Keys to Effective Vaccination of Calves

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Vaccinating Calves: Questions

- Can immunity of calves be improved by vaccination?
- How early can you vaccinate calves effectively?
- What about maternal antibody interference?

Immune Development: Prenatal Calf

- Immune system begins developing before calf is born
  - Thymus (T cell development) evident at 40 days gestation
  - Response to some viruses possible at 70 days gestation
  - By third trimester, can respond to many different infections
    - At birth, see serum antibody titers elevated before colostrum intake

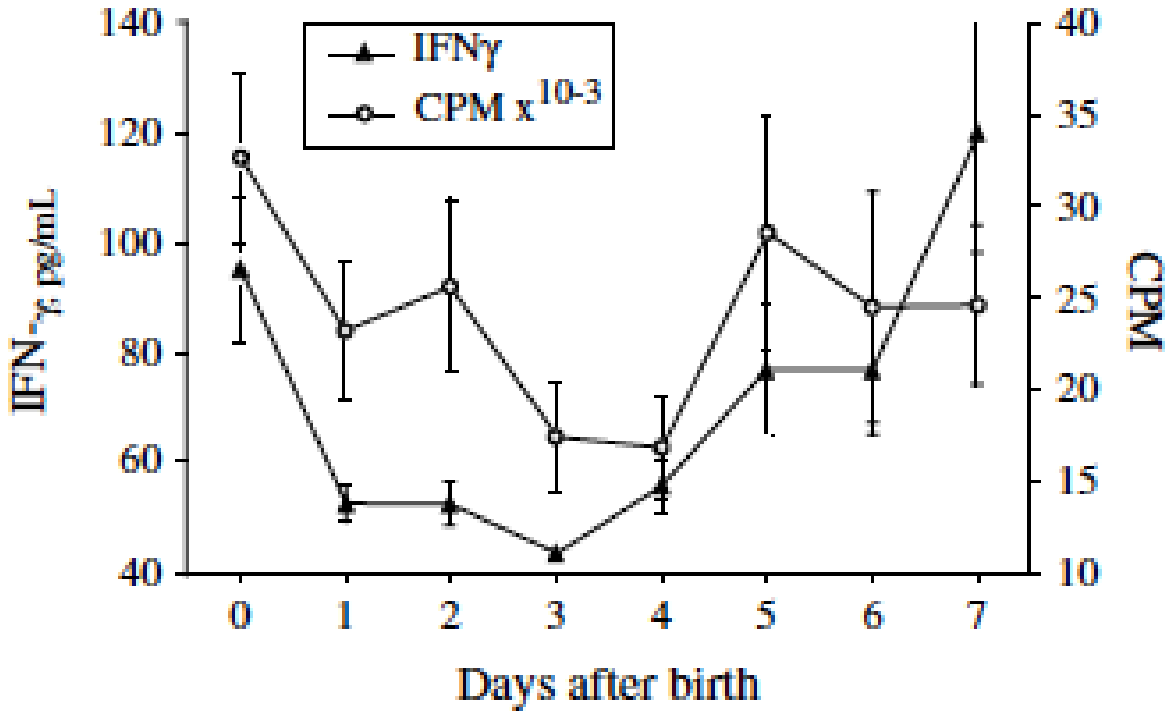
Immune Development, Neonatal Calf

- At birth, calf has no antibody in serum
  - Unless infected before birth
- Other issues
  - Serum complement levels lower than adults
  - Cell functions lower than adults
    - neutrophils
    - macrophages
    - antigen presenting cells
    - T and B cells

- Immune response of neonatal calf is functional, but naïve and immature

- Colostrum is a solution to this problem

Response of calf lymphocytes to mitogenic (nonspecific) stimulation in first week of life



Data from Kehrli, in Cortese 2009

- Calves vaccinated at 8 hours old were protected against *Mycobacterium bovis* challenge 15 weeks later

Buddle et al., 2003

- Colostrum-deprived calves exposed to coronavirus at 1 day of age were protected against challenge at 3 weeks

Heckert et al., 1991

- Calves vaccinated with ovalbumin at 2 days of age: antibody at 4 weeks
- Calves vaccinated with PPD at 2 days of age: skin test positive at 7 weeks

Nonnecke et al., 2012

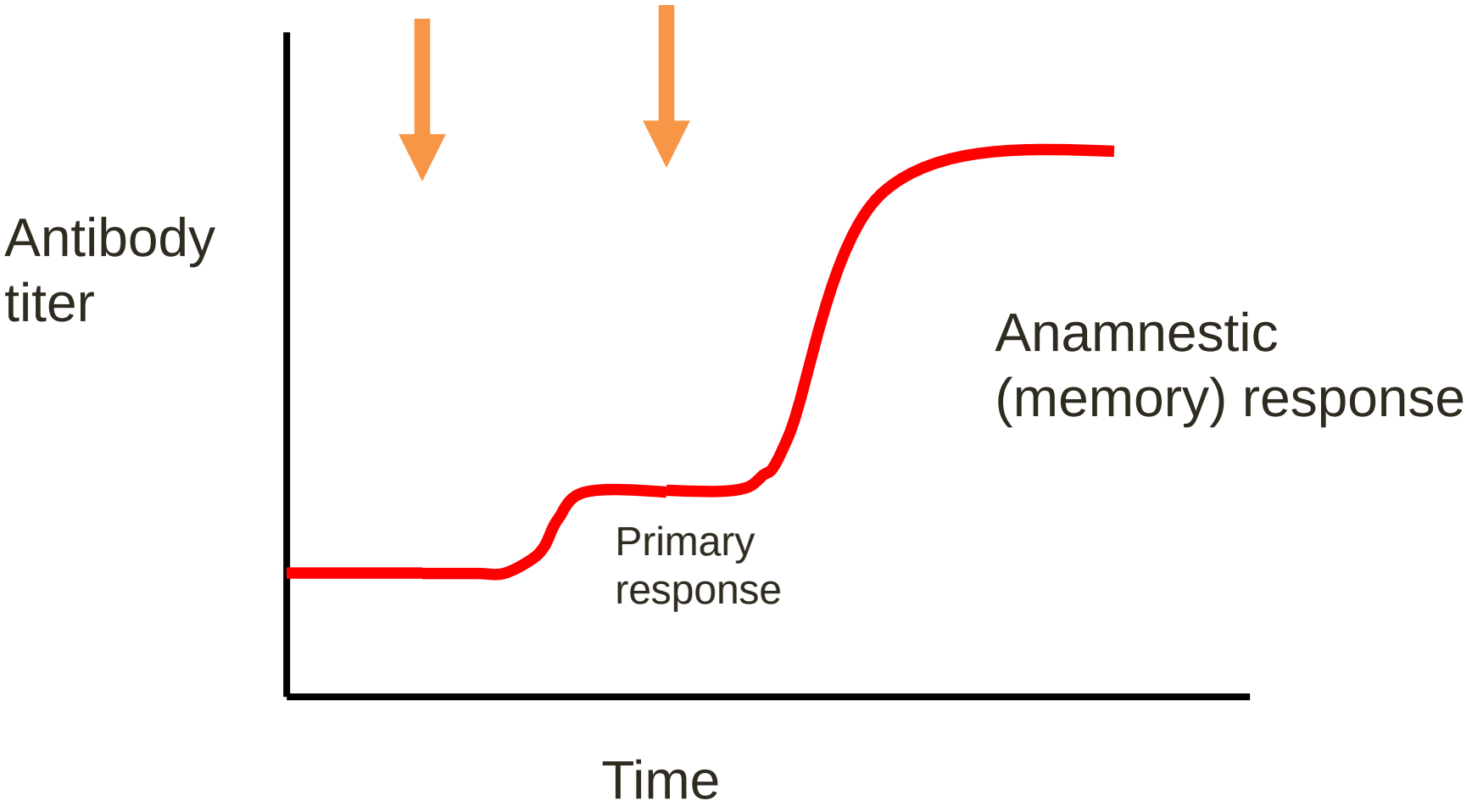
- Numerous studies show diminished immune responses in 1 – 2 week old calves, compared to juveniles or adults

