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Bovine Respiratory Disease

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Vaccination to Control BRD: What's the Latest?


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Disclosure and thanks

- Dr. Woolums has received support for research and consulting from
  - Bayer Animal Health
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  - Merck
  - Phibro
  - SAb Biotherapeutics
  - Zoetis

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- There is no single BRD vaccination protocol that fits all situations
- Need to consider
  - What are these animals likely to be exposed to?
    - Do vaccines against these agents exist?
    - What is the evidence for their efficacy?
  - Can the vaccine cause harm? What is the risk?
  - Will the financial cost of vaccinating be returned?
  - Can the vaccine be administered usefully, given the management on this operation?

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Core vaccines for cattle

American Association of Bovine Practitioners
AABP GUIDELINES 1

AABP VACCINATION GUIDELINES

http://www.aabp.org/committees/resources/VaccGuidelines2021.pdf

Core vaccines for cattle:

- Infectious bovine rhinotracheitis virus (IBRV)
- Bovine viral diarrhea virus (BVDV)
- Parainfluenza type 3 virus (PI3V)
- Bovine respiratory syncytial virus (BRSV)
- Multivalent clostridial vaccines (excluding *C. tetani* and *C. hemolyticum*)

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Where to find currently available vaccines

- https://www.aphis.usda.gov/animal_health/vet_biologics/publications/currentprodcodebook.pdf

USDA

Veterinary Biological Products

Licensees and Permittees
Prepared July 1, 2020

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- Why do we vaccinate?
  - To prevent infection?
  - To prevent disease?
  - To improve immunity?
  - To save money otherwise spent on treatment?
  - To decrease antimicrobial use?

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- Vaccines against common endemic pathogens usually don't prevent infection and disease in all vaccinated animals

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Rectal temperatures measured after IBRV challenge

Calves vac IN at 3-8 days of age

A and B: no maternal antibody

C: maternal antibody

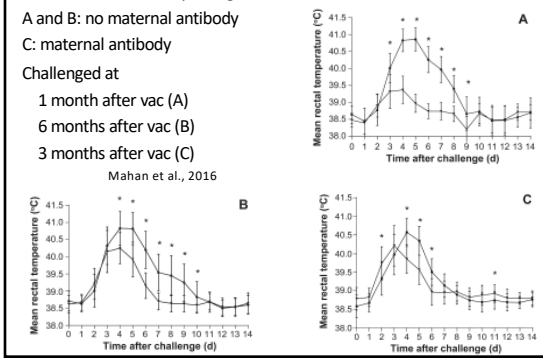
Challenged at

1 month after vac (A)

6 months after vac (B)

3 months after vac (C)

Mahan et al., 2016



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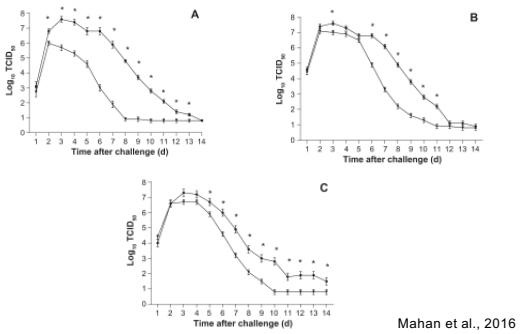
IBRV shedding after IBRV challenge



Mahan et al., 2016

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Modified live or killed (inactivated)?

- Most relevant to viruses (few live bacterial vax)
- Modified live:
  - Pros:
    - Replicating intracellular pathogen (virus) induces CMI through MHC I presentation
    - Cheaper
    - May give acceptable immunity after one dose
  - Cons:
    - May cause disease, including abortion
    - Require careful handling to keep agent in vaccine alive
      - Cold (but not frozen) storage

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Modified live or killed (inactivated)?

- Inactivated
  - Pros:
    - Won't cause disease (unless improperly inactivated at the manufacturer)
    - Storage and handling conditions not as critical
  - Cons:
    - Always contain adjuvants, which make local reactions worse
    - More expensive (contain more agent + adjuvant)
    - May not induce effective CMI (some can: ask for data)

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How do we know if a vaccine works?

