On behalf of the College of Veterinary Medicine, I would like to extend a warm welcome to you. The 2014 Minnesota Dairy Health Conference is part of the college's commitment to offering current research in practical contexts to both practitioners and producers. Your partnership in this educational process with us ensures improved management, healthy herds and a safer food supply.

Over the past year the private-public partnership at the Dairy Education Center has continued to flourish and we are very pleased to have this wonderful collaboration. In addition, I would like to highlight that Dr. Erin Royster joined our dairy team earlier this year. She will be working closely with the VDL's Udder Health Laboratory and will be providing her expertise in the assessment of parlor systems. The research of the members of our dairy group is also continuing to grow in the areas of lameness, reproduction, calf health, udder health, organic dairying and stockmanship.

We are thrilled to offer you a fabulous program covering an array of the latest applied research which features leading dairy industry speakers from across the United States and Canada. Joining this roster of presenters is a group I am especially proud to call my colleagues. Our dairy faculty and graduate students here at the University of Minnesota will further enrich the program by presenting their most current research.

In addition, I want to thank the sponsors and exhibitors of this annual conference. Your support makes this educational exchange possible. We especially appreciate the interest you take in our students' research, education and careers. I am fortunate to see the high level of quality in students entering the field of food animal veterinary medicine today and your mentorship and support of these students is critical to the industry.

And finally, a special thank you to Dr. Riki Sorge for her committee's steadfast and visionary leadership of this conference. The conference's scientific program remains vibrant and timely due to the attention and involvement of our entire dairy faculty here at the University of Minnesota's College of Veterinary Medicine.

Thank you for joining us.

Sincerely,

Trevor R. Ames, D.V.M., M.S., Diplomate ACVIM
Dean, College of Veterinary Medicine
University of Minnesota

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Minnesota Dairy Health Conference

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Economics of Culling

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Culling is an inevitable event in every dairy cow's life (in this context culling includes death on the dairy). Industry-wide herd turnover rates (percent of the adult inventory on a dairy that leaves within a year) certainly varies between farms. The differences between farms are due to a complex mixture of management, biology, policy, and economics (both real economics and farmer perceptions). There are also differences in industry-wide culling rates between countries. The differences between countries seem to be driven by industry management decision practices regarding raising females for beef, tolerance of low producing cows, the value of animals at slaughter relative to the cost of rearing replacement heifers and the survival of young females to calving age and, very importantly, by the margin between milk prices and feed cost.

Total U.S. national herd inventory of milking cows has been remarkably stable for the last decade or more, hovering slightly above 9 million cows. The average herd turnover rate on dairies in the United States is currently roughly 37 percent of the herd in a typical year. This number is driven by many factors and certainly varies farm to farm and year to year on a particular farm, but viewed from a national perspective, the single most important factor that drives the national cull rate is the number of available replacement heifers. As dairies do a better job of keeping heifer calves alive and of raising and breeding heifers, more heifers are available as replacements and one should expect the national cull rate of dairy cows to increase. Similarly, improved reproduction (shortened inter-calving interval), will have produce a slight increase in calves born per cow per year and will also impact the supply of replacement heifers. Notably, the wider use of sexed semen will also increase the number of replacements available unless producers compensate by breeding some cows with non-dairy semen and thereby hold total heifer births steady.

Prices of heifers sold in the open market has been increasing steadily for years, but recent increases have been particularly notable. Prices for selected markets as reported by Progressive Dairyman magazine for May 7, 2014 show that purchase price of a new Holstein heifer is about $2,000 across the United States.

Progressive Dairyman Market Watch			
7-May-14			
	top springer	top average	medium Holstein springer
Midwest	2,345	2,024	1,521
Minnesota	2,275	1,850	1,750
Wisconsin	2,800	2,500	1,650
Michigan	2,000	1,400	850
Missouri	2,350	2,150	1,250
Minnesota	2,300	2,219	2,103
East	2,038	1,838	1,400
New York	1,800	1,600	1,250
Kentucky	2,075	1,850	1,350
Pennsylvania	2,200	2,000	1,650
Georgia	2,075	1,900	1,350
West	2,301	2,104	1,840
Colorado	2,800	2,685	2,240
Washington	1,800	1,667	1,200
Idaho	2,490	2,360	2,157
Utah	2,140	1,959	1,993
Washington	2,175	1,800	1,600
California	2,400	2,150	1,850
overall	2,245	2,006	1,616

The cost of replacements on a dairy typically ranks third if properly accounted for, exceeded only by the cost of feed and labor. A fairly simple spreadsheet can estimate the cost of replacing cows with a new purchased heifer. In the example shown here, the annual cost of replacements on a dairy with a 33% annual exit rate, $2,000 nominal purchase price for a pre-fresh heifer and $900 cow cull value is about $500 per cow per year, or about $1.40 per cow per day. Viewed in terms of milk production, at $20/cwt for milk and $6 for the cost of feed to support a marginal cwt of milk production, it takes about 12 pounds of milk per cow per day to pay the costs of the replacement program. Farms that raise their own heifers should consider the value of their home-raised heifers to be what they could sell them for. If they can raise them for less than that price, then they are profitable heifer raisers. If they spend more than the market price to raise a comparable heifer, then their heifer rearing enterprise loses money.

	A	B	C	D	E	F	G	H
1	Cost to bring a productive heifer into a dairy							
2								
3	505	annualized payment to replace cows						
4		$ 1.38	cost per day of adult life		$ 20.00	milk price/cwt		
5		11.6	lbs milk per day to pay		$ 6.00	marginal feed cost/cwt		
6					85%	% herd milking		
7	$ 1,376	cash cost for a productive heifer (cost - cull cow income)						
8	$ 2,213	cost to bring a productive heifer into the herd						
9		5.0%	cost of cow loans (interest rate per year)					
10		$2,000	purchase price of the new heifer/replacement					
11		2.0	months before the heifer calves					
12		$ 50	pre-fresh carrying costs of a new heifer / mo					
13		6%	% of heifers culled in early lactation					
14			$ 700	cull value				
15		1%	% dead in early lactation					
16		7%	% heifers that don't enter milking string					
17		$ -	cost of disposing of a dead heifer					
18		$ -	net income from heifer culled in early lactation					
19	$ 837	effective salvage value						
20		$ 900	cull price when sold					
21		7.0%	probability of the cow dying on the dairy					
22		3.0	average life span of a cow (years)					
23			33%	average annual herd turnover rate				

Large mostly western dairy accounting firms publish income statements for client dairies and typically break out the cost of replacements as separate line items on the report. These estimates are likely conservative, since some costs actually spent on heifers are bundled elsewhere in the accounting (machinery, utilities, etc. depending on the operation). For 2011 – 2012, the cost per cow for replacements was about $250.

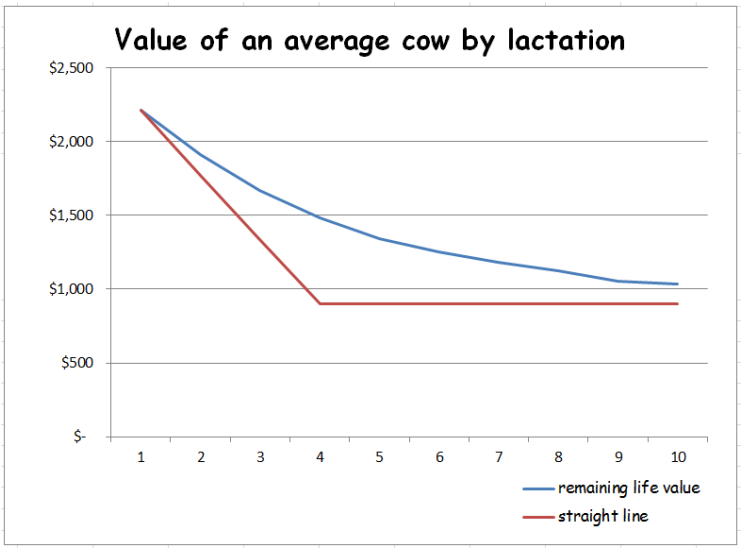
Moore Frazer replacement costs: large, western dairies

	2011	2012
region	replacement cost per adult cow	replacement cost per adult cow
Southern California	$ 316	$ 316
San Joaquin Valley	$ 259	$ 250
Kern County	$ 259	$ 253
Arizona	$ 265	$ 221
Idaho	$ 226	$ 220
New Mexico	$ 222	$ 159
Texas Panhandle	$ 269	$ 230
Pacific Northwest	$ 291	$ 260
average	**$ 263**	**$ 239**

Another approach to this question would be to simply calculate the annual depreciation of a cow based on the cash costs of bringing in the replacement and selling the slaughter cow (adjusting for death loss as above). For the same input numbers as above, this would look like the following and the estimate falls between the first spreadsheet estimate and the numbers from the accounting firm.

Straight line depreciation estimates of cost of replacements on a dairy	
$2,213	cost to bring a productive heifer into the herd
$ 837	effective salvage value
1,376	loss of value across the average cow's life
3.0	average life span of a cow (years)
$ 459	annual cost of depreciation for a cow

The depreciation approach assumes a straight line depreciation made at the start of the replacement's first lactation. Built into the example model is the presumption that the cow will last for 3 years. Some cows don't last that long, but some survive and produce for more than the average 3 lactations (actually about 2.7 in the U.S.). This means that some cows do not depreciate in a straight line fashion. They lose value more slowly than predicted at the start of their adult lives. A more complete model adjusts their value based on their expected lifetime production at a given point in their lives. Thus a cow starting her third lactation can be expected to have a better than zero chance of surviving that lactation and has more value than a straight line expectation would have predicted at the start of her adult life. For the example used in this calculation, a cow starting her fourth lactation is not worth only beef value ($900 in the example); she is worth close to $1,500. The slower rate of loss of value is driven by the conditional probabilities of being culled in any given lactation. Herds with lower culling rates of older cows retain those cows' value better than herds with high cull rates in older cows.



Thus viewed from an economic perspective, there is a significant advantage if a cow's productive capacity can be protected, she can be reliably be re-bred, and she survives into later productive lactations. Older cows in general make more milk than younger cows and if a cow has more than the average number of lactations her cost as a replacement can be spread over more total milk production while she is part of the dairy's herd inventory. Events and conditions that reduce her productivity (milk production) or longevity reduce her time in the herd and thus are to be avoided where practical. Diseases may impact either or both aspects (productivity and longevity) to a variable degree, but the impact on increased culling is often a major part of the cost of diseases. Poor reproductive performance, mastitis, and lameness are perhaps the most notable problems that impact the dairy by increasing premature culling.

At first blush, it certainly seems that a dairy should strive to reduce culling rate to reduce the cost of replacements per cow per year. Using the same inputs as the first spreadsheet, except using a 25% annual cull rate instead of a 33% cull rate, the results look desirable. Replacement costs drop from $505 per cow per year to $388; a "profit" of $117 per cow per year!

Cost to bring a productive heifer into a dairy				
388	annualized payment to replace cows			
	$ 1.06	cost per day of adult life	$ 20.00	milk price/cwt
	8.9	lbs milk per day to pay	$ 6.00	marginal feed cost/cwt
			85%	% herd milking
$ 1,376	cash cost for a productive heifer (cost - cull cow income)			
$ 2,213	cost to bring a productive heifer into the herd			
	4.0	average life span of a cow (years)		
		25%	average annual herd turnover rate	

One should view this kind of calculation with a large dose of healthy skepticism. This extra "profit" is true only if the cow that was not culled has retained her value, i.e. has remained productive, avoided repeated bouts of mastitis, is not lame, and continues to breed back, etc.

Maximizing the returns from a slot on the dairy:

Culling decisions are not made in the aggregate for a farm; the decision to cull cows is made on a cow by cow basis. The herd's annual cull rate is the result of a series of individual cow decision. Since all cows are ultimately culled, the decision is really a largely economic decision to replace a "used cow" (one that has lost value) with a "new cow" (one that will make more profit for the dairy in the long run than the culled cow). Businesses make these kinds of decisions routinely as they decide to replace capital assets (taxi companies replace old taxis, construction companies replace old backhoes, restaurants replace old stoves). The question in

each a case is the same. For the dairy, the question is: "would the dairy's long term profit be greater if this individual cow stays or would the long term profit be greater if she were replaced with a new milking heifer? (It is NOT just the next day's milk production and profit, but rather long term profit that matters.)

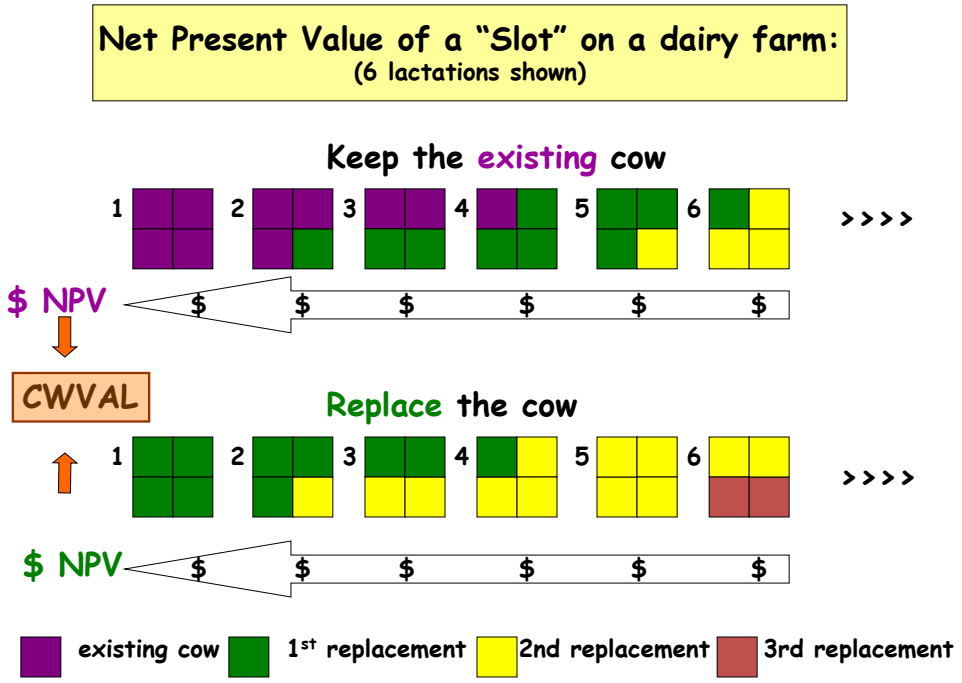
To answer that question, one ideally needs an answer to the question "What is the economic value of a cow on a particular dairy"? This is perhaps best considered by setting the cow herself aside for a moment and thinking in terms of the "slot" on the dairy she occupies. A "slot" is the capacity of the dairy to house, feed and otherwise care for a milking cow. The number of slots on a dairy may be defined by actual physical spaces (tie stalls or stanchions) or by a more conceptual capacity defined by bunk space, milking parlor capacity, land use permit restrictions, or farmer preference. If one accepts that a farm will have a certain inventory of milking cows, then a "slot" is one of those spaces in the inventory. The current cow in that slot will produce milk and consume feed and over time will experience an increasing risk of being replaced until finally she is removed and a new first lactation heifer fills the slot. The replacement then milks and eats, is replaced, etc. Each day out into the future, the slot will produce a certain amount of milk, consume a certain amount of feed and earn a certain amount of income over feed costs. On some particular day, the slot will also incur the cost of replacing the existing cow. The economic value of the slot is the net present value (NPV is the time discounted value) of that future stream of incomes over feed costs and replacement costs for that slot. This concept assumes that the other important costs of running the dairy or caring for a cow are generally independent of which cow is in the slot. While not strictly true (a particular cow may cost more for disease treatment or be bred with more expensive semen) this assumption is fairly robust in terms of herd level economic modeling.

For example, if the current cow in the slot is a young cow that produces well above the herd's average, then the NPV of the slot is enhanced by her presence in it. If she is a poor producer, then she detracts from the NPV of the slot by being in it. Cows that are pregnant (less likely to be culled) are more valuable than cows that are not pregnant. The current economic value of a cow ("cow value") is the NPV of the slot with her in it, minus the NPV of the slot were it instead occupied today by a new "typical" replacement heifer on that particular dairy (including the economic costs of bringing the replacement into the herd).

Given this conceptual framework, the cull decision is essentially a question of trading the existing cow in the slot with a new replacement, while incurring the costs of purchase and earning the beef / salvage value of the exiting cow. Neither the current cow nor the replacement heifer will remain in the herd forever. Another replacement animal will eventually replace either one. The most critical time period in terms of calculating this comparison in values for the slot between the two animals is the next several years and each animal's milk production across that

period. The replacement cost will inevitably be incurred some time in either case. It is a matter of the timing of those replacement costs, not whether they will occur.

Graphically, the concept looks like the following. At any time, a slot on a dairy has a predicted future given the particular cow filling the slot. If she stays, one can model the future milk income, feed cost, and future replacement events that will happen in the slot, with the (purple) cow staying for the moment but in the end being replaced at some series of possible future times. Alternatively, the cow can be replaced today with the dairy's average replacement heifer (green). This latter point is important. The long term profit of replacing the cow today depends on the dairy's own predicted production and costs for an average replacement heifer on that dairy.



Thus there are two possibilities for each future lactation: a future with the existing cow retained in the slot (at least for the moment) and a future with a new replacement heifer. Both lactation series can calculate the income over feed costs depending on the cow in the slot and her predicted production and the cost of and probability of a replacement event. This string of "income over feed and replacement costs" can be discounted back to present time values and summed. Each sum is then the predicted financial future for the slot, either with or without the existing cow. The difference between the two NPV (net present values) is the relative advantage (or disadvantage) of retaining the existing cow in the slot, her cow value (COWVAL). This number can be calculated in any herd that uses DairyCOMP as its herd software if the input parameters to the model are properly set up in the program.

A cow's value in comparison to a potential replacement fluctuates with milk production and price, slaughter value and replacement prices and depends as well on feed prices and several other variables, notably on her risk of being culled (sold or dead) in each lactation on that particular dairy. The decision to cull an existing cow or leave her in the herd also may be influenced by the dairy's supply of replacements and the dairy's willingness to purchase replacements if there are none available on farm. Of these factors, milk price is most important. As milk price **increases**, the value of an existing cow **decreases** in relation to the replacement heifer. This may not be intuitive, but it derives from the fact that cow's value is a **difference** between the current cow and her potential replacement. At high milk prices, the replacement does not need to be that much better than the current cow to justify incurring the expense of earlier replacement. Translated into farm policy, this means that if high milk prices are anticipated to be higher over the next year or more, then the dairy should cull for production more aggressively.

High producing cows hold their high value until some misfortune either reduces production (age or disease) or requires her removal (injury, failure to conceive, abortion, or death). Genetically poor producing cows have a low value essentially from the outset. Many should be culled as soon as their production deficiency is reliably identified.

Cost of Culling

When considering the cost of culling, there are actually three related questions one could ask:

1. What is the cost of culling a cow at the end of her problem-free productive life after she has naturally declined in production with advancing age such that she has lost enough cow value to make it worth replacing her?
    - This would be the ideal circumstance and some cows actually achieve this, but most do not.
        - The cash costs of such an event would be the cost of the new replacement (all factors considered) minus the money earned from sale of the cow for beef.
        - The economic cost of such a cull would be a tidy zero. The cow's cow value would have declined to being equal to the value of the new heifer in terms of future impact on the slot.
2. Far more realistic: What is the cost of "prematurely" culling a cow? This is, what is the cost borne by the dairy because a cow has lost her future value to the dairy sooner than one might have desired because she got mastitis or other illness, remained open, went lame, got injured, etc. and the better economic decision was to replace her?
    - The cost now is the difference between her value had she not suffered one of these value reducing events and her salvage value as beef (or zero value if she died). This is the stuff of calculation of the cost of culling for diseases. This is the loss that all dairies try to avoid by taking good care of their cows, managing

transition, cow comfort, foot trimming, teat dipping, earnest estrus detection or synchronization, etc.

- The simplest approach to answering this question is to use some version of the cow's average depreciated value given her age and the herd's average production for cows like her minus the beef price received.

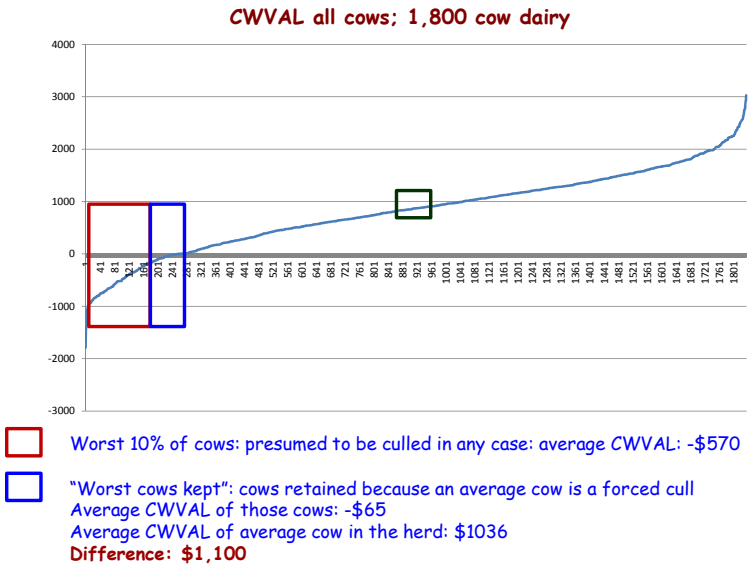
3. What is the cost of NOT culling the worst cow left in the herd? Said another way, what is the cost to the dairy of keeping the "worst kept cow"?
    - This is typically a cost that is invisible to the dairyman, but on many dairies it is a very large cost. This cost generally derives from the dairy's desire to reduce their cull rate for what seems like good economic reasons and/or the dairy's lack of adequate replacements and hesitance to purchase replacements in the open market.

Estimating the cost of keeping the "worst kept cow"

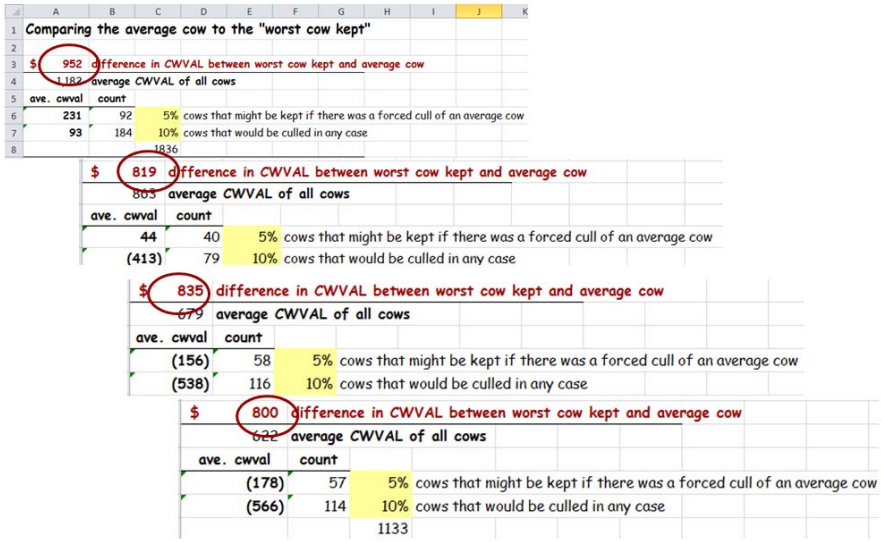
In the best of circumstances, the cost of keeping the "worst kept cow" on a dairy would be calculated using DairyCOMP to calculate each cow's COWVAL and simply finding the worst cow that was not culled. Her negative COWVAL would be the estimate of the cost of the mistake of keeping her.