- BUT: calves within a week of life CAN mount meaningful immune responses

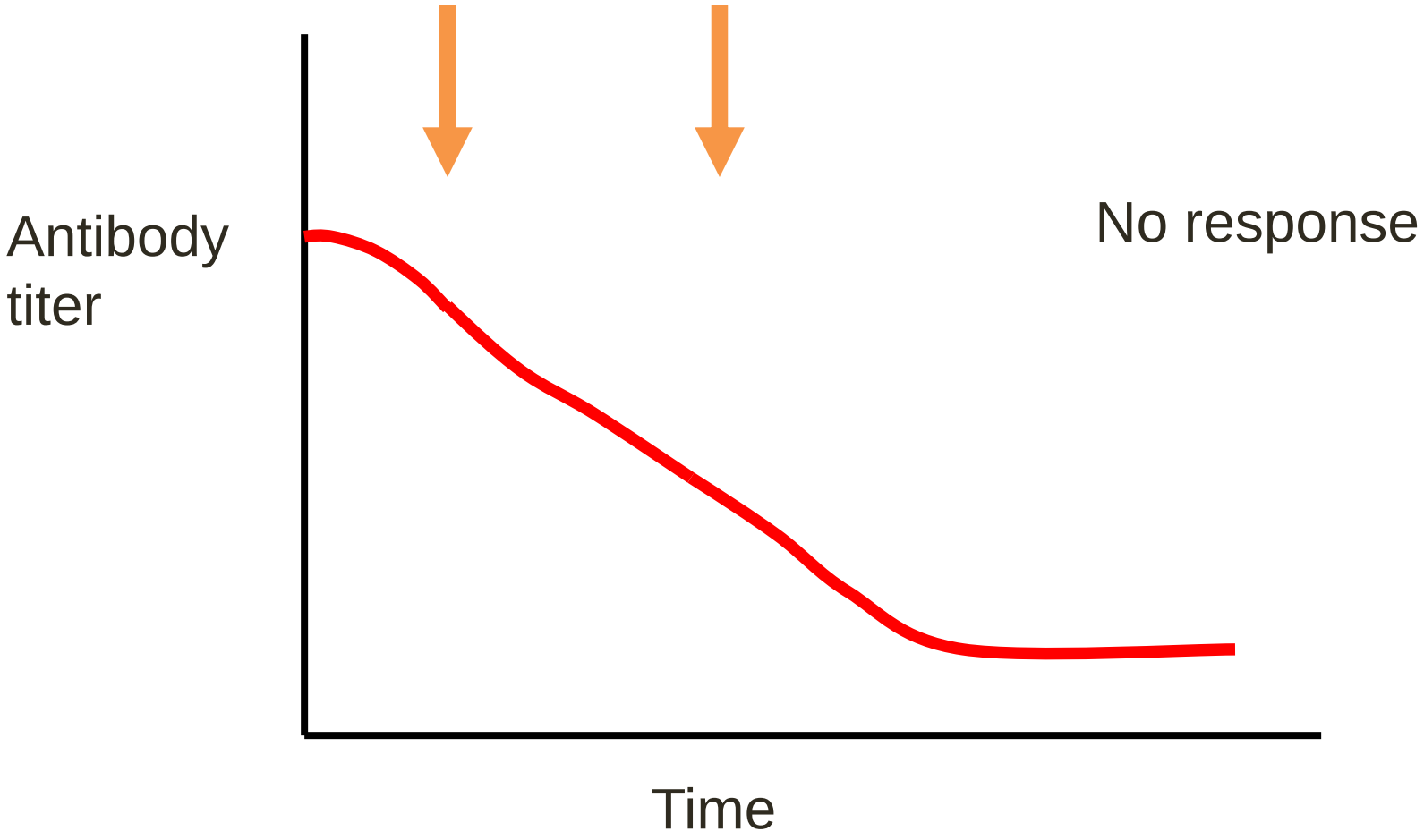
- Not clear when in first week is best time to vaccinate if vaccination is appropriate

Vaccination of calves and maternal antibody

- Vaccination in the face of maternal antibody (IFOMA) traditionally considered ineffective



