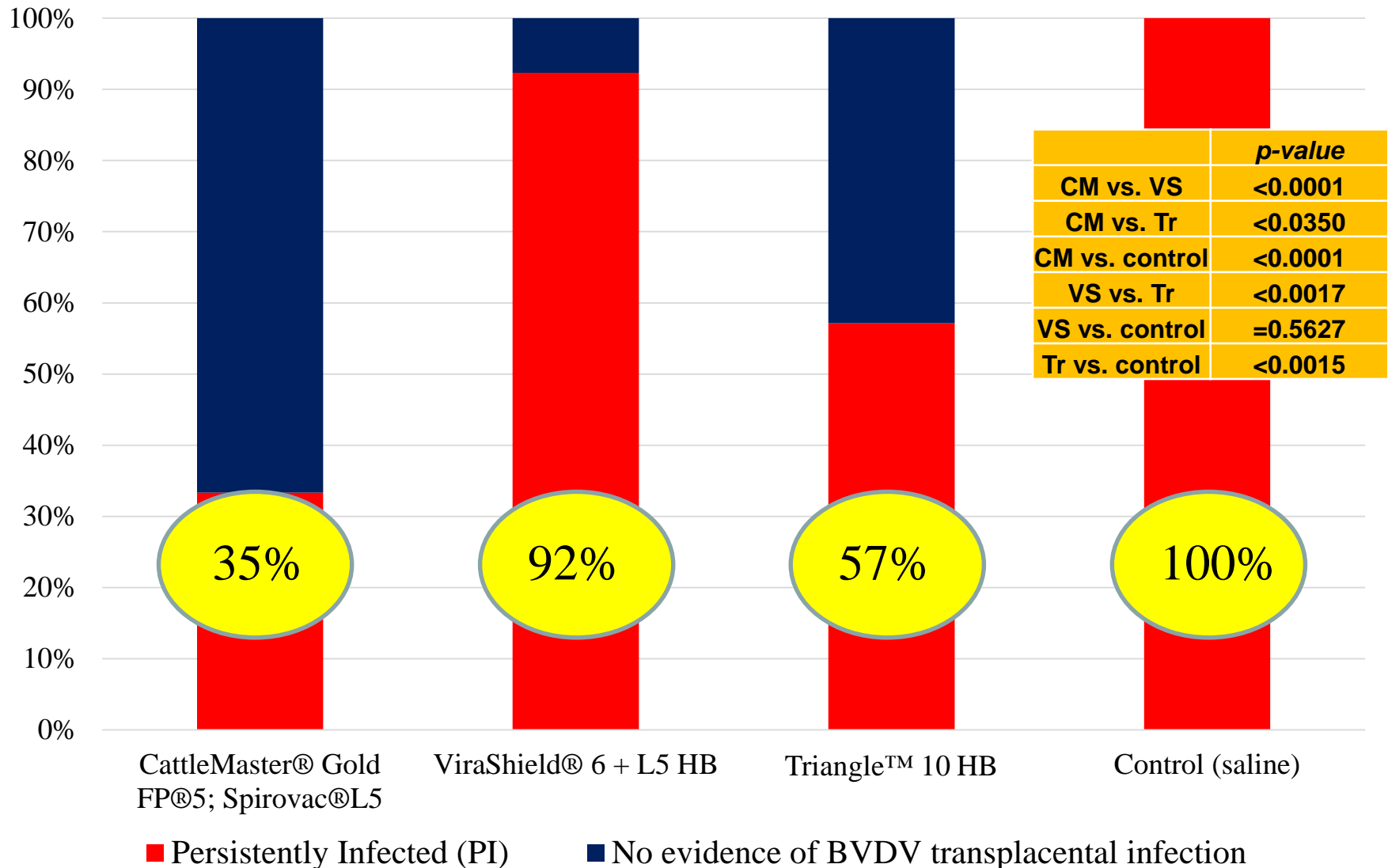
Proportion of cows with at least one positive result for BVDV on WBC passage between day 6-10 of exposure



