Pathogen based treatment – Prudent use of antimicrobials

OPERATIONS MANAGERS CONFERENCE
ProDairy 2019

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Overview

- Antimicrobial use in humans and animals
- Dairy farm antimicrobial usage
- Pathogen based treatment (PBT)

Pop quiz

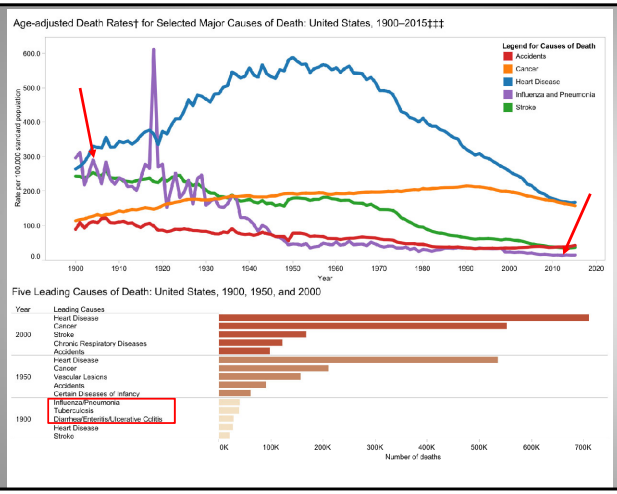
- What is the percentage of mastitis cultures that are culture negative?
- What percentage of mastitis causing organisms are treatable or respond to intramammary treatment?
- How many dairy producers in the room have a MAST No Treat protocol?

The role of antimicrobials in human and animal medicine

- Antimicrobials – medicine that inhibits the growth of or destroys microorganisms
  - Some antimicrobials specifically target bacterial cells
  - Human cells have a plasma membrane but lack a peptidoglycan cell wall structure
    - Beta-lactams selectively target bacteria with a peptidoglycan layer with no negative impact on human cells
- Antimicrobials have and continue to save millions of lives
- Antimicrobials improve human health
- Lifespan
  - 1930 – 60 years
  - 2016 – 78 years
- Use of antimicrobials in animal medicine
  - Lower mortality rate
  - Lower morbidity rate
  - Lower disease rates – increased risk of another disease when sick

What were the major killer of humans in the 1930?

What are the major killers of humans today?



Main causes of death in 1900's was from diseases caused by bacteria. Today bacterial deaths are very few compared to other diseases

CDC, NCHS

So what's the problem…?

- Concern from public health, food safety, and regulatory perspectives about the use of antimicrobials in food-producing animals….
- This is not new
  - In 1987 three out of five consumers viewed antimicrobial use in poultry and livestock as a "serious health hazard"
  - Historical data from 1937 to 1991 shows that food safety was the number one topic of discussion among consumers as it related to food
    - Food safety was of greater concern than excess consumption of a food product, pesticides residues in food, animal hormones and unsafe practices used to treat cattle
- The discussion is not that different today
  - Need to educate on prudent use not reduction

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Bulk tank milk testing

- Every load of milk is tested for the presence of Beta-lactam drugs
  - > 3.4 million loads tested annually
    - 0.011% test positive

Milk residue sampling survey

	Target farms	Non-target farms
antimicrobial negative	953	959
antimicrobial positive	11 (12)	4
antimicrobial positive (%)	1.15%	0.42%

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USDA Dairy 2014

- 90% of operations use IMM antimicrobials
  - 87% of cows with mastitis treated with IMM
  - 21% of cows affected with mastitis during lactation
  - 93% of cows are dry treated with an antimicrobial
- Not focusing on use of antimicrobials in non-lactating animals during this presentation
  - But…..

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History of antimicrobials in feed