Vaccination without maternal antibody



Vaccination with maternal antibody

Calf vaccination IFOMA

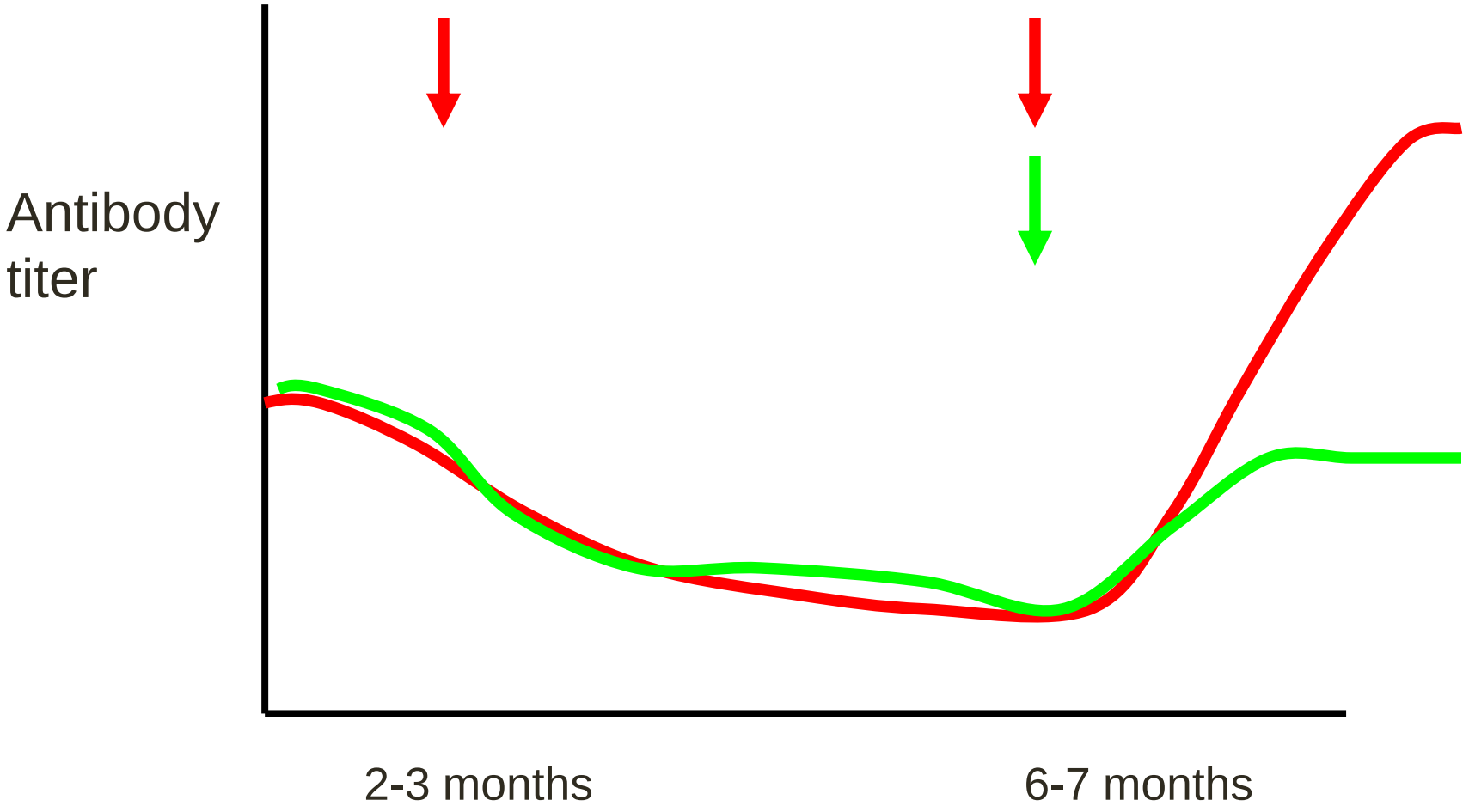
- Several studies indicate calves CAN respond to vaccination IFOMA
  - Anamnestic response when maternal antibodies gone
  - Measures of T cell responsiveness in absence of seroconversion
  - **Protection against later challenge**

Vaccination IFOMA and antibody responses

- 2-3 month old beef calves
  - Vaccinated with MLV IBRV + BVDV
    - IBRV SN titers 1:19
    - BVDV SN titers 1:35
- Control calves not vaccinated
- Both groups vaccinated again at 6-7 m.o.

Menanteau-Horta et al, 1985

- Calves vaccinated at 2-3 months seroconverted to BVDV
  - IBRV titers continued to fall
- At vaccination at 6-7 months, calves vaccinated IFOMA seroconverted rapidly to IBRV
  - Significantly higher titers than calves not vaccinated at 2-3 months



Vaccination IFOMA can prime for memory response when maternal antibodies are gone

Vaccination IFOMA and antibody responses—inactivated vaccine

- 2 – 3 month old beef calves

  IBRV SN titers: <1:2 – 1:128

  BVDV 1 SN titers: 1:20 - 1:1920

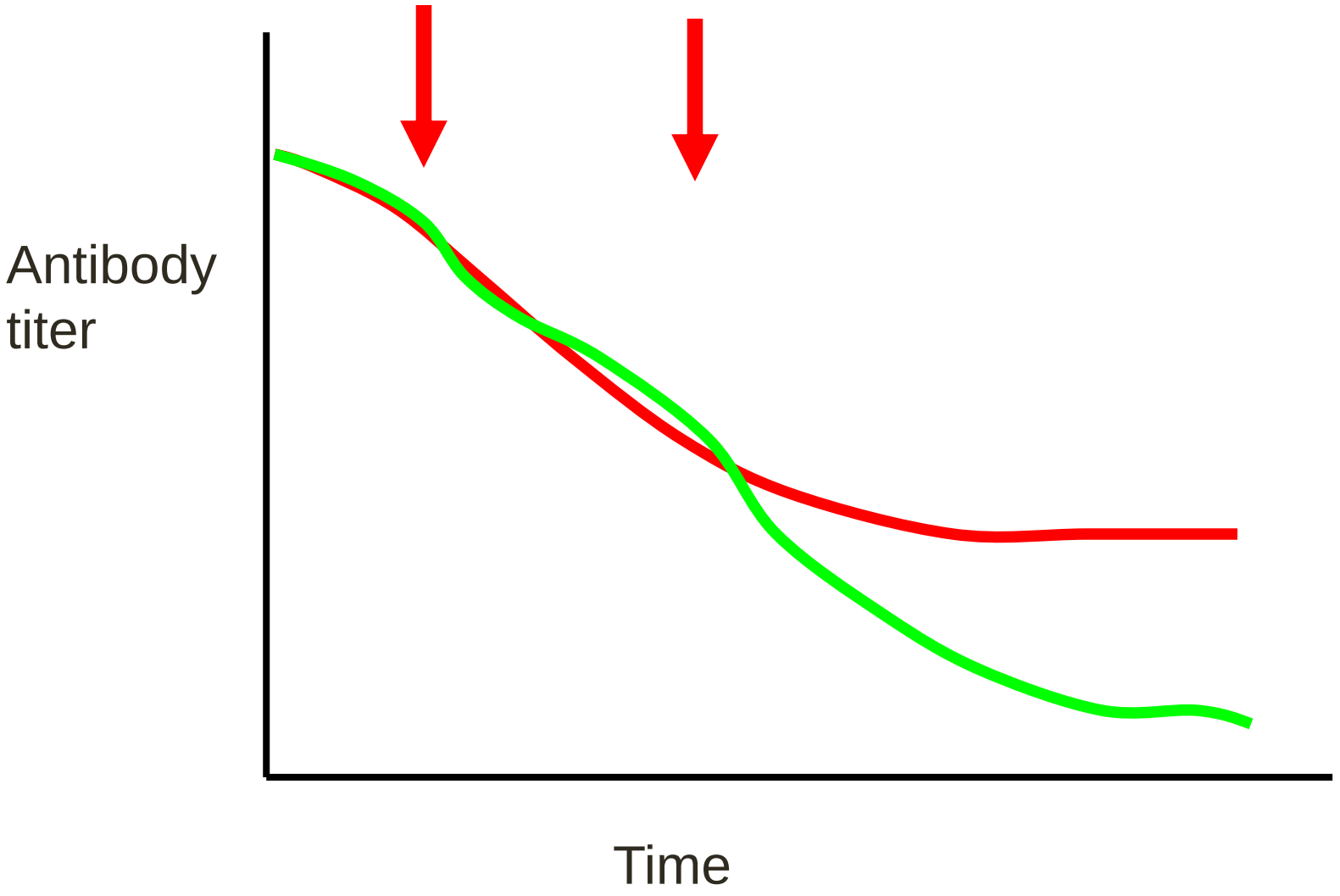
  BVDV 2 SN titers: 1:7.5 - 1:1280

  – Inactivated IBRV/BVDV/PI3/BRSV
    - Vira Shield® 5
    - ELITE® 4
    - Triangle® 4
  – Control group, no vaccine
  – Boosted 1 month later