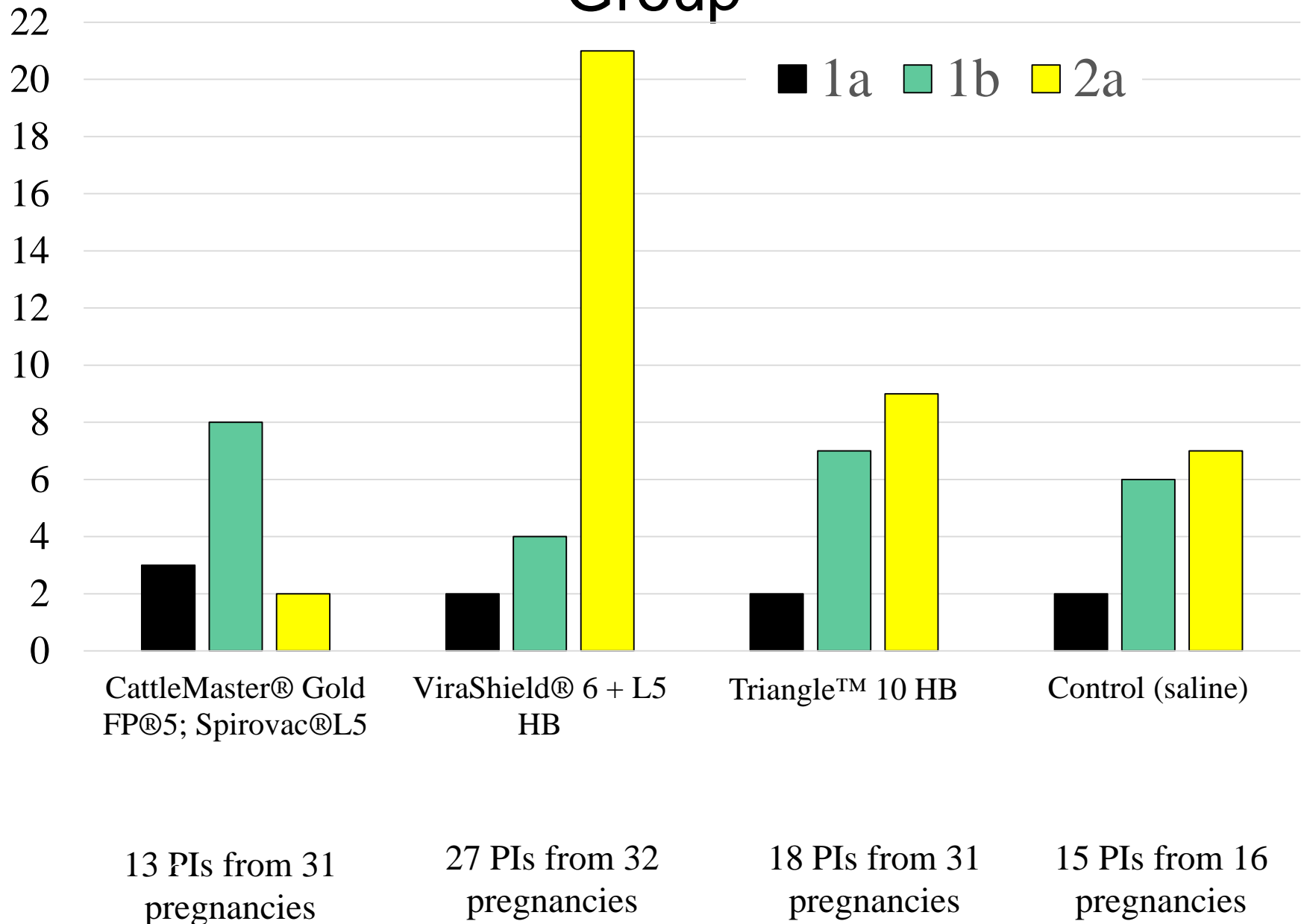
Infection Results – Fetuses and Calves (n=104)