- 1951 FDA approves antimicrobials for use in animal feed based on studies showing it helps chickens, pigs and livestock improve weight gain
- 1969 A committee of government experts in the U.K. concludes that the use of antimicrobials in animals has contributed to antimicrobial resistance in humans
- 1970 A U.S. task force, including scientists from the FDA and other agencies, recommends some antimicrobials used in humans be banned from use in animals
- 1977 The FDA proposes a ban on the use of penicillin and tetracycline in animal feed, unless pharmaceutical makers can show the practice is not a danger to humans
- 1980 FDA-commissioned report by the National Academy of Sciences finds little scientific data on antimicrobial resistance caused by feeding drugs to animals
- 1997 World Health Organization recommends antimicrobials used in humans should not be used to promote growth in animals.
- 1999 The European Union issues a ban on using popular human antimicrobials in animals for growth promotion due to risks to humans
- 2003 U.S. Institute of Medicine issues a report on the rise in dangerous bacteria, or superbugs. The group's recommendations include banning use of antimicrobials for growth promotion in animals.
- January 2012 The FDA orders limits on cephalosporin antimicrobials given to animals. The drugs are used to treat pneumonia and other diseases in humans.
- April 2012 The FDA outlines plans to phase out non-medical uses of more than 200 antimicrobials in animals over three years.
- 2015 FDA implements animal drug regulations regarding veterinary feed directive (VFD) drugs. FDA's current VFD regulation established requirements relating to the distribution and use of VFD drugs and animal feeds containing such drugs. This amendment is intended to improve the efficiency of FDA's VFD program while protecting human and animal health.

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- **60% of AMU in dairy is for mastitis or milk quality (MAST and dry cow)…**
- **Limited number of approved intramammary antimicrobials**
  - **5/6**

Product	Antibiotic	Bactericidal Bacteriostatic	Spectrum	Dosage	Milk Withholding	Slaughter Withdrawal	Product Indications
Boehringer Ingelheim Vetmedica, Inc.							
ToDAY®	Cephapirin Sodium	cidal	Broad	1 syringe repeat in 12 hours	96 hours	4 days	Treatment of mastitis in lactating cows caused by susceptible strains of *Streptococcus agalactiae* and *Staphylococcus aureus* including strains resistant to penicillin.
'PolyMast® (R)	Hetacillin Potassium	cidal	Broad	1 syringe repeat in 24 hours up to 3 days	72 hours	10 days	Treatment of acute, chronic or subclinical bovine mastitis in lactating cows caused by susceptible strains of *Streptococcus agalactiae, Streptococcus dysgalactiae, Staphylococcus aureus* and *Escherichia coli.*
Zoetis							
Pirsue® (R)	Pirlimycin Hydrochloride	static	Narrow	1 syringe repeat in 24 hours x 2 days 1 syringe repeat in 24 hours for > 2 days (up to 8 days)	36 hours	9 days 21 days	Treatment of clinical and subclinical mastitis in lactating dairy cattle against *Staphylococcus aureus* and *Streptococcus agalactiae, Streptococcus dysgalactiae* and *Streptococcus uberis.*
Spectramast® LC (R)	Ceftiofur Hydrochloride	cidal	Broad	1 syringe repeat in 24 hours x 8 days	72 hours	2 days	Treatment of clinical mastitis in lactating dairy cattle associated with coagulase- negative staphylococci, *Streptococcus dysgalactiae,* and *Escherichia coli.*
Merck							
Amoxi-Mast® (R)	Amoxicillin	cidal	Broad	1 syringe repeat in 12 hours for three treatments	60 hours	12 days	Treatment of subclinical mastitis in lactating cows due to *Streptococcus agalactiae* and penicillin-sensitive *Staphylococcus aureus.*
Dariclox® (R)	Sodium Cloxacillin	cidal	Narrow	1 syringe repeat in 12 hours for three treatments	48 hours	10 days	Treatment of bovine mastitis in lactating cows due to *Streptococcus agalactiae* and nonpenicillinase-producing *Staphylococcus aureus.*