In practice on many dairies, the reason that a "worst kept cow" is kept is that another better cow suffered some event that led to her being culled and the worst kept cow was kept instead. The economic impact of that event and that decision could be estimated by calculating the difference between the value of an average cow in the herd (this presumes the bad event happens to an average cow) and the value of the worst kept cow.

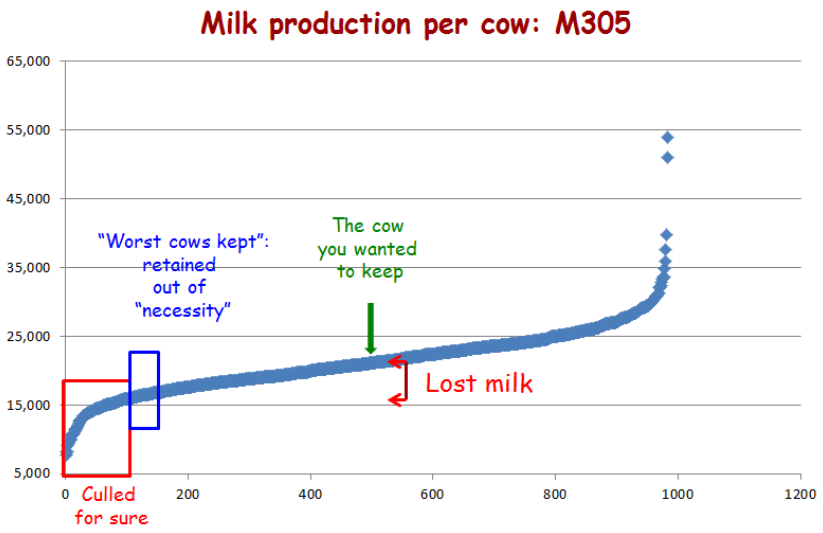
Graphically, this could be approximated (and calculated) as follows:



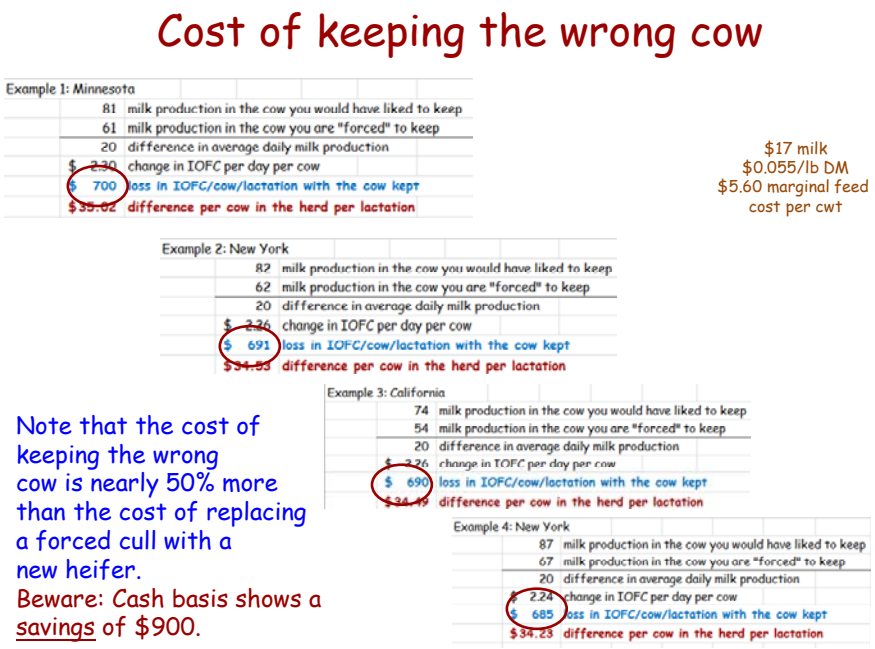
The graph shows the distribution of COWVALs across all of the cows in a large Holstein dairy. Some cows have very high COWVALs and some have negative COWVALs. The average cow in the herd has a COWVAL in this example of about $1,036 (green box). If one assumes the worst 10% of cows will be culled in any case (red box) and then calculates the average COWVAL of the cows between the worst 10% and the worse 15% of the herd, their average COWVAL is -$65 (blue box). So if a calamity happens to an average cow in the green box and she is culled and instead a cow in the blue box is retained, the economic impact of those circumstances is ($1,036 – (-$65)) = a loss of $1,100 to the dairy. It is very expensive to keep a bad cow just because you had to "spend" a replacement to accommodate culling an average cow that had to be culled. The same calculation on four large Holstein dairies shows that keeping the "worst kept cow" is a mistake that cows roughly $800 or more:



If the dairy does not have access to DairyCOMP and COWVAL, an approximation of the same idea can be calculated based on the distribution of actual milk production for cows. Using the same approach of assuming the worst 10% of cows will be culled in any case and comparing the production of the next worst 5% to the production of the average cow, the cost of retaining a "worst kept cow" can be estimated.



Using the same four example large Holstein dairies:



In these examples, the cost of keeping the "worst kept cow" is on the order of $700 loss compared to biting the bullet and buying a replacement and culling her. These numbers are in the same general order of magnitude as the values calculated using DairyCOMP. In either case, the loss from keeping this poor cow may look like a positive cash event (the dairyman does not need to buy a heifer), but the real economic event is a very significant loss.

Conclusion

The issue of culling and economics is complex and significantly dependent on what question one asks and the economic conditions and constraints operating at the time of the decision to cull or keep a cow. In general:

1. Replacement costs are a large part of the operating costs of a dairy and heifers are currently very expensive. Thus it makes sense for dairies to try to reduce the need to replace cows by taking excellent care of the cows they have.
2. Keeping poor cows for the sake of lowering a dairy's cull rate is a very costly mistake. Most dairies should cull more cows, even while working hard to reduce the need to do so.

The financial objective that relates to culling is not simply a low cull rate. The financial goal is to maximize milk income over feed and replacement costs from each slot on the dairy.

Vaccination of transition/adult cows, with special focus on respiratory disease vaccination

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Immunity in transition cows

It is well known that cows in the transition period experience significant physiologic, metabolic, and immunologic stress[7,10,13]. If not managed, these stresses can impair productivity and contribute to the development of disease that can have serious impact on the cow's quality of life, perhaps even leading to culling or euthanasia. Specific impacts on the immune response have been characterized; some of the most important are decreased response to vaccination, likely resulting from decreased lymphocyte function, and decreased function of neutrophils, which are the cells that first defend against infection. Thus, vaccination of cows in the transition period is unlikely to be as effective as vaccinations given at other times, although field trials are needed to clarify the practical importance of this, because useful immunity can be induced in cattle vaccinated 30-60 days post calving[3]. Decreased neutrophil function is likely a leading factor contributing to the development of infectious diseases such as mastitis and metritis in the transition period. Nutritional deficiencies or imbalances related to the transition period are important causes of immune dysfunction[7,13]. At this time it appears that the leading factors contributing to immune dysfunction are increased blood ketones and NEFAs, and relative deficiency of calcium. Deficiencies of vitamin E, selenium, zinc, and copper are also associated with depressed immune function in transition cows[7]; however, supplementation with these vitamins or minerals in excess of required amounts does not reliably improve immunity[6]. Careful attention to management of transition cows to prevent negative energy balance and hypocalcemia, and formulation of rations to ensure adequate concentration of vitamins and minerals, is warranted because these factors impact immune function and overall cow health.

Respiratory disease in adult dairy cows

Although anecdotal reports indicate that adult dairy cows can experience outbreaks of respiratory disease with high morbidity and an important impact on milk production, the epidemiology of respiratory disease in adult cows has not been well characterized. Surveys of U.S. producers carried out by the USDA National Animal Health Monitoring System indicated that respiratory disease is the cause of 11.3% of deaths that occur in adult dairy cattle. The relative lack of information regarding respiratory disease in adult cows is likely due to the fact that other diseases that affect reproductive performance and milk yield are of greater economic significance in this class of cattle. However, the few published descriptions of respiratory disease outbreaks confirm that the problem can on occasion be of major importance to individual herds. The risk

factors for respiratory disease in adult dairy cows have likewise not been described, but it is reasonable to surmise that risk factors important for other classes of cattle (e.g., feedlot cattle and dairy calves). Important risk factors that may contribute to the occurrence of outbreaks of respiratory disease in adult cows include introduction of new cattle into the group, contact with neighbor cattle across fencelines, or contact with youngstock; all of these groups could be a source of exposure to contagious respiratory pathogens. Recent transportation and poor air quality in housing are likely also important risk factors. Negative impacts of transition period events on immune responsiveness may also increase risk of dairy cattle for BRD; this may explain common anecdotal reports of dairy cows developing respiratory disease after calving. While the cost of respiratory disease in adult cows has not been estimated, the fact that respiratory disease accounts for approximately 10% of the adult cow deaths indicates that veterinarians and producers should be alert to signs of respiratory disease in adult cows so that timely treatment is implemented. Vaccines against common viruses that can contribute to respiratory disase (BHV-1, BVDV, BRSV, and PI3V) should be included in the annual vaccination protocols so that cows maintain immunity to protect themselves and also the calves that consume their colostrum.

Some research has indicated that cows can benefit from vaccination against respiratory pathogens. In one U.S. study, first parity cows that were given a 4-way vaccine containing BHV-1, BVDV, PI3V, and BRSV produced significantly more milk (3.1 pounds per day) in the first 21 weeks of their lactation than cows receiving a 3-way vaccine the effect of vaccinating adult dairy cows against respiratory pathogens[4]. Researchers in Sweden found that herds with evidence of recent BRSV infection produced less milk (1.3 pounds per day) than herds without evidence of BRSV infection[1], which supports the concept that vaccination to prevent BRSV infection could improve productivity of dairy cows. And a recent report indicated that first lactation milk production in Dutch dairy herds was significantly greater in herds that administred BRSV vaccines[9]. Taken together, this research suggests that at least BRSV vaccination may improve cow productivity, presumably by decreasing respiratory disease, because BRSV does not cause disease outside the respiratory tract.

Vaccinating cows to improve concentrations of antibody in calves

Vaccinating cows late in gestation is sometimes considered as a mechanism to improve calf immunity by increasing calf serum concentrations of passively transferred antibody. This is rational because antibody from the cow's serum is transferred into colostrum in the last month or two of gestation. If a cow's serum antibody titers are increased late in gestation, it follows that colostral antibodies should be increased, and serum antibodies in the calf consuming the colostrum should be increased. While this train of reasoning is logical, relatively little research has confirmed whether vaccinating cows late in gestation improves calf antibody titers, and less has confirmed whether the practice improves resistance of calves to disease. Vaccination of

dairy cows with a commercial clostridial vaccine at 6 and 2 weeks before calving significantly increased anti-clostridial antibody titers in calves at 3 days of age[5]. Similarly, vaccination of dairy cows with a *Mannheimia haemolytica* vaccine at 6 weeks and 3 weeks before calving increased antibody titers to *M. haemolytica* in calf serum at 2 – 7 days of age[8]. In a third study, vaccination of beef cows with a *M. haemolytica*/*H. somni* vaccine at either 4 weeks before calving or 7 and 4 weeks before calving increase serum antibody titers in calves at 28 day of age[12]. Although all of these studies showed that vaccination of cows in late gestation increased serum antibodies in calves, none evaluated whether disease was decreased in calves. A small study evaluating whether a single dose of inactivated multivalent viral respiratory vaccine given to dairy cows at dry off would increase antibody titers in calves at 2 – 7 days of age showed no effect of vaccination[10]. Two trials evaluated vaccination of late gestation cows to decrease calf diarrhea, with one showing a beneficial effect[2], and one showing no effect[14]. In summary, a small number of studies have shown that vaccinating cows late in gestation can improve antibody titers in calves; but more research is necessary to confirm that the practice can decrease disease in calves.

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Five Key Factors for Transition Cow Success

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Abstract

Field studies of transition cow management using Transition Cow Index ™ as the outcome variable have shown that housing constraints related to cow comfort are the major risk factors for fresh cow health in freestall dairies today. Key factors to improve fresh cow health are provision of sufficient bunk space so that all transition cows can eat simultaneously, minimizing social stress or the need to establish social rank during the prepartum period, provision of soft bedded surfaces for standing and resting, and sizing of stalls and packs to facilitate the motions of lying and rising for large, mature cows, and a high quality program by herd personnel for early identification of fresh cows that need medical attention.

Introduction

The phrase widely attributed to the management writer Peter Drucker, "If you can't measure it, you can't manage it" seems to have been especially pertinent to the development of our transition cow management advisory programs. Looking back, the development of the measurement tool Transition Cow Index™ (TCI) [1] has made possible our studies of transition cow management in the world of commercial dairies. It has allowed us to evaluate associations between housing systems and fresh cow health that are not financially possible for research institutions. Prior to our use of TCI, our clinical group would investigate complaints of "too many DA's, deads, RP's, etc" using primarily ration analysis techniques. Essentially, we were investigating poorly defined problems using very narrowly focused tools.

Our approach began to change following a field survey in Wisconsin using TCI which we conducted in 2005. TCI is a patented index where an expected first test-date milk yield is predicted for each cow in her second or greater lactation based upon the cow's previous performance, and that predicted value is subtracted from her actual first test-date performance. In this study, TCI values are expressed in units of first test-date 305-day projected milk yield. While TCI is calculated at the individual cow level, herd average TCI values vary greatly between herds and reflect overall fresh cow health and herd management of the transition programs. We surveyed the transition management practices of 50 Wisconsin freestall herds with an average size of approximately 600 cows. The herds represented a stratified random selection of herd average TCI values; meaning that equivalent numbers of herds were selected from each TCI category, i.e., <-1,500 lbs, -1,500 to -500 lbs, -500 to +500 lbs, etc. Another field study of transition cow management practices was conducted in 22 open lot dairies in the Southwest USA in the summer of 2009. From these surveys, a modest number of management practices have

emerged as associated with improved herd TCI scores. Knowledge of these key transition management practices has informed our investigation services, our education programs for veterinarians and veterinary students, and an ever-increasing planning service for dairies as they construct new facilities.

The key factors associated with improved herd average TCI scores relate to provision of sufficient bunk space so that transition cows can eat simultaneously when fresh feed is delivered, minimizing social stress or the need to establish social rank during the prepartum period, increasing cow comfort and minimizing lameness with deeply bedded stalls or packs and provision of ample space within the stall to lie down and facilitate rising, and an effective process to promptly detect fresh cows in need medical attention.

While ration formulations remain a part of our investigation services, variation in dry cow and close-up ration formulations in our survey work has not been associated with herd TCI averages. It would be a mistake to infer that ration formulations do not matter. Rather, it may be that the ration formulation services provided to larger herds are generally of good quality and variation between well formulated transition rations is not a major determinant of overall transition success in our industry today.

Bunk space

Sufficient space at the feeding fence for all transition cows to eat simultaneously appears to be the most important determinant of transition cow performance in our current industry. In very practical terms, we are recommending a minimum of 30 in of bunk space per Holstein cow in pre-fresh and post-fresh pens for a 90-min period after fresh feed is delivered and after every milking. A discussion of the studies that support this recommendation has been presented previously [2].

To determine feeding space/cow, it is important to focus on length of bunk as opposed to counting self-locking stanchions or headlocks. Headlocks come in a number of widths including 24, 27, and 30 inch intervals between each unit. Our video studies show that lactating Holstein cows fill a row of 24 in headlocks to a maximum of 80 % at peak feeding periods. This 80% maximal fill rate occurred in two and three row pens, each with various stall stocking densities, suggesting that the finding was independent of the number of cows per headlock. Converting these numbers, it suggests that lactating Holstein cows will voluntarily fill a bunk at a spacing of one cow per 30 inches. It is likely that pregnant prepartum cows would take even more space than lactating cows.

These recommendations for 30 in of space assume that the pens are equipped with lockups or other vertical dividers between feeding spaces. If the cows are fed at a post-and-rail feeder, additional space should be provided as dominant cows appear to clear subordinates sooner in these situations [3].

While we focus the most attention on bunk space in the close-up and fresh pens, the actual number of cows in these pens usually changes every day. If cows are transferred into the

close up pen on a weekly basis, and if cows move to calving pens on a daily basis, there will be wide weekly swings in the number of cows in the pen. The opposite dynamics characterize the fresh pens. In addition, there will usually be seasonal changes in stocking pressure that track seasonal infertility and recovery by 10 months. Because of these pen dynamics, it is more useful to focus on the longer term capacity of the pens.

The traditional approach to sizing close up and fresh pens is to calculate the average number of calvings per week by dividing the total number of calvings in the past year by 52 weeks per year. Then the average number of calvings/wk is multiplied by the target number of weeks in the pen. For example, if a dairy has an average of 20 calvings per week and the planned duration of stay in the close up pen is 3 weeks, most planning manuals suggest that the close up pen should be designed to house 60 cows. By definition, pens designed in this manner are overstocked half of the time.

We prefer to build special needs pens to accommodate the surges in numbers of special needs cows. Based upon a review of a number of Midwestern herd records, we have recommended sizing close-up and fresh pens for 140% of the average number of calvings. In the example from the paragraph above, we would recommend provision of not 60, but 84 stalls in the prefresh pen with an available bunk that is 240 feet in length. Sizing these pens on this basis will mean that these pens are overstocked less than 10% of the time. There are also times when pens sized on this basis appear to be substantially understocked, or as some would say, "grossly overbuilt". Our estimations of the impact of this practice suggest that this makes economic sense. Each stall and headlock in a prefresh pen has an impact on the start of somewhere between 10 to 15 lactations each year. Because of the multiplier effect on the start of the lactation of so many cows, it is critical that these facilities are excellent and available to all cows.

Pen moves and social stress versus stable social groups

Each pen move requires that a cow familiarize herself with the surroundings, as well movement into a new social group also creates stress as the cow establishes rank within the group [4]. The first 2 days after entry into a new social group are characterized by a dramatic increase in the number of agonistic interactions, most of them physical [5]. If no additional new cows enter the pen, the group becomes relatively stable. More recent work with mid-lactation cows has shown reduced time spent eating, increased feed evictions, and reduced milk yield following a pen move [6]. Minimizing the number of regroupings through the transition period is consistent with successful transition programs. In most situations, steps to reduce any moves will result in improved transition performance.

A concept of a *social turmoil profile* of a pen has been described [2]. In pens where cows enter at intermittent intervals, like a week or more, extended stays in such pens are considered more desirable than in pens with entries and departures every day. Daily entry pens are considered to be in constant social turmoil and every effort should be made to minimize the time that prepartum cows spend in these pens.

Cows are social animals. Isolation from the herd creates stress for a cow and separating a single cow into a separate calving pen for more than a couple of days appears to be a practice with high risks for fresh cow health.

Dry and Close-Up Pens

The traditional close-up pen is based upon cows entering the pen approximately 3 weeks prior to due date. For reasons of convenience, cows are separated from the far-day pen and moved to the close-up pen once or twice each week. In some systems, the cows deliver their calves in the close up pen, while in other systems they are removed to calving pens at various times relative to delivery.

Studies on the effect of the number of cows moved at one time have been conducted. Generally, movement of single animals should be avoided as it is believed that familiarity and social bonds among 3 to 5 moved animals may reduce the social stress of integrating within a larger group [7]. Sowerby and Polan did not find significant production differences between groups where between 2 and 14% of the cows were transferred at one time between lactating groups [8]. For reasons of both increased numbers of transferred cows and a decreased proportion of high turmoil days, a weekly move policy would appear to be preferable to more frequent entries.

Regardless of the frequency of new cow additions in our traditional close-up pen, each cow remains in a dynamic social system for a period of several weeks before calving. New arrivals tend to be involved in more agonistic interactions than the current residents of the pen. Brakel and Leis showed that during the first day after regrouping, the average moved cow was involved approximately double the rate agonistic interactions of the resident cows in the pen [9]. Moved cows will tend to maintain their rank relative to the other cows that were moved [10], but occupy a low rank with respect to the resident cows, even first-lactation, that already occupy the pen. However, the situation is sometimes more complex. Hook observed a complete reversal of the social rank of a group of six heifers with the removal of the high rank individual and the simultaneous introduction of a new heifer [11].

As we began applying these concepts to transition cow management, we proposed that the optimal transition cow pens would be based upon an *all-in* pen where a cohort of cows due to calve within a short period of time, such as a 7 to 14 day window, are assembled with no further additions through the calving process [2, 12]. The stable social group could be assembled at the time of the traditional close-up period of 3 weeks prior to calving date, or the groups could be assembled at dry off. In either system, social rank would be established in the first days after the group is assembled, but would be followed by relatively less turmoil in the weeks that precede calving. Depending on the planned duration of the dry period, there could be 4 or more separate cohorts of dry cows in the series of stable group pens. The usual policy would be to periodically move entire pens of cohorts intact into the next pen in order to keep the cows near due date in a location proximal to the calf delivery facilities.

Recent studies have examined the effectiveness of stable social groupings in the pre-partum period with neutral to positive results [13, 14, 15]. Even if there is no measureable positive health benefit, the practice appears to bring with it several benefits for herd management. First, the group is established long before calving date and even cows that deliver their calf a week or two prematurely are well established in a stable situation. Second, it eliminates the additional lockup of dry cows and removal of close up cows from that group. Third, monitoring dry matter intakes of close-up pens becomes more meaningful when the cows within each pen are stable in numbers and stage of pregnancy. Fourth, the size of the active calving group is usually smaller than the conventional 3-week close up group, reducing the size of the pen to be closely monitored for cows beginning to deliver.

In practical terms, even though there is an attempt to develop stable groups at dry off, it is typical to need to make some modest number of transfers between pens. Individual cows may be dried off early or late and may need to be transferred into a pen with cohorts more likely to calve at a similar time. Likewise, as the cows deliver and are transferred out to the fresh cow pen, there will ultimately be a situation where there is a single cows remaining. It is generally viewed as preferable to merge them with the next cohort of cows when two remain in the pen.

Calving Pens

Calving pens can refer to either a pen to which a cow is moved hours before delivering her calf or it could be a close-up pen where cows enter several weeks before their anticipated calving date and deliver the calf within the pen. If the calving pen has a stable social structure (no additions), extended stays are fine. If new cows are continually being added, we recommend that the duration of stay be limited to 48 hr maximum. Clinical data from field investigations by the Food Animal Production Medicine group at the University of Wisconsin show dramatic increases in ketosis and displaced abomasums and early lactation culling of cows that stay 3-10 d in daily-entry group calving pens [2]. When cows are moved to calving pens on a daily basis, they should be selected carefully so that minimal numbers spend more than 48 hr in these high turmoil pens.

It has become common to move cows to calving pens when the feet or head of the calf are showing. Moving cows to calving pens once calving has begun, commonly called “just in time” calving, effectively minimizes the time in high turmoil pens, but presents a new set of challenges. First, it requires round-the-clock labor to check and move cows. Freestall pens can be designed to facilitate this practice with the construction of two-row head-to-tail arrangements of the stall rows. With the tails of all cows visible from the central feed alley, the observer can monitor each cow without walking through and disrupting the pen. Second, workers must be monitored carefully in that they should not move cows into calving pens too early. In a report on moving cows when parturition was imminent [17], cows that were moved when in labor but with only mucus showing had 2.5 times the rate of stillbirths as cows that were moved when the calf’s feet or head were showing. When the close-up cows are in freestalls, there is a tendency of laborers to move cows into calving pens too early. By moving cows into the pens early, fewer

calves are born into the alleys and workers can avoid soiling their clothing when picking up slurry-covered calves. This tension between worker convenience and calf health needs to be monitored and managed in these "just in time" calving systems.