- Vaccines developed and marketed for decades
- Research results often presented
- When evaluating, consider outcomes measured
  - Antibody or cellular immune responses
  - Protection against experimental challenge
  - Protection in randomized controlled field trial
  - Results of systematic reviews and/or meta-analyses

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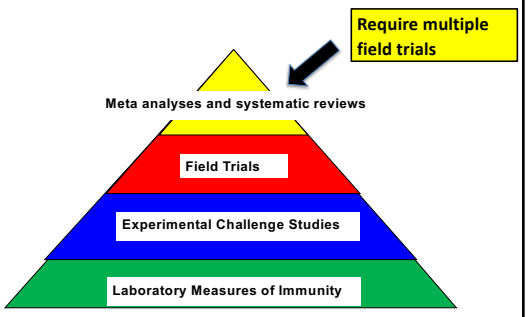
Hierarchy of evidence quality for clinical practice



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Laboratory measures of immunity: example

Duration of serum antibody responses following vaccination and revaccination of cattle with non-living commercial *Pasteurella haemolytica* vaccines

A.W. Confer*, R.W. Fulton†, K.D. Clinkenbeard* and B.A. Driskell*

This study was designed to determine the duration of serum antibody responses to Pasteurella haemolytica whole cells (WC) and leukotoxin (LKT) in weanling beef cattle vaccinated with various non-living P. haemolytica vaccines. Serum antibodies to P. haemolytica antigens were determined periodically through day 140 by enzyme-linked immunosorbent assays. At day 140, cattle were revaccinated, and antibody responses periodically determined through day 196. Three vaccines were used in two experiments (A and B), OneShot®, Presponse® HP†K, and Septimune® PH-K. In general, all three vaccines between 7 and 14 days induced antibody responses to WC after vaccination. Antibodies to LKT were induced with OneShot and Presponse. Revaccination at days 28 and 140 usually stimulated anamnestic responses. Serum antibodies to the various antigens remained significantly increased for up to 84 days after vaccination or revaccination. The intensity and duration of antibody responses were variable depending on the experiment and vaccines used. Vaccination with OneShot usually stimulated the greatest responses to WC. Vaccination with OneShot or Presponse resulted in equivalent primary anti-LKT responses. In experiment B, spontaneous seroconversion was found in numerous calves on day 112. Revaccination of those cattle at day 140 resulted in markedly variable antibody responses such that several groups had no increase in antibody responses.

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Assessing laboratory measurement of immunity

- Antibody or cell mediated immune responses
  - Indicates immune response occurred…
    - Antibody: important for bacteria or viruses
    - Cell mediated: important for viruses and intracellular bacteria
- Done alone, or, more often, as part of a challenge study or field trial
- Responses don't always correlate with protection

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Experimental challenge study: example

Comparison of humoral and cellular immune responses to a pentavalent modified live virus vaccine in three age groups of calves with maternal antibodies, before and after BVDV type 2 challenge

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[b] Boehringer Ingelheim Vetmedica, Inc., 5506 Corporate Drive, Suite 1600, St. Joseph, MO 64507, United States
[c] Veterinary Resources, Inc., 404 Douglas Ave, PO Box 866, Ames, IA 50010, United States

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Keywords:
Cell mediated immunity
Vaccination in the face of maternal antibody
Bovine respiratory disease vaccines

ABSTRACT

The aim of this study was to evaluate the ability of a pentavalent (BVDV types 1 and 2, BHV-1, BRSV, and PI-3) modified live virus (MLV) vaccine given to 1–2-, 4–5-, and 7–8-week-old calves with maternal antibodies to induce humoral and cellular immune responses and protect calves from virulent BVDV type 2. Eight calves in each age group were vaccinated and four served as controls. All calves were challenged intranasally with BVDV type 2, 12 weeks after vaccination. SVN titers to all five viruses declined in all groups after vaccination (except 4–5-week-old calves to BVDV type 1). After challenge, the SVN titers for both types of BVDV showed anamnestic responses in calves vaccinated at 4–5 and 7–8 weeks, but not at 1–2 weeks of age. In all groups, T cell subsets responded specifically to BVDV types 1 and 2 but not to BHV-1, BRSV, or PI-3 after vaccination by increasing their expression of activation markers (CD25, IFN-γ and IL-4). All vaccinated calves were significantly protected from BVDV type 2 challenge.

