Johne's Disease

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Should I be concerned?

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Johne's Disease

- Named after Heinrich Johne
  - Diagnosed the first (recorded) case of "pseudotuberculosis enteritis" in a cow in Germany – 1894
- First described in the USA by researchers at UPenn in 1908
- Caused by a bacteria
  - ***M****ycobacterium* ***a****vium* ssp. ***p****aratuberculosis* a.k.a. "**Map**"

MAP – the bug

- Intracellular pathogen
  - Can lives inside the goat's immune cells
  - Has a thick, waxy cell wall
- Very slow growing organism
  - In the animal
    - Clinical disease takes a long time to develop (12-18 months to years)
  - In the laboratory
    - Culture takes a relatively long time (8+ weeks to call a sample 'negative')

MAP – the bug

- Many unanswered questions remain:
  - How many ‘strains’ exist?
    - Do they vary in their ability to infect animals?
  - What is an infective dose?
  - Why do some animals become infected and not others?
  - Why do some goats develop clinical disease and not others?

How do we diagnose an infection?

- Detection of MAP organism
  - Culture (living organisms)
    - Solid or liquid media
    - Manure or tissue
  - PCR (DNA) (live or dead)
    - Manure or tissue
- Detection of antibodies
  - ELISA
    - blood

Stage 1 (Invasion phase)

- Infection with MAP is established
  - Oral inoculation of bacteria
  - Localizes in a fairly small section of gut
  - Usually – but not always! – occurs in very young animals

Stage 1 (Invasion phase)

- Subclinical infection
  - No weight loss or other clinical signs

- **No** antibodies detectable
- **No** shedding of bacteria

- **N**o risk to other animals

Susceptibility to infection

- Risk of infection depends on age at infection
  - Young animals are much more susceptible to acquiring an infection than older animals
  - *"Just a thimble of manure!"*
- Incubation period depends on dose of organisms ingested
  - Higher dose of MAP → faster progression of disease

When do new infections occur?*

- 5% - prior to birth; calf of a clinical, heavy shedder dam
- 75% - newborn and unweaned calves
- 10% - weaned and young heifers
- 10% - older heifers and cows
  - Animals may become infected as adults & develop clinical signs
  - Requires repeated, heavy doses?

*Estimated by R Whitlock

Stage 2 (Eclipse phase)

- Subclinical infection
  - No diarrhea, weight loss, etc.
- Antibodies not usually detectable (negative blood and milk ELISA)
- Occasional shedding of bacteria
- Pose small risk to herdmates

Stage 3 (Asymptomatic phase)

- Start to become clinically affected
  - Weight loss
  - Serum antibodies often detectable
  - Shedding bacteria in manure (i.e culture **+**)

- Kidding/stress may trigger increased shedding?
  - *Significant risk to other animals in herd*

Stage 4 (Clinical phase)

- Clinical disease!
  - Weight loss; Weight loss; Diarrhea (infrequent), occ. edema
- Good appetite
- Normal temperature (usually)
- Some “rule-outs” (other diseases to consider)
  - Internal parasites; Chronic malnutrition; Caseous lymphadenitis; Cancer

Stage 4 (con't)

- Most are positive on blood test (ELISA)
- Shedding ***lots*** of bacteria in manure
  - Many thousands of MAP organisms per day
  - Often show up as "heavy shedders" on culture
- Kids of stage 4 animals may be infected before birth