2/3 of that 60% is for Dry Cow Therapy

Product	Antibiotic	Bactericidal Bacteriostatic	Spectrum	Dosage	After Minimum Dry Period	Dry Period	Slaughter Withdrawal	Product Indications
Boehringer Ingelheim Vetmedica, Inc.								
ToMORROW®	Cephapirin Benzathine	cidal	Broad	1 syringe per quarter at dry off	72 hours	30 days	42 days	Treatment of mastitis in dry cows, when caused by *Streptococcus agalactiae* and *Staphylococcus aureus,* including penicillin-resistant strains.
'Dry-Clox® (R)	Cloxacillin Benzathine	cidal	Narrow	1 syringe per quarter at dry off	0	30 days	30 days	Treatment of mastitis in dry cows when caused by *Streptococcus agalactiae* and *Staphylococcus aureus* including penicillin-resistant strains.
Zoetis								
Albadry Plus®	Penicillin G. Procaine and Novobiocin Sodium	cidal	Broad	1 syringe per quarter at dry off	72 hours	30 days	30 days	Treatment of subclinical mastitis in dry cows caused by susceptible strains of *Staphylococcus aureus* and *Streptococcus agalactiae.*
Spectramast® DC (R)	Ceftiofur Hydrochloride	cidal	Broad	1 syringe per quarter at dry off	0	30 days	16 days	Treatment of subclinical mastitis in dairy cattle at the time of dry off associated with *Staphylococcus aureus, Streptococcus dysgalactiae* and *Streptococcus uberis.*
Merck								
Orbenin®-DC (R)	Benzathine Cloxacillin	cidal	Narrow	1 syringe per quarter at dry off	0	28 days	28 days	Treatment and prophylaxis of mastitis in dry cows due to *Staphylococcus aureus* and *Streptococcus agalactiae.*
WG Critical Care								
Quartermaster® (R)	Penicillin-Dihydrostreptomycin	cidal	Broad	1 syringe per quarter at dry off	96 hours	42 days	60 days	Reduce the frequency of existing infection and to prevent new infections with *Staphylococcus aureus* in dry cows.

Shouldn't be a complicated discussion…

Mastitis

- Define mastitis
  - Inflammation of the mammary tissue
    - Abnormal milk, swelling, warmth to the touch, sensitive to touch
    - Mastitis is indicated by inflammation or abnormal milk, etc. and that is why we have milk samples that culture negative
      - The organism may have been evacuated from the mammary gland by the time we see abnormal milk and collect a milk sample
  - Inflammation caused by response of immune system to invading organism or localized trauma
    - Not infection but inflammation
      - Why is the distinction important?
      - We cant treat inflammation with antibiotics

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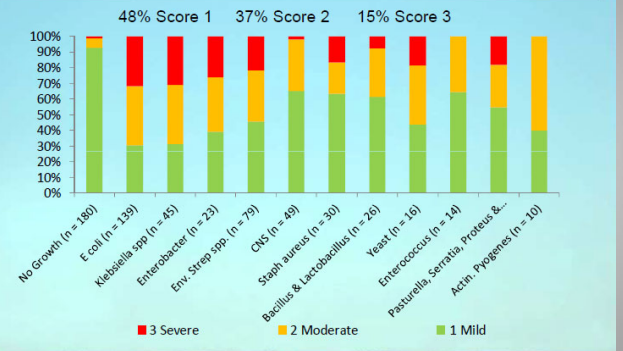
Almost All the Cases Are Mild

(622 cases from 52 farms)



Ruegg et al.

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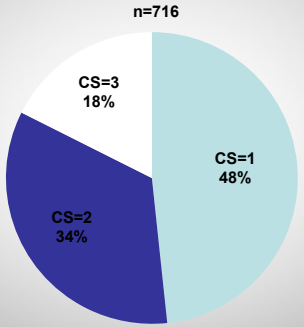
Severity Score Distribution

Clinical Mastitis on 6 NYS dairies 2016



Vasquez et al.

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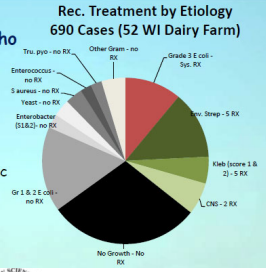
Judicious Antibiotic Usage

- **Do not administer antibiotics to cows who will not benefit**
  - Chronic Staph aureus
  - Mycoplasma bovis
  - Multiple infected quarters
  - Damaged teats
  - Other serious metabolic disease
  - Repeated previous treatment failures
  - Long history of chronically high SCC



< 40% of mastitis cases require treatment if we use cure rate as an outcome

J. Dairy Sci. 96:7538–7549
http://dx.doi.org/10.3168/jds.2012-6078
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Characterization of clinical mastitis occurring in cows on 50 large dairy herds in Wisconsin