Isolation pens, i.e., box stalls would appear to minimize social turmoil, but cows are social animals and separation from the herd is usually a stressful experience. If cows are moved to individual box stalls for calving, the duration of stay should be limited to a matter of a few hours.

Surface cushion in stalls, packs, and under shades

A loose, deeply bedded surface has emerged in our field studies as a major factor for improving fresh cow TCI scores. In freestall herds, sand based stalls were associated with more than a 1,000 lb TCI advantage over herds with mattress freestalls. Similarly, depth of loose bedding under shades emerged as a risk factor affecting herd average TCI scores in open lot dairies.

There is increasing evidence that locomotion scores increase for a substantial proportion of transition cows [17] and physiological mechanisms have been proposed where the same physiological changes that are associated with the loosening of the pelvis to accommodate parturition also relax the suspensory apparatus of the digit in the hoof [18]. The study of sand and mattress freestalls by Cook et al [19] showed that cows with elevated locomotion scores change their behavior on mattress stalls, but not on sand, may explain the substantial improvement in fresh cow performance on sand surfaces.

Any deep, loose surface will be an improvement over a hard surface. Mattresses covered with modest quantities of shavings or other materials are viewed as average, and any stall surface such as concrete or other firm packed materials covered with modest bedding should be considered a high risk to successful transitions.

Amply sized freestalls, packs, and shades

A deeply bedded pack is the probably the preferred housing for close-up cows in confinement housing. The guideline of 100 sq ft of space/cow [21] includes the bedded area only and assumes that cows have access to an external feeding alley or outside lot. If the feeding area is continuous with the bedded pack, the space should provide a minimum of 120 sq ft/cow with good bedding covering most of the area. The pack should be sized to accommodate surges in cow numbers as discussed in the section on bunk space above.

Prepartum freestalls, in particular, need to accommodate the ample dimensions of pregnant cows and allow for some clumsiness in their rising and lying motions. Stalls for prepartum Holsteins and Jerseys should be at least 50 and 45 in wide respectively [22]. Length is the distance between the outer corner of the rear curb to the point where the stall surface touches the brisket locator. If there is no brisket locator, the total stall length is the stall resting length.

This distance should be greater than 70 and 63 in for Holstein and Jersey cows respectively. Appropriate dimensions have been developed for cows of other breeds and various sizes [21, 22].

Evaluating the potential for *lunge, bob, and rise* should reflect assessments of 3 separate items in a freestall: a brisket locator that does not restrict rising motions including the forward swing of the front foot, freedom from impediments to the forward lunge of the head and shoulder, absence of *bob* zone obstructions, and the neck rail being sufficiently high and forward [21, 22]. For a stall to be considered low risk for Holstein cows, the total stall length should be at least 9 ft long with no obstructions to forward lunge and bob. If the stall is less than 9 ft, but the lower side rail is 11 in above the stall bed or less, it should allow side lunging and is considered an average risk for transition cows. If the stall is less than 8 ft and has obstructions to side lunging, such as lower divider rails greater than 13 in above the stall bed, the stalls present major risks to successful transition performance. Finally, the neck rail should be approximately 48-50 in above the stall surface.

In open lot dairies, transition cow facilities should provide at least 45 square feet of shade per cow with loose bedding at least 3 inches deep below the shade.

Effective screening program for cows needing attention

While difficult to assess, the primary determinant of the fresh cow screening and treatment program is the quality of the people and how much they care for the cows. Facilities that allow easy restraint without exciting the cows is also critical to these programs.

The optimal screening programs appear to use some form of appetite assessment. The practices of the herdspersons of the elite transition programs in our survey study were remarkably similar: delivery of fresh TMR while fresh cows were being milked, palpation of udders for fullness while being milked, observation of cow demeanor as the cows returned to the pen, i.e., does she go to feedbunk or does she lie down, and an assessment of appetite and attitude. Beyond process, the herdspersons in the elite herds knew and cared about the fresh cows under their watch. Effective screening requires both special people and facilities.

Back to the bunk space issue, it requires sufficient feeding space for all cows to eat simultaneously. Cows that do not lock-up, or cows that lock-up with suppressed appetite or signs of depression were examined. Other examination procedures including rectal temperature, observations for vaginal discharge, ketosis, displaced abomasum, lung sounds, etc., were conducted when primary assessments indicated further evaluation.

While formal screening programs in lockups for fresh cows are a desirable practice, the procedure needs to be efficient and not interfere significantly with the daily time-budget of the fresh cows. Screening procedures that lock cows up for a period of 1 hr or less/d are considered optimal. While cows are quite capable of compensating for a 1-2 hr change in routine, if lock-up is prolonged and in association with other stressors, such as overstocking, then the ability of the cow to compensate and *catch-up* on lying time may be exceeded. Cooper et al. showed that when cows were deprived of lying for 2-4 h/d, they only managed to recover approximately 40 % of

the lost lying time by 40 hr after the deprivation [23]. Extended lockup time adds substantially to the stresses of transition.

The location of the screening procedures has a substantial impact on the time constraints. If the cows have access to feed while being examined, feeding and the screening can proceed almost simultaneously. Screening time at a palpation rail, for example, must be weighted as riskier than equivalent time in lockups over feed.

This antagonism between holding time and the thoroughness of the screening procedure puts some severe constraints on the fresh pen.

Disclaimer

Obviously, this paper does not provide a comprehensive listing of risk factors for transition cows. However, the risk factors presented here are considered to be common problems in today's intensively managed dairies and virtually all dairies will realize improved fresh cow health if they correct deficits in the areas discussed in this paper.

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Cow Grouping And Stocking Density During The Dry Period: What Have We Learned So Far?

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Introduction

In spite of the advancements made in transition cow nutrition and management, many herds still have challenges during this critical period in the life of a dairy cow. Dairy cows are genetically driven to produce large amounts of milk in early lactation, and most cows will be in a state of negative energy balance during that time. Anything that affects the cow negatively, such as poor nutrition, housing or management, will exacerbate transition problems experienced by that cow. We have learned of the importance of cow comfort to improve health and productivity in our dairy herds. During the critical transition period, that is even more important.

What has been suggested in terms of cow grouping during the close-up dry period? Based on observations from a large dairy field study, Nordlund et al. (2006) recommended that producers adopt a stable social grouping during the prepartum period to minimize social disruptions. Cows with a similar calving date can be grouped together during the prepartum close-up period and stay in that pen until calving or calve in bedding pack pens. During this time no new cows are added to the pen until all to most of the current animals have calved. One disadvantage of the stable pen management system is the need for additional pens which increases building cost. Cook (2009) recommended sizing the pens to accommodate 140 percent of the average weekly calving rate with the stable pen management. At times, pens will be underutilized while a few remaining cows are awaiting parturition.

What about stocking density? In a study designed to evaluate the effects of a dietary supplement on productive and health parameters of prepartum cows and heifers housed together, it was observed that for every 10 percentage unit increase in stocking density above 80% of headlocks there was a 1.5 lb/day decrease in milk yield among first lactation cows (Oetzel et al., 2007). Based on this and a small number of other studies, a common industry recommendation is to limit stocking density for close-up cows to 80% or providing 30 inches of feedbunk space per cow.

Grouping Management Strategy Study

A study that examined a stable pen management versus a dynamic pen did not find a difference on the number of displacements from the feed bunk, dry matter intake, plasma NEFA concentrations and milk production up to 30 DIM (Coonen et al., 2011). In that study,

approximately one cow was added at a time to a small pen with only 10 cows. Additionally, cows in their study calved in the dry cow pen. It was unknown whether these results would be similar to movements of small groups of cows into a larger pen with cows then being moved to a calving pen as they near parturition (like feet showing or 'just in time' calving), similar to conditions experienced on large commercial dairies. Therefore, we conducted a study to compare a stable social group or all-in-all-out (**AIAO**) during the close-up prepartum period with a traditional pen management (**TRD**) that had weekly entrance of new animals in a large dairy setting.

The study was conducted at a large commercial dairy farm (6,400 lactating animals) in south-central Minnesota. For health and performance data we used a total of 567 primiparous and multiparous non-lactating Jersey cows allocated to 6 replications using two pens at a time, one for each treatment (AIOA or TRD). For the behavior portion of the study we used a total of 224 cows allocated to the two treatments with two replications. Cows assigned to the TRD treatment were moved to the study pen as a group of 44 cows and weekly thereafter groups of two to 15 cows were moved to the study pen to reestablish stocking density (~92% of headlocks). Cows assigned to the AIAO treatment were moved to the study pen in groups of 44 cows, but no new cows entered the AIAO pen until the end of the replicate. At the end of each replicate, a new TRD and AIAO group started but pens were switched.

When cows demonstrated signs of calving, farm personal moved the cows to an individual box stall. Video observation ceased when the cows left the dry period treatment pens. At day 1 post-calving, cows were moved into a freestall pen with 240 stalls and 260 headlocks stocked at 100% based on the number of stalls for 21 days. Plasma NEFA concentration was measured weekly from day −18 (prior to calving) to day 24 post-calving and plasma β-hydroxybutyrate (BHB) was measured weekly from day 3 to 24 post-calving. Cows were examined on days 1, 4, 7, 10 and 13 post-calving for diagnosis of uterine diseases, and had their ovaries scanned by ultrasound on days 39 and 53 post-calving to determine resumption of ovarian cycles.

Average stocking density was reduced for the AIAO (71.9%) treatment compared with the TRD (86.9%) treatment. Treatment did not affect the incidences of retained fetal membranes (TRD = 10.9, AIAO = 11.6%), metritis (TRD = 16.7, AIAO = 19.8%), and acute metritis (TRD = 1.7, AIAO = 3.6%). Concentrations of NEFA (TRD = 80.4, AIAO = 62.9 μmol/L) and BHB (TRD = 454.4, AIAO = 446.1 μmol/L) were not different between treatments. Percentages of cows that resumed ovarian cycles by d 39 (TRD= 70.8, AIAO = 63.1%) and 53 (TRD = 90.1, AIAO = 90.2%) were not different between treatments. Similarly, treatment had no effect on rate of removal from the herd (TRD = referent, AIAO [(adjusted hazard ratio (95% confidence interval)] = 0.85 (0.63, 1.15)) or rate of pregnancy (TRD = referent, AIAO = 1.07 (0.88, 1.30)). Finally, treatment did not affect energy-corrected milk yield (TRD = 75.9, AIAO = 75.7 lb/day).

Behavioral observations showed a treatment × week interaction for mean daily number of displacements from the feed bunk. The TRD treatment had more displacements from the feed

bunk during weeks 1, 3, and 5 ($P < 0.05$) than AIAO treatment, whereas there were no differences between the treatments during weeks 2 and 4. There was a treatment by week interaction for daily feeding times ($P < 0.001$). Cows housed in the AIAO treatment spent 39 fewer minutes per day eating during week 1 than TRD treatment. During week 2 of the study, the AIAO treatment had a 25 minutes/day longer average daily feeding time than the TRD treatment ($P < 0.05$), with a tendency of longer feeding time during week 3 of the study ($P = 0.054$). There were no differences between the treatments in feeding times during weeks 4 and 5. There were no differences in maximum feed bunk occupancy occurring at fresh feed delivery (0500 h) with 64.9 and 68.6% of cows eating at that time for the TRD and AIAO, respectively (Figure 1). In general, the AIAO treatment had a greater percentage of feed bunk occupancy during periods of low feeding activity.

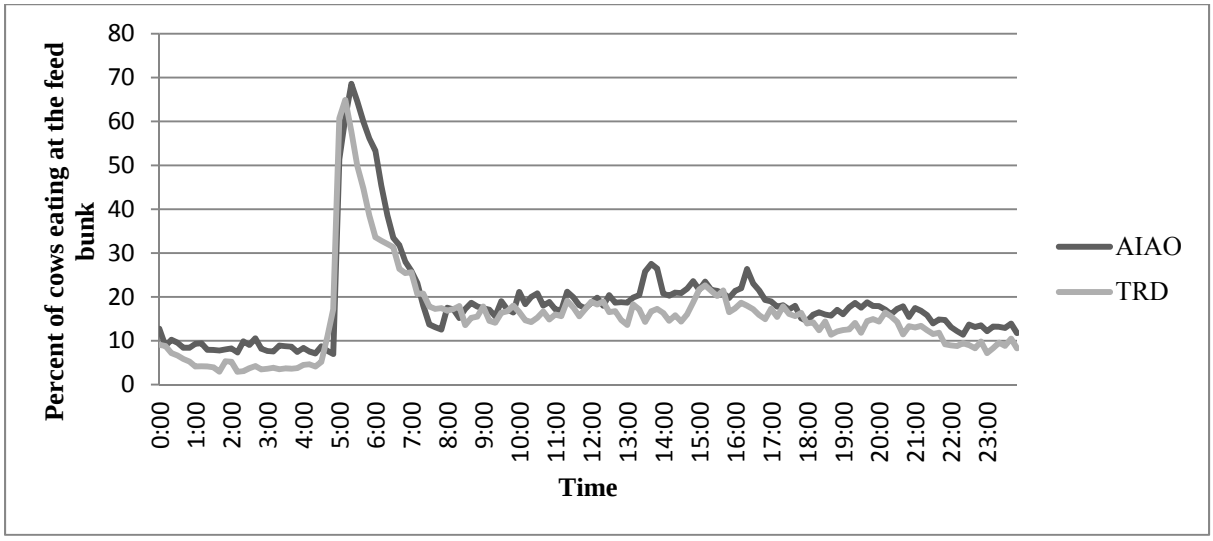

Figure 1. Percentage of cows eating at the feed bunk over a 24-h period for a stable (AIAO, all-in-all-out) or a weekly entrance of new animals (TRD, traditional) pen management during the close-up prepartum period. Significant differences in percentage eating were found for feeding periods 0030-0450, 1320-1330, 1650, 1720, 2200-2210, and 2320-2340 h.

The AIAO grouping strategy had fewer displacements from the feed bunk than the TRD and this was evident during all weeks of the repetition except during week 2 and 4 when the treatments did not differ. Even when accounting for changes in stocking density the AIAO treatment still had a lower displacement rate than the TRD treatment. The AIAO cows spent fewer minutes eating daily than the TRD cows during week 1, whereas having a longer feeding time during week 2.

Our results (with Jersey cows and approximately 92% feed bunk stocking density) indicate the AIAO treatment reduced negative social behaviors and altered daily feeding times. However, the AIAO treatment did not improve health, metabolic, reproductive, or productive parameters compared with the TRD treatment.

Stocking Density Study

We hypothesized that increasing prepartum stocking density would affect behavior and metabolic parameters and consequently affect health and performance of dairy cows in early lactation. The objectives of study were to determine the effect of increasing prepartum stocking density from 80% (**80SD)** to 100% (**100SD**) of headlocks on the day of regrouping on behavior, metabolic, health, reproductive, and productive parameters of dairy cows. We used 324 animals (141 first-calf heifers, 183 cows) for the 80SD treatment and 404 animals (173 first-calf heifers, 231 cows) for the 100SD treatment.

Daily average stocking densities based on number of headlocks (80SD = 74.1%, 100SD = 94.5%) and stalls (80SD = 80.8%, 100SD = 103.1%) were different ($P < 0.01$) between treatments; therefore our goal of a 20% unit difference in stocking density between treatments was achieved.

Incidences of peripartum diseases were not different between 80SD and 100SD treatments (Table 1). Similarly, incidences of DA and mastitis in the first 60 d post-calving were not affected by treatment. Percentages of cows with locomotion score > 2 at 0, 35, and 56 days post-calving were not different between treatments. Similarly, treatment did not affect the likelihood of cows being removed from the herd within 60 d post-calving. The rate at which cows in the 100SD treatment were removed from the herd [adjusted hazard ratio (AHR) (95% CI) = 1.02 (0.75, 1.38)] did not differ from that of cows in the 80SD treatment. The mean intervals from calving to removal from the herd were 258.3 days for the 80SD treatment and 262.5 days for the 100SD treatment.

Body condition score was not affected by treatment. Concentration of NEFA (80SD = 251.5, 100SD = 245.9 μmol/L) was not different between treatments. Similarly, concentration of BHB (80SD = 508.2, 100SD = 490.9 μmol/L) was not different between treatments.

The percentage of cows characterized as cyclic by 35 and 45 DIM was not different between treatments. Similarly, the likelihood of cows being inseminated in estrus and the DIM at first postpartum AI were not different between treatments. The percentage of cows diagnosed pregnant 31 and 66 days after first and second postpartum AI was not different between treatments and the incidence of pregnancy loss between 31 and 66 days after first and second postpartum AI was not different between treatments. The interval from first to second postpartum AI and the DIM at second postpartum AI were not different between 80SD and

100SD treatments. Average daily milk, fat and protein yield from calving to 155 DIM were not different between treatments.

Table 1. Effects of prepartum stocking density (80SD vs. 100SD)[1] on incidence of postpartum health disorders, lameness, and removal from the herd within 60 d postpartum

Items	80SD,%	100SD,%	AOR (95% CI)	*P*–value
Retained fetal membranes	5.1	7.8	1.55 (0.78, 3.07)	0.19
Metritis	21.2	16.7	0.71 (0.46, 1.09)	0.11
Acute metritis	9.9	9.4	0.87 (0.45, 1.66)	0.64
Vaginal purulent discharge at 35 ± 3 DIM	5.8	7.9	1.41 (0.65, 3.05)	0.35
Mastitis up to 60 DIM	2.9	4.6	1.94 (0.70, 5.39)	0.18
DAs up to 60 DIM	1.0	0.7	0.76 (0.10, 5.80)	0.78
Locomotion score > 2 at 1 ± 1 DIM	0.6	0.0	0.26 (0.02, 3.19)	0.27
Locomotion score > 2 at 35 ± 3 DIM	3.8	2.6	0.66 (0.25, 1.75)	0.37
Locomotion score > 2 at 56 ± 3 DIM	3.5	2.1	0.56 (0.12, 2.69)	0.44
Removed within 60 DIM	6.1	5.1	0.84 (0.38, 1.83)	0.63

[1]80SD = cows housed in prepartum pens with 80% target headlock stocking density (38/48); and, 100SD = cows housed in prepartum pens with 100% target headlock stocking density (48/48).

Body condition score was not affected by treatment. Concentration of NEFA (80SD = 251.5, 100SD = 245.9 μmol/L) was not different between treatments. Similarly, concentration of BHB (80SD = 508.2, 100SD = 490.9 μmol/L) was not different between treatments.

The percentage of cows characterized as cyclic by 35 and 45 DIM was not different between treatments. Similarly, the likelihood of cows being inseminated in estrus and the DIM at first postpartum AI were not different between treatments. The percentage of cows diagnosed pregnant 31 and 66 days after first and second postpartum AI was not different between treatments and the incidence of pregnancy loss between 31 and 66 days after first and second postpartum AI was not different between treatments. The interval from first to second postpartum AI and the DIM at second postpartum AI were not different between 80SD and

100SD treatments. Average daily milk, fat and protein yield from calving to 155 DIM were not different between treatments.

The 100SD treatment resulted in a greater number of displacements from the feedbunk than the 80SD treatment independent of parity. Feeding time was reduced for nulliparous animals in the 80SD treatment compared with the 100SD treatment but feeding time was greater for parous animals in the 80SD treatment than those in the 100SD. Interestingly, stocking density had no effect on lying time of prepartum cows but first-calf heifers in the 80SD treatment had more lying bouts per day than first-calf heifers in the 100SD treatment.

In conclusion, increasing average daily stocking density by 20 percentage units (from 80 to 100%) affected behavior of prepartum animals. On the other hand, changes in behavior associated with elevated stocking density had no impact on metabolic status or health, reproductive, and productive parameters.

Acknowledgments

Numerous undergraduate students and interns helped with data collection. Study was partially supported by the University of Minnesota Rapid Agricultural Response Fund, Novus International, and AES funds.

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Update on management of transition cows

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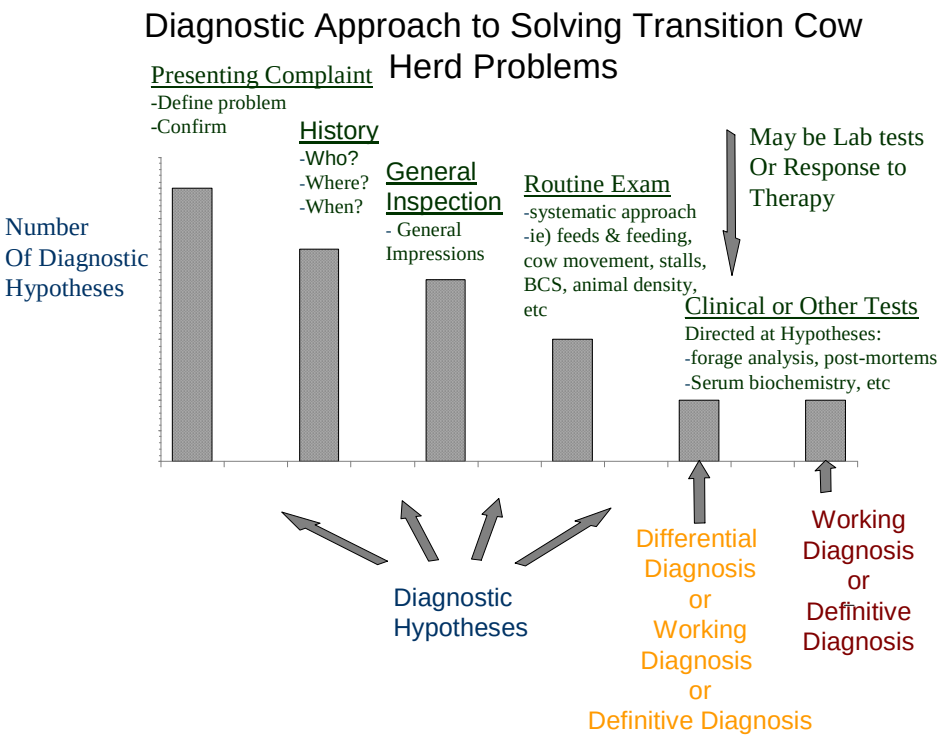
Introduction

There seem to be multiple recommendations for best management of transition cows. The reality is that some strategies work on some farms but not others. Rather than make broad sweeping recommendations, a guideline for transition cow investigations is perhaps more revealing. Unraveling the cause of transition cow problems is a complex task. The "cause" will always be multifactorial, meaning that there will be multiple components that have ultimately contributed to the eventual problem. Since this is the case, often investigations will stop once one issue has been identified. A solution or remedy directed at this one particular issue may fail to alleviate the big problem. The investigation will then continue until the next issue is identified. This process is frustrating and lacks a systematic approach. Recognizing the multifactorial nature of disease and using a systematic approach to problem solving can help with making a more efficient diagnosis and often remedy the transition cow problem much faster.

Overview of the diagnostic approach

The diagnostic approach to herd investigations is similar to that used at the individual animal level. In our Ruminant Health Management group at the Ontario Veterinary College in Guelph we teach our students the hypothetico-deductive approach to making a diagnosis. This method consists of generating and refining diagnostic hypotheses through the presenting complaint, history, general inspection, routine exam, and clinical tests. This method can be applied to individual sick animals or to herd level problems. In addition, employing the W-5 (what, who, where, when, why) criteria is critical to solving and correcting transition cow issues. Since most transition cow problems are multifactorial, the challenge is to identify and address the most critical factors contributing to the problem. Finally, monitoring outcome success is an important and often overlooked part of the herd investigation.

Understanding the diagnostic process
(figure adapted from Dr. Ken Bateman, OVC, University of Guelph)



W5 of case investigation: what, who, where, when, why?