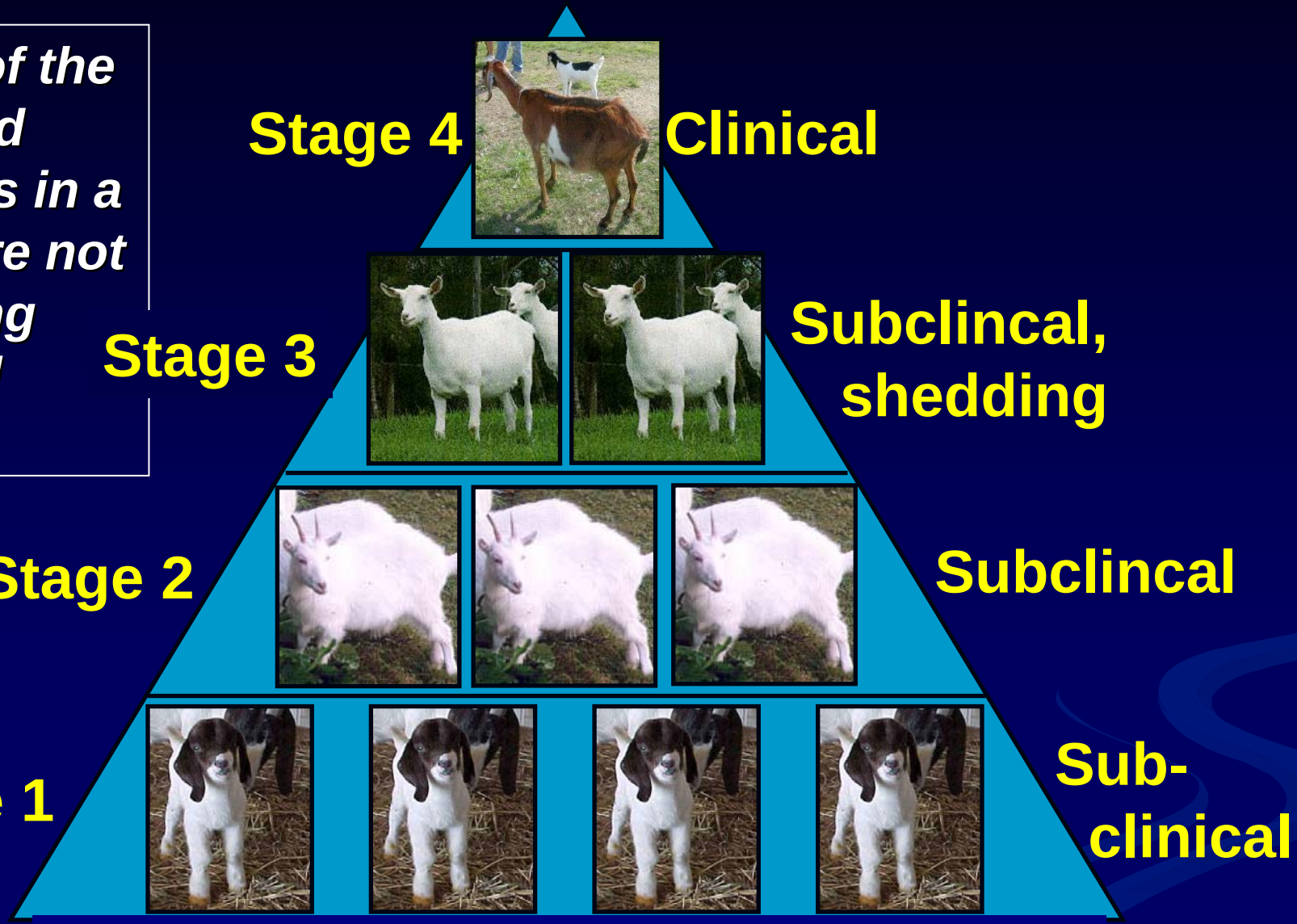
In utero & milk transmission (cattle)*

- Clinical (stage 4)
  - ~25% calves infected prior to birth
  - ~30% milk samples positive for MAP
- Asymptomatic heavy shedders (stage 3-4)
  - ~18% fetuses positive for MAP
  - ~19% milk samples positive
- Asymptomatic light shedders (stage 2-3)
  - ~0% fetuses positive
  - ~5% milk samples positive

*Very likely similar numbers are true for goats?

The iceberg principle…

~95% of the infected animals in a herd are not showing clinical signs



Images from: www.das.psu.edu/goats/ , www.jackmauldin.com , Oklahoma State University

Contamination of environment

- Manure slurry
  - survived for 252 days
- Pasture
  - freezing temperature - 245 days
  - shade & lower temps favored survival
- Survival in water
  - Does not replicate; Survives normal chlorination
    - River water - 165 d.
    - Tap water - 520 d.

So, MAP...

- is an insidious bacterial infection...
- that is difficult to diagnose...
- and impossible to treat!

- It can be found in milk...
- can survive well in the environment...
- and can survive chlorination.

- ***NOT*** a pleasant bug to deal with!!

A link with Crohn's Disease?