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Assessing Experimental Challenge Studies

- Was a nonvaccinated (control) group included?
  - Were both groups alike? Randomly allocated?
- Did meaningful disease occur in controls?
  - **Were evaluators blinded to grouping?**
- Was there **statistically** and **clinically** significant difference between controls and vaccinates?
- Was the vaccination regimen similar to field use?
  - What was the duration between vaccination and challenge?

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Field trial: example

Field evaluation of a *Mycoplasma bovis* bacterin in young dairy calves

Fiona P. Maunsell[a,*], G. Arthur Donovan[b,1], Carlos Risco[b,2], Mary B. Brown[a,3]

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Calves
Vaccination

ABSTRACT

Mycoplasma bovis is an important cause of pneumonia, otitis media and arthritis in young dairy calves, and there is a critical need for improved preventative strategies for this pathogen. We conducted a randomized, placebo-controlled, double-blinded field trial to determine the efficacy of a commercial *M. bovis* vaccine for the prevention of *M. bovis*-associated disease in calves. Calves ($n = 373$) on 3 Florida dairies with a history of *M. bovis* infection received an *M. bovis* bacterin or a placebo, administered subcutaneously at 3, 14 and 35 days of age. One of the herds did not experience *M. bovis*-associated disease; for calves in the remaining 2 herds, the incidence risk for respiratory disease, otitis media and arthritis from 3 to 90 days of age was 0.64, 0.28 and 0.02, respectively. Vaccination had no effect on the age at first treatment for *M. bovis*-associated disease, incidence of respiratory disease, mortality, weight gain, or nasal colonization with *M. bovis* in the first 90 days of life. In one herd, vaccination was associated with an increased risk of otitis media. There was no association between *M. bovis*-specific serum antibody titers and morbidity in vaccinated calves. Under the field conditions in this study, this vaccine was not efficacious for the prevention of *M. bovis*-associated disease in young dairy calves.

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Assessing Field trials

- Were the cattle and management representative of your practice?
- Were animals randomly allocated to their groups?
- Were **concurrent** (not historical) controls used?
- Did important disease occur in any group? How diagnosed?
  - **Were evaluators blinded to treatments?**
- Were meaningful outcomes measured?
- Was protection against specific agents (or all disease) measured?
- Were there **statistically** and **clinically** significant differences between vaccinated cattle and controls?

adapted in part from Ribble, 1992

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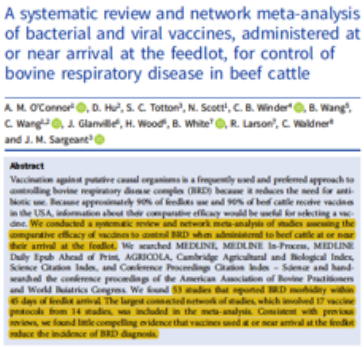
Systematic review and meta-analysis: example



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

A. M. O'Connor[1], D. Hu[2], S. C. Totton[3], N. Scott[1], C. B. Winder[4], B. Wang[5], C. Wang[5,2], J. Glanville[6], H. Wood[6], B. White[7], R. Larson[7], C. Waldner[8] and J. M. Sargeant[3]

Abstract

Vaccination against putative causal organisms is a frequently used and preferred approach to controlling bovine respiratory disease complex (BRD) because it reduces the need for antibiotic use. Because approximately 90% of feedlots use and 90% of beef cattle receive vaccines in the USA, information about their comparative efficacy would be useful for selecting a vaccine. We conducted a systematic review and network meta-analysis of studies assessing the comparative efficacy of vaccines to control BRD when administered to beef cattle at or near their arrival at the feedlot. We searched MEDLINE, MEDLINE In-Process, MEDLINE Daily Epub Ahead of Print, AGRICOLA, Cambridge Agricultural and Biological Index, Science Citation Index, and Conference Proceedings Citation Index – Science and hand-searched the conference proceedings of the American Association of Bovine Practitioners and World Buiatrics Congress. We found 53 studies that reported BRD morbidity within 45 days of feedlot arrival. The largest connected network of studies, which involved 17 vaccine protocols from 14 studies, was included in the meta-analysis. Consistent with previous reviews, we found little compelling evidence that vaccines used at or near arrival at the feedlot reduce the incidence of BRD diagnosis.