Presenting complaint

This is the "What". The first step is to define the problem and the second step is to determine if it is actually a problem or not. Calculate incidence of the problem using the appropriate denominator (correct population at risk) and compare this number to the target, goal, or industry standard. Finally, the problem timeline needs to be addressed. Is it a new problem or an old problem? Establish the timeline by tracking the disease incidence over time. For example, the problem is new this year, new this month, new this week, etc. Note, good records make this process much easier.

For example: A herd complains of fresh cow problems in the last month. A fresh cow problem could be anything (hypocalcemia, subclinical ketosis/fatty liver, metritis, mastitis, etc). Is the problem related to a specific disease or disease syndrome? Is it happening right at calving, within the first two weeks, or later? Is the problem either restricted to or absent from a parity group. We don't expect to see milk fever problems in first parity heifers for example.

Develop the history

Who – Demographics: parity, birth or calving cohort, purchased or home, etc
Where – specific location of occurrences (pen, barn, etc)
When – calendar time (dates) and animal time (DIM)
Why – The most difficult to understand – What has changed? Asking what has changed is usually not very fruitful. However, asking specific questions about what might have changed can be useful. Have you switched to a new bunker silo? Has the labour situation recently changed? Have you had an increase in the number of cows calving?, etc.

General inspection (Step back and look – Big picture things)

The general inspection consists of understanding the cow perspective on the farm. Walk through the cows from two perspectives:

1. A day in the life of a cow (understand the farm routines)
2. A year in the life of a cow (understand management flow from dry to calving to lactation)

Look for anything that is obviously wrong such as:

- Empty Bunks
- Overcrowding
- Low or High BCS
- Cow comfort issues
- Fine rations or Sorting
- Etc.

Routine examination

The routine exam may revisit areas found to be abnormal in the general inspection. This is a systematic approach to walking through the farm that addresses issues relative to the Diagnostic Hypotheses. This would usually include:

- Cows – evaluation of BCS, grouping, frequency of group changes, etc
- Feeds and Feeding- assessment of quality, particle size, diet changes, etc.
- Bunk Management – gathering information on frequency of feeding, push-ups, etc
- Headlocks and Stalls – assessment of overcrowding
- Environment – Ventilation, Stall design, Bedding, Floors, Water
- Management Routines and Prevention/Treatment Measures
- etc

Clinical tests

This is the final stage of the diagnostic process that is used to help confirm or refute Diagnostic Hypotheses. Tests might include the following: post mortems, serum or blood parameters, forage and VFA analysis, rumen pH, urine pH, etc.

Concept of the tipping point

It is important to understand that all disease syndromes have complex causes and therefore are multifactorial in nature. In working through any investigation, there will most likely be several factors that have been identified as problems and many of those will have existed for sometime. This leads to the question, why now? Often it is the combination of these factors that is important, with the last change tipping the problem over into an obvious and large clinical issue. The challenge is to identify the key factors that need to be addressed to tip the scale back toward health.

Key strategies for prevention of metabolic disease

Management guidelines

Since metabolic disease problems occur in early lactation, recommendations for prevention have focused on the nutritional management of the dry and transition cow. The goals of the transition diet (specifically designed to prevent energy-related metabolic disease) are to maximize dry matter intake and to provide optimal energy density (Oetzel, 1998). Avoidance of ketogenic feedstuffs and the reduction of overconditioning cows in late lactation and the early dry period have also been suggested as aids in prophylaxis. Strategies for prevention of hypocalcemia are similar with the added attention to potassium concentration in the diet and possibly managing the diet through dietary cation anion balance. The challenge with adding anionic feed additives to the dry cow diets is the attention to detail required for successful implementation. Many farms simply do not have the management skills or resources to effectively utilize this tool and in fact may limit intake by over-acidifying the dry cow diet. Maximizing dry matter intake and maintenance of a consistent intake through the last three weeks prior to calving is likely the hallmark of a successful transition cow program. High fibre diets have been effective in reducing excess energy in dry cow diets, particularly in the early dry period, and for maintaining rumen fill. These diets are aimed at reducing the risk of increased insulin resistance, a suspected cause of so-called ‘Type-II’ ketosis. However, the main advantage of these diets is limiting energy in the first half of the dry period. One must remember that NDF still limits intake; so excessively high NDF diets can reduce or limit dry matter intake. Additionally, challenges exist, in smaller herds in particular, in the compromise between the correct energy concentration in the

diet for a one group dry cow diet, that still allows a smooth transition onto the lactating cow diet. Too high an energy concentration and cows gain weight and the 'low-energy' dry cow diet is ineffective. Too low an energy concentration and there could be rumen adaptation issues onto the highly digestible and higher starch lactating cow diet. For these reasons, many herds have reverted back to a more traditional two-group dry cow approach, but with renewed emphasis on a low energy far-off diet. Osborne (2003) indicated that a dry matter intake (DMI) of less than 12 kg per cow per day in the last 3 weeks prior to calving substantially increased the subsequent risk of subclinical ketosis postcalving (Odds Ratio 5.7, $p < 0.05$). Achieving group DMI targets above an average of 12 kg per cow per day should be a goal for the close-up group. More important than ration formulation and ration ingredients, close attention should be paid to cow comfort and environmental issues. These factors include but are not limited to adequate pen space or stall space per cow, adequate feed bunk space, sufficient and comfortable bedding, adequate water supply and minimization of heat stress. The frequency of group changes and additions to groups around transition is a huge stressor that should be limited as much as possible. Recent research has identified several social stressors as being associated with suboptimal herd performance. These include mixing of primiparous and multiparous cows precalving, and the use of individual calving pens.

Prevention tools

In addition to good nutrition, certain products have been found beneficial in improving transition cow health Propylene glycol has been used successfully for the prevention of subclinical ketosis (Emery et al, 1964; Sauer et al, 1973). Several studies have been conducted with varying doses and durations of treatment. Generally, propylene glycol is more effective when drenched because the bolus effect provides a stronger insulin response (Christensen et al, 1995). A dose in the range of 300 to 500 ml (or 10 to 16 oz) is sufficient when started on the day of calving and administered for 3 days.

A series of meta-analysis of monensin studies in lactating dairy cattle has clearly demonstrated that monensin through the transition period reduces BHBA, NEFA, acetoacetate; and increases glucose (Duffield et al, 2008a,b,c). These important improvements in metabolic parameters result in a reduced risk of clinical disease, including reductions in the incidence of displaced abomasum, clinical ketosis, and mastitis. In addition, cows administered monensin through transition produce significantly more milk, particularly those cows at highest risk of ketosis. Monensin delivered through a controlled-release capsule is more consistent at improving metabolic indicators of health. For most effective control the monensin capsule should be administered precalving (ideally 3 to 4 weeks prior to expected calving).

Rumen protected choline has been shown to influence liver glycogen and triglyceride (Piepenbrink and Overton, 2003), but not in all studies (Zahra, 2004). A topdress of 56 g per day

of rumen protected choline during the transition period did not affect BHBA, NEFA, liver glycogen or liver triglyceride. However, milk production was significantly increased in choline treated cows and this effect was more pronounced in cows that were over-conditioned.

Several studies have demonstrated an improvement in dry matter intake through transition with the feeding of yeast products. However, impacts on metabolic parameters and clinical health outcomes have not been investigated to date.

Conclusions

Herd variation for metabolic disease incidence problems are wide and herd level risk factors are poorly described. However, herd level risk factors most likely involve combinations of management, feed quality and nutritional programs, cow comfort, environment, and other variables that influence dry matter intake. Routine monitoring programs for subclinical ketosis is beneficial on many dairies and can serve as an important early warning system for metabolic disease problems, as well as a highly useful means of assessing effects of management or nutritional changes..

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Monitoring programs for ketosis & hypocalcemia

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Introduction

Metabolic monitoring has its roots in metabolic profiling developed in Compton, England in the 1970's. Since that time automated laboratory machines and enzyme kits to measure a battery of serum or blood constituents is widespread and commonplace. However, ease of sample collection and submission is not justification for conducting metabolic herd testing. Serum analytes have more value when used appropriately in the diagnostic process or as part of a specific objective in herd monitoring programs for metabolic disease. Profile testing should not be used in place of other more appropriate procedures, such as ration evaluation and physical examinations. The transition cow represents the target with the most utility for metabolic profiling.

Most periparturient abnormalities have some metabolic element as a component of the sufficient cause of clinical disease. Negative energy balance, fat mobilization and subsequent elevations in ketone body concentrations play a contributing role in the expression fatty liver syndrome, clinical ketosis, and abomasal displacement. A negative energy balance during transition may also increase the risk of retained placenta, metritis, and mastitis through impaired immune function. In addition to energy balance, nitrogen balance and calcium homeostasis are disrupted through parturition. Therefore, several biochemical parameters may be useful for monitoring cows in the transition period.

Objectives of metabolic monitoring

There can be two main objectives for conducting serum metabolite testing in periparturient cows. Although these objectives may overlap, it is worth stating them for clarity.

1. Cow-level interpretation – There is a problem with this cow and treatment and/or further examination may be warranted.
2. Herd-level interpretation - There is a potential problem with the current herd management that needs to be investigated.

Cow and herd level interpretation can be conducted with the same samples but they differ in that we are differentiating between an individual or group problem. In our opinion the group interpretation is the strongest reason for conducting the tests regardless of whether it is an ongoing monitoring program or a herd-problem investigation.

Serum metabolites to consider

Circulating concentrations of non-esterified fatty acid (NEFA) and β-hydroxybutyrate (BHBA) measure the success of adaptation to negative energy balance. NEFA reflects the magnitude of mobilization of fat from storage. BHBA indicates the completeness of oxidization ("burning") of fat in the liver. Ketone bodies (BHBA, acetone and acetoacetate) are intermediate metabolites of oxidation of fatty acids; as the supply of NEFA to the liver exceeds the ability of liver to completely oxidize the fatty acids to supply energy, the amount of ketone body production increases. Ketone bodies can be used by muscle as an alternative fuel source to glucose, sparing glucose for milk production (Herdt, 2000a). However, ketone production does not result in as much net energy release as does complete oxidation of fatty acids. Additionally, increasing concentrations of ketones are thought to suppress feed intake.

Glucose is the primary metabolic fuel, and is absolutely required for vital organ function, fetal growth, and milk production. In dairy cows, the massive energy demand to support milk production is partly met through gluconeogenesis. Glucose concentrations are under tight homeostatic control. Therefore, although glucose has a central role in metabolism, it is a poor analyte for monitoring or investigating herd problems (Herdt, 2000b). However, recently we have discovered a poetenial role for glucose measurement in assessing treatment success. Ketotic cows with low serum glucose responded to parenteral supplementation with vitamin B12 in addition to oral propylene glycol,. However, ketotic cows with normal serum glucose did not benefit from the B12. Aspartate aminotransferase is an enzyme that becomes elevated with cell damage and may be elevated in cows with fatty liver disease. Although there have been associations between AST and subsequent occurrence of displaced abomasums (Geishauser et al, 1997), the test lacks both sensitivity and specificity. For energy balance NEFA and BHBA are the best two measures.

Calcium demand is tremendous immediately postpartum and monitoring serum calcium in cows less than a week following calving may have some utility but before or beyond this time period, it makes no sense to measure calcium. Low serum calcium concentrations (subclinical hypocalcemia) have been linked with increased risk of early lactation culling (Duffield et al, 2005; Roberts et al, 2012) and reduced milk production (Chapinal et al, 2012). Effective cowside monitoring of both NEFA and calcium is currently not available because of the absence of cowside tests for either analyte.

Haptoglobin is an acute phase protein that becomes elevated under situations of inflammation. However, this inflammation indicator is non-specific and could reflect for example dystocia, mastitis, metritis or displaced abomasum. However, despite its non-specific nature haptoglobin may also have utility for monitoring transition cows.

Currently the strongest data exists for the use of NEFA and BHBA testing in transition dairy cows. The remainder of this article will focus on these two analytes.

Key associations of NEFA and BHBA with health and performance in transition dairy cows are:

- High NEFA in the 2 weeks before calving is associated with
  - 2 to 4 times increased risk of LDA (Cameron et al, 1998; LeBlanc et al, 2005)
  - 1.8 times increased risk of retained placenta (RP) (LeBlanc et al 2004)
  - 2 times increased of culling before 60 days in milk (DIM) and 1.5 times increased risk of culling over the whole lactation (Roberts et al, 2012)
  - Decreased milk production (Ospina et al, 2011; Chapinal et al, 2012)
  - Deceased reproductive performance (Ospina et al, 2011)
- Subclinical ketosis (BHBA > 1200 – 1400 μmol/L) in early lactation is associated with
  - 3 to 8 times increased risk of LDA (Geishauser et al, 2000b; LeBlanc et al 2005; Duffield et al, 2009)
  - increased risk of metritis (Duffield et al, 2009)
  - Decreased probability of pregnancy at first AI (Walsh et al, 2007; Ospina et al, 2011)
  - Decreased milk production (Duffield et al, 2009; Ospina et al, 2010; Chapinal et al, 2012)
  - Increased duration and severity of mastitis (Suriyasathaporn, 2000)

Monitoring NEFA and BHBA

Cow selection

By most definitions, the theoretical testing period for transition cows would extend from 3 weeks prior to calving until 3 weeks after calving. Practically however, the most important time periods are:
1. during the last week prior to calving 2. within the first 2 -3 weeks after calving.

Precalving

It is unusual for cows to develop subclinical ketosis (SCK) precalving because the etiology of the condition depends on the homeorhetic drive for milk production. However, cows in an energy deficit precalving will start mobilizing energy reserves in the final week before parturition. This can be measured via serum or plasma NEFA. The challenge for this precalving sample is predicting when the animal is going to calve. In the past, establishment of a serum bank and retrospective submission of samples relative to calving have been recommended. However, recent data suggests that assessment of samples obtained within a week of expected calving is a practical approach that seems to provide meaningful information (Leblanc et al, 2005).

Postcalving

A routine ketone testing program should commence after calving. The primary risk period for SCK is the first month of calving. The first 2 weeks postcalving is the time of peak incidence. In addition, the median days from calving to diagnosis of clinical ketosis and displaced abomasum is around 11 days. Thus, in order to try to prevent subclinical disease from becoming clinical disease (if that is possible), cows must be identified earlier. For these reasons, a SCK monitoring program should focus on the first 2 to 3 weeks of lactation.

Required sample size

The number available for testing depends on the herd size. For both BHBA and NEFA it is proportion rather than mean measurements that are important. A good thumb rule for evaluating a herd is to interpret data based on 12 samples. This is based on the following:
in a close-up or fresh cow group of up to 500 cows, assuming that detection of a prevalence of subclinical disease of 10% is the threshold of interest, to have 75% confidence of detecting the problem, 13 samples are required (Dohoo et al, 2003). Oetzel (2004) proposes using 12 samples for simplicity of interpretation. In small herds, this may require repeated sampling over time.

Test selection

NEFA

This test should only be used precalving on samples obtained within 1 week of expected parturition. It can be used within 2 weeks of parturition based on the work of Ospina et al (2011) but a lower cutpoint of around 0.3 mmol/L should be used. The data for NEFA is frequently right skewed and thus averages can be very misleading. One suggested threshold is 0.5 units/L. In recent work, cows within 1 week of calving with serum NEFA above this threshold were at a 3.5 times greater risk of subsequently developing a displaced abomasums (Leblanc et al, 2005). Whole herd interpretation is best made by calculating a proportion of cows above a threshold value, however, there is limited data on an appropriate goal for this parameter. In a muti-herd 1060 cow study near Guelph, 30% of cows were above 0.5 U/L during the last week prior to calving (Leblanc et al, 2005).
The potential of NEFA as a monitoring tool is further highlighted by research conducted at the Elora dairy research center (Osborne, 2003). Of 136 transition cows evaluated, 24 had BHBA concentrations ≥ 1400 μmol/L of serum in the first week post-calving (17.6%). There was a significant association between NEFA concentration in the week prior to calving and BHBA concentration in the first week post-calving. A nearly 5-fold increased risk of SCK was noted when the NEFA concentrations in the week before calving were greater than 0.7 mmol/L

(*OR*=4.8, *P*=0.04) (Osborne, 2003). Our research group currently uses 0.4 mmol/L for cows in the last week prior to expected calving and 0.3 mmol/L for cows two weeks prior to expected calving for all research and herd investigations.

BHBA

In contrast to NEFA, serum BHBA should only be used postcalving. The first two weeks are the primary risk period for subclinical ketosis, defined by a serum concentration of 1400 umol/L BHBA or greater (Duffield, 2000). A reasonable goal is to have less than 2 cows per 10 with BHBA above 1400 umol/L in the first 2 weeks post-calving. Many other studies have been conducted and threshold ranges can be defended between 1000 and 1400 umol/L depending on study and outcome. Our research group has been using 1200 umol/L for recent research and for herd investigations.

Sample Handling

Both NEFA and BHBA can be measured with either plasma or serum. Both analytes are subject to interference with hemoglobin in the sample, thus, hemolysis will artificially elevate measurements and should be avoided. Both NEFA and BHBA are subject to changes relative to time of feeding. Samples meant to compare performance on the same farm should be obtained at approximately the same time of day. The most severe swing in values in our experience appears to be with NEFA with highest values obtained just before first feeding. Therefore it is best to sample herds at some point after the first feeding of the day. NEFA concentrations could be slightly falsely elevated if serum were not separated within 12-24 h of blood collection, or if samples were not kept chilled (Stokol and Nydam, 2004). Serum can be kept frozen for at least 1 month without affecting NEFA results. Samples should be collected from the tail vein (not the milk vein) and ideally chilled, separated within a few hours, and then frozen or shipped chilled for receipt at the laboratory within 1 to 2 days. However, delay of up to 24 hours for separation, and kept at room temperature for 1 day or refrigerated for < 3 days does not substantially affect results (Stokol and Nydam, 2004).

Cowside tests

Milk ketone tests

Most milk ketone tests measure acetone and acetoacetate through a reaction with nitroprusside which causes a colour change from white to pink or purple. These tests in general are poorly sensitive in milk (<40%) but highly specific (>90%) (Duffield, 1997; Geishauser et al, 1998). One exception is the milk ketone test that measures BHBA. It was once marketed in Europe as "Ketolac BHB", in Japan as "Sanketopaper", and in Canada as "Keto-Test". This test has a

much higher sensitivity in milk (>70%) and reasonably good specificity (>70%, up to 90%) (Oetzel, 2004). This is a semi-quantitative test that allows choosing a lower threshold for screening to increase sensitivity, and a higher threshold for diagnosis to increase specificity.

Urine ketone tests

The urine ketone tablet tests are based on the same nitroprusside reaction as the milk powder ketone tests. These tests are highly sensitive (approaching 100%) but are poorly specific. Thus, they are great tests for ruling out subclinical ketosis with a negative test result. However, their use overestimates a subclinical ketosis problem because of a high probability of false positive reactions (see Table 1). However, recent work out of Minnesota suggests that a 5 to 10 second interpretation using the Ketostix in urine is just as accurate as the Keto-Test in milk (Carrier et al, 2005).

Blood tests

The human device Precision Xtra glucometer used with the ketone strips (sold by Abbott laboratories) is a highly accurate cowside test for measuring blood BHBA. Several studies have documented Sensitivies and Specificities in the low to mid 90's. This test is the most accurate cowside test available.

Selection and interpretation of cowside tests

There are two possible actions resulting from screening a group of fresh cows with a ketone test. One action might be to treat all positive animals with the goal to prevent subsequent development of clinical disease. In this case, a high predictive value of a positive test is desired so that normal animals are not unnecessarily treated. The second action might be to compare the percent of positive reactors to a goal for determining the effectiveness of either the transition ration or some prophylactic measure in reducing the incidence of subclinical ketosis. In this situation, the apparent prevalence is the parameter that actually would be used. Note from Table 1 that the urine Acetest tablet would substantially overestimate the prevalence of subclinical ketosis, while the Ketocheck™ test would grossly underestimate the prevalence. Despite a consideration of the inherent sensitivity and specificity of these two tests, their utility for group level decision making is questionable. The Acetest might be used with an adjustment in the apparent prevalence goal. The Ketocheck test is simply too insensitive to be useful. However, both the Keto-Test and the Ketostix are useful tests for group level monitoring and for individual animal identification.

Table 1. Use of cowside ketone tests in screening programs for identifying subclinical ketosis.

Test	20% Prevalence			40% Prevalence			60% Prevalence		
	PV +ve	PV -ve	Apparent Prevalence	PV +ve	PV -ve	Apparent Prevalence	PV +ve	PV -ve	Apparent Prevalence
Keto-Test® using 100 μmol/L	62%	93%	23%	81%	83%	35%	91%	68%	48%
Ketocheck™ (milk)	90%	86%	8%	96%	70%	16%	98%	51%	23%
Urine Acetest Tablet	38%	100%	53%	62%	100%	65%	78%	100%	76%
Urine Ketostix	83%	94%	19%	93%	87%	34%	97%	74%	48%
Precision Xtra (blood) using 1.4 mmol/L	89%	99%	22%	95%	97%	40%	98%	94%	59%

PV +ve: Predictive Value of a pos. test result. PV –ve: Predictive Value of a neg. test result.

Other tests

Herd disease records

Herd records are important tools for monitoring the incidence of periparturient disease. However, it is highly critical that standardized disease definitions are in place to allow comparison from year to year and from farm to farm. Producers should set goals for the minimizing the incidence of metabolic disease. Herd consultants should periodically review herd performance relative to these goals. In addition, intervention levels should also be considered. Several diseases are associated with increasing age and this must be taken into account when assessing herd performance. For example, in monitoring and comparing herd incidence of milk fever and clinical ketosis, it is important to stratify this by parity. A high proportion of first lactation animals will likely give a herd a much lower incidence of milk fever and clinical ketosis, since risk increases with age.

Dry matter intake

Clearly cows that are mobilizing NEFA precalving will have suboptimal dry matter intake. In a recently completed project, serum BHBA concentration in the first week post-calving was significantly associated with the average DMI in the week prior to calving (Osborne, 2003). There was a significant increase in the risk of subclinical ketosis (BHBA ≥ 1400 μmol/L of

blood serum) if the DMI was below 12 kg/d (*OR*=5.7, *P*=0.05) in the three weeks prior to calving. If the DMI in the week prior to calving was below 11 kg/d, there was a greater risk of an animal developing subclinical ketosis in the first or second week post-calving (*OR*=2.9, *P*=0.05) (Osborne, 2003). Thus, measuring and monitoring the dry matter intake in the close-up group every week has utility. However, beware of group demographics relative to time of expected calving and parity, which can influence these parameters dramatically. Fresh cow intakes are generally less useful because we are primarily interested in the intakes of cows within the first three weeks postcalving. If a fresh cow group exists, it is often composed of cows that may be several months postcalving. Larger farms are more likely to have more useful opportunities for measuring dry matter intake because of the ability to group cows into parity and smaller days in milk windows.

DHI test day data

Since milk fat and milk protein percentages are altered in sublinical ketosis, these parameters have been investigated for their utility in defining subclinical ketosis. Among all protein and fat parameters, a protein to fat ratio of ≤ 0.75 was the best test for diagnosing subclinical ketosis, at the cow level, in a Canadian study (Duffield et al, 1997). However, the protein to fat ratio was not a good test overall, having a sensitivity of 58% and a specificity of 69%. There is good European data that supports using milk acetone measured in routine DHI samples. A big problem with both this and protein to fat ratio is the frequency of sampling. Subclinical ketosis is prevalent in the first few weeks postpartum. However, DHI testing frequency is typically every 30 to 40 days. Thus the interval of sampling is too infrequent to hold great utility. However, the incorporation of milk acetone into in-line sampling methodology that could be done daily, holds tremendous promise.