L. Oliveira,[1] C. Hulland, and P. L. Ruegg
Department of Dairy Science, University of Wisconsin, Madison 53706

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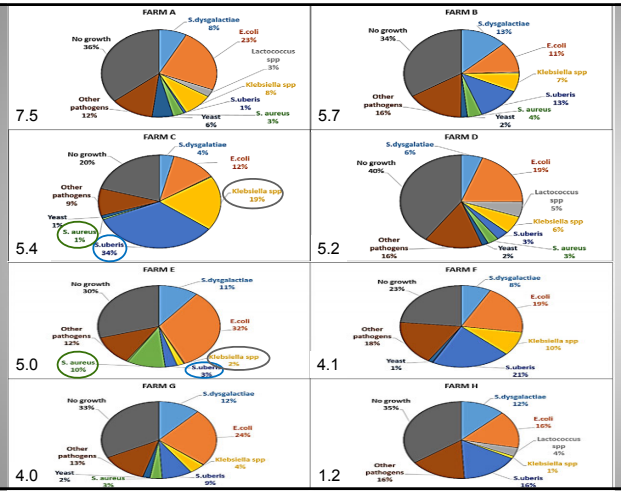

Monthly mastitis incidence risk of 4.8%

Treatable:
Streps

Non-treatable:
Gram-
Staph aureus
CNS
No growth
Lactococcus?

9 – 38% treatable

Alanis et al. - unpublished

Pathogen Based Treatment Decisions for Clinical Mastitis

- How could delaying treatment of mastitis by 24 – 48 hours be beneficial to milk quality and clinical outcome?
  - Not all cases should/need to be treated!
  - ~85% of cases are mild or moderate
    - Delaying treatment ~ 24 hours doesn't change outcome
    - Don't need systemic treatment
  - ~15% of cases should be treated immediately and systemically

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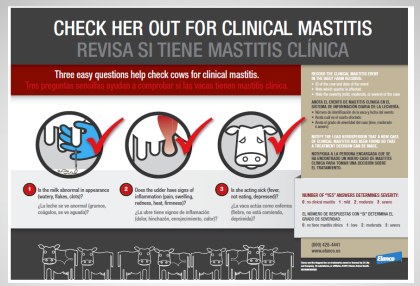
Clinical mastitis score



- Clinical severity score of 1, 2 or 3
  - 1: abnormal milk
  - 2: swelling or inflammation
  - 3: systemic or down cow
- What percent of mastitis cases are clinical score 3?

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Design Summary

Randomize cows into two groups:

1. Treat **all** cows with mild/moderate mastitis with 5 days of Spectramast (BT)
   a. Cull *Myco*, *Staph aureus*, *Prototheca*

1. Treat **some** cows based on pathogen ID (ToDay or NOT) after 24 hours (PB)
   a. Treat *Streps*, CNS *Staphs* with Today 2x
   b. Cull *Myco*, *Staph aureus*, *Prototheca*
   c. *Not treat others*

2. *Cows with CS=3 given systemic therapy and not included in analysis*

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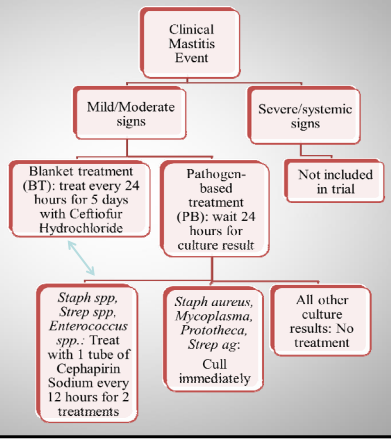
Materials and Methods



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1. Compare treatment "success"
   a. Next test-day LS
   b. Next test-day milk production
   c. Duration of clinical mastitis signs
   d. Risk of being sold/dead at 30 and 60 d after event
   e. Time out of tank

2. Determine risk of chronic *E. coli* in untreated cows compared to treated cows

Does waiting >24 hours for pathogen ID and then treating only Streps and Staphs with Today 2x v. treating with Spectramast 5x change:

- the length of clinical mastitis signs? – **NO**
  - 4.5d in 24 hr (PB)
  - 4.8d in Spectramast (BT)
    - P= 0.12

Does waiting ~24 hours for pathogen ID and then treating only Streps and CNS Staphs with Today 2x v. treating with Spectramast 5x change:

- LS at next test day – **NO**
  - 4.3 in 24 hour group (PB)
  - 4.3 in Spectramast group (BT)
    - P= 0.70

Does waiting ~24 hours for pathogen ID and then treating only Streps and CNS Staphs with Today 2x v. treating with Spectramast 5x change:

- Milk Production at next test day – **NO**
  - 77.8 lbs in 24 hr group (PB)
  - 76.3 in Spectramast group (BT)
    - P= 0.42

Does waiting >24 hours for pathogen ID and then treating only Streps and Staphs with Today 2x v. treating with Spectramast 5x change:

- the risk of being sold/dead - **NO**
  - Survival at 30d
    - OR = 1.6 (95% CI:0.7-3.7) for remaining if in PB
    - 3.7% PB v. 5.8 BT
    - P=0.31
  - Survival at 60d
    - OR = 1.4 (95% CI:0.7-2.5) for remaining if in PB
    - 9.3% PB v. 11.1% BT
    - P=0.53

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Descriptive Results

- 725 cases of clinical mastitis
  - 16% had CS=3 (n=114)
    - 37 cows culled and excluded for Staph aureus or Mycoplasma
    - 85 others excluded for other diseases, protocol errors, etc.
- 246 Pathogen Based / 243 Blanket Therapy
  - PB: 167 = no treatment; 79 ToDay 2x
  - BT: 243 = Spectramast 5x

Pathogen	PB (%)	BT (%)
No growth	26	21
NSO	7	7
CNS	2	3
Strep spp.	31	33
Gram negative	34	33
Yeast	0.4	2
T. pyogenes	0.4	0.8
Other	0	0.8

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PBT Summary

- 3 less days of milk withhold
  - No differences in:
    - Days to clinical cure
    - Post MAST milk yield
    - Post MAST LS
    - Risk of cull in 1-2mo following MAST
- Over 65% of mild/moderate mastitis will NOT be treated with antimicrobials if this protocol is employed
- Every farm has different mastitis causing organisms
- $25,000 in economic benefit to the farm / 1,000 cows when using PBT vs. blanket treatment
  - 5% Mastitis incidence rate
  - $15/cwt

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Economics: Milk $15/cwt

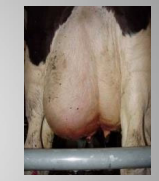
Assumptions	
On Farm Labor Rate/Hour	$ 15.00
Per Tube Cost-Spectramast	$ 3.80
Per Tube Cost- ToDAY	$ 3.10
Milk Price/cwt	$ 15.00
Daily Production (lbs)-Mastitis Cow	60
Clinical Mastitis Incidence/Month	5%
Culture Based Therapy	
IMM Treatment Rate	35%
No IMM Treatment Rate	65%

Per Cow Estimates	Blanket Therapy	Culture Based Therapy	
Materials and Labor		IMM Therapy	No Treat
Antibiotic Cost	$ 19.00	$ 6.20	$ -
Labor Cost	$ 7.50	$ 3.75	$ 1.25
Culture Cost	$ -	$ 6.00	$ 6.00
Total	$ 26.50	$ 15.95	$ 7.25
Lost Milk Income			
Days of Nonesaleable Milk	8.8	5.8	5.8
Total Lost Milk	528	348	348
Lost Income	$ 79.20	$ 52.20	$ 52.20
Direct Cost per Case	$ 105.70	$ 68.15	$ 59.45
Calculations Projected to 1000 Cows			
Clinical Cases Treated per Year	600	210	390
Total Costs / 12 Months	$ 63,420	$ 14,311.50	$ 23,185.50
Total Cost / Treatment Strategy	$ 63,420		$ 37,497
Difference			$ 25,923

Table By: Michael Capel and Daryl Nydam; adapted by Rick Watters

QMPS 24 hr: 6 - 7d/wk service

- Cows gets mastitis
- Milk samples taken
- Events entered into computer
- Courier picks up samples
- Accessioned at lab
- Pathogen results reported 24 hours after pick-up
- Protocol driven treatment/automated treatment assignment in DC305