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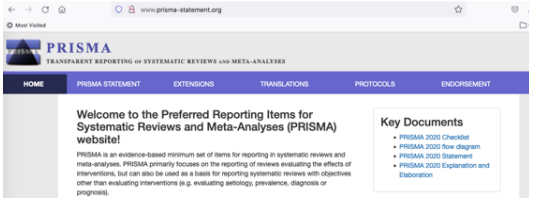
Guidelines for assessing systematic reviews and meta-analyses



www.prisma-statement.org

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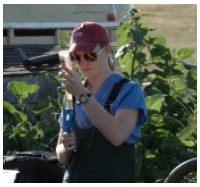
Do BRD Vaccines Work?

- Currently marketed vaccines have shown protection against experimental challenge
  - Requirement for licensure
- Field trials, systematic reviews, and meta-analyses lacking for many vaccines



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- Vaccines for endemic respiratory agents decrease disease and improve productivity SOMETIMES
  - Evidence suggests some vaccines are more effective than others
  - Keep up to date on the current information regarding vaccines you use
  - Remember some sources of information (e.g. the manufacturer) may have a reason to present you with biased information

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- Clients need realistic expectations
  - Vaccines rarely prevent infection completely
  - Vaccines rarely prevent disease in all vaccinates
  - Vaccines should be viewed as a tool to LIMIT disease and not necessarily PREVENT it
- Vaccines are one of multiple tools needed to limit disease

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Vaccinated Animals Got Disease Anyway: Why?

- Consider factors related to vaccine administration
  - MLV vaccines mishandled
    - Not kept cool
    - Old product previously reconstituted
    - Disinfectants in multidose syringes
  - Poor timing of administration
    - Animals already incubating disease
    - No booster given when needed

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Vaccinated Animals Got Disease: Why?

- Consider factors related to ability of host to respond to vaccination:
  - Animals already sick
  - Nutritional deficiency
    - protein, energy
    - copper, zinc, selenium
    - Vitamin E, B vitamins
  - Very high levels of maternal antibody (calves)
    - Vaccination in face of moderate levels CAN work

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Vaccinated Animals Got Disease: Why?

- Consider vaccine given and actual pathogen exposure
  - Were animals infected with agents not included in vaccines given?
  - Were animals infected with strains or serotypes of pathogens not in vaccine?
  - Was challenge overwhelming?
    - Management problems

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Rational Use of BRD Vaccines

- Remember basic principles
  - Animals need time to respond to vaccination
    - 14 – 28 days—longer is better
  - **Booster vaccination is always ideal**
    - Once or twice at 1- to 2-month interval
    - More than this may be counterproductive
    - Annual boosting after initial series usually needed
    - For viruses: if only one dose possible, use MLV
  - Pay attention to the vaccine label recommendations

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- If an animal is already infected, vaccination can't help much (or at all)
  - Time vaccination to occur 14 – 28 days before expected exposure
- If an animal is vaccinated for one agent but gets infected with another, vaccination won't help
  - Diagnostic microbiology may help guide vaccine choices
  - Vaccines not available for all agents that cause BRD
- Ensure good management to help control BRD
  - Good vaccines can be overwhelmed by poor management

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Case Examples

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Case example #1

- 27 Dairy herds with calf respiratory disease in previous year
  - Evidence of BRSV infection in previous year in 20
- 9 herds: calves vaccinated with MLV BRSV twice at 4 to 5 week interval
- 8 herds: calves not vaccinated
- 10 herds: half calves vaccinated, half not
- Calves 2-10 months of age at vaccination
- Vaccinated in August

