

Evolution of Respiratory Vaccines



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What's on the “Menu” today?

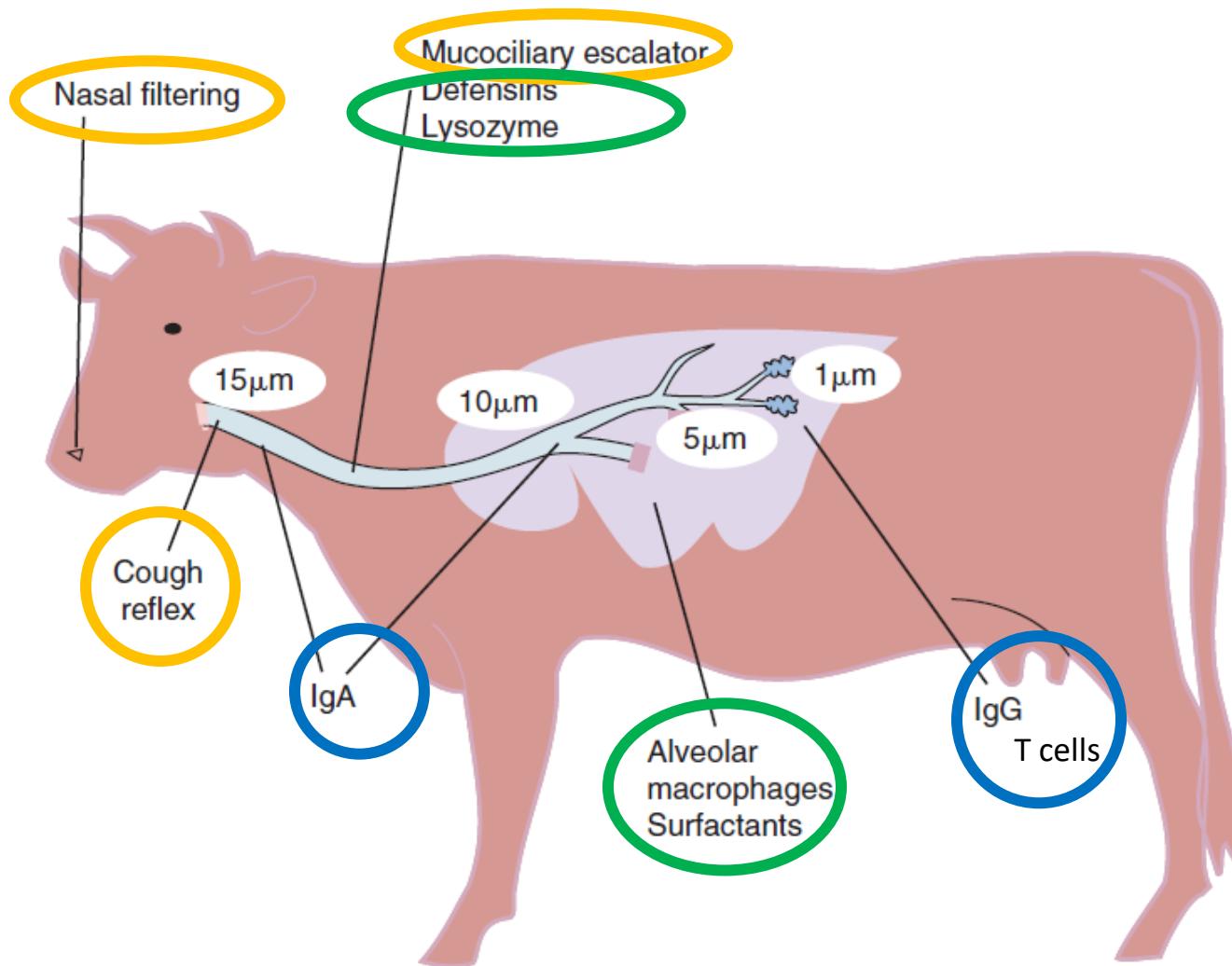


- Some basic Immunology
- Types of vaccines and how they work
 - Some evidence to show they *actually* work
 - How we can maybe improve the way they work by re-thinking how we give them

How do you or a steer defend against the world: 3 layers of defense

NON-SPECIFIC DEFENCES		SPECIFIC DEFENCES
1. SURFACE BARRIERS	2. INNATE IMMUNITY	3. ADAPTIVE IMMUNITY
<ul style="list-style-type: none">• Intact skin• Mucous membranes• Chemical secretions	<ul style="list-style-type: none">• Phagocytic leukocytes• Inflammation• Fever	<ul style="list-style-type: none">• Lymphocytes• Antibodies• Memory cells

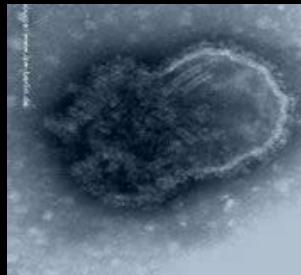
Overview of “**Barriers**” and **Innate** and **Acquired** Immune Responses in the bovine respiratory tract....



From Tizard, Veterinary Immunology, 9th edition

Generally, the life style of the “Bug” determines the immunological Response

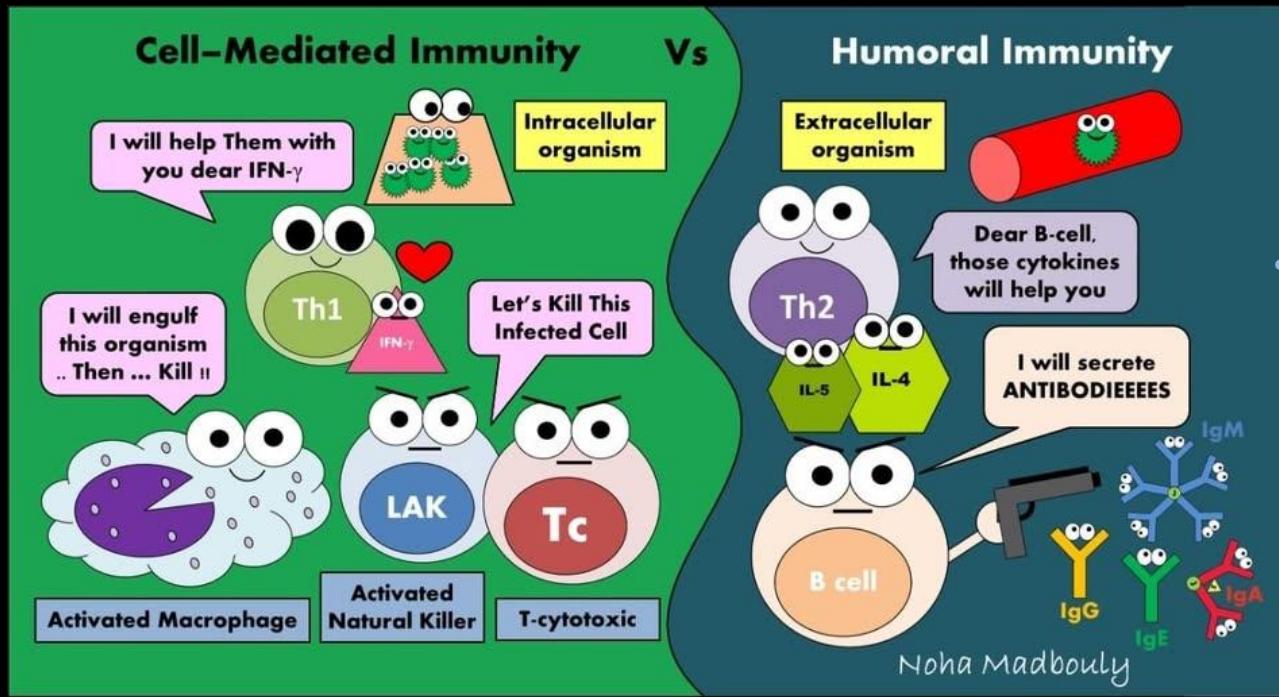
- Intracellular pathogens (viruses)



- Extracellular pathogens (Bacteria)