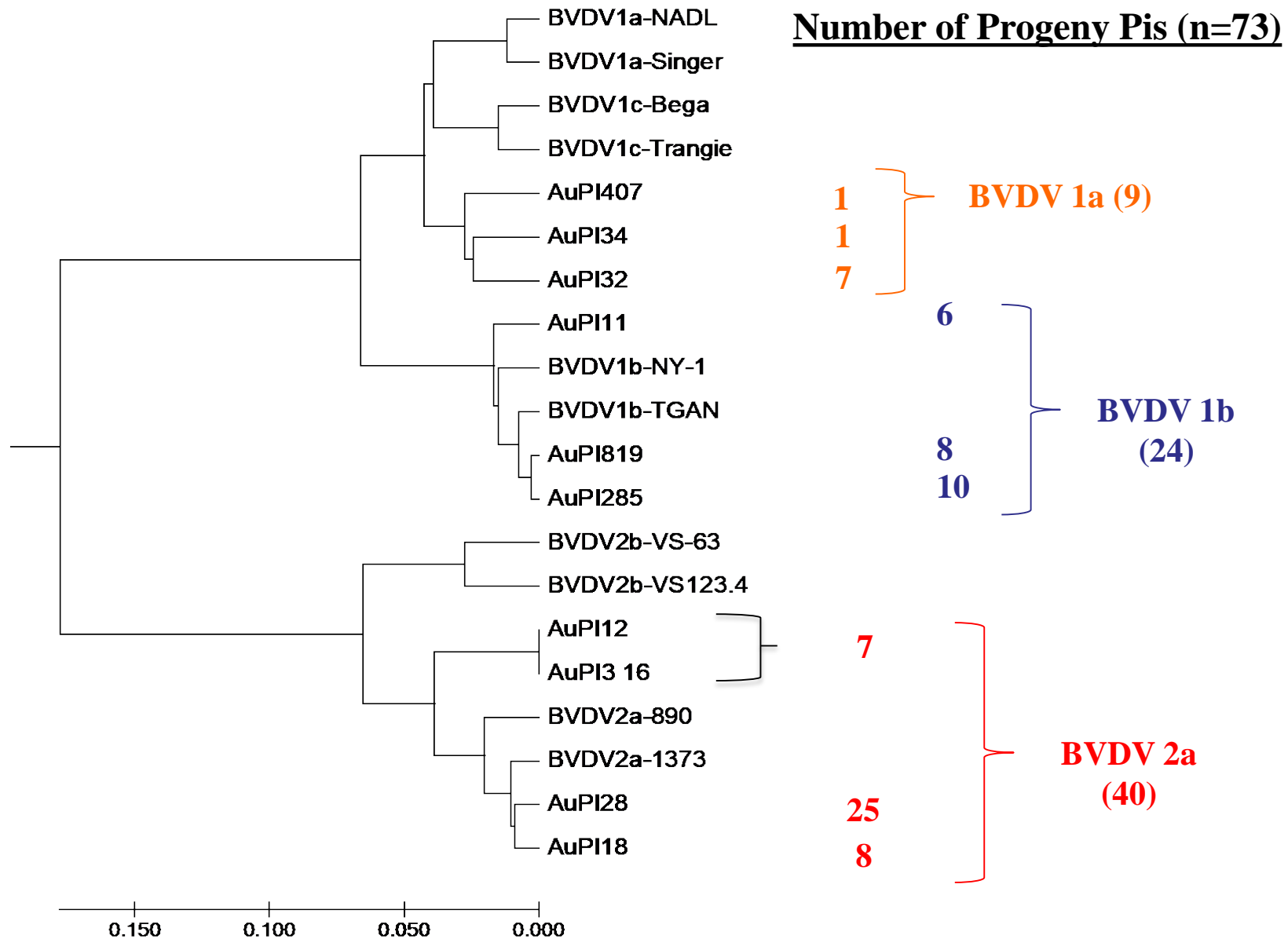


Infection Results – Live-born Calves (n=92)