Verhoeff et al, 1984

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- Calves had low serum titers to BRSV at vaccination (78% seronegative)
- Calves examined by vet weekly from October to January
- **BRSV infection** occurred in
  - 6 of 8 nonvaccinated herds
  - 2 of 9 completely vaccinated herds
  - 9 of 10 partly vaccinated herds
- **Signs of respiratory disease** seen in
  - 4 of 8 nonvaccinated herds
  - 1 of 9 completely vaccinated herds
  - 1 of 10 herds partly vaccinated herds

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Key points, Case #1

- MLV BRSV vaccination associated with decreased disease in vaccinated herds
- INFECTION with BRSV was decreased only when all calves were vaccination
  - Vaccinating half of calves decreased disease but not infection
- Calves got 2 doses of vaccine
  - Can't say if 1 dose would have same effect

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Case example #2: Intranasal vs injectable viral vaccination of high-risk cattle at arrival

- 525 high-risk steers and bulls
- Allocated by pen (n = 12/pen) to receive
  - Intranasal MLV 3-way (Inforce3) + parenteral BVDV1 + BVDV2 (Bovishield BVDV)
  - Parenteral MLV -5 way (Bovishield)
  - No vaccine
- 15 pens per treatment
- Health monitored for 70 days

Powledge et al., 2022 doi.org/10.1093/jas/skac249

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Results

No difference in BRD morbidity or mortality between groups

	No vac	IN vac	SQ vac	P value
BRD 1x	55%	59%	58%	0.83
BRD 2x	31%	32%	31%	0.98
BRD 3x	25%	17%	22%	0.47
Chronic BRD	7%	3%	8%	0.37
BRD mortality	11%	5%	8%	0.37
Antimicrobial treatment costs	$18.96	$19.08	$19.12	1.00

Powledge et al., 2022

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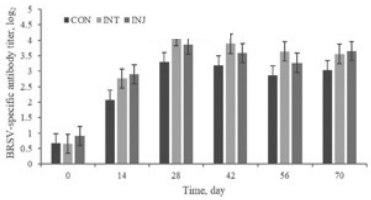
Results: antibody titers to BRSV



Significant effect of time ($P < 0.01$), no effect of treatment, no treatment x time interaction.

Powledge et al., 2022

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Key points, case #2

- Neither IN or SC vaccination was better than no vaccination in this trial
- BRSV was already present when cattle were vaccinated
  - Non vaccinated cattle seroconverted to BRSV
- Vaccination was too late for BRSV protection

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Case example #3

- Weaned beef calves destined for feedlots
- Single ranch of origin
  - Shipped immediately at weaning OR
  - Kept on farm 45 d., no vac OR
  - Kept on farm 45 d. and MLV viral vac (Titanium 5) and *M. haemolytica* vac (Presponse)
- Vac calves boosted 2 weeks later
- Calves not vac at farm were vac and boosted at feedlot

Step et al, 2008

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- Calves kept on ranch 45 days before shipment had significantly lower feedlot respiratory morbidity in first 42 days
  - 6% for weaned 45 d.
  - 10% for weaned 45 d. and vaccinated
  - 35% for shipped immediately
- No significant difference if calves vaccinated on ranch
- Health costs (but not total costs) higher for calves shipped immediately
  - No difference for vac vs nonvac groups

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Key points, Case #3

- Vaccination component of a preconditioning program was not related to improved health during receiving period
- Early weaning before shipment did improve health during receiving period

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So ***WHY*** do vaccinated cattle get BRD anyway??


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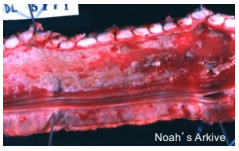
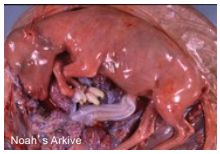
- Vaccines have led to historic benefits when used to protect against disease caused by single organisms
  - smallpox
  - polio
  - rabies
  - infectious bovine rhinotracheitis due to IBRV
  - abortions due to BVDV





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- In contrast, BRD is a multifactorial syndrome caused by the interaction of
  - One or more of a dozen or more viruses

    AND/OR
  - Opportunistic commensal bacteria

    AND/OR
  - A variety of host and environmental factors

Maybe it's no surprise we haven't made more progress on BRD with vaccination?