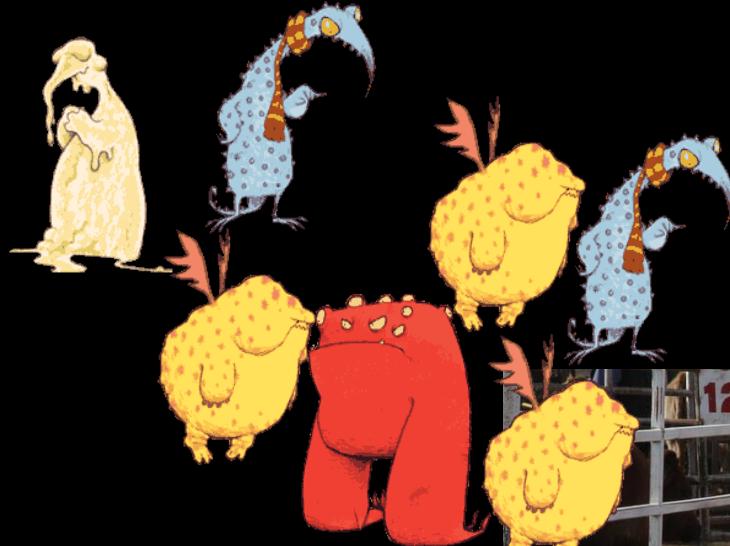


**T cells
recognize
“processed”
antigens**

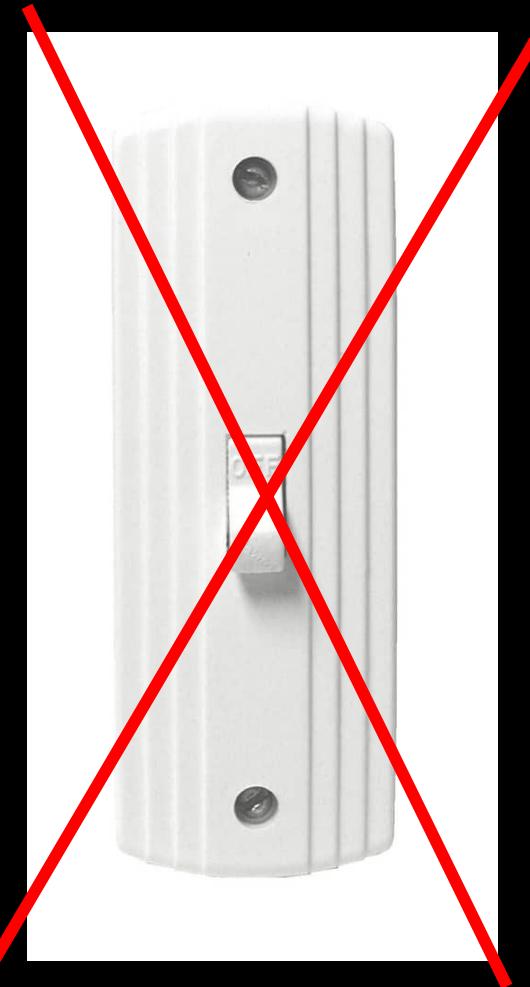


**B cells
recognize
native whole
antigens**

Think of infectious disease as a RACE between a “bug” and a host.....



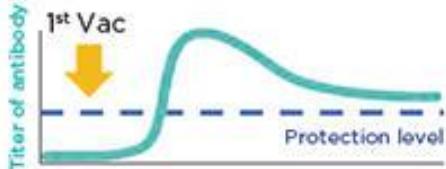
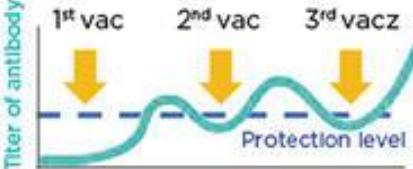
Think of the immune response as a rheostat, *not* an on-off switch!



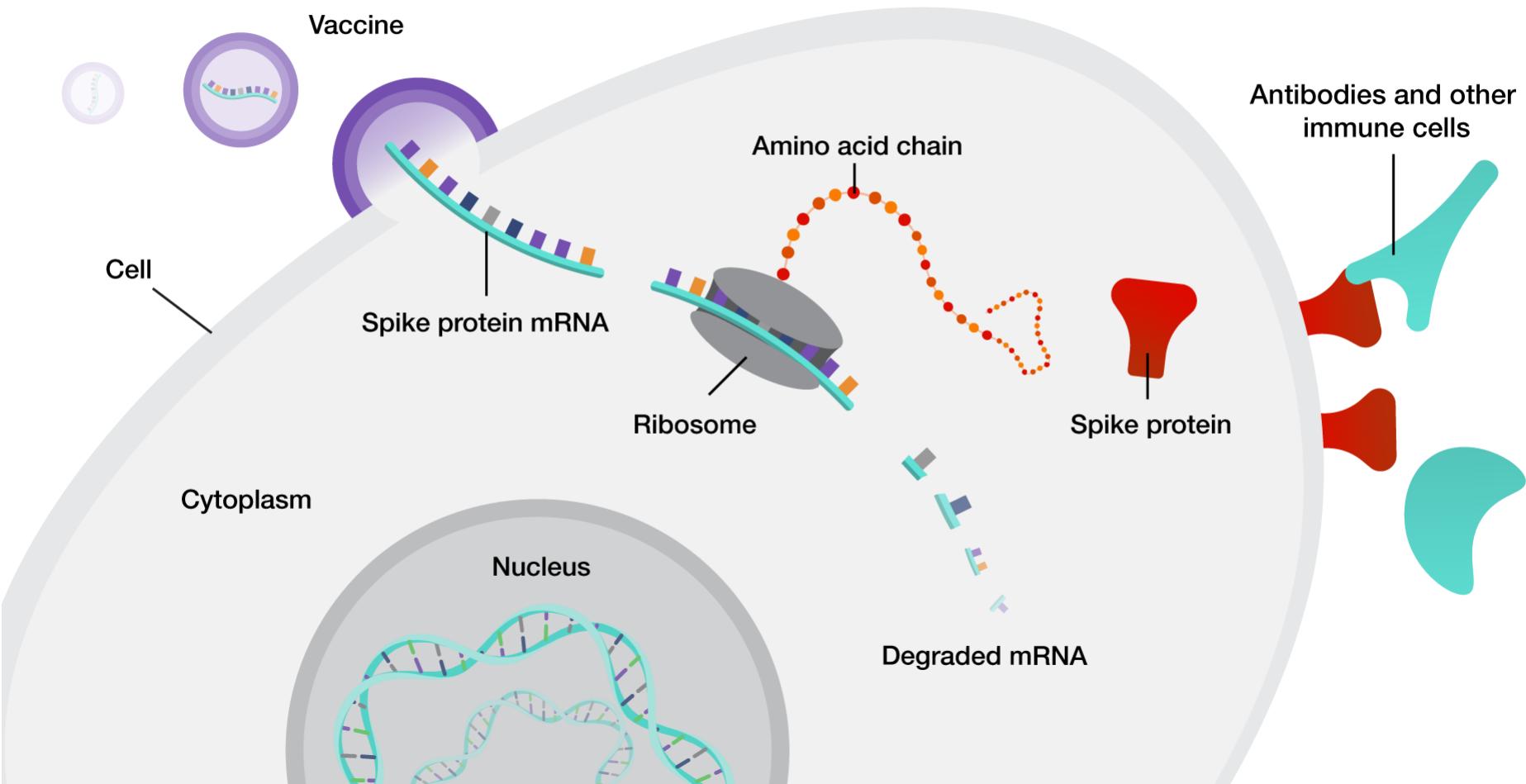
Reasonable Expectation: Vaccines, properly applied, *reduce* the size of the dead pile, they don't *prevent* it!



Basic vaccine types used in cattle for the last 50 years

	Live vaccine	Inactivated vaccine
1. Development	Attenuated virus Replicate in the host	Inactivated form of virus, protein etc. Non-replicating in the host
2. Effectiveness	Induce antibody and cellular immune response	Induce only antibody
3. Safety	Takes time for safety testing Strong immune response Long-term vaccine efficacy	Capable of rapid preparation Weak, transient Short-term vaccine efficacy
4. Economical aspect	 Potential reversion to virulence Lower cost of manufacturing	 Non-replicating Need Large number of vaccine

How do RNA vaccines work?