Kaeberle et al, 1998

- At 6-7 months of age, calves in Vira-Shield group had significantly higher titers to IBRV, BVDV 1, and BVDV 2 than control calves

- Administration of some inactivated vaccines IFOMA induces persistence of serum antibody
  - Boosting may be important



Vaccination IFOMA can prolong titers

Vaccination IFOMA and antibody responses—effect of age

- Dairy calves vaccinated with *M. haemolytica* vaccine (Presponse®)
  - 2 and 4 weeks old
  - 6 and 8 weeks old
  - Control group not vaccinated
- No difference in titers at 2 weeks of age

Hodgins and Shewen, 1998

- At 10 weeks of age, leukotoxin neutralizing titers significantly higher in calves vaccinated at 6 and 8 weeks
  - Not significantly higher in calves vaccinated at 2 and 4 weeks

- Magnitude of titer and age may impact efficacy of vaccination IFOMA in very young calves

Vaccination IFOMA and T cell responses

- Beef calves vaccinated IFOMA at 10 days old
  - MLV/inactivated 4-way (CattleMaster 4®)
  - Control group not vaccinated
- At 22 days old
  - No difference antibody titers
  - Significantly higher lymphocyte responses to IBRV and BRSV in vaccinates

Ellis et al, 1996

- Vaccination IFOMA stimulated specific T cells, even though no apparent effect on antibody production

Summary

- Vaccination of calves IFOMA can:
  - Prime for a memory response after maternal antibodies are gone
  - Increase the half-life of serum antibodies
  - Stimulate T cell responses

- Not as reliable in calves < 1 month old

Vaccination IFOMA and resistance to disease

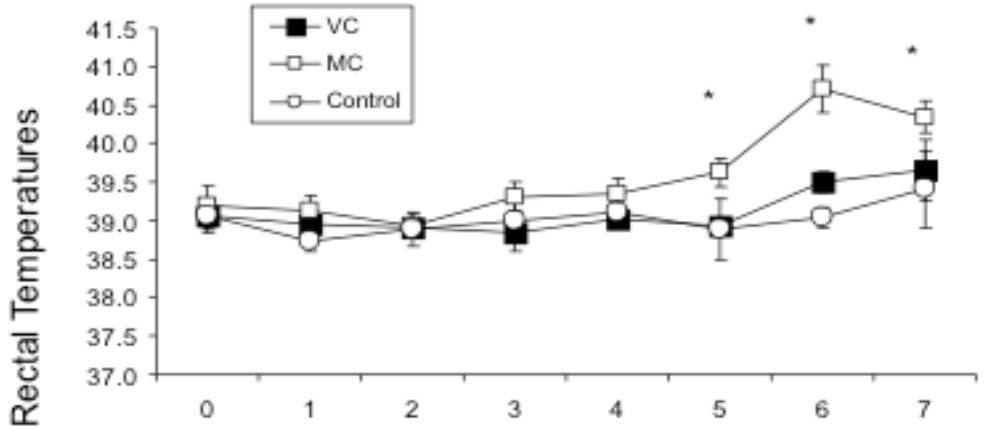
- Increased resistance to disease: best measure of value of vaccination IFOMA

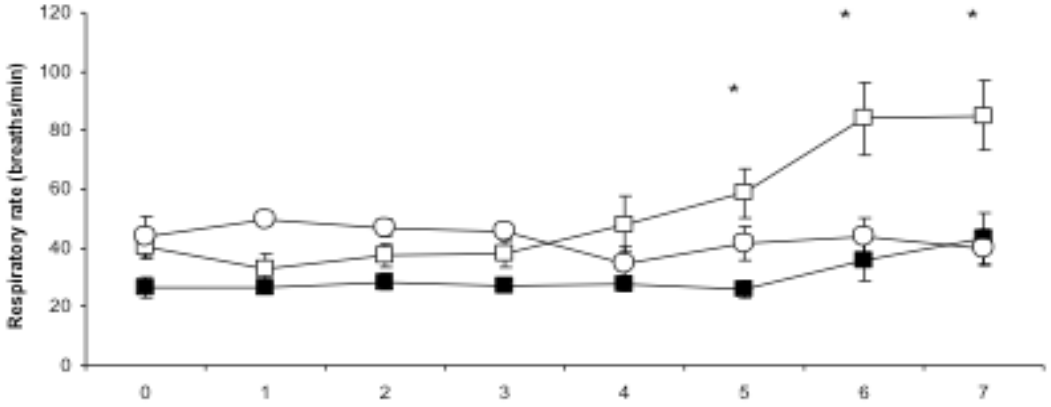
- Effect has been measured in response to
  - Experimental challenge
  - Naturally-occurring disease

Vaccination IFOMA and resistance to disease

- 4 to 6 week old Holsteins
  - SN titers 1:4 – 1:64
  - "Vaccinated" IN once with MLV (hi pass) BRSV
  - Challenged on d. 30 with virulent BRSV
  - Clinical signs evaluated for 7 days
  - BRSV-specific IFN-γ production in several sites evaluated

Woolums et al, 2004





Woolums et al., 2004

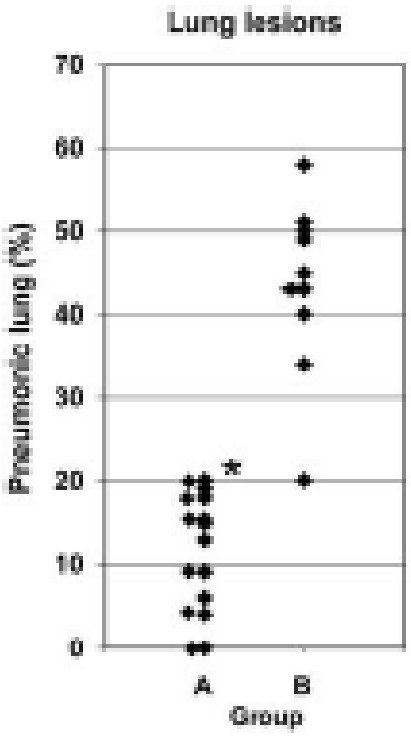
- A single dose of MLV BRSV IN given IFOMA protected calves from virulent challenge one month later