- On-farm culture also works for Pathogen Based Treatment decision making

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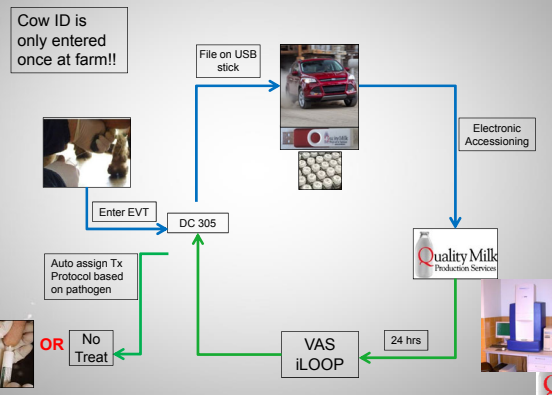
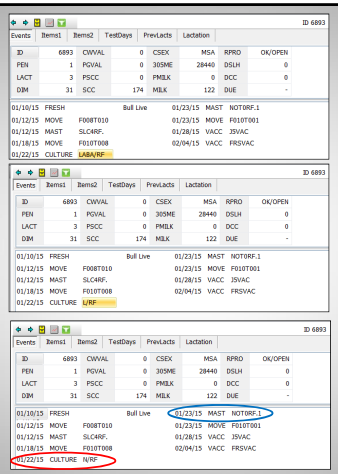
Data and Sample Flow





When Cow Entered

When Sample at Lab

24 Hour Results

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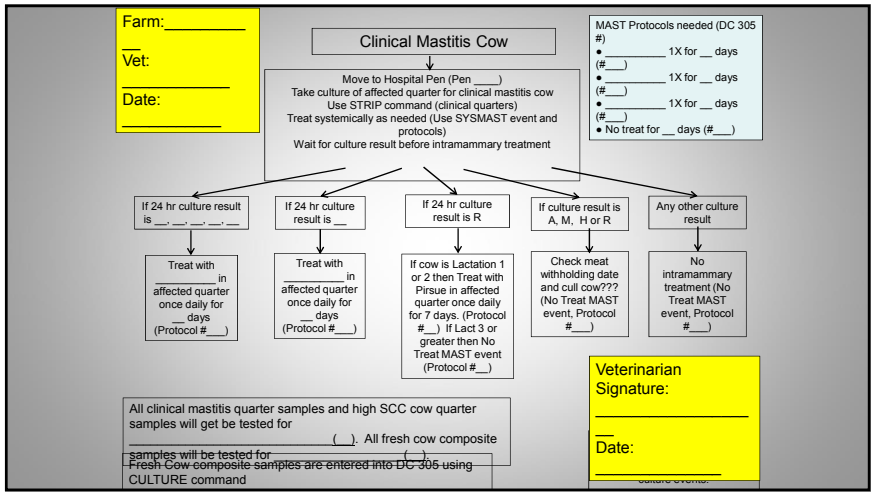
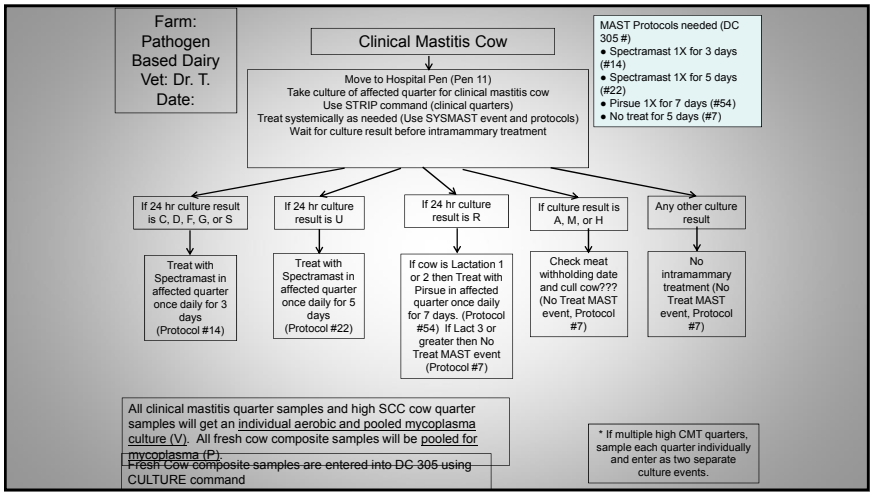
Review MAST treatment protocols - DVM

- When was the last time that you reviewed your MAST treatment protocols?
- How many farms have a MAST no treat protocol?