Key Facts for Consumers

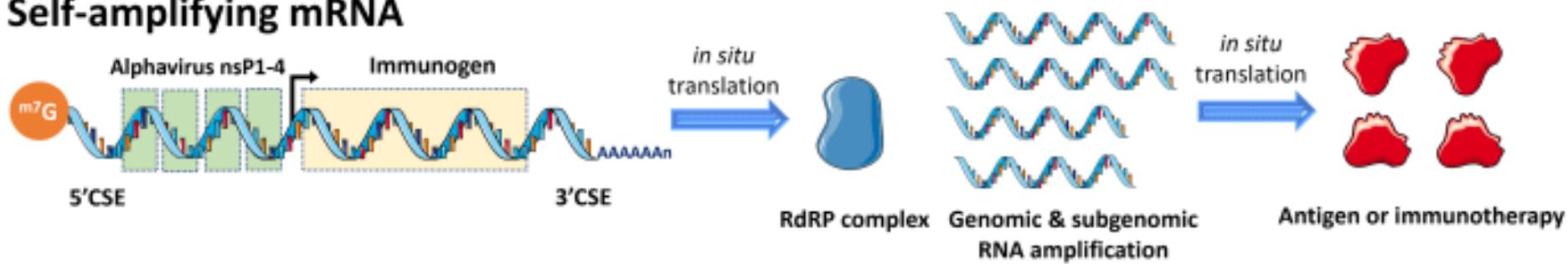
- **No Genetic Modification:** mRNA vaccines do not alter the animal's DNA; they provide temporary instructions to cells to build a protein that triggers an immune response.
- **No Residue in Meat:** mRNA is highly unstable and degrades within hours or days. Additionally, mandatory **withdrawal periods** ensure that any vaccine components are cleared from the animal's system long before processing

The *FUTURE*? “self-amplifying” RNA vaccines

Conventional mRNA



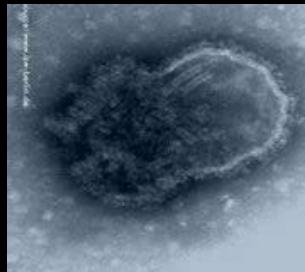
Self-amplifying mRNA



RNA and saRNA vaccines act like MLV vaccines: they stimulate *both* **CMI** and **antibody** responses

Generally, the life style of “Bug” determines the type of vaccine to use

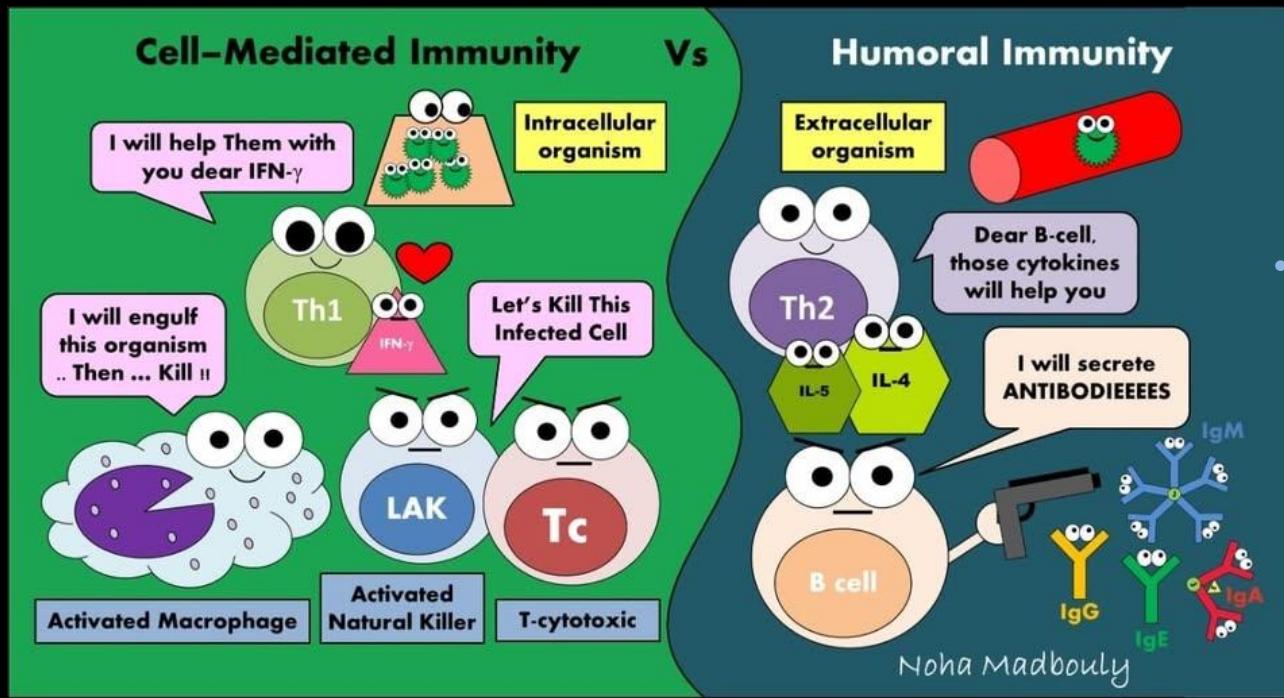
- Intracellular pathogens (viruses)



- Extracellular pathogens (Bacteria)

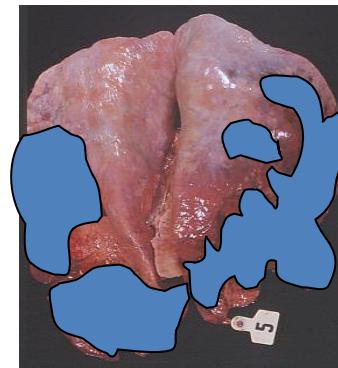


Modified-live vaccines



Inactivated (“killed”) vaccines

Outcome variables of efficacy in **BRSV** challenge model



- **% pneumonic lung**
 - Image analysis
- **Arterial pO₂**
 - Percutaneous aortic puncture
- Nasal shed
- Clinical signs
 - Respiratory rate / character
 - Rectal temperature



How well do commercial injectable MLV vaccines for **BRSV** “work”?

Vaccine 18 (2000) 907–919

The efficacy of modified-live bovine respiratory syncytial virus vaccines in experimentally infected calves

Keith West^{a,*}, Lyall Petrie^b, Carrie Konobay^a, Deborah M. Haines^a, Victor Cortese^c, John A. Ellis^a

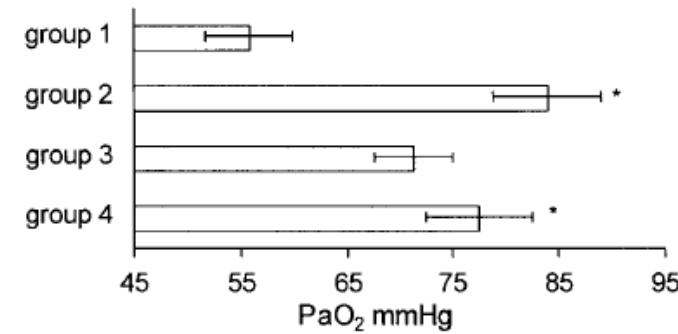
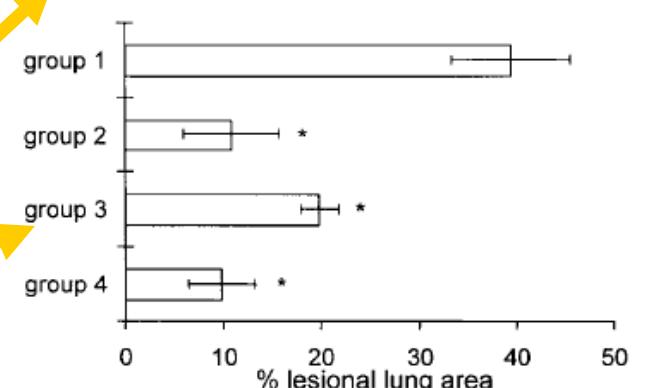
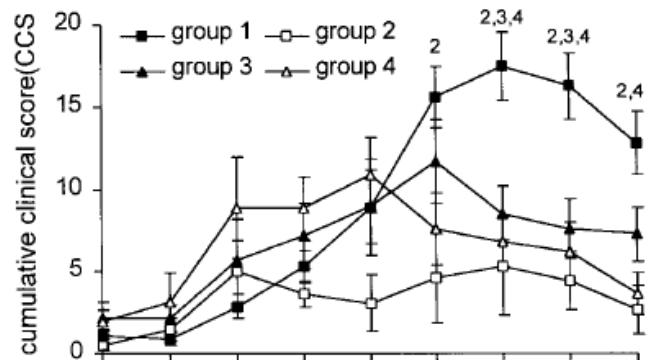
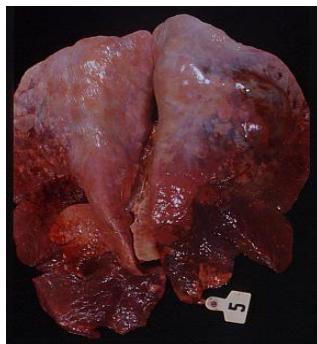
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^cAnimal Health Group, Pfizer Inc., 812 Springdale Dr, Exton, PA 19341-2803, USA

Received 26 January 1999; accepted 30 June 1999

- Seronegative calves
- Vaccinated with 1 of several *injectable* MLV vaccines; challenged 2 weeks later
- Reduction in clinical signs, (viral shed)
- Reduction in pulmonary lesions
- Reduction in compromise of pulmonary function (pO₂)



Parenteral **BHV-1** vaccines...how well do they work????