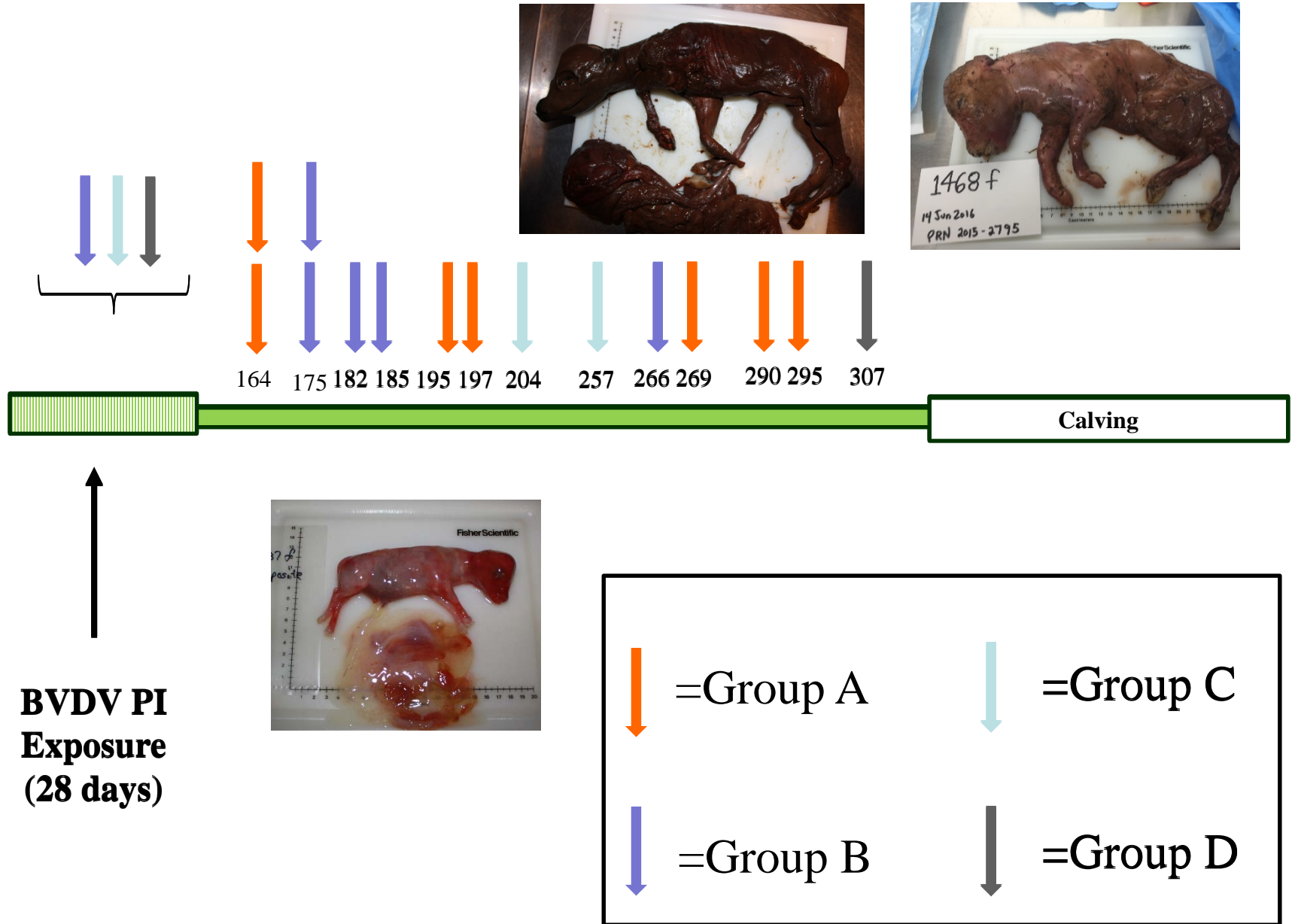
Total Number of BVDV genotypes by Group