- Protection was associated with virus-specific IFN-γ production in respiratory lymph nodes and pharyngeal tonsil

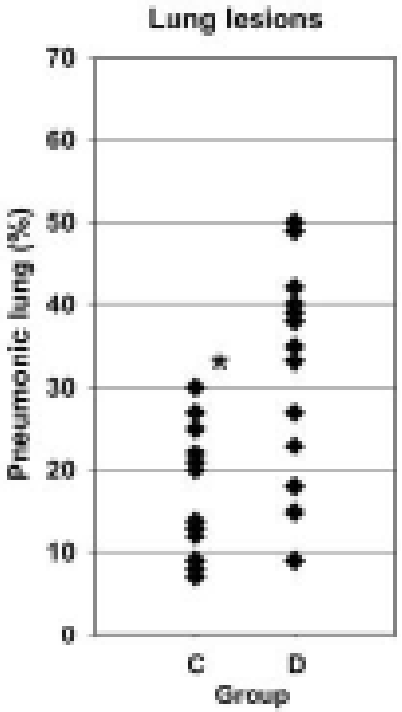
- Duration of protection following IN vaccination IFOMA may not be long

- This may be particularly true for BRSV

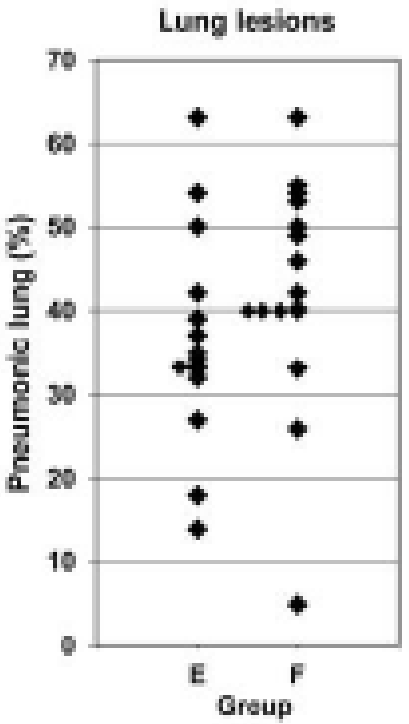
Disease in calves challenged with BRSV after IN vaccination IFOMA at 3 – 8 days of age



7 weeks post vac



9 weeks post vac



14 weeks post vac

Ellis et al., 2013

Vaccination IFOMA and resistance to disease: BHV-1

- Three separate but related trials: effect if IN vaccination on disease due to BHV-1 challenge
  - 3 – 8 day old calves
  - Trial A and B: calves had no maternal antibody
  - Trial C: calves had maternal antibody
- Calves vac IN once with INFORCE 3 (BHV-1, BRSV, PI3V)
- Control calves: same vaccine but no BHV-1

Mahan et al., 2016

Rectal temperatures measured after IBRV challenge

Calves vac IN at 3-8 days of age

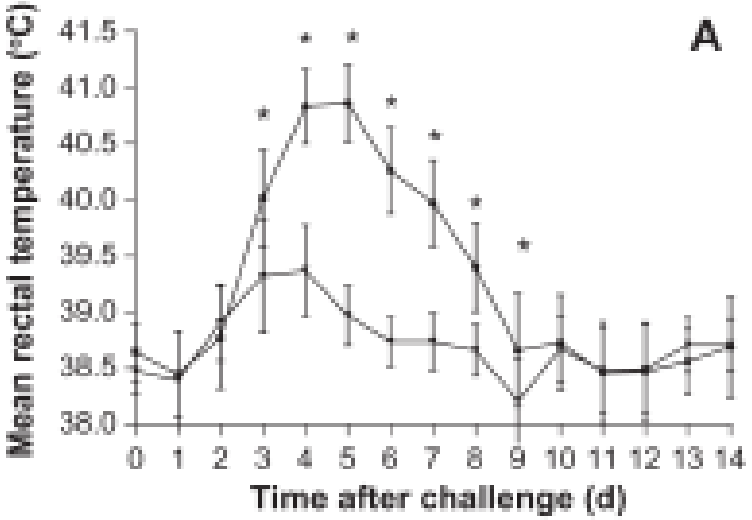
A and B: no maternal antibody

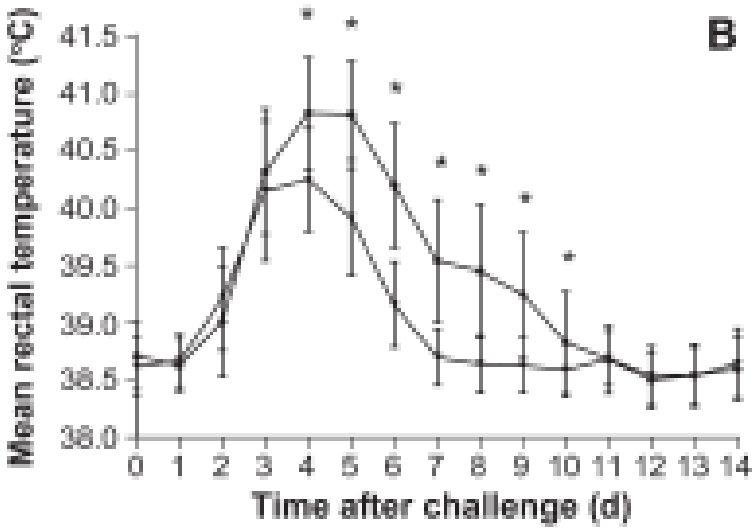
C: maternal antibody

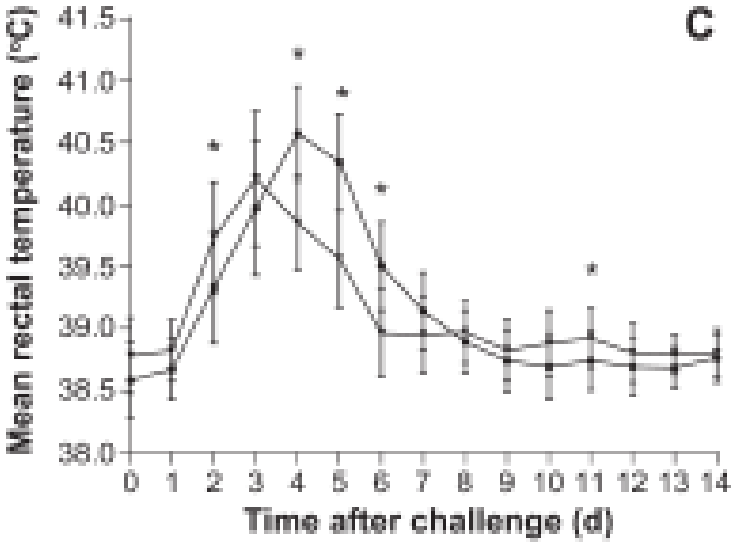
Challenged at

- 1 month after vac (A)
- 6 months after vac (B)
- 3 months after vac (C)