Identifying high risk herds

Herd incidence of certain diseases may be useful to decide whether a herd has a problem with subclinical ketosis. Using data from a 25 herd study conducted in Guelph in 1995/1996, the median cumulative herd incidence of subclinical ketosis was 41% in the first two months postcalving, which crudely broke down into a threshold of 20% in week 1 and week 2 postcalving. Summary data for each herd from each cows first DHI test postcalving was used to assess the protein to fat ratio as a test at the herd level for classifying a herd as a high or low incidence herd for subclinical ketosis. If more than 40% of cows in the herd at 1st DHI test had a protein to fat ratio of less than or equal to 0.75, those herds were likely to be problem herds. This test had a sensitivity of 69%, and a specificity of 83%. Although more work needs to be done on herd level indicators of subclinical ketosis, herd level protein to fat ratios appear to be better indicators of herd level issues than individual cow protein to fat ratios are of identifying cows with subclinical ketosis problems.

Additional analysis indicates that the herd incidence of displaced abomasum is positively associated with the probability of a herd having a high incidence (>20% in the first 2 weeks of lactation) of subclinical ketosis. In addition, if herds had greater than 10% of transition cows with a BCS ≥ 4.0 at 3 wks precalving, that herd was extremely likely to have a problem with subclinical ketosis.

Economics of monitoring

For the herd level monitoring interpretation, the savings achieved is in identifying a problem sooner rather than later, since nearly all problems will eventually be identified. A conservative estimate of the economics of a biweekly program suggests that a routine monitoring program would payback if one major problem was identified earlier than traditional means every 4 to 5 years. The economics of individual cow testing depends on the efficacy of treatment, accuracy of the test, cost of the therapy and prevalence of disease.[7]

Conclusions

Given the cost of subclinical ketosis, the fact it is a common problem in early lactation, and the strong association with clinical disease, monitoring programs for subclinical ketosis during the first few weeks of lactation may be warranted. There are several cowside tests for subclinical ketosis available. However, only Ketostix in urine, Ketotest in milk, or Precision Xtra for blood have sufficient documented accuracy to be useful in a monitoring program.The appropriate design and frequency of a subclinical ketosis monitoring program will depend on the purpose of the program and the frequency of disease within the herd. Utilization of a technician in peripartum monitoring programs might be a way to ensure compliance and benefit both the herd and the veterinarian.

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Success factors for transition cow management and lameness

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Introduction

Lameness is a painful, costly disease that affects productivity of cows through its effect on milk production, culling and reproductive performance. In addition, lameness is also a major animal welfare concern as it is highly prevalent and more importantly recognizable by consumers.

Worldwide, clinical lameness prevalence estimates range from 20 to 30%. Estimates of the prevalence of foot lesions found at hoof trimming are much higher however, ranging from 40 to 70% of cows (Cramer et al, 2008). Types of lameness due to foot lesions can be broadly categorized into infectious (digital dermatitis heel horn erosion, foot rot) and hoof horn (ulcers, white line disease, hemorrhage). Although infectious lesions are the most common type of lesions in most herds, hoof horn lesions are far more costly due to their effects on milk production and culling.

Economic losses due to hoof horn lesions are difficult to quantify yet it is becoming apparent that cows affected with hoof horn lesions are usually cows with higher production potential and production losses start prior to a lameness diagnosis. Typical production losses for cows with hoof horn lesions range from 200-500 kg plus these cows are also at increased risk of culling. Infectious lesions, on the other hand, do not appear to have an association with long term productivity and are a source of short term inconvenience.

Fortunately for the dairy industry the knowledge exists to prevent and reduce the impact of lameness. This knowledge can be summarized into the following four success factors.

1. Low infection pressure
2. Good horn quality and hoof shape
3. Low forces on the feet
    a. Good cow comfort
    b. Good cow flow
4. Early detection and prompt effective treatment of lame cows.

The implementation of these success factors requires a management approach that is similar to the dedication and approach most producers have to improving udder health.

The focus of this paper is on the process of the developing a foot health program. It will outline a foot health program that can be used to reduce the level and impact of lameness. This foot health program has 6 components and focuses on controlling the major risk factors for both infectious and hoof horn lesions. The reader will find specific recommendations absent. This is due to the

fact that recommendations are farm specific and on farm particulars need to be considered.

Foot Health Programs Components:

1. Record and use lesion data from lame cow trimmings.
2. Find lame cows early and treat them quickly and appropriately.
3. Provide a housing environment that ensures cows’ feet are comfortable, clean and dry.
4. Disinfect and clean cows' feet regularly.
5. Ensure cows' feet have a proper weight bearing surface through proper hoof trimming by a trained individual.
6. Minimize metabolic stresses especially nutritional and transition problems.

1. Record and Use Lesion Data:

The recording and use of foot lesion data from clinically lame cows is necessary to the development of a foot health program and for its continuation. This data is necessary for the design of a good foot health program as knowledge of the type and stage of lactation of the lameness event allows the prevention program to be tailored to the specific farm instead of being created for the average dairy farm. Continued recording of foot lesion data allows for the monitoring and adjusting of the foot heath program as farm dynamics evolve.

Recording of foot lesion data starts with the person doing the hoof trimming. Ideally this person records lesions in a standardized manner to allow proper communication between the hoof trimmer and the farm's advisory team. It is equally important that the person who identifies and treats the lame cows uses the same terms as the person doing the routine preventative hoof trimming so there is continuity in the data collected.

The recording of foot lesion data does not have to be complicated. At minimum what is recorded is the cow's ID, the date, the lesion and the treatment. Additional data on location and size of the lesion is of lesser value from a monitoring perspective and should not become an impediment to the recording of the necessary basic information. Regardless of recording method it is necessary that this data gets entered into the on-farm software to allow both cow and herd level interpretations to be made.

2. Find and Treat Lame Cows Early

The second and probably the most important part of the foot health program is to create a protocol for early detection and treatment of lame cows. It is quite likely that the dairy industry can make the biggest change in lameness prevalence by addressing the lack of detection and treatment of lameness.

The primary reason to focus on the detection and treatment of lameness is to improve the well-being of the cow. Compared to a cow with either metritis, mastitis or a displaced abomasum, the

time between noticing her as diseased and implementing a treatment is usually delayed considerably for the lame cow. Typical comments are: “Oh we’ll see how she does in a couple of days”, or “The hoof trimmer is coming in a month”, or “Maybe a shot of antibiotics will fix that swollen claw”. Since lameness can quickly develop into a chronic disease, early intervention will result in reduced duration of pain, quicker return to productivity and reduced chance of chronicity.

3. Clean, Dry and Comfortable

This part of the foot health program focuses on the key risk factors for both infectious and hoof horn lesions.

3.1 Clean and Dry

The organisms responsible for digital dermatitis, foot rot and heel horn erosion are anaerobic bacteria that thrive in wet and moist conditions. For this reason the major focus to control infectious foot lesions should be to ensure that the cow’s feet are clean and dry. No amount of foot bathing will overcome an environment where the cow’s feet are constantly coated with manure. In free stalls manure and wetness are a fact of life, but measures can still be taken to reduce exposure to wetness by ensuring proper drainage and avoiding pools of water in cow traffic areas.

Although alley scrapers are used a as labour saving device, several research studies have shown an association with increased scraping frequency and higher prevalence of digital dermatitis (Cramer et al., 2009). Therefore scraping of alleys should occur at times when cows’ feet do not get coated by a “tsunami” of manure several times a day and timing of the scraper should be such that the majority of cows are not standing in the alleys when it is running. For barns with slats, alleys should also be scraped and robotic alleys scrapers are an effective way to accomplish this.

Currently, no clinical trial has been done with alley scrapers to prove the association with digital dermatitis prevalence. However, observations of feet in alley scraper barns reveal a thicker coat of manure on the front wall of the claw as opposed to manually scraped barns. This thicker coat would create a more anaerobic environment.

One of the best ways to reduce exposure to manure is to increase the amount of time cows spend lying down in a well bedded stall. A well bedded stall will serve 2 functions; entice the cow to lie in it thereby reducing manure exposure and the secondly the deep bedding will have a cleansing action on the feet.

3.2 Comfortable

Hoof horn lesions such as sole ulcers, white line lesions and hemorrhage are caused in a large part by movement of 3rd phalanx (P3) in the claw capsule. The downward movement of P3 causes compression of the corium resulting in the production of inferior horn. Depending on several factors including the duration and extent of movement by P3, different lesions can

develop. The exact cause of the movement of P3 is still open for debate, but enzymes and mediators that act on ligaments and the thickness of the digital cushion are all thought to play a role.

For hoof horn lesions to develop there needs to forces acting on the corium both from the exterior and interior of the claw. This occurs when a cow is standing as there is pressure exerted on the corium by P3 and a counter pressure by the surface she is standing on.

The major risk factor that should be controlled for to prevent hoof horn lesions is standing time. Any change to cows' environment that can be made to reduce standing time is going to result in less lameness as it removes weight bearing from the corium. This focus on cow comfort needs to go beyond the stall and needs to consider the cow's time budget to discover areas of “avoidable” standing time. A typical cow stands approximately 12 hours/day split up in 2.7 hrs for milking, 4.3 hrs for feeding 2.5 hrs for time in the alley and 2.7 hrs in the stall (Gomez and Cook, 2010). Herd level factors that influence standing time on individual farms include parlour and holding pen size, stocking density, social make up of groups, heat abatement strategies and management procedures like fresh checks and synchronizing programs.

The above factors all affect standing time and are in addition to the effects that stall design and management has on standing time. There is not enough space to address each of these factors individually in this paper. For the design a foot health program the impact of each of these factors needs to considered and if short comings are identified, additional management efforts will need to be devoted to other areas to compensate for these deficiencies.

4. Disinfect and Clean Regularly

Once we have addressed the cleanliness of the cow's feet, the reality is that most herds still require the regular use of a proper footbath to clean and disinfect feet. For most herds it is likely not the type of product used that is responsible for the lack of apparent control of infectious lesions. Even though there are few clinical studies to prove the efficacy and economics of most current foot bath products, no product will be effective if it is not used regularly and effectively. What defines regular is likely herd dependent but just like teat dipping is a standard practice twice daily, foot bathing should be standard practice daily on all free stall herds.

A good footbath protocol starts with thinking of a footbath as a preventative tool, similar to teat dipping, and not as a treatment tool. There is a role for antibiotics in footbaths as a treatment solution, however in most cases these should be short term in nature and not used on an ongoing basis.

On most farms digital dermatitis control would improve if footbaths were run more frequently. Does this mean that there needs to be disinfectant in the bath every time? Potentially, but even having a cow walk through a footbath with water alone or with a small amount of soap will have a cleansing action and over time remove the caked manure on the foot. This cleansing will result in a cleaner foot so when a disinfectant is used 3-5x/week, it will be more effective. An additional benefit to running cows through a footbath more frequently is that the footbath

becomes part of the cow's routine and running a footbath does not automatically mean a longer milking time.

For a footbath to be effective we need contact time with the disinfectant and in this case more is better. One way to do this is to increase frequency of use, but the other way is to increase the number of "dips". If we consider the length of a cow and how far apart her feet are and then watch cows walk through a six foot footbath, it becomes obvious that 6 foot footbaths were meant for the cow to stand in and not to walk through. Recent work out of Wisconsin has shown that over 60% of cows get less than 2 "dips" in a 6 foot footbath (Cook, 2010 pers. comm.). Unfortunately, 6 foot long footbaths are common both in the portable and permanent concrete form. The ideal footbath is at least 8-10 feet long, narrow (20 inches) and have a minimum of 2 feet high side walls to avoid cows stepping on the side and to keep solution in the bath. Minimum water depth should be at 4-6 inches. Higher curbs at the entrance and exit of the footbath will force cows to take more steps again increasing the number of "dips". To create good cow flow through the footbath the ideal location for a footbath is not in the return lane but in the area that links the parlour to the barn. If this is not possible, then having the footbath at the very end of the return alley will allow for better cow flow out of the parlour.

Spraying the cows feet either in head locks or in the parlour is an alternative to a regular foot bath program but can quickly become a labour issue. Whether spraying or foot bathing, it is important to remember to include dry cows and heifers in the control program.

5. Proper Balanced Weight Bearing

Hoof trimming plays an important preventative role in a foot health program. In most of our current housing environments an imbalance is created between horn growth and wear. Preventative hoof trimming attempts to remove the excessive growth and redistribute the forces that occur within a cows' foot to avoid excessive pressure on the sole ulcer location. Several excellent texts exist that describe a functional trimming technique based on the method developed by Dr. Toussaint Raven. The basis of this method is to transfer weight bearing from the overgrown outside claw to the inside claw and to create a flat weight bearing surface to walk on. Unfortunately, no research exists that evaluates different trimming techniques. However, for any trimming method the goal of trimming is to prevent or treat lameness and any horn that is removed from cows' foot should meet these criteria.

Hoof trimming should only be done by trained personnel, who have knowledge of the anatomy of the foot as it is possible to do a lot of damage with improper hoof trimming. The required frequency of hoof trimming is cow dependent but in most cases cows should be examined at least twice a year. An examination does not necessarily mean that the foot is trimmed, but twice a year a judgment is made about the length and shape of her feet. Some chronically lame cows will benefit from more frequent trimmings and if a hoof trimmer makes regular visits to a herd this becomes much easier to implement.

6. Minimize Metabolic Stress

The transition period is also a time of great metabolic stress thus in a foot health program this time period cannot be ignored. Recent work has shown increased standing behaviour in transition cows not only leads to traditional transition cow problems, but also foot lesions (Proudfoot et al., 2010) This finding provides another reason to treat transition cows properly and ensure they go through a stress free calving. Additionally, recent work from Cornell has shown that there is a relationship between body condition score, the thickness of the digital cushion and lameness rates. Although still preliminary, these findings suggest that cows that lose a lot of body fat during early lactation also lose a lot of shock absorptive capacity in their feet increasing their risk of lameness (Bicalho, et al., 2009).

Traditionally nutritional factors and nutritionists have received a lot of the blame for lameness problems in herds. Surprisingly, the evidence in the literature for a causal relationship between subclinical acidosis and lameness is very weak. Based on our current understanding of the digital cushion, suspensory apparatus and the effect that mediators and enzymes have on the tissues and structures inside the claw, the diet the cow eat is likely less important than how she eats it. Factors that increase standing time or create periods of slug feeding such as available bunk space, consistency and quality of the actual feeds and ration delivery, and behavioural factors likely play a bigger role than the actual “paper” ration.

To minimize metabolic stress and to promote proper horn growth and integrity the role of trace minerals and vitamins in a foot health program cannot be ignored. Whilst supplementing trace minerals should be considered in most herds it is important to remember that to gain the maximal benefit from these products they should be fed in the dry period and during lactation.

Conclusion

By focussing on lameness success factors the dairy industry can prevent lameness from becoming a major animal welfare issue. The implementation of this knowledge requires a dedicated management approach to foot health similar to the one that exists for udder health. The keys of this program are to detect and treat lame cows early, focus on clean, dry and comfortable feet that are regularly disinfected and evaluated, and ensure cows do not experience metabolic stresses at key periods in their lactation. Following these principles will reduce lameness levels in the dairy industry but will require a concerted effort by all sectors of the industry including producers, hoof trimmers, veterinarians, nutritionists, researchers, dairy supply companies, and contractors.

Note

This paper was adapted from a paper presented at the Western Canadian Dairy Seminar in 2010.

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KEYNOTE: Values, Trust and Science, Building Trust in an Age of Radical Transparency and Unbridled Social Media

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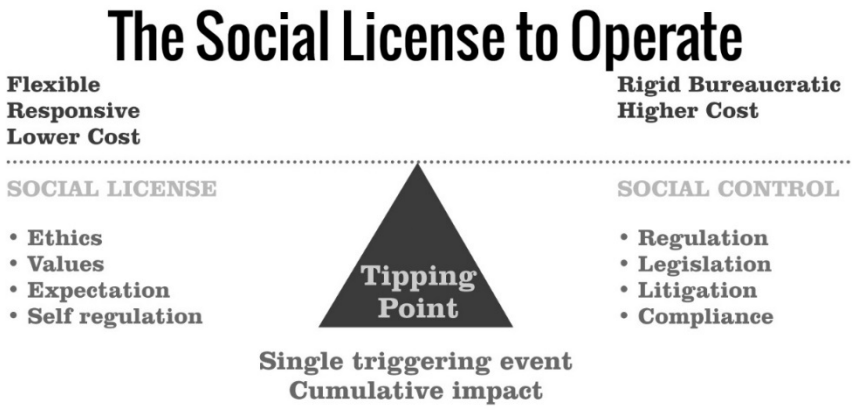
- Every organization operates with some degree of social license. Once lost through a single event or a series of events, it is replaced by social control (legislation, regulation).
- Today's operating environment mandates transparency. In this age of social media, food system stakeholders must develop new models for authentic engagement.
- A truly sustainable system is ethically grounded, scientifically verified and economically viable.

The social license to operate

Every organization, no matter how large or small, operates with some level of social license. A social license (illustrated below) is the privilege of operating with minimal formalized restrictions based on maintaining public trust by doing what's right. You are granted a social license when you operate in a way that is consistent with the ethics, values and expectations of your stakeholders. Your stakeholders include customers, employees, the local community, regulators, legislators and the media.

Once lost, either through a single event or a series of events that reduce or eliminate public trust, social license is replaced with social control. Social control is regulation, legislation, litigation or market action designed to compel you to perform to the expectations of your stakeholders. Operating with a social license is flexible and low cost. Operating with a high degree of social control increases costs, reduces operational flexibility and increases bureaucratic compliance.



Source: CMA Consulting, LLC

A U.S. case in point - Arthur Anderson and Enron. Prior to the collapse of Enron, public accounting firms operated with a fairly broad social license. The accounting industry had established the Financial Accounting Standards Board to regulate the implementation of Generally Accepted Accounting Principles by Certified Public Accountants. The accounting industry created a structure for self-regulation based on the expectations of their stakeholders which included investors, banks, the Securities and Exchange Commission, financial media and others.

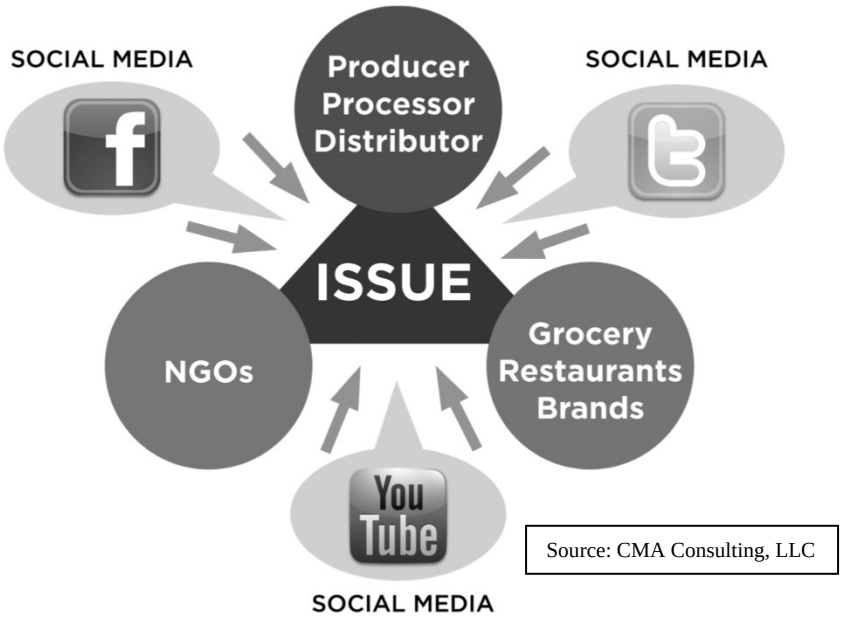
Stakeholders relied on the industry to operate in a way that maintained public trust and in return the public was willing to grant accountants broad social license. The Enron debacle cost the accounting profession its social license. That single event was the tipping point that compelled Congress to replace the social license of the accounting profession with the Sarbanes-Oxley Act, a law that requires extensive reporting and verification of financial information by publicly traded companies. According to research by Foley & Lardner, the average cost for a public company to comply with Sarbanes-Oxley is between $10 and $15 million per year. Those are costs that could have been returned to shareholders as dividends, or reinvested in research and development.

The question then becomes, what can be done to maintain public trust that grants the social license and protects freedom to operate?

Transparency is no longer optional

Today, anyone with a cell phone is a cinematographer. Research over the past four years clearly indicates that consumers increasingly go online to look for information to answer their questions about food. The power of social media to change the food system became clear in 2012 when concern over Lean Finely Textured Beef (LFTB) by a mommy blogger in Houston created an online firestorm that drove leading branded food companies, restaurants and grocery chains to eliminate a product that was supported by science.

In today's age of unbridled social media, food system stakeholders have to develop new models for authentic engagement. Growing skepticism about food safety and the use of technology fuel online communities that are raising issues and making their voices heard with increasing volume and frequency. In this dynamic new environment (illustrated below) producers, processors and distributors are inextricably linked to their customers and NGOs interested in food issues. The question for food companies is no longer "*will you be transparent,*" but rather, "*how will you protect your social license in an age of radical transparency?*"



Source: CMA Consulting, LLC

New models for building trust

The food system has an incredible challenge and opportunity ahead. By mid-century we have to more than double food production to meet the needs of more than 9 billion people. We have to produce more food by the end of this century than we've produced in the last 10,000 years combined. To meet that challenge we have to embrace new models of public engagement that build and maintain public trust and our social license to operate.

We need stakeholders who control social license to understand that while our systems have changed and our use of technology has increased, our commitment to doing what's right has never been stronger. We need to be able to verify our claims with objective science and we have to be able to continue to operate profitably if we want to survive. We need to adopt systems and practices that are ethically grounded, scientifically verified and economically viable. (model below)

It is only by achieving and maintaining this balance that we can create systems that are truly sustainable. Each side of the sustainability triangle has stakeholders focused on maintaining the strength of that side, even at the expense of maintaining balance. There may be times when stakeholders have to look beyond short term self-interest to foster truly sustainable food systems.

If food system practices are not ethically grounded they will not achieve broad-based societal acceptance and support. If they are not scientifically verified there is no way to evaluate and validate the claims of sustainability, and if they are not economically viable they cannot be commercially sustained. For a system to be truly sustainable, it has to be ethically grounded, scientifically verified and economically viable. This model encourages stakeholders to look for balance in an effort to find true sustainability.

Ethically Grounded

Those who focus on ethics want food system practices that are consistent with the shared values of compassion, responsibility, respect, fairness and truth. They want to ensure that our increasingly sophisticated and technologically advanced food system doesn't put profits ahead of ethical principles and that science is not used as moral justification. When this side of the triangle is out of balance, critics claim there is no scientific basis for the claims being made and that the ethical demands will jeopardize the economic viability of the system.

Scientifically Verified

Those with a primary interest in scientific verification are data driven. They want specific, measurable, and repeatable observations to provide the basis for their objective decisions. They believe science can provide the insight and guidance necessary to make reasonable determinations about how food systems should be managed. When this side of the triangle is out of balance, critics claim the organization is relying on science while ignoring ethical considerations and that research may be done and recommendations made without consideration of the economic impact.

Economically Viable

Those responsible for the "bottom line" are focused on profitability. They work every day to respond to demand, control costs and increase efficiency to maximize the return on investment. They have to manage the increasingly complex demands of competing in a global marketplace with volatile commodity markets and ruthless competition. When this side of the triangle is out of balance, critics claim profits outweigh ethical principles and that business decisions are made without the benefit of scientific verification, placing those decisions at risk when questioned by those who value validation.