Efficacy of a combination viral vaccine for protection of cattle against experimental infection with field isolates of bovine herpesvirus-1

John A. Ellis, DVM, PhD, DACVP, DACVM; Sheryl P. Gow, DVM, PhD; Noriko Goji, DVM; Clinton Jones, PhD; Aspen Workman; Gail Henderson; Carrie Rhodes, BSc; Glenn Alaniz, BS; Todd R. Meinert, PhD; Cassius M. Tucker, DVM

Objective—To determine whether a combination viral vaccine containing a modified-live bovine herpesvirus-1 (BHV-1) would protect calves from infection with virulent field strains of BHV-1 for weeks or months after vaccination.

Design—Randomized controlled trial, performed in 2 replicates.

Animals—63 weaned 4- to 6-month-old crossbred beef calves seronegative for antibody

- ***Reduction in clinical signs***
- ***Reduction in viral shedding***
- ***Reduction in lesions***

37 days after vaccination.

Conclusions and Clinical Relevance—Administration of the combination modified-live BHV-1 vaccine yielded significant disease-sparing effects in calves experimentally infected with virulent field strains of BHV-1. (*J Am Vet Med Assoc* 2009;235:563-572)

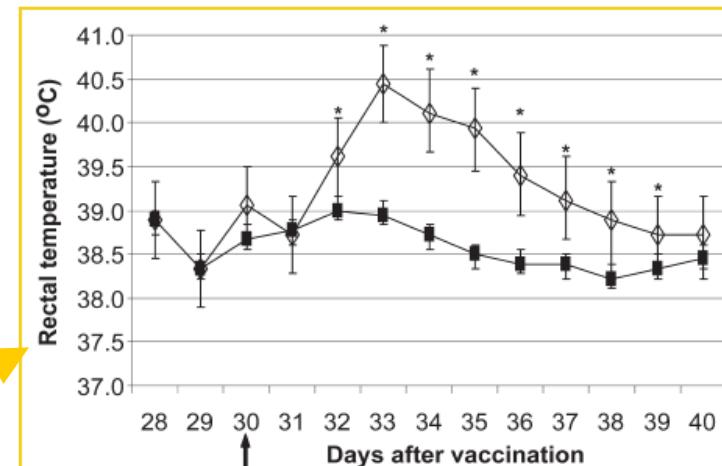
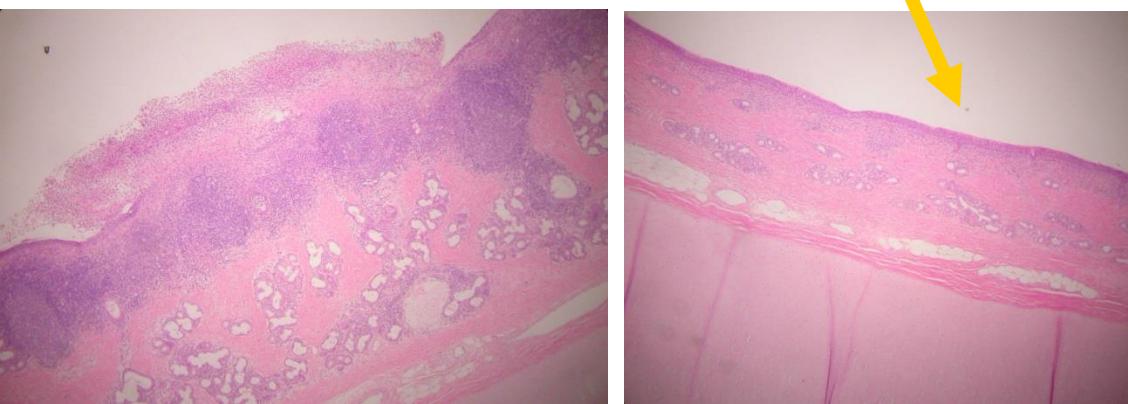


Figure 1—Mean \pm SE rectal temperatures at various time points in calves vaccinated with a combination modified-live vaccine with (squares; $n = 20$) or without (diamonds; 10) BHV-1 8 days after weaning and challenged with BHV-1 strain P3 30 days after vaccination. Arrow indicates time of challenge. To convert temperature from Celsius to Fahrenheit, multiply value by 9/5 and add 32. *Values are significantly ($P < 0.05$) different between groups on indicated day.

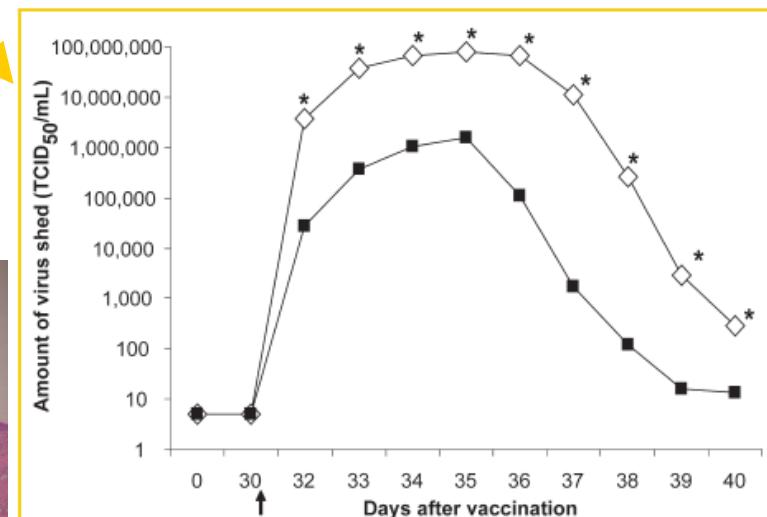


Figure 5—Mean amount ($TCID_{50}/mL$) of virus shed in nasal secretions at various time points in calves vaccinated with a combination modified-live vaccine with (squares; $n = 20$) or without (diamonds; 10) BHV-1 8 days after weaning and challenged with BHV-1 strain P3 30 days after vaccination. See Figure 1 for remainder of key.

Clinical immunity to **BHV-1**...how long does it last?

- Given the logistical difficulties in maintaining cattle in isolation for extended periods after vaccination and prior to experimental infection, there have been relatively few studies that have examined duration of immunity to BHV-1 vaccines. Available data indicate the duration of immunity to conventional parenteral BHV-1 vaccines is at least 4-6 mo....*but begins to wane shortly after vaccination!!!*

Longevity of protective immunity to experimental bovine herpesvirus-1 infection following inoculation with a combination modified-live virus vaccine in beef calves

John Ellis, DVM, PhD, DACVP, DACVM; Cheryl Waldner, DVM, PhD; Carrie Rhodes, BSc; Van Ricketts, DVM

Objective—To determine whether a combination viral vaccine containing modified-live bovine herpesvirus-1 (BHV-1) would protect calves from infection with a recent field isolate of BHV-1.

Design—Randomized controlled trial.

Animals—Sixty 4- to 6-month-old beef calves.

Procedure—Calves were inoculated with a placebo 42 and 20 days prior to challenge (group 1; n = 10) or with the combination vaccine 42 and 20 days prior to challenge (group 2; 10), 146 and 126 days prior to challenge (group 3; 10), 117 and 96 days prior to challenge (group 4; 10), 86 and 65 days prior to challenge (group 5; 10), or 126 days prior to challenge (group 6; 10). All calves were challenged with BHV-1 via aerosol. Clinical signs, immune responses, and nasal shedding of virus were monitored for 14 days after challenge.

Results—Vaccination elicited increases in BHV-1-specific IgG antibody titers. Challenge with BHV-1 resulted in mild respiratory tract disease in all groups, but vaccinated calves had less severe signs of clinical disease. Extent and duration of nasal BHV-1 shedding fol-

causal organism was eventually identified as a herpesvirus, and bovine herpesvirus-1 (BHV-1) was first isolated in 1956 from affected cattle in California and Colorado.³ A subsequent study⁴ revealed that BHV-1 was a common predisposing factor for shipping fever pneumonia in feedlot cattle.