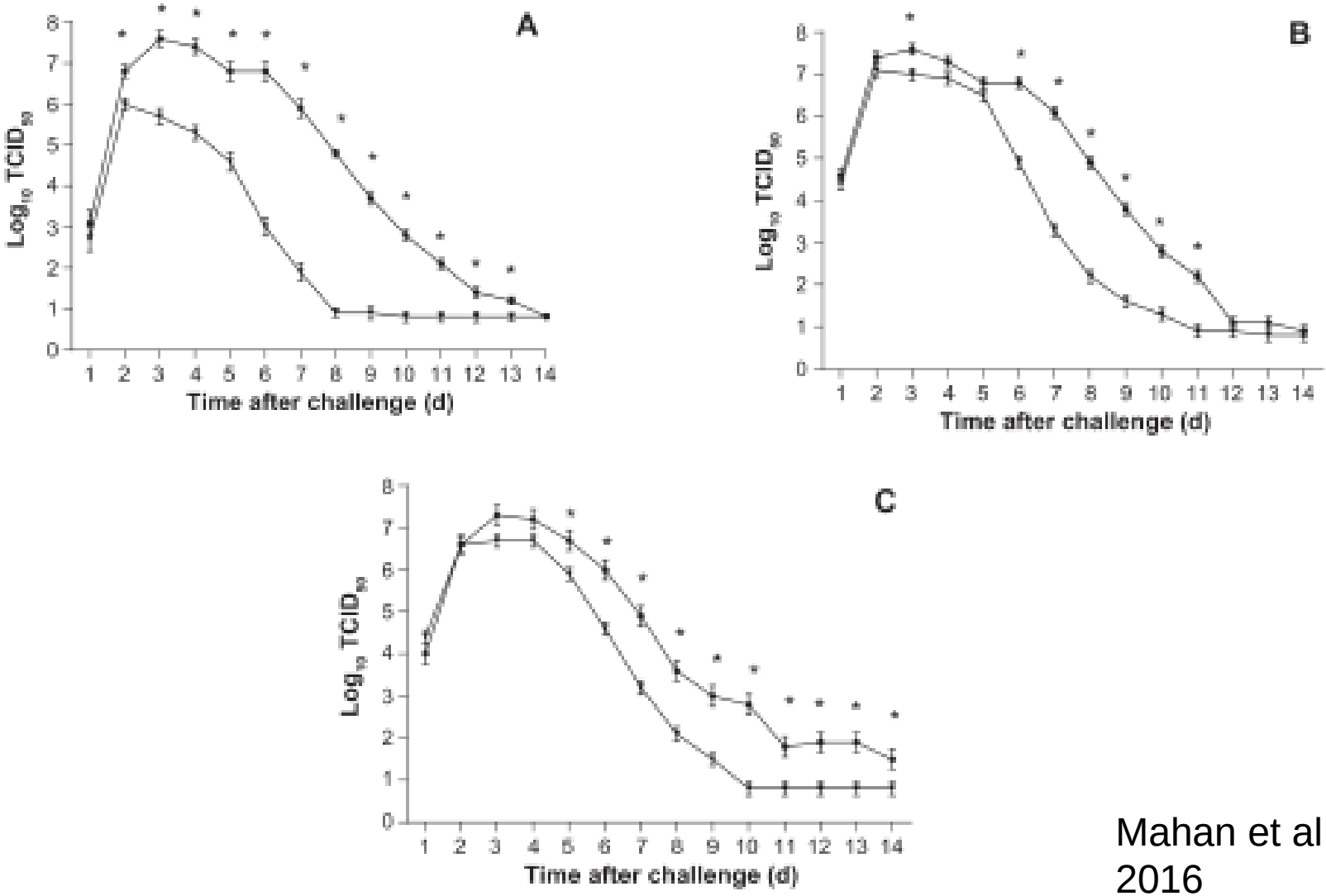
Mahan et al., 2016







BHV-1 shedding after BHV-1 challenge

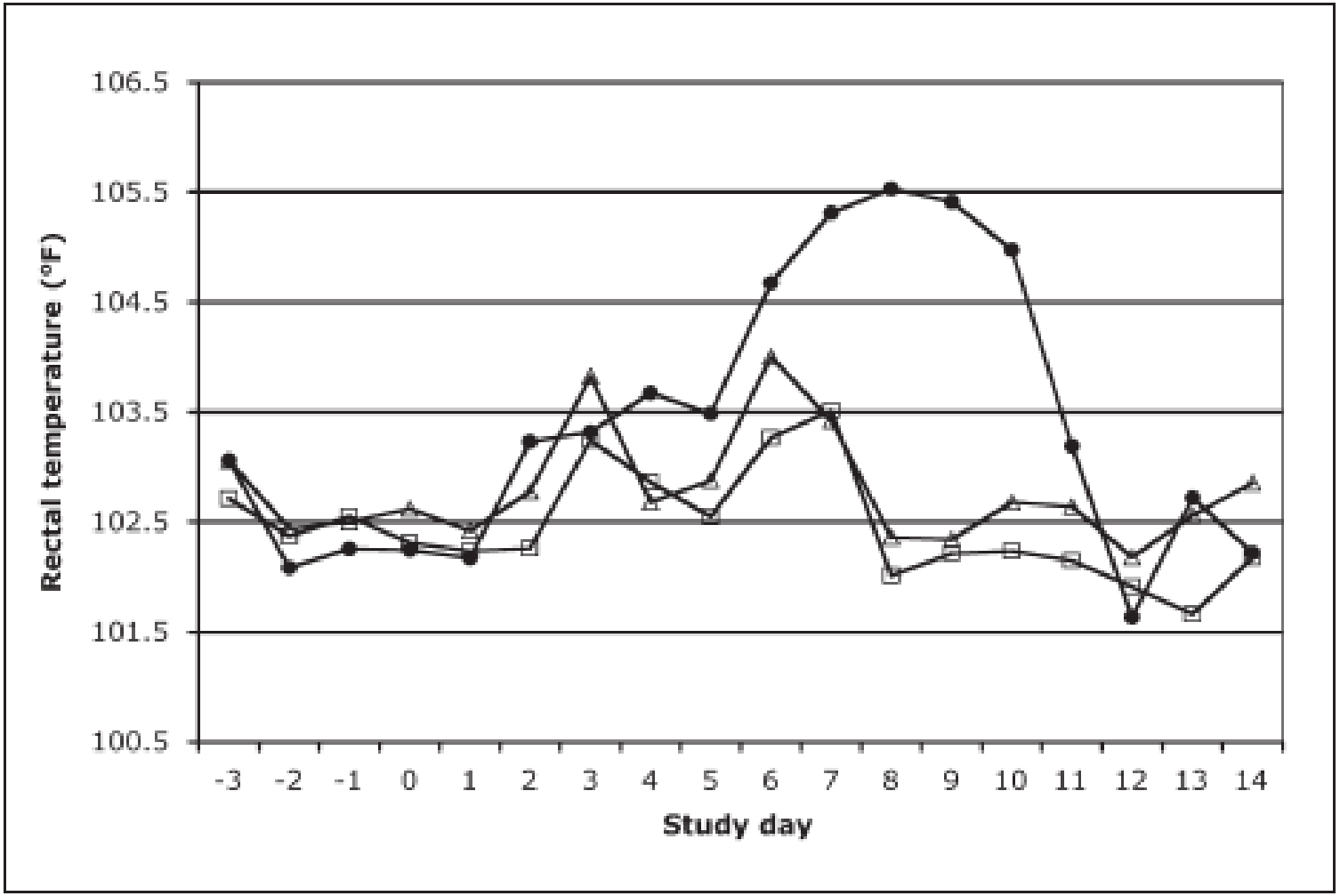


Mahan et al., 2016

Vaccination IFOMA and resistance to disease: BVDV

- 5 week old calves
- Fed colostrum with or without BVDV antibody
- Vaccinated MLV adjuvanted 5-way (Pyramid® 5)
- BVDV 2 SN titers at vaccination 1:128 – 1:2048
- Control group: no antibody, no vaccine
- Challenged with BVDV2 at 3.5 months

Zimmerman et al, 2006



● NO antibody, NO vac

□ NO antibody, vac

△ antibody, vac

Zimmerman et al., 2006

- Calves in the no vac group were positive for virus in buffy coats after challenge