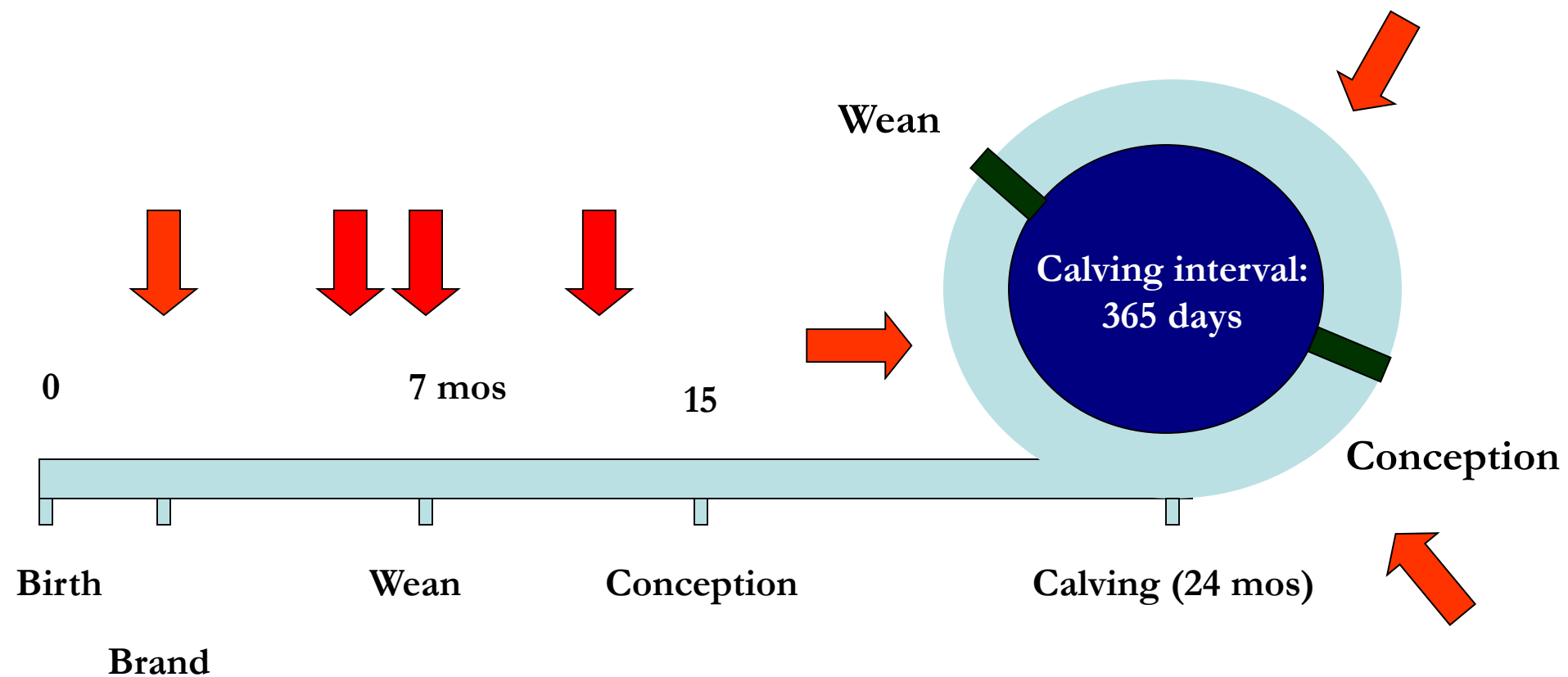


Sequence of Abortion – All cows (110 pregnancies – 18 abortions)