- No consensus on this point!
- Some evidence shows an ***association***
- Very difficult to prove ***causation***

Mycobacteria and Crohn's disease — Personal view

Is Crohn's disease caused by a mycobacterium? Comparisons with leprosy, tuberculosis, and Johne's disease

Robert J Greenstein

Although Crohn's disease is considered to be autoimmune in origin, there is increasing evidence that it may have an infectious cause. The most plausible candidate is *Mycobacterium avium* subspecies *paratuberculosis* (MAP). Intriguingly, Koch's postulates may have been fulfilled for MAP and Crohn's disease, even though they still have not been met for *Mycobacterium leprae* and leprosy. In animals MAP causes Johne's disease, a chronic wasting intestinal diarrhoeal disease evocative of Crohn's disease. Johne's disease occurs in wild and domesticated animals, including dairy herds. Viable MAP is found in human and cow milk, and is not reliably killed by standard pasteurisation. MAP is ubiquitous in the environment including in potable water. Since cell-wall-deficient MAP usually cannot be identified by Ziehl-Neelsen staining, identification of MAP in human beings requires culture or detection of MAP DNA or RNA. If infectious in origin, Crohn's disease should be curable with appropriate antibiotics. Many studies that argue against a causative role for MAP in Crohn's disease have used antibiotics that are inactive against MAP. However, trials that include macrolide antibiotics indicate that a cure for Crohn's disease is possible. The necessary length of therapy remains to be determined. Mycobacterial diseases have protean clinical manifestations, as does Crohn's disease. The necessity of stratifying Crohn's disease into two clinical manifestations (perforating and non-perforating) when interpreting the results of antibiotic therapy is discussed. Rational studies to evaluate appropriate therapies to cure Crohn's disease are proposed.

Lancet Infect Dis 2003; **3**: 507–14

Crohn's disease[1,2] is a disease of unknown aetiology that is increasing in incidence in the USA,[3–5] Canada,[6] and around the world.[7–9] It is associated with immune dysregulation.[10–12] I review the increasing evidence that Crohn's disease is caused by *Mycobacterium avium* subspecies *paratuberculosis* (MAP).

The thesis that Crohn's disease is infectious, and may be caused by MAP, is usually discounted or even ignored.[13] There are multiple reasons for this scepticism. One is that mycobacteria are not seen using standard mycobacterial cell wall (Ziehl-Neelsen[14]) staining techniques. An additional and more compelling concern is that in most antibiotic clinical trials, Crohn's disease has not been cured. The apparent value of immune modulation and the identification of a "Crohn's-related gene" are additional reasons to question bacterial culpability. Despite this

Creeping mesenteric fat

A B

Mucosal cobblestoning

Figure 1. Mucosal cobblestoning in bovine Johne's disease (B; courtesy A J Cooley, School of Veterinary Medicine, University of Wisconsin) compared with that seen in Crohn's disease (A). Additionally, note the creeping mesenteric fat, that is so characteristic of Crohn's disease, on the serosal surface of the specimen from Johnes's disease (arrow).

ongoing controversy, several European governments are concerned about[15–17] and are addressing the possibility of a causal connection between MAP and Crohn's disease.[18,19] The government of the UK has decided to exercise the precautionary principle concerning a possible link between Crohn's disease and MAP, and has decided to eradicate MAP from the food chain. This action is not contingent on demonstrating an unequivocal link between MAP and Crohn's disease.[19]

Mycobacteria are effective pathogens

Mycobacterium tuberculosis infects about one-third of humankind today.[20] However, only an estimated 5–10% of those exposed have a lifetime risk of developing active tuberculosis.[21] An even smaller minority of those who are infected are killed by the disease.[22] Nevertheless, *M tuberculosis* has killed about one billion people over the past two centuries.[23] I suggest that MAP is an equally effective and even more insidious pathogen than *M tuberculosis*. It infects many species and yet, in human beings, is more difficult to detect than *M tuberculosis*.

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So, is there MAP in milk??

- United Kingdom milk studies
  - retail milk was PCR and culture positive
- USA - Marshfield Clinic study
  - 702 retail milk samples – culture & PCR
  - Viable (living) MAP organisms found in about 3% of retail milk samples
    - Present in very low numbers
    - Could not ‘rule out’ post-asteurization contamination!

What about goat's milk??

- "*Seventy-nine (23.0%) goat's tank-milk*… samples* [in Switzerland] *were PCR-positive for insertion sequence 900**, *providing presumptive evidence for the presence of M. avium paratuberculosis*"

Journal Dairy Science, 2003

* Raw/unpasteurized milk

** Does **not** necessarily mean that any or all of these bacteria were alive…but it seems very likely that at least some were!