Pathogen based treatment at QMPS

- > 100,000 cows in NY state on PBT
  - Where was this number 5 or 10 years ago?
  - Where will this number be 5 or 10 years from now?
  - Approximately 35% of cows managed with On-farm culture
- NY state most likely has the highest adoption rate of PBT than any other state given the ability of QMPS to promote the program state wide
- NY State Dairy Statistics
  - 4,400 farms
  - 623,000 cows

Dry cow therapy

- 2014 NAHMS, USDA survey indicated that 93% of cows undergo dry treatment
  - 9.39 million dairy cows in US – 2017
  - 4 tubes/cow
    - Blanket treatment of all cows to control contagious mastitis
- What about selective dry cow therapy?
  - Does every quarter of every cow need to be treated with intramammary antimicrobials at dry off?

Selective dry cow therapy (SDCT)

- Articles in press over past couple of years on SDCT
- Since 2012 no preventive antimicrobials allowed in Netherlands
  - Bulk tank SCC 170,000 country wide
  - Reduced antimicrobial usage by 28%
- New Zealand Veterinary Association states by 2020 only cows with an existing intramammary infection at dry off can be treated
- Strep ag and Staph aureus smaller issue today
- From 70 – 95% of cows are culture negative at dry off


MILK QUALITY

Why think about selective dry cow therapy now?

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SDCT

- An approach abolishing the dry treatment of all animals is not suggested
  - There are animals that will benefit from intramammary antimicrobials and these animals should be dry treated
- How do we identify which animals to treat and not treat at dry off?
  - Quarter level culture
    - Treat quarters that were culture positive
    - Reduced antimicrobial usage by 28%
      - Patel, Gordon et al 2017
  - SCC data
    - SCC < 200,000 cells/ml on last three tests no treat
      - 53% of cows low risk
        - » Rajala-Schultz/Ruegg
  - Use of on-farm data and test day
    - <200,000 cells/ml at last test
    - Average of last three test days < 200,000 cells/ml
    - ≤ 1 clinical case of mastitis during lactation
    - No current symptoms of mastitis
    - No mastitis in last 30 days
      - 64% of cows low risk
        - » Vasquez et al. 2018

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SDCT

- Slow adoption from NE to SE to NW to MW
  - Farms are working closely with veterinarians
  - Superior milk quality should be achieved prior to taking on SDCT
  - Using multiple criteria to determine if cow is eligible for no treat may be beneficial
    - Error on the side of treating a few more versus not treating cows that should be treated

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Potential antimicrobial reduction

- 30 – 65% no treat with PBT
  - Stop treating negatives to full on PBT
- 50 – 65% no treat with SDCT
  - Use farm records to determine who to treat and not treat
- 20% of dairy operation antimicrobial use for mastitis
- 40% of dairy operation antimicrobial use for dry treatment
  - Potential to reduce antimicrobial usage by 30 – 50 %
    - Not reduction but prudent use

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What if…?

- What would happen if antimicrobials were banned for use in food-producing animals?
  - Inhumane? - YES
  - We don't want to find out
- What can we do to promote prudent or efficacious use of antimicrobials in the dairy industry and the food-producing animal industries?

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Discussion

- Antimicrobials are necessary for humane treatment of animals
- Two pronged **science based** approach to **prudent** use of antimicrobials
  - PBT
  - SDCT
- Pathogen based treatment in NY
  - No increase in SCC, New and Chronic Infection rates at farms using PBT
  - No increase in chronic MAST at farms using PBT
- Internationally antimicrobial usage has decreased with no negative impact on animal health

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Pop quiz - review

- What is the percentage of mastitis cultures that are culture negative?
  - 30-40%
- What percentage of mastitis causing organisms are treatable or respond to intramammary treatment?
  - 10 – 40%
- How many dairy producers in the room will have a MAST No Treat protocol after today?

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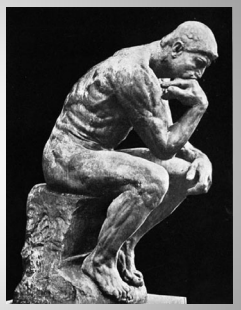
Questions

- Without bacteria we wouldn't be alive
  - Humans require bacteria for carbon, nitrogen and to digest food
    - Cycling of chemical elements – converting nitrogen to ammonia or nitrates to be absorbed by plants, which we eat and absorb to create amino acids and nucleic acid
    - Digestion – without bacteria we wouldn't break down all food – obtain more nutrition from food because of bacteria
- Without antimicrobials we would have a shorter lifespan
- It's not about whether or not we should use antimicrobials, but instead implementing prudent use management strategies for antimicrobial use on dairy operations.



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