Because of the substantial economic losses associated with BHV-1 infection in feedlot cattle, modified-live⁵ and inactivated⁶ virus vaccines were developed shortly after the initial isolation of the virus and are still commonly used today to control the clinical effects of BHV-1 infection.⁹ Despite label instructions recommending vaccination of healthy cattle prior to exposure to the agent in high-stress situations, BHV-1 vaccines have traditionally been administered to calves at the time of feedlot arrival and are tacitly expected to induce immunity lasting throughout a feeding period of 180 days or more. However, losses associated with BHV-1 infection continue despite routine vaccination of cattle, and in recent years, there has been an apparent increase in the number of reports of outbreaks of IBR among vaccinated feedlot cattle (so-called vaccine

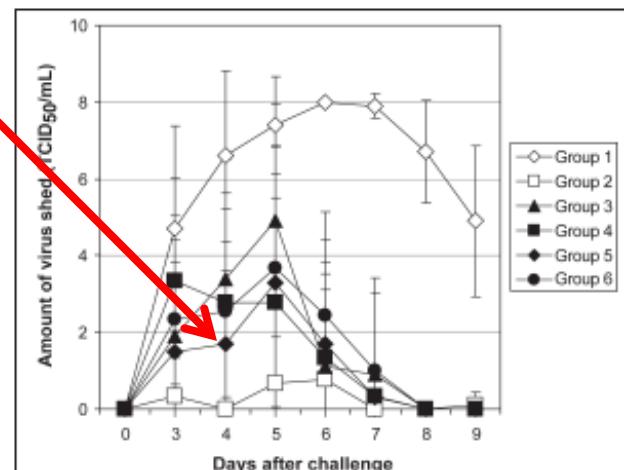


Figure 2—Mean \pm SD amount of virus shed (TCID₅₀/mL) in nasal secretions following challenge of feedlot calves with virulent BHV-1. See Figure 1 for key.

Standard of Practice

- Vaccinating on arrival at feedlot.....



....and then hoping for an immunological miracle...
or blaming the vaccine (company) if there is no
miracle...



A systematic review and network meta-analysis of bacterial and viral vaccines, administered at or near arrival at the feedlot, for control of bovine respiratory disease in beef cattle

O'Connor, A. M. and Hu, D. and Totton, S. C. and Scott, N. and Winder, C. B. and Wang, B. and Wang, C. and Glanville, J. and Wood, H. and White, B. and Larson, R. and Waldner, C. and Sargeant, J. M.

Anim Health Res Rev (2019) 20: 143–162

DOI: [10.1017/s1466252319000288](https://doi.org/10.1017/s1466252319000288)

Summary of findings:

- Identified **53 vaccine studies** reporting BRD within 45 days of arrival.
- Included **17 vaccine protocols** across 14 studies in the connected network.
- Found **little compelling evidence that arrival vaccination — of any vaccine type or route — reduces BRD morbidity in feedlot cattle.**

So, should we just stop vaccinating?

Key Takeaways

- Do not stop vaccinating — but adjust protocols based on risk.
- High-risk cattle benefit most from aggressive vaccination, including intranasal + injectable combinations.
- Arrival vaccines have limited short-term BRD effect in low-risk cattle, but viral immunity must still be maintained.
- The O'Connor vaccine meta-analysis does not argue against vaccination, but rather against relying on arrival vaccination alone for short-term BRD control.

Developing **LOW RISK**
cattle should be the
goal!



➤ J Am Vet Med Assoc. 1955 Jun;126(939):463-7.

Infectious necrotic rhinotracheitis of cattle

N J MILLER

Miller (1955)

- Typical morbidity: ~30%
- Peak morbidity: reached within 12–15 days
- Potential morbidity: up to 100% in acute outbreaks

osu

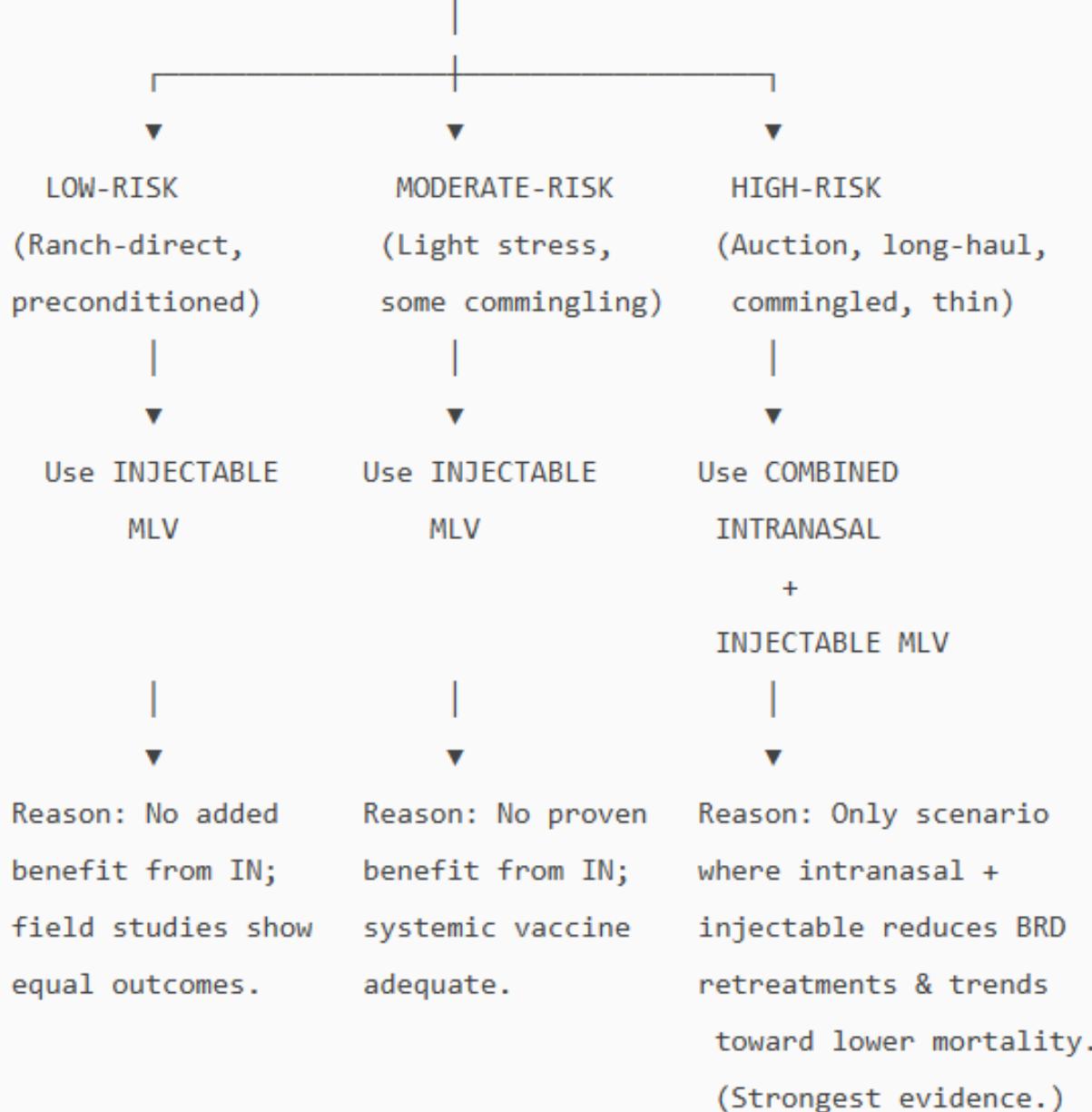
Modern Data

Modern IBR rarely appears as explosive, high-morbidity outbreaks in feedlots due to:

- Widespread vaccination
- Latent virus dynamics
- Improved management
- IBR often acting as *part* of BRD, not a standalone epidemic



What is the RISK CLASS?





Bottom Line

- High-risk vaccinated cattle still experience more BRD than low-risk cattle, but **combined intranasal + injectable vaccination provides significant clinical benefit**, reducing retreatments and likely reducing mortality.

cambridge

- Low-risk vaccinated cattle have low morbidity/mortality regardless of vaccine route, and **no field trial shows improvement** with intranasal or prime-boost methods.

avma

- **Injectable MLV alone** remains the standard for low-risk cattle.
- Combined IN + IJ is the evidence-supported strategy *only* for high-risk groups.

No published field studies show that giving an intranasal (IN) respiratory vaccine on arrival *worsens* BRD outcomes.

Developing **LOW RISK**
cattle should be the
goal!