If we can't operate a system that maintains a balance of practices that are ethically grounded, scientifically verified and economically viable, it will collapse. That collapse may subject producers, processors, restaurants or retailers to undue pressure that includes consumer protests or boycotts, unfavorable shareholder resolutions, uninformed supply chain mandates, regulation, legislation, litigation or bankruptcy.

Maintaining balance is never easy. Success demands an increased level of communication and engagement and willingness to look for solutions that are ethically grounded, scientifically verified and economically viable for each segment of the food system. Only by working with stakeholders across the food chain can we maintain the integrity of the sustainable system.

Conclusion – It's about trust

As we increase both the distance most consumers have from farming, food processing and the level of technology we implement in food production we have to dramatically improve our ability and commitment to build trust with our customers and other stakeholders who grant social license. This will require a new way of thinking, a new way of operating and a new way of communicating.

To be successful we have to build and communicate an ethical foundation for our activity and demonstrate our commitment to practices that are ethically grounded, scientifically verified and economically viable.

Writing Protocols

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Protocol sophistication will vary depending on the autonomy of the individuals treating cattle. Regardless of how extensive a protocol is, it is important that all of the people who will be using it have ownership in developing the contents, monitoring results, and updating the protocol. In addition to benefits to the production facility, detailed protocols and records of education and agreement related to the protocols are very important to the veterinarian in the case of a violative drug residue or regulatory inspection.

Several basic inclusions are required to allow consistent application of treatments and evaluation of what happens after these treatments are administered.

- Characterization of the disease challenge
- Case definitions
- Regimen design
- Consistent application of treatment protocols
- Outcome evaluation

What should be included in a complete dairy protocol?

Mastitis
- Environmental
- Contagious

Lameness
- Footrot
- Hairy heel wart
- Sole ulcers/whiteline

Respiratory disease
- Adult cow
- Neonatal
- Heifers

Metabolic disease
- Ketosis
- Hypocalcemia
- Fatty liver
- DA

Metritis

Neonatal

Pneumonia

Enteric disease

For comparison, what should you expect to be covered in a feedlot protocol?

- Respiratory disease
  - Low risk (expected morbidity ≤ 10%, case fatality 1-2%)
  - High risk (expected morbidity > 10%, case fatality > 2% up to 10%)
  - Heavy cattle within 30 days of harvest (withdrawal times are now a primary consideration)
  - Acute interstitial pneumonia (AIP)
  - Tracheal edema (Honkers)
  - Diphtheria (relatively rare in the feedlot)
- Gastrointestinal disease
  - Acidosis
  - Bloat
  - Coccidiosis
- Musculoskeletal disease
  - Footrot
  - Toe and sole abscesses
  - Undifferentiated lameness (e.g., sprains)
  - Hairy heel wart (Strawberry footrot)
- Central nervous system disease
  - Polioencephalomalacia
  - Thrombolic meningoencephalitis
  - Listeriosis
- Miscellaneous
  - Rectal, vaginal, and uterine prolapses
  - Calvers and abortions
  - Anaphylactic shock
  - Bullers
  - Pinkeye
  - Abscesses

Required inclusions in a treatment protocol

Characterization of the disease– Why is the animal sick? This requires an investment in diagnostic tests and post-mortem exams. The clients will start with the case definition, but your job is to be determining why these cases are occurring and working to minimize the need to use the protocol.

Case definition – The description of an animal that meets your requirements for receiving treatment or for treatment success/failure.

Regimen – Consists of the drug, dose, route, duration, frequency, and slaughter withdrawal. The regimen should be complete to the detail of needle size and injection or administration site.

Case definition examples: These bovine respiratory disease examples need to be characterized as important or misleading criteria. Any disease has similar challenges.

- Depression (see the example scoring system below)
- Nasal discharge
- Ocular discharge
- Rumen fill/appetite
- Rectal temperature
- Auscultation?

You may want to institute a scoring system to give some basic foundation to training new personnel and helping "adjust the dial" of current personnel or clients. The scoring system below is simple yet allows discussion of just how depressed (and by inference, how advanced in disease) an animal is.

Depression Score	Clinical Signs
0	Normal, no signs of depression
1	Slower than pen mates but still perks up when approached and does not appear weak, actively follows your movements with a raised head
2	Stands with head lowered, will perk up when approached but will return to depressed stance, moves slowly and falls towards back of group, may display signs of weakness such as incoordination
3	Obviously very weak, difficulty in moving with group, raises head only when approached closely
4	Moribund, unable to rise

Applying treatment guidelines

It just isn't possible to accurately evaluate a practice or procedure that is not consistently applied. One source of inconsistency is applying different treatment regimens for bovine respiratory disease depending on initial rectal temperature or apparent severity of disease. I haven't found any data to support that these practices increase treatment efficacy.

Should we routinely change (rotate) antimicrobials?

There has been minimal publication on this subject concerning food animal therapeutic applications. There are two core questions:

- Does cycling have an impact on treatment efficacy?
- Does cycling reduce resistance development?

There is no data to suggest an affirmative answer to either question. Another common question is "should we rotate drugs for second and third treatments"? If you are finding adequate first treatment response in the majority of animals, the lack of efficacy noted in some animals at the end of the first treatment regimen is likely more closely associated with degree of disease advancement and time needed for response rather than interaction between the pathogen and the antimicrobial. In these cases, it is probably not going to be a problem to continue therapy with the initial antimicrobial for animals not classified as first treatment successes.

Example Treatment Guideline

These treatment guidelines are an example of a feedlot protocol for respiratory disease in cattle. It is critical that the guidelines contain…

- A case definition for initial case selection and success/failure determination
- A detailed regimen description including drug, dose, route (needle description and volume/site if appropriate), duration, and frequency.
- Any safety information for handling the drug that is different from other drugs.
- A slaughter and/or milk withdrawal time
- A case definition for success/failure and the disposition of animals for each outcome

The guidelines should be routinely reviewed with the client and/or their employees. The secret to a consistently applied protocol is the crew having ownership in the contents. It is absolutely imperative that all agree to communicate prior to changing any aspect of the protocol.

Respiratory Disease

Case definition - The animal is usually depressed (moves slowly, hanging head, drooping ears, "knuckling" of hind fetlocks) and may also have:

nasal or eye discharge - Clear nasal discharge does not necessarily indicate respiratory disease, and may be normal early in the morning or during dry/dusty conditions.

sunken flanks - Decreased rumen fill indicates decreased feed intake. This may be used as supportive evidence that the animal has respiratory disease, but really indicates that the animal needs to be examined for why it is not eating. A full rumen should not keep you from examining an animal with other signs of disease; sick animals eat too.

diarrhea (scours) - Diarrhea may accompany respiratory disease. However, also evaluate the animal for other digestive disorders such as acidosis.

Low Risk Cattle - Yearling cattle and low-stress calves where we expect to treat less than 10% for respiratory disease and expect less than 0.5% to die from respiratory disease.

Low Risk Treatment #1 - Slaughter withdrawal 28 days

Day 0	**3-day miraclemycin** - 4.5 mL/100 lbs. subcutaneously in the neck, 16 gauge, ¾" needle, maximum of 10 mL/site.
Day 1 (24 hours)	Observe only
Day 2 (48 hours)	Observe: Animals which have shown no response may be moved to treatment #2 ahead of schedule, but this should be < 5% of the cattle. Low risk status should be reconsidered if ≥ 5% of the cattle have not responded by this time.
Day 3 (72 hours)	Make your final decision on this day. Two options: discontinue treatment (the animal has recovered), or advance to treatment #2.

Case definition for success/failure determination - Cattle classified as treatment successes are displaying no or only minimal clinical signs as described in the initial case definition. Determining rectal temperature is not necessary if the animal appears

clinically normal. Cattle classified as failures, and moved to the next treatment, are those displaying visible depression or respiratory disease symptoms. These cattle will be moved to treatment #2.

Continue the guidelines with the next treatment option and other disease protocols.

Avoiding Carcass Residues

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Introduction

Dairy cattle end their careers in the beef industry, and what happens towards the end of their dairy career has a huge impact on the reputation and safety of the beef industry. Two main components of carcass quality are drug residues and injection site lesions. There are high risk behaviors which contribute to problems in each of these areas.

Avoiding Violative Carcass Residues

In the U.S., it's simple to avoid violative carcass residues, just use the product exactly as labeled and observe the withdrawal time. The label regimen includes disease indication, dose, route, duration, frequency, and injection site. A mechanism for checking withdrawal times prior to shipping of cull cows should be instituted just as for returning cows to the milking string after a milk withdrawal time. A system where the cow does not ship until her withdrawal time has been checked is a basic tenant of residue avoidance programs.

If the product is to be used in any manner inconsistent with the label, then a veterinarian must prescribe this use within a veterinarian-client-patient relationship and the regulations of the Animal Medicinal Drug Use Clarification Act (AMDUCA) must be followed. The veterinarian is responsible for determining an exaggerated slaughter and milk withdrawal time; the Food Animal Residue Avoidance Databank (FARAD) is the best source for assigning extended withdrawal times. If FARAD can't provide a withdrawal time, it is a good indication that sufficient data do not exist to assign a withdrawal time for this extralabel use, and the drug should not be used for this purpose.

Foreign markets lead to some challenges in that we have different maximum residue limits (MRLs) in different markets. Their withdrawal times may be based on different formulations (you need to check), and different calculation procedures, so without the appropriate information we can get in trouble by just adapting foreign withdrawal times. If you are selling into a system where a food animal product will be sold into a foreign market, you must work with the purchaser to assure that the proper withdrawal times are observed.

Four Basic Tenants of Residue Avoidance

Here are 4 concepts which I feel are very important in avoiding violative residues.

1. Serum/plasma doesn't necessarily represent tissue concentrations. And, elimination characteristics in serum/plasma are not necessarily the same as the tissues, which may differ dramatically amongst themselves. Sometimes veterinarians have relied on serum or plasma drug elimination estimates to approximate extended withdrawal times for extralabel use. Besides the potential difference between the blood and target residue tissues, the science behind residue depletion can be complex, so back to FARAD.

2. Drug elimination from edible tissues can behave very differently beyond and below existing data (i.e., you can't extrapolate beyond the available residue depletion data to predict behavior at lower concentrations, it might be the same or it might not). One of the reasons you might not be able to safely use a product is because it has no tolerance and there are no data to show when the drug reaches an undetectable concentration using current technology.

3. If a foreign market is a possibility, get help.

4. Zero is getting smaller and smaller. Technologies such as advanced mass spectrometry systems are making it possible to detect lower and lower concentrations of residues. If there is no tolerance for an extralabel drug, then any detected in meat, milk, or eggs is volative.

Development of Tolerances in the United States

To understand how violative residues can happen, it is important to understand the science that goes into establishing how much of a drug or metabolites can remain in a tissue at slaughter, and how withdrawal times are established to assure that this concentration is not exceeded. The progression of arriving at a withdrawal time is NOEL, ADI, safe concentration, tolerance, and finally a withdrawal time.

First, toxicity studies are used to determine a No Observable Effect Level (NOEL). A safety factor is then applied to the NOEL based on the type of toxicity studies used in developing the NOEL, which creates an Acceptable Daily Intake (ADI, in µg /kg). The ADI is less than the NOEL. This ADI is for total residues of the drug. The ADI is taken times a 60 kg human to come up with the total ADI (total µg which may be consumed in a day).

This total ADI is then divided by the grams of intake for each of the edible tissues to come up with the safe concentration for total residues of the drug in each tissue. The total estimated daily

intake for each of the potential target residue tissues is used for each of the tissues in this calculation: muscle 300 g, liver 100 g, fat 50 g, and kidney 50 g. If the drug is labeled for lactating dairy cattle, the ADI is split between each of these tissues and milk. If the drug does not have this approval, then no ADI is partitioned to milk, and the total ADI is used to determine the safe concentration for each of the 4 tissues. Generally half of the ADI is allocated to the tissues and half to the milk. The same goes for laying chickens; the ADI is partitioned between the chicken tissues and eggs. For an explanation of the calculations, see pages 15 and 16 of guidance # 3 from the FDA Center for Veterinary Medicine (FDA/CVM GFI #3)

The Code of Federal Regulations (CFR) for tolerances is a historical document reflecting the procedures in place at the time of the establishment of that tolerance (21 CFR Part 556). For example, many of these tolerances were established with a muscle consumption value of 500 g, resulting in a lower safe concentration than would be established with the current value of 300 g. The sponsor may ask the CVM to recalculate the safe concentrations and tolerances for the tissues based on the new consumption value and the existing ADI. For example, liver consumption is now 100 g rather than 250 g (food factor of 0.5 x 500g for meat, is the way they used to figure it).

If the safe concentration is left as total residues, you have a maximum residue limit (e.g., European Union), where the regulatory method specifies the parent drug and metabolites to be measured (e.g., chlortetracycline and 4-epichlortetracycline). In the U.S., we focus on the marker residue, which is either the parent drug or a key metabolite. This is done by determining the % of the total residues represented by the marker residue at or near the withdrawal time. For example, if the marker residue comprises 40% of the total residues, then the tolerance for this marker residue is 40% of the total safe concentration for all residues. With that understood, it is now clear that a MRL of 100 ppb would be more stringent that a tolerance of 100 ppb. The tolerance is for one specific compound, which may be the parent compound or a dominant metabolite. The MRL would include this compound and whatever additional metabolites (or perhaps the parent) are included in the regulatory method.

In the U.S., the tolerance for a carcinogen is zero, and the withdrawal time is based on a non-carcinogenic metabolite being at a concentration which indicates that the carcinogenic parent drug (and perhaps carcinogenic metabolites) is not detectable. If the work were done again today for these compounds, the withdrawal time would have to be extended for some due to the ever decreasing criteria of “non detectable”.

How do zero tolerances happen? If there are no established tolerances or MRLs, then any amount detected is violative. Of course the MRL can be set at zero, too, such as in the case of carbadox (swine feed medication) in muscle for Japan, Hong Kong, Korea, and about everywhere else. In the U.S., the tolerance for the marker residue is 0.03 in the liver, indicating

that no carcinogenic compounds could be detected in edible tissues when the marker residue is at this concentration.

Recent Big Changes for Residue Testing and Criteria in Cull Dairy Cows

The Food Safety Inspection Service (FSIS) has determined that since no tolerance is listed for dexamethasone for any animal species in 21 CFR part 556, that the tolerance is therefore zero and any amount detected will be violative. This is in spite of there being no required withdrawal time on the label for dexamethasone, which is labeled for applications in cattle, including ketosis. Therefore, a withdrawal time is now necessary to attempt to achieve a residue concentration below the applicability level of the new FSIS mass spectrometry testing method, which is 50 ppb (FSIS 9 CFR parts 417). This interpretation of the tolerance for dexamethasone affects all food animal species. The best source for new, extended withdrawal times is FARAD which will base the recommendation off of the dose, route, duration, and frequency of administration being used.

Another big change for residues in cull dairy cows is the FSIS and FDA interpretation that tolerances established in cattle do not apply to dairy cattle unless dairy cattle are specifically included on the label. For example, if florfenicol (Nuflor, Merck Animal Health) is used for the label indication of bovine respiratory disease in beef cattle (excluding veal calves) or dairy cattle (females, under 20 months of age), the label withdrawal time is 38 days for the 40 mg/kg subcutaneous dosing regimen (Florfenicol label, Animal Drugs @ FDA). The tolerance for cattle which is the basis for this withdrawal time is 3700 ppb of florfenicol amine (the marker residue) in the liver, which is the target residue organ (21 CFR Sec. 556.283).

With the current interpretation, if used in a dairy female bovine aged 20 months of age or older (the same as the lactating cow definition of the FDA/CVM), then the tolerance becomes zero. Any concentration above the FSIS mass spectrometry applicability level of 100 ppb would be violative. This is 37 times less than the tolerance established for beef cattle. The veterinarian involved in the decision for any extralabel use of florfenicol in lactating dairy cows should consult with FARAD to determine a substantially extended withdrawal time.

This change is only for drugs without lactating dairy cattle on the label. Antibiotics such as ceftiofur (Naxcel, Excenel, Excede, Pfizer Animal Health) and Liquamycin LA-200 (Pfizer Animal Health), which have lactating dairy cattle on the label, will have any residues evaluated according to the tolerance established for the drug by the FDA/CVM.

What Goes Wrong When Residues Occur?

The top 10 residues in cull dairy cows, in order of occurrence, from 2005 to 2010 are (FDA compliance and Enforcement):

- Penicillin
- Flunixin (only cattle that are positive for antibiotics are tested for flunixin)
- Sulfadimethoxine
- Gentamicin
- Ceftofur
- Sulfamethazine
- Oxytetracycline
- Neomycin
- Tilmicosin
- Tetracycline

Penicillin is an excellent example of a drug available over-the-counter for which the label is not commonly followed. Alterations in dose, route, volume per injection site, and injection site are common, and require careful construction of an extended slaughter withdrawal time in conjunction with a veterinarian.

Common causes of residues are (FDA compliance and enforcement):

- Exceeding the approved dose
- Shortening the withdrawal period
- Using a drug in an extralabel manner without the required veterinary involvement
- Using a drug in an unapproved species (e.g., lactating dairy cow)
- Altering the site of administration from the label indication
- Giving the wrong drug by mistake

Other big deficiencies leading to the occurrence of violative residues are the lack of written treatment guidelines which serve as the basis for personnel training, and the lack of treatment records.

How Quality Assurance Has Been Addressed

The precursor to Beef Quality Assurance (BQA) began in the late 1970s as the Beef Safety Assurance program. In the early 1980s, the Beef Safety Assurance program focused on making sure beef was free from chemical residues. Beef Quality Assurance Programs funded by checkoff dollars began in individual states in the early 1990s, about the same time that the Beef Quality Task Force was started. A real milestone that I remember is the first National Beef Quality Audit in 1991. This was a real eye opener as to what our injection practices were

causing in carcasses in the packing plants. These types of data drive real changes in the industry, such as our changes in injection practices for clostridial vaccines. Repeated audits encouraged the industry to continue with education initiatives as key indicators improved over the next decade. Today, the beef industry continues an emphasis on subcutaneous injections and the proper locations for all injections.

The first National Market Cow and Bull Beef Quality Audit was conducted in 1994. During the 1990s, states with large populations of dairy cattle adapted BQA principles to implement dairy quality assurance programs which were also geared to producers. A transportation BQA manual came out in 2006, followed by the national BQA trainers manual in 2008 and the initiation of the BQA awards program (for both beef and dairy) in 2009. Also in 2009, the BQA Feedyard Assessment program began, and the National Dairy Animal Care & Quality Assurance Manual was released. And most recently, in 2010, The BQA stocker/cow-calf, seedstock assessment manual was made available.

The Beef Quality Assurance program started in the 1970s and has continued to expand across different production segments to address subjects such as residues, carcass quality, and animal handling. This history and the documents may be accessed at the BQA site (Beef Quality Assurance). The National Dairy Animal Care and Quality Assurance Producers Manual may be downloaded directly from this website (Dairy BQA manual). This manual encompasses the National Beef Quality Assurance Guidelines issued by the National Beef Quality Assurance Program and the Principles & Guidelines set forth by the National Dairy Animal Well-Being Initiative.

Between state and national initiatives, a lot of good people have worked hard to provide the basis for quality assurance in cull dairy cattle, including a big emphasis on violative residue avoidance. The lack of individual recognition of the multiple state efforts in beef and dairy quality assurance in this article by no means is intended to ignore these efforts.

Putting It All Together In a Plan

One of the programs specifically focused on residue avoidance in cull dairy cows is the Wisconsin Veterinary Medical Association and Professional Dairy Producers of Wisconsin Hazard Analysis and Critical Control Points (HAACP) plan (WVMAs HAACP Plan). This plan started when Wisconsin was identified as leading the nation in dairy beef residues in 2009. The plan focuses on 6 key points.

- A veterinary-client-patient relationship
- A drug list detailing all drugs used on the dairy and how they are used
- Developing protocols based on the farm and skill sets of employees

- Standard operating procedures (SOPs)
- Records
- Oversight by a veterinarian focused on drug use, protocol/SOP drift, identification of problem cows

Perhaps one of the most compelling slides in the WVMA presentation on this HAACP plan states that true jeopardy is having protocols and not following them. This HAACP plan does a nice job of summarizing the messages of many organizations working to assure carcass quality from dairy beef. If you combine this plan with the common problems the FDA/CVM found in residue violation cases, the road map is obvious.

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Antimicrobial Resistance in Human and Veterinary Patients

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We can split this discussion into two parts, not necessarily unrelated. The first is what resistance challenges we might see in infectious diseases of food animals that arise from our use in animal agriculture. The second part is any effect we may have on human therapeutics.

These proceedings discuss

- The definition of resistance
- Selection for resistance
- Resistance challenges in human health
- Resistance challenges in veterinary species
- Transfer of resistance from animals to humans
- Tetracyclines as an example in cattle

To discuss the relevance of food animal antimicrobial use to human therapeutics, we first need to outline the resistance challenges in both human and veterinary medicine. This presentation attempts to summarize some of the major concerns in resistance development along with key articles explaining relevance, epidemiology, and prevalence. It is not intended to be an exhaustive review of the literature and the interested practitioner should use the cited literature herein as a basis for continued, extended reading. But before we can discuss resistance, we must define resistance.

What kind of resistance are we talking about?

We sometimes become confused as to the type of "resistance" we are talking about. As clinicians, you are concerned about clinical resistance, based on clinically derived breakpoints. These approved breakpoints are developed and approved by the Clinical and Laboratory Standards Institute Veterinary Antimicrobial Susceptibility Testing Subcommittee (CLSI VAST) based on the following.

- Clinical outcomes coupled with pathogen susceptibility data
- MIC distributions of wild type isolate collections
- Pharmacokinetic/pharmacodynamic modeling

These breakpoints are intended to give guidance on the probability of the antibiotic working on a combination of a pathogen, antimicrobial, disease, animal species, and specific treatment

regimen. Once you deviate from any of these, the predictive value of the breakpoint is greatly diminished.

The second type of "resistance" is related to changes in population profiles of "wild type" susceptibility distributions. Instead of a clinical breakpoint, these are now referred to as an "epidemiological cutoff". These cutoffs are defined to indicate a change from the original population minimal inhibitory concentration (MIC) distribution, and may be developed to indicate appearance of resistance genes. Regardless, they are not necessarily correlated to clinical response and it is very important to understand what changes based on epidemiological cutoffs convey in relation to clinical efficacy. One of the outcomes of using both epidemiological cutoffs and clinical breakpoints is that different monitoring systems may be declaring "resistance" at different MICs.

So where do resistant organisms come from?

Here is the basic question.

- Do resistant organisms develop from spontaneous mutations in your patient (or a population of patients, such as in some food animal applications) during antimicrobial use and then proliferate within the favorable climate of antimicrobial selection pressure?
- Or, are they already present at a low prevalence level and then proliferate in the new environmental "rules" imposed by the presence of antimicrobials (clonal dissemination and selection)?

My impression from the literature and sitting through and participating in meetings, debates, and outright arguments is that dissemination of resistant bacterial clones is a primary driver in what we are seeing in human and veterinary medicine. Spontaneous mutations can and do occur, but the rapid changes in resistance over broad areas, and also the similarities between isolates suggests that the spread of clones is a primary driver. Clones may be inaccurate in that it implies that it is the spread and proliferation of a single organism, when in fact what really matters is the spread and dissemination of genetic elements that code for resistance.