Odds & Ends

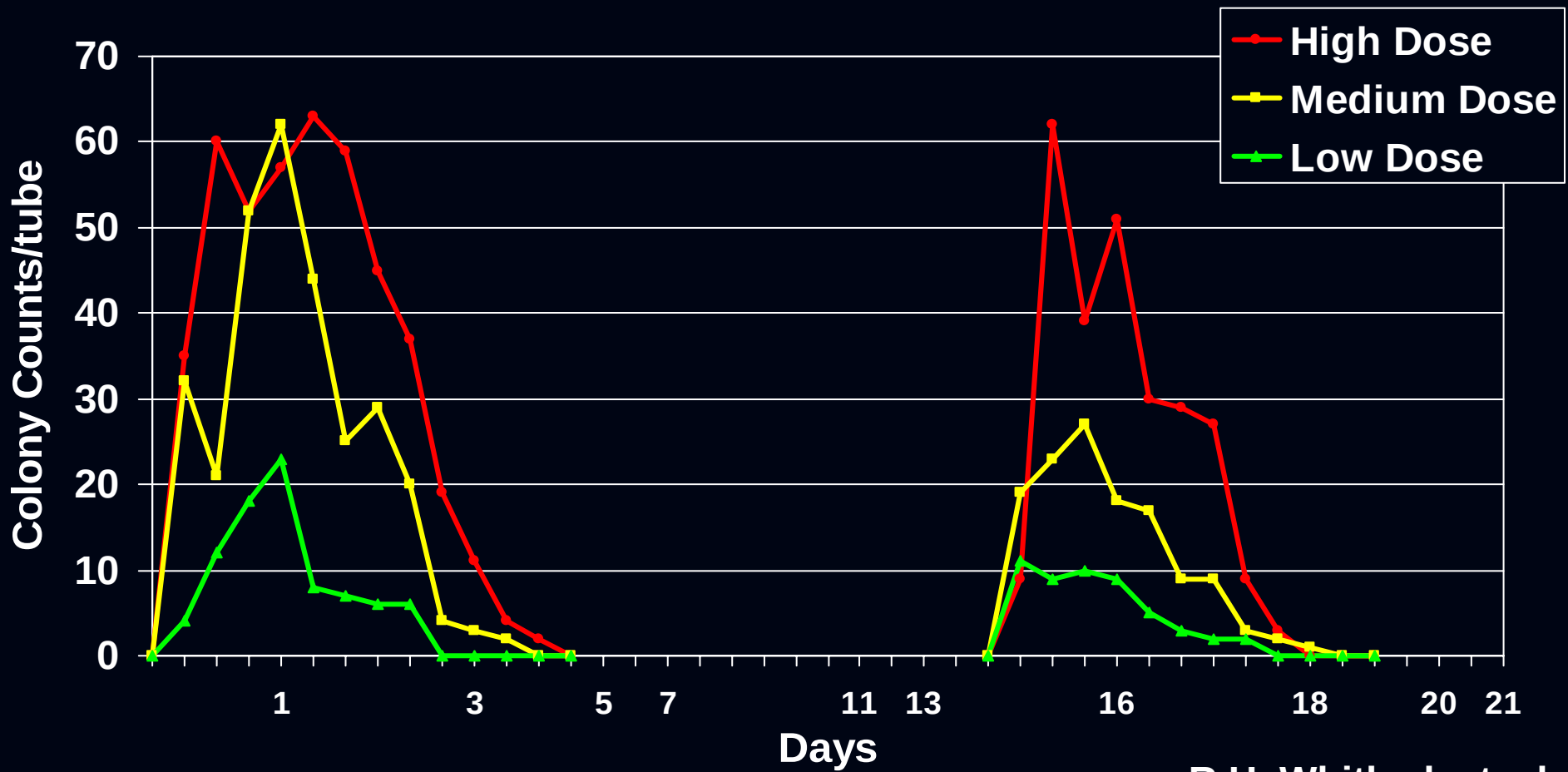
- Transmission by deer?
  - 400 hunter-sampled deer in NY state (100/yr over 4 years)
  - 1 positive animal - from on/near a heavily infected dairy farm! (Stehman, 1999)

- So its possible, but may not be very likely!