Standard of Practice

- Vaccinating young calves with *injectable* vaccines...



....is this really the best way to develop **LOW RISK** cattle..... Why or why not?

NO! It's because maternal antibodies block injectable vaccines... but, remember, the “blocking” (inhibitory) effect of maternal antibodies is a rheostat; *not* an on-off switch!



Do maternal antibodies block priming of injectable BRSV vaccines..???

Can Vet J 2014;55:1180–1185

Inhibition of priming for bovine respiratory syncytial virus-specific protective immune responses following parenteral vaccination of passively immune calves

John Ellis, Sheryl Gow, Michael Bolton, William Burdett, Scott Nordstrom

Vaccine 38 (2020) 298–308



Protection against bovine respiratory syncytial virus in calves vaccinated with adjuvanted modified live vaccine administered in the face of maternal antibody

Elizabeth A. Kolb ^{a,1}, Robin E. Buterbaugh ^a, Carol L. Rinehart ^a, Douglas Ensley ^b, George A. Perry ^c, Karim W. Abdelsalam ^a, Christopher C.L. Chase ^{a,d,*}

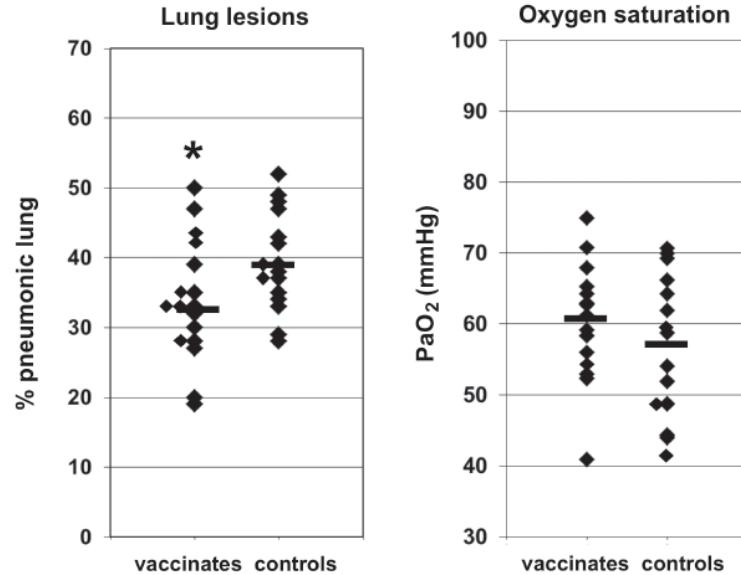


Figure 2. Scatter plots of the percentage of lungs affected with pneumonic lesions and arterial oxygen concentrations after BRSV challenge of BRSV-seropositive calves that were either vaccinated parenterally with a commercial combination modified-live virus vaccine containing BRSV, or control-vaccinated, and that were challenged with BRSV approximately 11 weeks after vaccination. Lines indicate median values in each group. *indicates significant difference between groups.

Calves vaccinated at 3-9 days of age;
mean VN titer 1:64

YES!, at levels consistent with good passive transfer; it's not all or none!!!

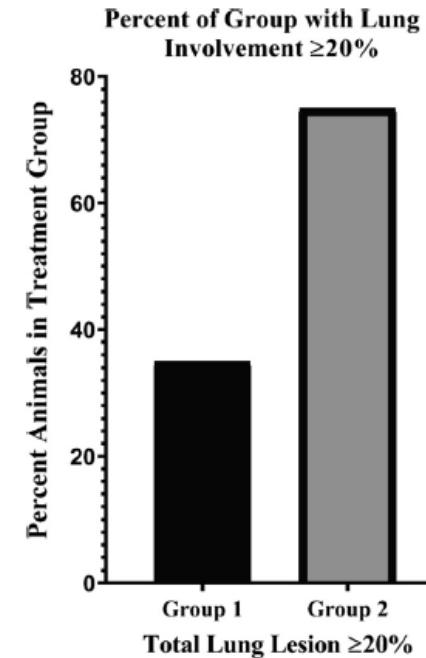
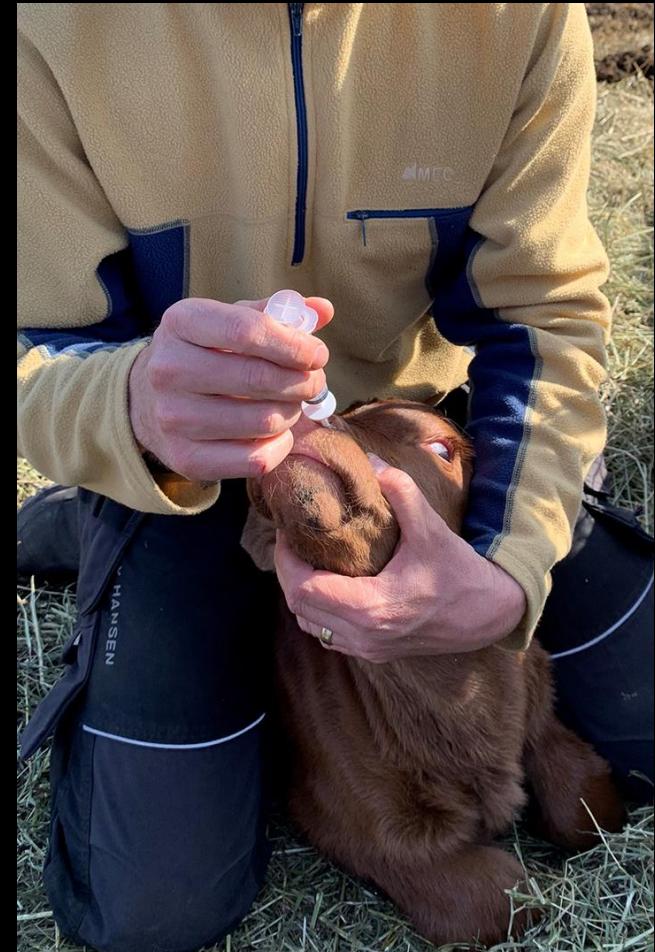