Another very basic concept is that selection for a resistant pathogen or bacteria may be due to an entirely different selection pressure than the antimicrobial in which we happen to be interested. Multiple-drug resistance mechanisms allow co-selection for resistance traits. And, it doesn't even have to be an antimicrobial in the way we typically think of them. Co-selection by environmental disinfectants can co-select for antimicrobial resistance, as demonstrated for pine oil for *E. coli*, and triclosan for *Pseudomonas aeruginosa*.[1,2] The presence of pathogens such as Vancomycin-Resistant Enterococci (VRE), *Pseudomonas*, and Methicillin-Resistant *Staphylococcus aureus* (MRSA) on surfaces, pagers, and stethoscopes has been well documented in human studies.

We don't cause the original spontaneous mutations. But, once these mutations take hold in an environment, we are responsible for aiding in selection and spread. As Pogo said, "We have met the enemy and he is us".

What are the challenges on the human side of medicine?

Hospital acquired infections. One publication gives us a quick look into the challenges in human hospitals. These data are from a Centers for Disease Control and Prevention (CDC) summary.[3] The objective was to describe the frequency of selected antimicrobial resistance patterns among pathogens causing device-associated and procedure-associated healthcare-associated infections (HAIs) reported by hospitals in the National Healthcare Safety Network (NHSN). Data were collected on HAIs reported to the Patient Safety Component of the NHSN between January, 2006 and October, 2007. These HAIs included…

- Central line-associated bloodstream infections
- Catheter-associated urinary tract infections
- Ventilator-associated pneumonia
- Surgical site infections

Overall, 463 hospitals reported 1 or more HAIs: 412 (89%) were general acute care hospitals, and 309 (67%) had 200-1,000 beds. There were 28,502 HAIs reported among 25,384 patients. The 10 most common pathogens accounting for 84% of reported HAIs were…

- Coagulase-negative *staphylococci* (15%)
- *Staphylococcus aureus* (15%)
- Enterococcus species (12%)
- Candida species (11%)
- *Escherichia coli* (10%)
- *Pseudomonas aeruginosa* (8%)
- *Klebsiella pneumoniae* (6%)
- Enterobacter species (5%)
- *Acinetobacter baumannii* (3%)
- *Klebsiella oxytoca* (2%)

As many as 16% of all HAIs in this report were associated with the following multidrug-resistant pathogens.

- Methicillin-resistant *Staph. aureus* (8% of HAIs),
- Vancomycin-resistant *Enterococcus faecium* (4%),
- Carbapenem-resistant *Pseudomonas aeruginosa* (2%),

- Extended-spectrum cephalosporin-resistant *Klebsiella pneumoniae* (1%),
- Extended-spectrum cephalosporin-resistant *E. coli* (0.5%),
- Carbapenem-resistant *A. baumannii*, *K. pneumoniae*, *K. oxytoca*, and *E. coli* (0.5%).

"Bad Bugs, No Drugs" report of the Infectious Disease Society of America

In 2004, the Infectious Disease Society of America (IDSA) came out with their "Bad Bugs, No Drugs" report.[4] This report was updated in 2009, implicating the same organisms as primary challenges for antibiotic resistance in human medicine.[5] The primary pathogens were termed the "ESKAPE" pathogens because they escape attempts at antimicrobial therapy.

E*nterococcus faecium*
S*taphylococcus aureus*
K*lebsiella pneumoniae*
A*cinetobacter baumanii*
P*seudomonas aeruginosa*
E*nterobacter* spp.

In the 2009 report, these pathogens were still implicated as being responsible for the majority of U.S. hospital infections. In addition, CDC data show rapidly increasing rates of infection due to Methicillin-Resistant *Stapylococcus aureus* (MRSA), Vancomycin-Resistant Enterococci (VRE), and fluoroquinolone-resistant *Pseudomonas aeruginosa*. The report stated that more people now die of MRSA infection in U.S. hospitals than HIV/AIDS and tuberculosis combined. In addition, several very resistant Gram (-) pathogens are emerging as significant pathogens in the U.S. and around the world: Acinetobacter species, multidrug-resistant *Pseudomonas aeruginosa*, carbapenem-resistant *Klebsiella* species and *E. coli*. The carbapenems (e.g., imipenem and meropenem) are our most powerful beta-lactam antibiotics, and the appearance of widespread resistance to these antimicrobials is very alarming.

Centers for Disease Control and Prevention Report – Antibiotic Resistance Threats in the United States, 2013

The Centers for Disease Control and prevention recently released a report describing the major antibiotic resistance threats to human health.[6] In this report, the major threats were classified as threat levels of urgent, serious, and concerning.

> **Microorganisms with a threat level of urgent** – These are high-consequence antibiotic-resistant threats because of significant risks identified across several criteria. These threats may not be currently widespread but have the potential to become so and require urgent public health attention to identify infections and to limit transmission.

Clostridum difficile
Carbapenem-resistant Enterobacteriaceae
Drug-resistant *Neisseria gonorrhoeae*

Microorganisms with a threat level of serious – These are significant antibiotic-resistant threats. For varying reasons (e.g., low or declining domestic incidence or reasonable availability of therapeutic agents), they are not considered urgent, but these threats will worsen and may become urgent without ongoing public health monitoring and prevention activities.

Multidrug-resistant *Acinetobacter*
Drug-resistant *Campylobacter*
Fluconazole-resistant *Candida*
Extended spectrum □-lactamase producing Enterobacteriaceae (ESBLs)
Vancomycin-resistant *Enterococcus* (VRE)
Multidrug-resistant *Pseudomonas aeruginosa*
Drug-resistant non-typhoidal *Salmonella*
Drug-resistant *Salmonella typhi*
Drug-resistant *Shigella*
Methicillin-resistant *Staphylococcus aureus* (MRSA)
Drug-resistant *Streptococcus pneumoniae*
Drug-resistant tuberculosis

Microorganisms with a threat level of concerning – These are bacteria for which the threat of antibiotic resistance is low, and/or there are multiple therapeutic options for resistant infections. These bacterial pathogens cause severe illness. Threats in this category require monitoring and in some cases rapid incident or outbreak response.

Vancomycin-resistant *Staphylococcus aureus* (VRSA)
Erythromycin-resistant Group A *Streptococcus*
Clindamycin-resistant Group B *Streptococcus*

Resistance challenges in veterinary medicine (including zoonotic concerns):

Weese has published an excellent review of antimicrobial resistance issues in companion animals (2008).[7] The primary organisms addressed in this review are as follows.

- *Staphylococcus aureus* and *Staphylococcus pseudintermedius*: both methicillin susceptible and resistant.
- Enterococci: *Enterococococcus faecium* and *Entercoccus faecalis*.
- *Streptococci*: *Strep. zooepidemicus* and *Strep. Equi* in horses, *Strep. canis*
- *Escherichia coli*
- *Salmonella*
- Pseudomonas

The issue of MRSA highlights issues of zoonotic interactions from multiple veterinary species.

Methicillin-Resistant *Staph aureus* (MRSA): a 2008 review article has summarized literature on animal occurrence, including cattle, dogs, cats, sheep, chickens, horses, rabbits, seals, and psittacine birds.[8] Significant research has been conducted evaluating the potential for exchange of isolates between people and their pets.

Kottler, et al., evaluated the prevalence of MRSA in people and pets in the same household.[9] The sample consisted of one human nasal swab and one dog or cat nasal and fecal swab from 586 households. *Staph aureus* was classified as methicillin resistant (MRSA) or susceptible (MSSA). Pulsed-field gel electrophoresis (PFGE) and *spa*-typing were used to characterize the relatedness of *S. aureus* and MRSA between pets and humans. There was no difference in MRSA prevalence in households with human healthcare workers, veterinary healthcare workers, or without healthcare workers. The following table displaying prevalence of MSSA and MRSA in humans and pets is adapted from the publication.

	MSSA	MRSA
Humans	21.5%	5.6%
Pets	7.9%	3.4%

In 4 of the 586 households (0.7%), the MRSA found in humans was the same strain as that found in the pet.

Faires, et al., evaluated the prevalence of concurrent infection in households where either a person or pet had a diagnosed MRSA colonization.[10] In part 1 of the study, 22 households were identified as having an MRSA infection in a pet (19 dogs and 3 cats). In these households, 10 of 56 humans (17.9%) were also colonized with MRSA. In part 2 of the study, 8 households were identified where humans had MRSA cultures from dermal abscesses. In only 1of these households was MRSA also isolated from a pet. In almost all cases of co-colonization or infection, the isolates were indistinguishable by PFGE.

O'Mahony, et al., evaluated MRSA isolates from dogs, horses, a cat, a rabbit, and a seal in Ireland along with isolates from 10 caregivers.[11] The PFGE results for the equine MRSA isolates were indistinguishable from the results for those isolates originating from the caregivers for the horses.

Several studies have evaluated risk factors for infection with MRSA in companion animals. Faires, et al., evaluated risk factors for 40 MRSA infected dogs compared with 80 MSSA infected dogs.[12] The highest prevalence of both infections was in ears and skin. The statistically significant risk factors for MRSA infection as compared to MSSA infection included the use of any antimicrobial prior to diagnosis (odds ratio 2.84), use of fluoroquinolones (OR 3.58), use of β-lactams (OR 3.58), or intravenous catheterization (OR 3.72).

A retrospective study in horses in Canadian and American referral hospitals evaluated MRSA infections in 115 horses.[13] The infections originated both in the referral hospitals and in the community, with the frequency of both being approximately equal. Community acquired infections were significantly associated with previous hospitalization and previous gentamicin therapy. Hospital-acquired MRSA infections were significantly associated with infected incision sites.

Increasing attention in the literature has been paid to MRSA in swine and potential zoonotic concerns. There is extensive literature on types and occurrence of MRSA in farm workers. While swine workers and veterinarians have been demonstrated to have nasal carriage of the MRSA type found in swine herds, epidemiological studies suggest that colonization is primarily limited to those working with the swine and further transmission is limited to familial communities of these exposed workers.[14] In the U.S., the human community-acquired outbreak strains are different from animal strains. In the Netherlands, a new type of MRSA (ST 398) is epidemiologically associated with pig and cattle farmers and is said to be > 20% of carriage in humans.[15] MRSA has also been identified in bovine mastitis isolates.[16] The authors of a 2012 study using single nucleotide polymorphisms (SNPs) to evaluate 89 CC398 MRSA isolates proposed that this MRSA originated in humans as a methicillin-susceptible isolate and then acquired tetracycline and methicillin resistance in livestock, but also lost phage-carried human virulence genes.[17] MRSA CC398 has been documented to cause disease in humans, although it is not a major player in MRSA-associated disease in humans and appears to be a poor long-term colonizer.[18,19]

MRSA is an example of a resistant organism (which may also be multi-drug resistant) that brings the issue of treating our veterinary patients together with concerns about the effect of this pathogen's presence on our clients. There are no free lunches, as pathogens which have developed resistance to one main line of therapy will likely also develop resistance to the next great thing in therapy.

Bovine respiratory disease pathogens: Another area of resistance concern involves the pathogens for bovine respiratory disease as displayed in isolates originating from high-risk calves in the United States. Lubbers and Hanzlicek published a retrospective analysis of Mannheimia haemolytica susceptibility results during 2009-2011 from the Kansas State Diagnostic Laboratory.[20] The percentage of isolates showing resistance to at least 3 of our main classes of antibiotics used for BRD were 42%, 46%, and 63% in 2009, 2010, and 2011 respectively.

Has the transfer of resistance from food animals to humans been demonstrated?

The Pew Trust recently funded a paper which summarized evidence for a link between food animal use of antimicrobials and therapeutic resistance in humans.[21] This paper, by Marshall and Levy, evaluated evidence for animal to human spread of antibiotic resistance. Ten references were cited which detailed some type of similarity between an isolate of a bacteria in food animals (5 papers for human colonization and 5 for infection) which were related to direct or indirect animal contact. Only one of these papers documented adverse effects in the humans, that being a Salmonella Newport hamburger-borne outbreak. These are basically what there is out there.

In my opinion, it is clearly shown that bacteria can be exchanged between animals and humans, either directly or through food, and that theses pathogens may be resistant. The challenge relating to interpreting the effect and importance of these relationships is shown by the fact that few of the isolates shown in these references are included on the "ESKAPE" list.
Some notable quotes from this article include the following.

"In the above examples, the link to nontherapeutic antibiotic use in the farm animals is still circumstantial and largely implied, often because the authors do not report any statistics on farm use of antibiotics. Interpreting these studies is also difficult because of the widespread resistance to some drugs in bacteria of both animals and humans and the ubiquitous nature of resistance genes. Moreover, the same farmer may use antibiotics for both therapeutic and nontherapeutic purposes."

"The complexities of the modern food chain make it challenging to perform controlled studies that provide unequivocal evidence for a direct link between antibiotic use in animals and the emergence of antibiotic resistance in food-borne bacteria associated with human disease."
"While this concrete evidence is limited, a small number of studies have been able to link antibiotic-resistant infection in people with bacteria from antibiotic-treated animals. While not necessarily involving NTAs, these studies substantiate the considerable ease with which bacteria in animals move to people."

We can agree on these passages. It certainly is hard to link the findings in these 10 references to specific drug uses. I especially agree that sorting out the uses for increases in rate of gain and feed efficiency is not based on any type of evidence.

"For example, a multidrugresistant *Salmonella enterica strain in a 12-year-old Nebraska* boy was traced to his father's calves, which had recently been treated for diarrhea. Isolates from the child and one of the cows were determined to be the same strain of CMY-2-mediated ceftriaxone-resistant *S. enterica."*

"It is now believed that the 1992 multiresistant *Vibrio cholerae epidemic in Latin* America was linked to the acquisition of antibiotic-resistant bacteria arising from heavy antibiotic use in the shrimp industry of Ecuador (13, 156)."

My confidence in the authors being straight up about interpretation of the articles is shaken by the interpretation of the Salmonella article. In this reference, the authors of the original paper (Fey, et al.) didn't do what I did; they didn't actually visit the farms or interview any of the involved people.[22] The facts are that only one, 1 gram vial of Naxcel was dispensed for treatment of the calves in the 4 affected herds, and that was only for the index case prior to culture and susceptibility results becoming available. How do Marshall and Levy know that the calves were treated, or that treatment contributed to the resistance of the Salmonella? They don't, but is doesn't stop them and many others from the insinuation that antibiotic use in food animals caused this resistant organism to be present. In fact, if the original authors would have done their field work, they would have found that geese were very prevalent on the calving grounds (a major flyway), that the isolate suddenly appeared in close temporal association in all herds, and that the isolate was gone the next year and not seen since. All of these point to a transient presence, most likely introduced by migratory water fowl. This organism was unable to find a niche due to antimicrobial use or any other factor. So, an article documenting the transmission of an enteric pathogen from a food animal population in which it was transiently present is now used as an indictment of antimicrobial use in animals.

The sum of evidence and the nature of the argument is best summed up by the following conclusion statement from the Marshall/Levy article.

"Data gaps continue to fuel the debate over the use of NTAs in food animals, particularly regarding the contribution and quantitation of commensal reservoirs of resistance to resistance in human disease. Nonetheless, it has been argued reasonably that such deficits in surveillance or indisputable demonstrations of animal-human linkage should not hinder the implementation of a ban on the use of nontherapeutic antibiotics."

That is the essence of the argument. The cited reasonable argument is a letter to the editor. I am certainly not arguing that there is not a link between food animal bacteria and foodborne pathogens. Nor do I argue that there is no evidence to show that resistant organisms can travel through the food chain, or be directly transmitted to humans. However, we are establishing a level of evidence for evaluation of all uses of antimicrobials in food animals, not just growth promotant uses and the arguable classification of "nontherapeutic", and this level of evidence for singling out individual use classes is troublesome.

Tetracyclines as an example in cattle

There are extensive, transmissible resistance genetic elements out there for the tetracyclines. A 2010 review of the tetracycline resistome noted 1,189 different reported resistance genes present in 84 bacterial genera, which included 354 bacterial species.[23] These genes comprise 41 classes, with three major mechanisms.

- Actively pumping the drug out of the cell
- Enzymatic degradation of the drug
- Protection of the drug binding site

Another paper has documented the methods by which these genes are transferred between bacteria.[24]

- Gram-negative and Gram-positive genes coding for tetracycline efflux are generally associated with plasmids.
- tet(S) and tet(O) encode for ribosomal protection and are located both in the chromosome and in conjugative plasmids
- tet(M) and tet(Q) (also ribosomal protection) are typically associated with conjugative transposons
- Other mechanisms include enzymatic inactiviation (tet(X) and tet(37)
- Mosaic genes have also been described, which are combinations of individual genes (e.g., tet(O/32/O)

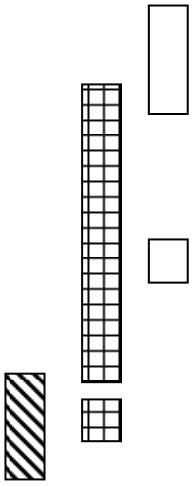
From these inputs, it is apparent that there are multiple options for tetracycline class resistance and that the mobility of these genetic options are well documented.

The next point for consideration is the breadth of regimens and the use classifications across these regimens. Here is the range of in-feed approvals for tetracyclines in cattle, with the highest dosing regimens at the top. These are spaced to illustrate the range of doses. (CTC = chlortetracycline, OTC = oxytetracycline, TC = tetracycline)

CTC: 10 mg/lb BW for up to 5 days
CTC: 400 g/ton to provide 10 mg/lb per day in calves up to 250 lbs
TC: 22 mg/kg for 3-5 days in calves

OTC: 0.5 to 2.0 g/hd per day

CTC: 350 mg/hd per day in beef cattle under 700 lbs
CTC: 0.5 mg/lb per day in beef cattle over 700 lbs
CTC: 350 mg/hd per day in beef cattle
CTC: 25-70 mg/hd per day in calves 250-400 lbs
CTC: 70 mg/hd per day in growing cattle over 400 lbs
CTC: 0.1 mg/hd per day in calves up to 250 lbs



Rate of gain/Feed efficiency

Prevention or control claims

Treatment claims

From this illustration, it is apparent that focusing on the rate of gain/feed efficiency claims as the "subtherapeutic" bogeymen implies that somehow there is a line where selection for resistant organisms increases or decreases based on label claims. Obviously, there is no science-based information to drive this assumption, but rather, in my opinion, it is based on selecting the most politically acceptable route for an initial removal of food animal antimicrobial uses. The challenge in allowing the rate of gain/feed efficiency antimicrobials to be removed based on the "precautionary principle" is that we then end up with this precedent in evaluating the prevention/control claims.

How can we put the dose ranges above in some kind of context as to the potential for selecting for tetracycline-resistant organisms? First, we need to evaluate what kind of dose it takes to alter the intestinal flora and/or select for resistant organisms in the gut. But, even before that, just how much tetracycline remains active in the gut anyway? My analysis of 7 published studies (rats, mice, humans, pigs) found a range of 0.2% to 13.4%, with an additional outlier showing 67% in rats.

These data were derived from experiments where they determined the actual active amount still functioning in gut contents or feces. Some difficulty is brought into this because we don't know exactly how this varies between different areas of the gut, and the resulting effects in various areas of the gut. So right away it is apparent that the low doses have even less drug surviving to have an effect in the gut.

The next step is to determine just how much drug needs to be present, and active, in the gut to have an effect on the flora. Several studies have evaluated this level.
Carmen, et al. (2006) evaluated three concentrations of tetracycline in a chemostat system inoculated with human fecal flora. Concentrations of 0.15, 1.5, and 15 μg/ml were used in the systems, equivalent to daily doses of 0.025, 0.25, and 2.5 mg/kg per day in a 60 kg human (based on fecal concentration data by van Marwyck, 1958). Statistical analysis identified the lowest and middle concentrations as having no observable adverse effect on the bacterial population.

Perrin-Guyomard, et al. (2001) used a human-flora-associated (HFA) mouse model to evaluate water tetracycline concentrations of 0, 1, 10, and 100 mg/liter administered for 8 weeks.[25] Upon further calculation, these are equivalent to doses of 0, 0.125, 1.25, and 12.5 mg/kg BW. The authors cited the highest dose as being capable of disrupting the capability to resist *Salmonella* infection by a resistant isolate. At the lowest dose, there were transient increases in percent resistant *Bacteroides fragilis* and Enterococci. These effects were more pronounced at higher doses.

Tancrede and Baraket (1987) administered 2, 20, or 2000 mg/day to human volunteers for 7 days. In 60 kg humans, this would be equivalent to 0.03, 0.33, 33 mg/kg per day.[26] The low dose caused no change in % resistance in the dominant anaerobes. The two high doses did induce changes in resistance.

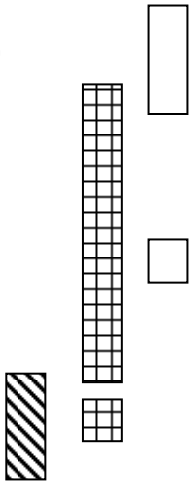
The gastrointestinal tract characteristics of the human and human flora associated mouse are obviously quite different from the bovine, but as our only means of evaluating this effect, we see a pattern in these 3 studies of daily doses of 0.25 and 0.03 mg/kg per day having no effect in two of the studies. In the other study, a dose of 1.25 mg/kg caused no change in the ability for resistant *Salmonella* to colonize the gut, while the low dose of 0.125 mg/kg per day caused some transient increases in resistant flora. These mixed results highlight the uncertainty in this type of modeling, but do support a conclusion that effects are dose dependant, and that the lowest doses cause the least effect.

Now let's look at the dose ranges of tetracycline shown above and evaluate them in the light of calculated mg/kg per day.

CTC: 10 mg/lb BW for up to 5 days (22 mg/kg)
CTC: 400 g/ton to provide 10 mg/lb per day in calves up to 250 lbs (22 mg/kg)
TC: 22 mg/kg for 3-5 days in calves (22 mg/kg)

OTC: 0.5 to 2.0 g/hd per day (5.5 mg/kg for 500#)

CTC: 350 mg/hd per day in beef cattle under 700 lbs (1.9 mg/kg for 800#)
CTC: 0.5 mg/lb per day in beef cattle over 700 lbs (1.1 mg/kg)
CTC: 350 mg/hd per day in beef cattle (1.1 mg/kg for 700#)
CTC: 25-70 mg/hd per day in calves 250-400 lbs (0.62 mg/kg for 250#)
CTC: 70 mg/hd per day in growing cattle over 400 lbs (0.22 mg/kg for 700#)
CTC: 0.1 mg/hd per day in calves up to 250 lbs (0.002 mg/kg for 100#)



Rate of gain/Feed efficiency

Prevention or control claims

Treatment claims

Even with all the uncertainties of model application, it is apparent that singling out growth promotion claims as the most likely candidate for removal does not focus on the most likely culprits for changes in gut flora resistance. The growth promotion claims may have an effect, but we will have to address effects of the prevention/control claims sooner or later, and the precedents set for the growth promotion claims will follow us through to the others.

What actually happens when tetracyclines are put in the feed of cattle?

The effect of chlortetracycline addition to feed at 22 mg/kg per day has been shown to be transient when evaluated in light of resistance profiles of *E. coli*.[27] In another study, including chlortetracycline in the feed for extended periods at a daily dose of approximately 0.03 mg/kg per day during a backgrounding and feeding phase in feedlot cattle increased the % of E. coli in the feces that were resistant to tetracyclines.[28] A third study found that administration of chlortetracycline at 350 mg/head per day for 197 days caused a decrease in E. coli diversity and "…an increased linked inheritance of ampicillin and tetracycline resistance genes and prevalence of specific strains at day 197."[29]

These studies demonstrate measurable effects of regimens that may or may not reflect actual use durations or doses in practice. However, the overall conclusion is yes, we can cause enteric flora changes with the tetracyclines in cattle.