Odds & Ends

- “Pass-through” culture positives
  - Can animals be fecal culture positive due to environmental contamination?
- Culture-negative heifers were tubed (into the rumen) with low, medium or high doses of MAP-infected manure
- Manure samples cultured at regular intervals

“Pass Through” Experiment



R.H. Whitlock et. al.

How do we deal with it??

Some of the challenges of JD...

- Diverse management & housing styles
- Not as much experience with managing JD as with dairy cattle
- More difficult to detect late-stage animals

Some of the challenges of JD...

- Poor diagnostic test performance
  - Infected animals are often test-negative
  - False positive tests may occur
- Not all test-positive animals are an immediate economic liability to the herd
- Difficulty of purchasing negative or low-risk replacements?
- No regulatory ‘incentive’

Managing JD on the farm

- ***National Voluntary Bovine Johne's Disease Control Program***

- "Risk assessment" approach
  - Develop a (*meaningful)* herd plan to deal with, and prevent Johne's Disease

- Collaborative effort: herd vet, farmer and other key advisors/personnel

Resources

www.jd-rom.com/riskassessment.asp *

www.johne's.org

www.vetextension.psu.edu

* These dairy and beef risk assessment documents are also available on the CD handed out at the workshop. They should be adapted to your specific management style, housing conditions, etc.

Risk of Fecal*-oral transmission

A. Calving Area Risk Factors (Place an X in the box to the right of the management practice that most closely signifies the risk for that item.)	0.	1 V. Low	2. Low	3.	4.	5 Moderate	6.	7.	8. High	9.	10. V. High
1. Multiple animal use [Single pen → Dense crowded group]											
2. Manure build-up risk for calf ingestion [Clean dry → Dirty wet]											
3. Area also used for sick cows [Never → Always]											
4. Presence of JD clinicals / suspects [Never → Always]											
5. Manure soiled udders / legs [Never → Always]											
6. Calves born in other cow areas [Never → Always]											
7. Time calves stay with dam [<30 minutes → >24 hours]											
8. Calves nurse dam [Never → Most or all]											

Notes / C

Maximum score = 80. Your herd score is _____. Consider the imp

Estimate the risk for spreading Johne's in the calving area: **Very L**

ry Herds

***r Johne's Disease*")**

	Risk Level	Score
	Lowest	0 to 2
	Moderate	3 to 7
	Highest	8 to 10
re-contaminated.	Lowest	0 to 2
	Moderate	3 to 7

*** Also risk of colostrum/milk-oral transmission**

Are calves/kids allowed to nurse?

Are cows' / does' udders, legs, and flanks soiled with manure?

Can feed become contaminated with adult goats' manure?

http://hoeggergoatsupply.com/

http://hambydairysupply.com/

bedford.extension.psu.edu

Building the elements of the testing strategy for Johne's management plan. See Step 5 in t
'How to Do' handbook, page 8, for guidelines.

1. What is the testing scheme expected to accomplish and how will it help reach plan objectives? **Determine level of infection, high shedders**
2. What test (s) will be used? **Fecal culture**
3. Who will be tested? **All animals 24 months and older**
4. When? **Mid-March**
5. What decision (s) will be made on results? Consider higher vs. lower risk 'test-positive' cattle. **Cull high shedders**

Johne's Management Plan

What are the objectives of the herd plan? ☒ Determine status of herd ☐ Prevent JD introduction into herd ☒ Prevent further spread
☐ Establish test negative status ☒ Reduce the infection in herd ☐ Other

Management practice to reduce identified risks for Johne's disease in this herd	How does practice benefit and/or integrate with existing health / management objectives	Priority Lo, M, or Hi	Person(s) in charge
Relocate kidding area to clean pasture frequently		**High**	**Jeff**
Feed pasteurized cows' milk or milk replacer		**High**	**Annie**
Whole herd fecal culture		**High**	**Jeff**

Take home messages

- Find out if you have Johne's Disease in your herd; fecal culture (pooling?), tissue samples (necropsy/slaughter), etc.
- Develop a Johne's herd management plan that will…
  - Prevent (any more) Johne's from coming onto the farm…
  - Reduce the number of infected animals in the herd over time

Take home messages

- Think of ways to reduce fecal-oral transmission of disease
  - Maintain CLEAN & DRY kidding facilities
  - Feed off of the ground
  - Minimize exposure of youngstock to adult manure
  - Etc…