  - no calves in either vaccinated group was positive for virus

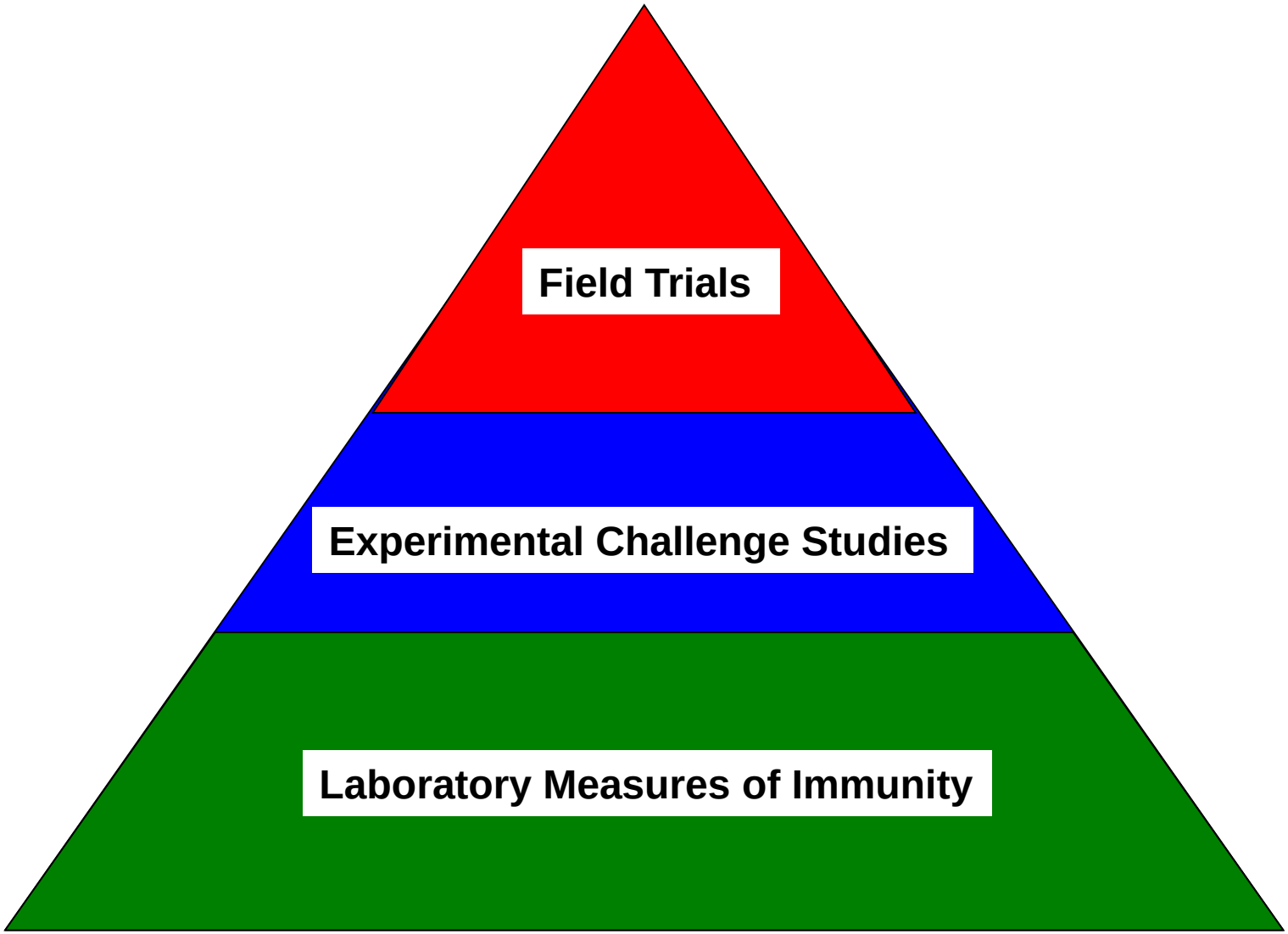
- 3 of 7 calves in no vac group died after challenge
  - No calves in vaccinated groups died

- Maternal antibody did not prevent the development of a protective response to vaccination
  - Also: vaccination of 3 – 5 week old seronegative calves was safe and effective

- Summary, BVDV studies
  - maternal antibody can protect calves from virulent BVDV challenge
  - calves vaccinated IFOMA develop immunity that is protective
    - even after maternal antibodies are gone

- Other research: T cells mediate the immunity associated with vaccination when maternal antibodies are gone