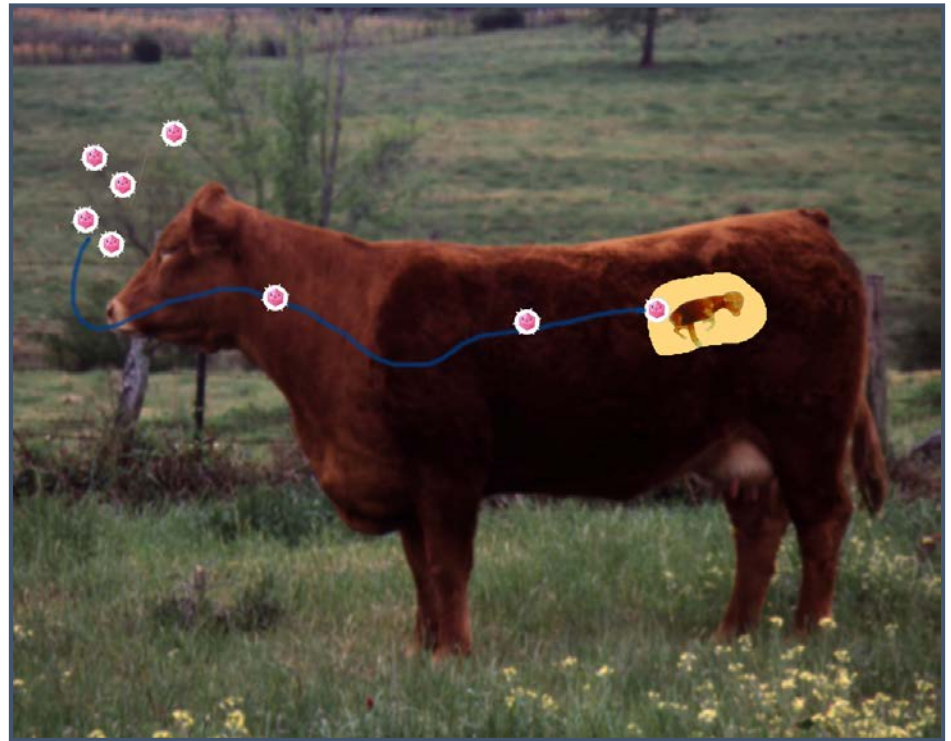
Note: Number below arrow indicates study day



Summary: Timing and Choice of Vaccination



Questions?



AUBURN UNIVERSITY

COLLEGE OF
VETERINARY MEDICINE

walzpau@auburn.edu



Controlling BVDV

1

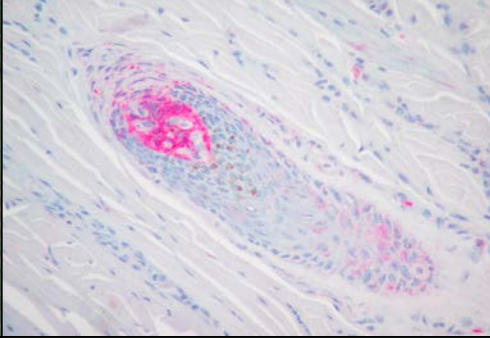
Surveillance to detect

2

Vaccination to keep in check

3

Biosecurity to protect



Comparison of fetal protection among three multivalent killed virus vaccines following exposure to cattle persistently infected with BVDV



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Funding provided by
Zoetis Animal Health

Situation:

Vaccines for bovine reproductive pathogens must provide fetal and abortive protection against *Bovine viral diarrhea virus* (BVDV).

Safety concerns associated with MLV vaccines have led some producers to utilize only KV vaccines in prebreeding and annual revaccination herd health programs.

Thus, a comparative assessment of the fetal and abortive protective efficacy resulting from pre-breeding vaccination of cows with different KV vaccines is needed.

92 cows in Phase I of study (51 cows; 41 heifers):

Group A: CattleMaster® Gold FP®5; Spirovac®L5 (n=28)

Group B: ViraShield® 6 + L5 HB (n=27)

Group C: Triangle™ 10 HB (n=24)

Group D: Saline; Saline (n=13)

18 cows in Phase II of study (5 cows; 13 heifers):

Group A: CattleMaster® Gold FP®5; Spirovac®L5 (n=3)

Group B: ViraShield® 6 + L5 HB (n=5)

Group C: Triangle™ 10 HB (n=7)

Group D: Saline; Saline (n=3)

110 total pregnancies in study (56 cows; 54 heifers):

Group A: CattleMaster® Gold FP®5; Spirovac®L5 (n=31)

Group B: ViraShield® 6 + L5 HB (n=32)

Group C: Triangle™ 10 HB (n=31)

Group D: Saline; Saline (n=16)