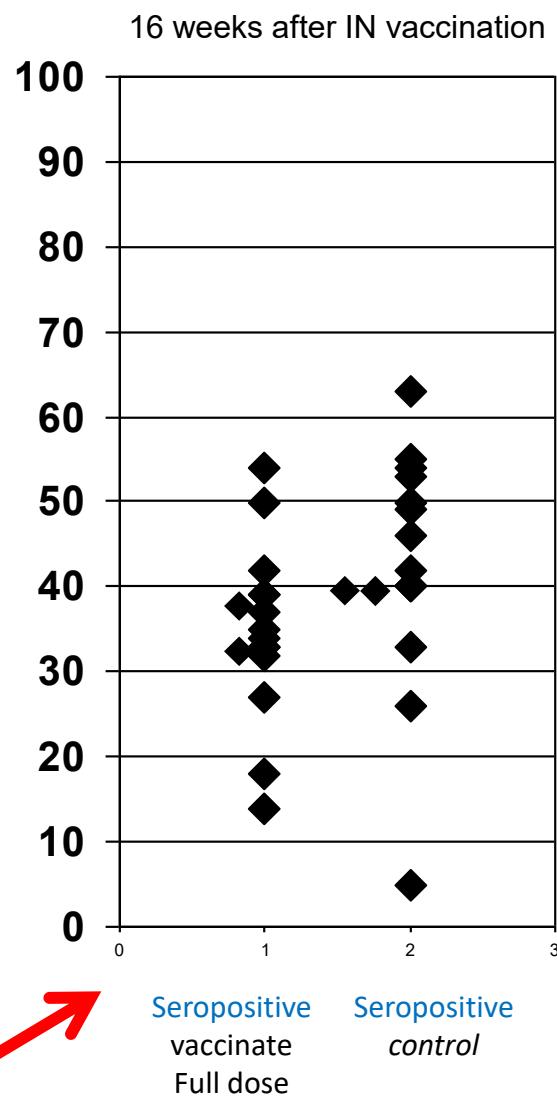
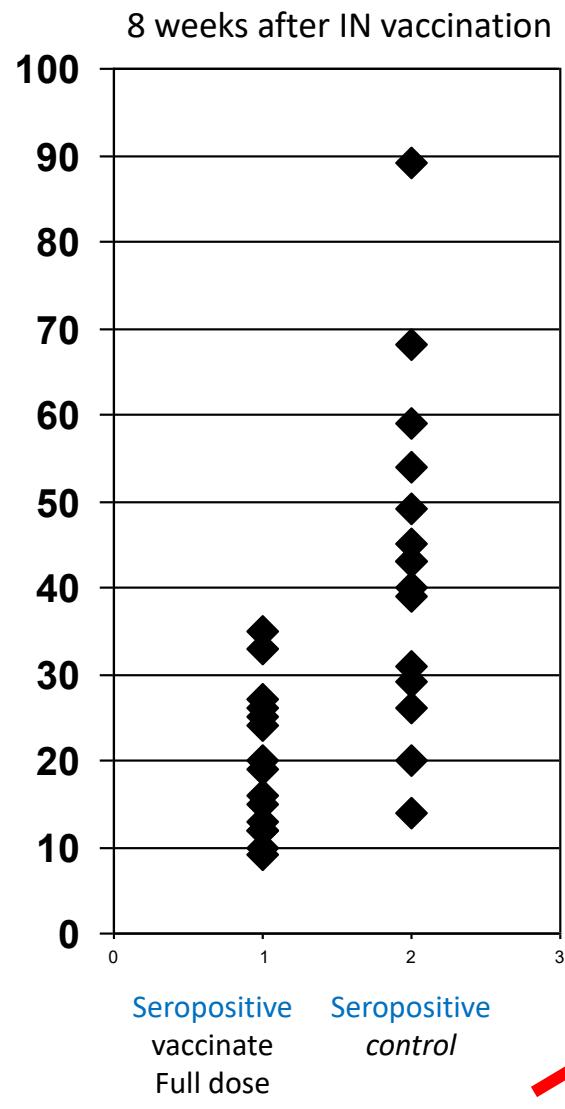
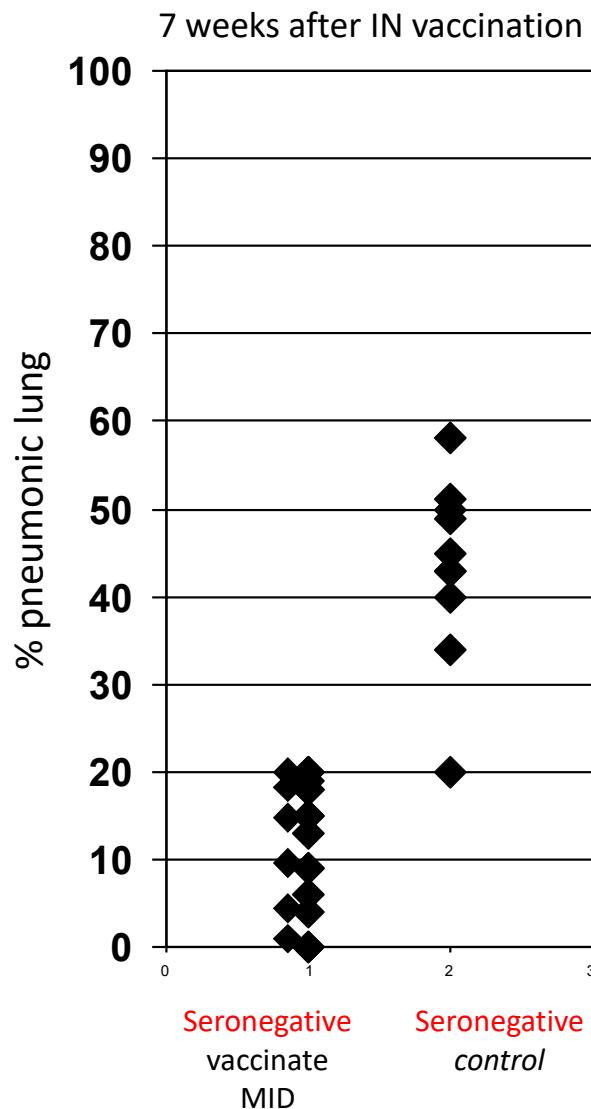
Fig. 4. Percentage of Animals with Total Lung Lesion Involvement ≥20%. Group 1 (Vaccinates) and Group 2 (Control). The number of animals in each group with a total lung lesion involvement of 20% or more were compiled. The remaining percent of animals by group had lesion scores that were less than these parameters. There was a statistically significant reduction in lung lesions in Group 1(vaccinates) compared to the controls ($P < 0.05$) as well as a reduction in the number of animals with significant lung involvement.

Calves vaccinated at 30 days of age;
mean VN titer 1:16???

What happens in a “herd” to assure its survival from infectious diseases...and how can we improve on that with vaccination?



IN BRSV vaccines “override” maternal antibodies...



but have short DOI; what's the best boost??....

No Difference!!
Ellis, et al. JAVMA, 2013

The (Heterologous) *Prime/Boost* approach to Immunization

- The Concept: Expose the immune system to *different forms* of an antigen by *different routes* to achieve broadest most durable response

Review

Vaccine 34 (2016) 413–423

Prime-boost vaccine strategy against viral infections:
Mechanisms and benefits

Kimia Kardani ¹, Azam Bolhassani ^{*,1}, Sepideh Shahbazi

Department of Hepatitis and AIDS, Pasteur Institute of Iran, Tehran, Iran

>2,700 papers in “prime/boost” search on Medline



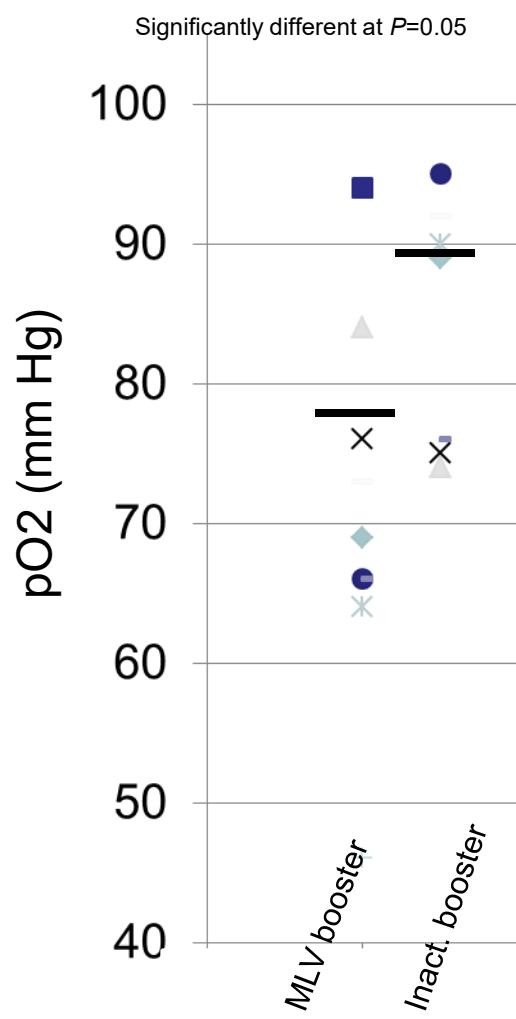
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Table 1
Preclinical and clinical trials for prime-boost vaccine strategies.