Endsley et al., 2004


Field Trials
Experimental Challenge Studies
Laboratory Measures of Immunity

Case Studies

Case #1, preweaning beef calves

- 65 head cow-calf operation
- BRD in nursing calves 3 to 4 months old

Case #1, preweaning beef calves

- 30% of calves have signs, 2 have died
  - Necropsy of 1 calf: BRSV and *Mannheimia*
- Three pregnant heifers purchased from neighbor 2 months ago

Case #1

- Herd evaluation
  - Dam body condition and nutrition acceptable
  - Calving season lasts 5 months
  - Cows not vaccinated or dewormed regularly
    - vaccinated once 2 years ago with killed 5-way
  - Calves not handled until weaning

- Plan to help limit disease in calves now:
  - Consider treating all calves in herd with long-acting antibiotic
  - OR increase surveillance and treat calves with signs of diminished activity
  - Vaccination in face of outbreak?
    - Often done
    - Evidence for benefit anecdotal
    - BRSV vac can be harmful in BRSV outbreaks

- Plan to prevent this problem in future:
  - Improve maternal antibody to respiratory viruses in calves?
    - Get cows on annual program of 5-way vaccination

- What about boosting cows late in pregnancy?
  - Can increase antibodies in calves
    - Studies have most often tested 2 doses to cows
  - Little evidence for decreased disease in calves

- Effect of cow vaccination on preweaning calf BRD
  - 430 cows randomly allocated to receive either
    - inactivated 5-way viral respiratory
    - no vaccine
  - cows vaccinated 40 days (mean) from calving

- BRD diagnosed in 12% of calves before weaning

- Incidence of calf BRD not different between groups (OR = 0.8, p = 0.54)
  - 13% in calves from unvaccinated dams
  - 10% in calves from vaccinated dams
- Trend toward a gender effect seen; heifers from vaccinated dams had less BRD (p = 0.07)

Smith et al., 2013

- What about vaccinating the calves?
  - MLV best for this application
    - Must be safe for use in contact with pregnant cows
    - If killed, look for data showing efficacy in animals with maternal antibody
  - TWO doses ideal
    - Consider giving at 2 months and 3 months
  - Viral vaccine
    - Consider IN first dose, IM second dose
  - *M. haemolytica* vaccine may also help

Case #2: Dairy calves

- Dairy milking 1600 cows
- Pneumonia in calves after they leave hutches and go to group pens at 14 days of age
  - 18 – 25 calves per group pen
  - group pens ≈ 15 feet wide x 30 feet long
  - automatic feeder (CF1000, DeLaval)
- Calves are given intranasal IBR/PI3 vaccine at 2 days of age
- Given IM MLV 5-way vaccine immediately before being turned into group pens

Case #2: Dairy calves

- 50% of calves treated for pneumonia in past month
- 5 calves out of 200 have died

- Necropsy of 2 calves: pure culture of *Histophilus somni*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5598
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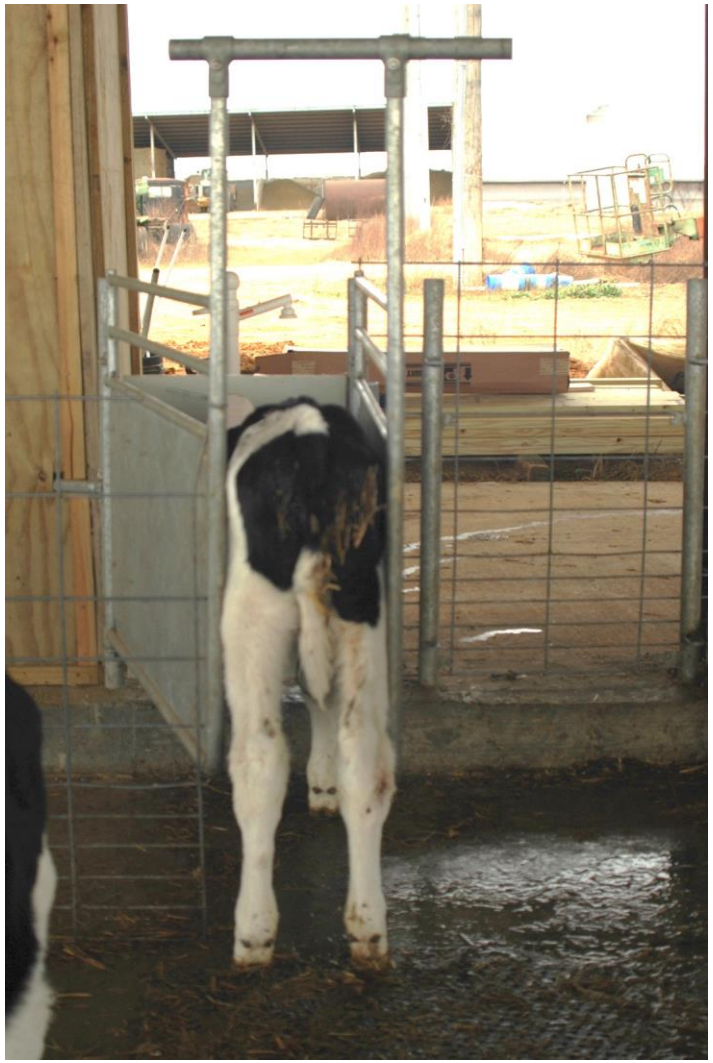


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Case #2: Management issues to consider

- In hutches
  - colostrum delivery
  - body condition
- In groups
  - group sizes
  - group age range
  - function of automatic feeder
- In both
  - timely identification and treatment of BRD cases
  - consistent adherence to treatment protocols

Case #2: use of vaccines

- Intranasal IBR/PI3 at 1 day of age
- IM 5-way at move to group pens

- Could this approach be improved?
- What might be better?

Take home messages: calf vaccination

- Young calves can respond to immune stimulation
  - As early as 1 day of life
  - Reliability of response inversely correlated with age
    - Especially in calves with good passive transfer

- Adult immune responses present by 5 – 8 months

Take home messages: calf vaccination

- Passive antibody blocks immune responses sometimes but not always
  - Blocking greatest in first month of life
  - Calves 2 – 3 months old: blocking not much problem
  - Really need more research confirming effect on disease

Take home messages: calf vaccination

- If vaccinating in first 6 months of life, 2 doses advised
  - 1 – 2 months between doses
  - Try to time second dose 1 month before expected challenge

Take home messages: BRD vaccination

- BRD vaccines must show efficacy in challenge studies to be licensed
  - But challenge studies are relatively artificial
- Clinical trial evidence supports vaccines for:
  - *Mannheimia haemolytica*
  - BRSV
- We need more clinical trials to know how BRD vaccines work in “real life”

Take home messages: BRD vaccination

- When BRD vaccines appear to fail, review factors related to
  - vaccine handling
  - timing of vaccination
  - agents in vaccine vs agents infecting cattle
  - ability of host to respond
- Help producers remember that vaccines are just one of many management tools needed to prevent BRD