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- We don't have many field trials demonstrating efficacy of BRD vaccines to decrease morbidity or mortality
- Most trials reported have likely been underpowered to detect differences
  - Too few animals or farms included

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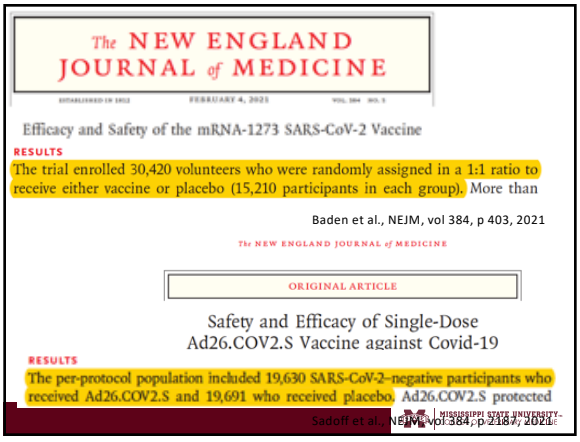

The NEW ENGLAND JOURNAL of MEDICINE

Efficacy and Safety of the mRNA-1273 SARS-CoV-2 Vaccine

RESULTS

The trial enrolled 30,420 volunteers who were randomly assigned in a 1:1 ratio to receive either vaccine or placebo (15,210 participants in each group). More than

Baden et al., NEJM, vol 384, p 403, 2021

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Safety and Efficacy of Single-Dose Ad26.COV2.S Vaccine against Covid-19

RESULTS

The per-protocol population included 19,630 SARS-CoV-2–negative participants who received Ad26.COV2.S and 19,691 who received placebo. Ad26.COV2.S protected

Sadoff et al., NEJM, vol 384, p 2187, 2021

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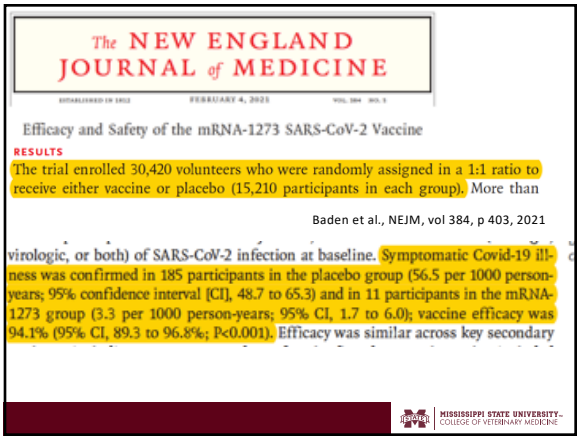

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virologic, or both) of SARS-CoV-2 infection at baseline. Symptomatic Covid-19 illness was confirmed in 185 participants in the placebo group (56.5 per 1000 person-years; 95% confidence interval [CI], 48.7 to 65.3) and in 11 participants in the mRNA-1273 group (3.3 per 1000 person-years; 95% CI, 1.7 to 6.0); vaccine efficacy was 94.1% (95% CI, 89.3 to 96.8%; P<0.001). Efficacy was similar across key secondary

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- To make progress understanding the impact of vaccines on BRD, we need large field trials, properly designed, and replicated
- Field trials are expensive and risky
- Could public-private partnerships address this need?

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Take home messages

- All fully licensed vaccines have been proven efficacious to decrease disease in experimental challenge studies
  - Required by USDA
- Results of field trials do not always agree with challenge studies
  - We need more field trials confirming efficacy of vaccines we regularly use

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Take home messages

- If vaccines seem to have failed to induce protection, review factors that may have contributed
  - Vaccine handling and administration
  - Ability of cattle to respond to vaccination
  - Disease due to agents not in vaccines
  - Overwhelming management problems
- Help producers understand realistic expectations for vaccines
  - Especially for respiratory disease prevention

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Questions?

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