Pathogen	Prime	Boost	Type	Antigen	Response	Preclinical (Animal model)	Clinical (Phase)	Ref.
HIV	DNA	MVA	DNA/virus	HIV-1 IIB Env, Gag, RT, Rev, Tat, Nef, SIV Gag, Pol	High Antibody and CTL; Low viral load	Macaques	–	[55]
MVA + cholera toxin	MVA + cholera toxin	Virus/virus	HIV-1 IIB Env	HIV-1 Gag, Pol, Net/Env	High Antibody, cytokine chemokine and CTL			
DNA	Replicon-defective adenoviral vector (ADV)	DNA/virus	HIV-1 Env gp120	High Ab, CTL, IFN- γ				
DNA	ADV, or recombinant vaccinia virus (VV)	DNA/virus	TAB 13	High IFN- γ , IL-10				
DNA	MVA or VV	DNA/VLP	Env proteins, Gag	High Ab and lymph proliferation, poor neutralization				
DNA	Protein (p55Gag virus-like particles)	DNA/VLP	HIV Gag	High IFN- γ and Cytotoxicity				
DNA	p55Gag virus-like particles	DNA/VLP	HIV Env (gp120, gp140, gp150)	High Ab and IFN- γ , neutralization				
DNA	ADV	DNA/virus	HIV gp120	High CD8+ T cell arm response				
DNA	Packaged amplicon particles (13')	DNA/virus	HIV Gag	No change in immune response against core				
ADV (E1-deleted adenoviral vector)	ADV (E1-deleted adenoviral vector)	Virus/virus	HIV Gag	High Ab and protec				
DNA	DNA/protein	Env	HIV-1 gp160/gp41	High Ab, Long term neutralization Ab				
HIV-1 gp160 DNA	Peptide HIV-1 gp41	DNA/peptide	HIV-1 gp160/gp41	Long term Ab, High and neutralization				
DNA	VV/Protein	DNA/virus or protein	Env	Long term Ab, High and neutralization	DNA	Canarypox	DNA/virus	Capsid/E1/E2/NS2/NS3 proteins
DNA	MVA	DNA/virus	CTL epitopes	High CD8+ T cell	DNA	lambda nanoparticles	DNA/virus	High IFN- γ , Low virus titers
DNA	MVA	DNA/virus	Tat, Rev, Nef, Gp41	High T cell respons	HCV core			Highest level of lymphocyte proliferation, Th1 response
DNA	Protein	DNA/protein	HIV-1 Gp120	High Ab and neutral Ab				A significant increase in polyfunctional IFN- γ /TNF- α
MVA	FPW	Virus/virus	V3 loop of gp120	High IFN- γ	DNA HCV 1a NS3/4A (chronVac-C)	Modified vaccinia virus Ankara vaccine expressing genotype 1b NS3/4 (5B (MVATG16643)	DNA/virus	High Ab and cytokines
SVF	MVA	Virus/virus	HIV immunogen from HIV-1 clade A	High IFN- γ /Long te				High Ab and virus clearance from lungs
CpG + protein	ADV	Protein/virus	Gag	CTL induction				100% protection
Rabies virus	VSV	Virus/virus	Env	High IFN- γ				Monkey
SFV	FPV	Virus/virus	TAB9 multi-epitopes	High Ab, IFN- γ and neutralization activ	HSV-2	Liposome-encapsulated protein MVA	DNA/protein	High Th1 response
Influenza virus (V3 loop of gp120)	VV/MVA (gp160)	Virus/virus	V3 loop of gp120/gp160	High IFN- γ , Low vi	Equine herpesvirus 1	Glycoprotein D EHV-1 Glycoprotein D	DNA/virus	Mice
DNA gp160/Rev	VLP	DNA/VLP	gp160/Rev	60% protec				Mice
Multigene DNA gp160subtypes A,B,C/Rev/B/Gag-A/B/RTmutB/CRP01-AEHIV-1Env subtype E/Gag-Pol subtype A	MVA (HIVIS03) CRP01-AEHIV-1Env subtype E/Gag-Pol subtype A	DNA/virus	gp160subtypes A,B,C/Rev/B/Gag-A/B/RTmutB/CRP01-AEHIV-1Env subtype E/Gag-Pol subtype A	High IFN- γ and IgG IgG1 ratio	Human T cell Leukemia/ Lymphoma virus type 1 (HTLV-1)	HBsAg		[113]
				Increase the env-specific humoral and cellular immune response, compared to the homologous protocol	Classical Swine fever virus	ADV		
				Low dose intraderm HIV DNA elicits high and broader immune responses compare higher dose	HPV	Recombinant Vaccinia or Adenovirus or poxvirus/tumor cell-based vaccine	DNA/viruses or cells	100% protection
				intramuscular injection	E6/E7 DNA	E6/E7		Pigs
				High levels of (ADCC)-mediating antibodies	pNGVL4a/Sig/E7 (detox) HSP70			Mice
					DNA			[114]
					Recombinant fusion protein			[115]
					HIV1/6 E6 and E7 (TA-HPV)			[116]
					Recombinant Vaccinia expressing			[117]
					HIV1/6 E6 and E7 (TA-HPV)			[118]
					Therapeutic effects			[119]
								[120]
								[121]
								[122]
								[123]
								[124]
								[125]

Comparing responses to MLV versus Inactivated boosters for BRSV: The inactivated booster conferred superior clinical immunity when neonatally IN-primed calves were challenged at weaning(6 months of age).....

Arterial pO₂ day 7 after challenge



Mean total clinical scores on day 7:
Inactivated vaccinees 0.3
MLV vaccinees 1.1

Comparison of virus-neutralizing and virus-specific ELISA antibody responses among bovine neonates differentially primed and boosted against bovine coronavirus

Nathan E.N. Erickson, Stacey Lacoste, Michelle Sniatynski, Cheryl Waldner, John Ellis

- Study 1 and Study 2 had 33 and 22 **commercial cross neonatal beef calves**, respectively.
- **Procedure** Study 1 compared BCoV-neutralizing antibody concentrations of control calves with 3 groups of calves differentially vaccinated with mucosal and/or systemic BCoV modified live virus (MLV) vaccines. Study 2 compared specific and neutralizing antibody concentrations among mucosally BCoV primed groups of calves that were differentially systemically boosted.
- **Bottom line results:** In Study 1, calves that were mucosally primed and systemically boosted had higher BCoV-neutralizing antibody concentrations than the only control group at weaning. In Study 2, boosting mucosally primed calves by injecting inactivated or MLV vaccine resulted in anamnestic BCoV-specific antibody responses at weaning
- **Conclusion:** Neonatal mucosal priming and systemic boosting resulted in anamnestic BCoV antibody responses at weaning.

Comparison of postweaning bovine respiratory disease treatment rates between non-vaccinated control beef calves and calves variably primed and boosted using commercially available bovine coronavirus vaccines

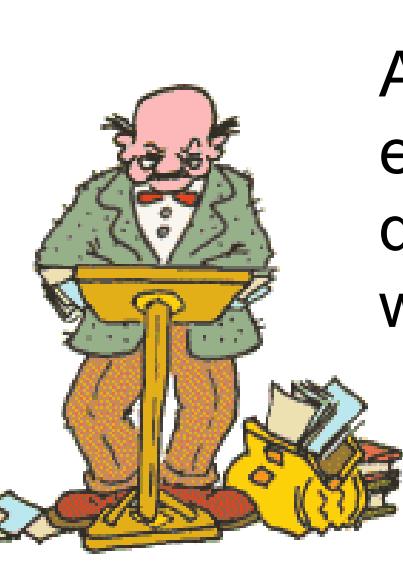
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- **Commercial heifer and steer beef calves** born in April and May 2022.
- **Procedure** Calves were randomly enrolled into 3 treatment groups. Those in 2 groups [V1 ($n = 160$) and V2 ($n = 160$)] were administered a mucosal priming dose of 1 of 2 commercial BCoV vaccines; those in the 3rd group [CTL ($n = 151$)] were unvaccinated against BCoV. The V1 and V2 groups were boosted by intramuscular injection pre-weaning with the same vaccine used for priming
- **Bottom line results:** Postweaning BRD treatment rates for V1, V2, and CTL were 7%, 9%, and 14%, respectively. The CTL calves had 2.23 greater odds of receiving treatment for BRD than V1 calves. There were no differences in odds of treatment between CTL and V2 calves or V1 and V2 calves
- **Conclusion:** In a herd with previously diagnosed BCoV BRD cases, prime-boost vaccination of calves is associated with a difference in odds of BRD treatment post-weaning compared to not vaccinating calves against BCoV.

Comparison of pre-weaning bovine respiratory disease treatment rates between non-vaccinated control and variably primed and boosted beef calves receiving commercially available bovine coronavirus vaccines

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- **Beef calves** of mixed sex and breed at a privately owned ranch in north-central Alberta with a history of BRD were randomized into a clinical vaccine trial.
- **Procedure** At birth, 447 calves were enrolled into the vaccine (VAC) group and administered an intranasal dose of BCoV vaccine, and 439 calves were enrolled as controls (CON). Most VAC calves ($n = 389$) also received an intramuscular dose of BCoV vaccine at an average of 49 d (SD: 7 d).
- **Bottom line results:** Weaning weights were higher for VAC calves ($P = 0.04$) and, despite increased costs due to vaccination, revenue for VAC calves was an average of \$10.50/head higher.
- **Conclusion:** Vaccination of neonatal calves with BCoV vaccine reduced the frequency of BRD treatment and total mortality and improved weaning weights and revenue potential in this herd.



An approach to improving overall vaccine efficacy...getting **LOW RISK** cattle.....we really don't need new vaccines we just need to rethink the way we're using the ones we have

Suggested protocol for use of
intranasal and ***injectable*** vaccines

- **Prime** with ***intranasal***
 - *Can be safely done at young age*
 - *Override maternal antibodies*
 - *Prime mucosal and systemic immune response*



- **Boost** with ***injectable***
 - *Better (systemic) memory response*
 - *No head gate needed*