Summary:

This presentation just scratches the surface of the literature as to the resistance challenges in human and animal health, and the interaction within the two. In my opinion, the major questions related to the use of antimicrobials in food animals are in relation to *Campylobacter*, *Salmonella*, and *E. coli*. The issue of MRSA is currently one of colonization with a more minor contribution to human disease from zoonotic sources, but this relationship bears watching in the future. However, it is obvious that food animal uses have little if any direct contribution to a large portion of the most critical human antimicrobial resistance issues.

In several parts of the world, the verdict has been returned on growth promotant uses of medically important (for human therapy) antimicrobials as evidenced by removal, or pending removal of these applications. Our next challenge will be to balance risk and benefit of antimicrobial uses for prevention and control of disease in food animals.

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Evolving Drug Use Regulations in Food Animals

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The pace of change in antimicrobial regulations for food animals continues to accelerate. There are 6 key areas with potential for extremely rapid change in the next 5 years. These areas are (1) the withdrawal of growth promotion uses of antimicrobials, (2) expansion of antimicrobial use reporting requirements, (3) continued legislative initiatives to remove antimicrobial uses for prevention or control of disease in food animals, (4) FSIS residue testing activities, (5) use of the AMDUCA regulations as a regulatory tool to attempt to decrease use of targeted drug classes in food animals, and (6) the potential for an FDA/CVM hearing on the hazard status of the use of tetracyclines and penicillins in animal feed.

Key Area 1: Guidance 209, Guidance 213, and Veterinary Feed Directive Proposed Rule

Links to the 3 documents discussed herein are available on the FDA Center for Veterinary Medicine website at http://www.fda.gov/AnimalVeterinary/NewsEvents/ CVMUpdates/ ucm378166.htm

Guidance 209 – April, 2013 (Final Document)

This guidance document puts forth two principles for which the FDA Center for Veterinary Medicine will seek voluntary compliance.

Principle 1: The use of medically important antimicrobial drugs in food-producing animals should be limited to those uses that are considered necessary for assuring animal health. This means that any antimicrobial drug listed as medically important for human therapeutics in Appendix A of Guidance 152 will no longer be legal to be used for improvement in feed efficiency or rate of gain after implementation of this guidance. Guidance 209 specifically applies to antimicrobials used in the feed or water for food animals. The FDA states that they feel this principle applies to all antimicrobials used in food animals; however, Guidance 209 does not address over-the-counter injectable antimicrobials such as procaine penicillin G and long-acting 200 mg/ml oxytetracycline products (e.g., Liquamycin LA-200®).

Principle 2: The use of medically important antimicrobial drugs in food-producing animals should be limited to those uses that include veterinary oversight or consultation. This means that the remaining uses of medically important antimicrobials in the feed and water of food animals

(prevention, control, and therapy) will require authorization by a veterinarian through a veterinary feed directive. Additives for milk replacer are approved as feed additives, so they are included in this requirement.

This list of medically important antimicrobials in Appendix A of Guidance for Industry #152 includes these antimicrobial groups with current feed or water use labels (with examples of in-feed or in-water approved antimicrobials). The groups listed may have other drugs that are used in humans, but the examples listed are those used in food animals. These groups will be affected by Guidance documents 209 and 213.

- Aminoglycosides: gentamicin, neomycin
- Lincosamides: lincomycin
- Macrolides: tylosin, tilmicosin (Pulmotil® currently requires a VFD in swine and cattle)
- Penicillins (natural): penicillin G included in combination products
- Streptogramins: virginiamycin
- Sulfonamides: Includes both potentiated (e.g., trimethoprim/sulfa) and non-potentiated sulfonamides. There are no current feed or water potentiated sulfa approvals in the U.S.
- Tetracyclines: chlortetracycline, oxytetracycline, tetracycline

The list of medically important antimicrobials does not include the following antimicrobials with food animal labels. They will not require a VFD or prescription in the future based on Guidance 209, nor will they lose growth promotion claims on the label, unless added to the list of medically important antimicrobials in the future.

- Ionophores: monensin, lasalocid
- Flavophospholipol: bambermycins (e.g., Flavomycin®, Gainpro®)
- Bacitracin
- Tiamulin

The list of medically important antimicrobials in Guidance 152, Appendix A, includes these antimicrobial groups for which there are no current food animal feed or water use labels in the United States. Extralabel use in feed is prohibited in the United States. Extralabel use in water is allowed when in conformance with the Animal Medicinal Drug Use Clarification Act (AMDUCA) regulations.

- Penicillins – Penase resistant, antipseudomonal, and aminopenicillin groups
    - Aminopenicillin examples are amoxicillin and ampicillin
- Cephalosporins – first, second, third, fourth generations and cephamycins
    - Ceftiofur is the third generation cephalosporin labeled for use in food animals with injectable and intramammary approvals
    - Cephapirin is the first generation cephalosporin approved for intramammary use in dairy cattle.

    - Cephalosporins are prohibited from any use in food animals which does not conform to the label regimens, meaning that use in water is prohibited since there are no labels including use in water.
- Carbapenems – another beta-lactam group (related to penicillins and cephalosporins) with no veterinary labels
- Monobactams - another beta-lactam group (related to penicillins and cephalosporins) with no veterinary labels
- Quinolones – the forerunner group to the fluoroquinolones, there are no veterinary labels from this group
- Fluoroquinolones – Enrofloxacin was once labeled for water use in poultry but this label was removed by the FDA/CVM in 2005. The sarafloxacin label for water use in poultry was withdrawn by the sponsor in 2000.
    - Enrofloxacin is labeled for injectable treatment and control of respiratory disease in cattle (including dairy heifers less than 20 months of age) and in swine.
    - Danofloxacin is labeled for injectable treatment of respiratory disease in beef cattle.
    - Extralabel use of the fluoroquinolones is prohibited in food animals.
- Glycopeptides – no veterinary labels and prohibited for extralabel use in food animals
- Oxazolidones – no veterinary labels
- Pyrazinamide – no veterinary labels
- Isoniazid – no veterinary labels
- Rifamycins – no veterinary labels
- Chloramphenicol – no food animal labels and prohibited for extralabel use in food animals
- Metronidazole – no veterinary labels and prohibited for extralabel use in food animals
- Polymyxin B – veterinary labels are ophthalmic preparations

A list of affected products, sponsors, and withdrawn products is available on the FDA/CVM website.[1] There are 283 affected products, including new animal drug applications ("pioneer"), abbreviated new animal drug applications ("generic"), and combination new animal drug applications (which can be either pioneer or generic).

Guidance 213 – December, 2013

This guidance document puts forth nonbinding recommendations for companies to comply with Guidance 209. There was a 3 month period for companies to communicate with the FDA/CVM regarding their intent to comply with the voluntary recommendations in Guidance 209. After this 3 month period, a 3 year period began for companies to comply. After this period, the FDA/CVM would likely take steps to accomplish these goals through other regulatory routes. On March 26, 2014, the FDA/CVM released an update indicating that 25 of the 26 affected

sponsors have indicated they will comply with Guidance Documents 209 and 213. [2] This participation accounts for 99.6% of the affected products.

A company may remove the label indications for growth promotion and insert label requirements for veterinary authorization without being subjected to other requirements such as updating the label in other areas (e.g., microbial safety). The guidance document also provides suggested pathways for companies who elect to pursue prevention, control, or therapeutic claims for the regimen previously labeled as a growth promotion claim. The document also makes it clear that generic versions of original proprietary labels must alter their labels to reflect any changes in the original label.

Veterinary Feed Directive (VFD) proposed regulation – December, 2013

This proposed regulation has 5 key changes in the existing VFD regulation

- User friendly reorganization of the VFD rule
- Increased flexibility for licensed veterinarians issuing VFDs
    - The current regulation requires veterinary "supervision" for a VFD to be written. The proposed regulation changes this to "supervision or oversight".
    - The proposed regulation removes the explicit veterinary-client-patient relationship (VCPR) provision and replaces it with the requirement that veterinarians ordering the use of VFD drugs must be "in compliance with all applicable veterinary licensing and practicing requirements". This defers the VCPR standard to the veterinary profession and the individual states to determine the requirements of a valid VCPR.
    - The veterinarian will be required to specify duration of use, approximate number of animals to be fed the medicated feed, and level of VFD drug in the feed. However, they will not be required to specify the amount of medicated feed to be dispensed.
- Continued access to Category I type A medicated feed articles by unlicensed feed mills
    - Currently, a VFD drug is automatically a Category II medicated feed, which means that the type A feed article for that drug would only be available to the limited number of licensed feed mills. The proposed regulation would not require a VFD drug to automatically become a Category II medicated feed.
- Increased flexibility for animal producers purchasing VFD feeds
- Lower recordkeeping burden for all involved parties
    - Duration of record keeping is proposed to be dropped from 2 years to 1 year

Key Area 2: Regulatory or legislative initiation of antimicrobial use reporting

Current antimicrobial use reporting in the United States consists of aggregate reporting of drug classes based on sales figures reported to the FDA/CVM by sponsors as required under the Animal Drug User Fee Act (ADUFA) of 2008. The FDA/CVM has recently asked for comment on a new form or reporting these sales data, but this proposal does not seem to include more detailed information on actual drug use by species, which to my understanding is not possible from the reported aggregate sales data which are reported.[3]

Legislative pressure has been applied in an attempt to bring about more detailed reporting. Senator Diane Feinstein put a hold on the Animal Drug User Fee Act (ADUFA) this year in an attempt to force inclusion of increased reporting requirements, which was not successful.

Representative Henry Waxman has introduced the "Delivering Antimicrobial Transparency in Animals (DART) Act of 2013" as HR 820. As of 3/1/2013 it had been referred to the Subcommittee on Health.[4] This bill would require increased reporting of antimicrobial sales for all food animal antimicrobials, and requires reporting by end users of antimicrobials in the feed.

The FDA/CVM has recently asked for input on how increased antimicrobial use data might be collected for food animal uses. This input has been collected and the FDA/CVM is considering how additional antimicrobial use information might be collected. I have no idea where this will end up, but anticipate some increased reporting burden in the future.

Key Area 3: Will we see legislative prohibition of the use of antimicrobials for prevention or control of infectious disease?

Bills which purpose to drive the evaluation of prevention and control uses, but which in fact would result in their removal for at least a protracted period of time, continue to be introduced. Representative Louise Slaughter has again introduced the latest edition of the PAMTA act, "Preservation of Antibiotics for Medical Treatment Act of 2013" (HR 1150).[5] This bill has 55 cosponsors. This bill does not outright prohibit the use of antimicrobials in food animals for anything but individual therapeutic use, but sets a very high bar with a very short timeline to retain their use, clearly with the intention of establishing unattainable benchmarks.

On the senate side, Senator Dianne Feinstein has introduced the "Preventing Antibiotic Resistance Act of 2013" (S 1256). This bill has 5 cosponsors and is very similar to PAMTA.[6]

These bills have typically not made it out of committee to the floor, and have been repeatedly introduced over the last decade.

Key Area 4: Will there be continued confusion by the USDA Food Safety Inspection Service in the area of food animal drug testing cutoffs for violative/nonviolative residues?

The USDA Food Safety and Inspection Service has recently initiated a new testing procedure, including a multi-residue monitoring (MRM) mass spectrometry test. [7] The FSIS has also determined that the tolerances developed for the use class on the label shall not apply to any other use class. For example, tolerances developed for Florfenicol in the liver of beef cattle will not apply to the liver of a cull dairy cow, and therefore the effective tolerance is the "applicability level" of the FSIS testing method (lowest positive result to be called positive).

In this process, FSIS started to issue notices of violative residues to producers supplying carcasses in which any residue of dexamethasone was detected. This is because no tolerance for dexamethasone is listed in 21 CFR part 556.[8] However, the FSIS was made aware by the FDA/CVM that no tolerance is listed because the safety of the drug at the time of approval did not require that a tolerance be developed. The FSIS announced in a December 6, 2013 constituent update that they were suspending testing for dexamethasone.[9]

However, this issue highlights a problematic lack of communication between the FSIS and the FDA/CVM at the appropriate scientific level. There is also a need for FSIS to establish improved communication with food animal practitioner organizations; the notice that this standard was being applied to dexamethasone was in the form of the first violation notices. The FSIS has been made aware that publishing in the Federal Resister is not an effective form of communication with food animal veterinarians.

Also included in the MRM are both enrofloxacin and the primary metabolite, ciprofloxacin. In cattle, the marker residue is ciprofloxacin, which is quantified with the official regulatory test to determine if the amount detected is violative. In swine, the marker residue is enrofloxacin, although small quantities of ciprofloxacin may be detectable. The FSIS has detected ciprofloxacin in pigs and classified that as a violative residue because there is no swine tolerance for ciprofloxacin in 21 CFR Part 556, even though the marker residue (enrofloxacin) was below the tolerance. This is an inappropriate designation of a new marker residue and will hopefully be corrected in the near future; the marker residue being below the tolerance eliminates the need to evaluate other residues because they were accounted for during the approval process. This issue again indicates that communication between FSIS and the FDA/CVM must be improved, and that FSIS needs to seek input on testing cutoffs beyond just presence or absence of a tolerance in 21 CFR Part 556.

Another issue is that of packing plants placing high pressure on suppliers for non-violative residues. In no case should producers be punished for detected but non-violative residues. As an industry, we must be very aggressive in pushing back against such actions, and any implied need

to do so by USDA personnel. There should also not be any pressure applied to extend withdrawal times for label use of drugs beyond the label withdrawal times. These withdrawal times have been determined to be safe during the approval process, and under no circumstances should we tolerate the precedent of extending them for animals being slaughtered for domestic consumption.

Key Area 5: Will there be another use of the AMDUCA regulations for regulatory action directed towards a drug class for food animal species?

The Cephalosporin ELDU prohibition is an example of a very troubling precedent.[10] The primary concern is that even though there was absolutely no evidence to separate concerns regarding label and extralabel use, the action was taken directed at extralabel use. The use of the AMDUCA regulations as a lower-resistance regulatory pathway is troublesome to those who invested considerable effort in both the act and the regulation promulgation process, resulting in legalizing extralabel use in veterinary medicine.

There is also a concern over species inclusion. Regardless of the lack of evidence to indicate a concern for swine, this species is included in the prohibition. In the evidence cited for cattle, the authors of two of the papers state in the discussion that you really can't make the conclusion from the paper for which they are used in the FDA decision, which in my opinion was obvious from reading the articles. The FDA also left out key articles related to cephalosporin use in cattle that were not supportive of their stance on the issue. The key evidence which really supported the ELDU ban was for the injection of chicken eggs and the resulting change in susceptibility profiles of surviving *Salmonella*. The evidence for concern in cattle was paltry at best, and nonexistent for swine.

The cephalosporin ELDU prohibition is a product of the need for a visible action on cephalosporins due to pressure on the FDA/CVM, and the selection of the easiest route to enact regulatory action on the drug class. Just to be clear about this prohibition, there are multiple misperceptions involved in the document. For example, the Agency implies that the label regimen is the best to minimize selection for resistance. In fact, there is absolutely no evidence to support this claim. The label regimen is developed based on efficacy, not on suppression of resistance selection. We don't even have evidence to support optimal duration of antimicrobials for therapy, let alone the relationship of duration and magnitude of exposure to the potential for selection of resistant organisms during therapeutic protocols.

The prohibition allows the use of ceftiofur for extralabel indications but not with an extralabel regimen. The result of having the ability to use an antimicrobial for off-label indications but not

the ability to adjust the dosage appropriately is completely nonsensical, and is likely to contribute to selection for antimicrobial resistance.

The most telling direct quote from the order of prohibition was from the section refuting the allegation that the FDA/CVM was relying on the precautionary principle. *"In the preamble to the final rule, FDA addressed the question of what type of evidence would be necessary by saying that the risk determinations that would lead to prohibition of an extralabel use typically will involve documented scientific information. However, the Agency believes that it is not limited to making risk determinations based solely on documented scientific information, but may use other suitable information as appropriate."* In other words, there is a drastically different standard of evidence between what is required of a drug sponsor submitting a new animal drug application, and what is required of the FDA CVM.

While the current FDA/CVM leadership is committed to prevention and control uses being classified as judicious, therapeutic uses of medically important antimicrobials, future leadership may not share this view and the precedent of the evidence standards in the cephalosporin ELDU prohibition are troublesome.

Key Area 6: Will the FDA Center for Veterinary Medicine be forced to hold hearings on whether the use of penicillins and tetracyclines in animal feed is a hazard to human health?

In 2011, The National Resources Defense Council (NRDC), the Center for Science in the Public Interest, Food Animal Concerns Trust, and the Union of Concerned Scientists, filed a lawsuit against the FDA/CVM in the U.S. District Court for the Southern District of New York.[11] This lawsuit sought to force the FDA/CVM to act on the 1977 Notice of Opportunity for a Hearing (NOOH) which sought to address the use of tetracyclines and penicillins in animal feed. On March 22, 2012, the magistrate judge ruled that the U.S. Food and Drug Administration must act on the 1977 NOOH regarding in-feed use of tetracyclines and penicillins in animal feeds.[12] The FDA/CVM had withdrawn this NOOH in December of 2011. The FDA Commissioner (Margaret Hamburg), Secretary of Health and Human Services (Kathleen Sebelius), and Director of the FDA/CVM (Bernadette Dunham) appealed this decision in the United States Court of Appeals, Second Circuit, on May 21, 2012.[13]

The history leading up to the NOOH and subsequent activities of the FDA/CVM on this issue were detailed in a presentation by two FDA/CVM representatives at a the symposium "Public Health Implications of the Use of Antibiotics in Animal Agriculture" held as part of the Annual Meeting of the American Society of Animal Science in August of 1985. [14] In 1981, the FDA/CVM was instructed by the house appropriations committee to hold in abeyance any

implementation of the proposed withdrawals pending the results of studies to evaluate the relationship of feed use of these antimicrobials to human health.

The NRDC has previously filed a petition with the secretary of Health and Human Services to declare the subtherapeutic use of penicillin and the tetracyclines in animal feeds an imminent hazard to the public health (Nov 20, 1984). The FDA/CVM held a "legislative type" hearing on January 25, 1985 to evaluate the evidence. If the Secretary would have found the use of these antimicrobials to be an imminent hazard to public health, a formal evidentiary public hearing before an administrative law judge would have been required for removal of these uses.

Obviously, the use of these antimicrobials in feed has not been withdrawn as of the writing of these proceedings. However, should the appeal be unsuccessful, then the hearing may be held and the drug sponsors and the industry will likely be put in the position of having to defend these uses. The definitions of the terms "subtherapeutic" and "nontherapeutic" will be crucial as to what uses are considered in the hearing, especially in relation to uses for prevention and control of disease. Also in play will be the ability, or perceived ability, of GFI #209 to achieve the goals of the original 1977 NOOH. In my opinion, if this hearing occurs, it will be a telling precedent for the future of uses of antimicrobials for the prevention and control of diseases in food animals; it won't just be about tetracyclines and penicillins.

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Needlestick Injuries in Livestock Workers and Prevention Programs

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Introduction

Veterinary medicine and agriculture have historically lacked needlestick injury (NSI) research, education, and mitigation due to the relative absence of zoonotic blood-borne pathogens and the "perceived" benign nature of the injury. However depending on the procedure/pharmaceutical used, these injuries may include mild/severe bacterial or fungal infections, lacerations, local inflammation, vaccine/antibiotic reactions, amputation, miscarriage, and death. The **objective** of this report is to identify published case reports and case series/surveys on human needlestick exposure to veterinary biologics, and to review literature and educational documents describing needlestick prevention strategies for agricultural workers and veterinarians.

Methods

An electronic database search was conducted using PubMed© and CABI©. Key search terms: PubMed© - "Needlestick Injuries" [MeSH] veterinar*, "Vaccination/veterinary"[MeSH]) AND "Occupational Exposure"[MeSH], "Vaccination/veterinary"[MeSH]) AND "Occupational Exposure"[MeSH]; CABI© - needlestick injuries.sh. Article inclusion criteria were those detailing NSI in agricultural workers only. Abstracts of all search results were read and relevant articles compiled into a RefWorks© database. References cited within articles were examined to locate additional articles.

Results

Fifty-six articles were identified. Literature consisted of case reports (n=14), survey/case series articles (n=11), prevention guidance documents (n=6), and background articles (n=25). A total of 48 cases were found. Twenty-four identified injury location: 13 (54.2%) NSI to the hands: three to the right, eight to the left, and two were not specified. Eight injuries were to the legs (33.3%): five to the right and three were not specified. Of the 48 cases, 11 (22.9%) involved oil-adjuvanted vaccines. The remaining products included: other vaccines, antibiotics, analgesics/sedatives, and hormones. Forty-six (95.8%) of 48 cases reported seeking medical attention. Of the six survey/case series articles: two focused on oil-adjuvant products, one on Brucellosis RB51 vaccine, and three on tilmicosin. General recommendations from guidance documents included: proper animal restraint, avoid recapping needles, do not bend needles, do

not put needle caps in your mouth, provide appropriate training, provide sharps containers, report injuries, seek medical attention.

Conclusion

NSI in agriculture workers and veterinarians can result in injury and loss of work. It appears that NSI awareness is limited among workers. There is a need for comprehensive programs to prevent NSI on livestock operations.

Organic Dairy Farms in Minnesota

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Organic agriculture has tremendously increased in the previous decade in the United State. The number of organically certified dairy cows has increased by 6-fold from approximately 38,196 in 2000 to 249,766 cows in 2008 (NASS, 2012) and organic dairy herds represent approximately 3% of dairy herds in most States, including Minnesota. To produce organically, dairy producers have to adhere to the regulations of the National Organic Program (NOP) of the USDA-AMS (USDA, 2012). Third party certifiers audit the farms to ensure compliance with the NOP. The rules require that ruminants over 6 months of age are receiving a minimum of 30% of their dry matter through pasture for 120 days/year, are fed and bedded on organically certified feedstuffs only and only drugs and their route of administration that are specified in the NOP may be used on organic farms. The use of antibiotics, hormones and most paraciticides is principally prohibited. The exceptions are Ivermectin, Fenbendazol, Moxidectin if a heavy infestation is diagnosed by a veterinarian. Animals that are treated with antibiotics have to leave the dairy and cannot be sold as organic anymore. However, if the allowed substances are ineffective in treating a sick animal, then organic farmers must not withhold antibiotics or other effective therapies just to save the organic status of their animals. Organic advocates claim that organic cows are healthier, while opponents of organic agriculture fear that the lack of antibiotics may pose a risk for animal welfare, should an animal get seriously sick. Some recently conducted studies have found little difference in health events or bulk tank somatic cell counts between organic and conventional farms (Sato et al., 2005; Cicconi-Hogan et al., 2013) while others found lower reported incidence of clinical mastitis in organic herds (Richert et al., 2013).

Therefore, in 2012, a pilot study was conducted in Minnesota to capture management practices and health incidence on organic and conventional herds in Minnesota. All organic herds (n=114) were invited to participate. In addition, conventional herds were enrolled in the similar region. At the visit, a questionnaire about management practices and health was administered and environmental fecal composite samples were taken for detection of *Mycobacterium avium* subsp. *paratuberculosis (MAP),* a bulk tank sample was collected, fecal grab samples of 20 breeding age heifers was collected for parasite egg count (Wisconsin sugar float method) and a representative sample or all of the mature cows (if herd < 100 cows) was assessed for lameness (score 1-5), body condition (score 1-5), hock (score 1-3) and hygiene (1-4).

In the end 35 organic herds and 38 conventional herds participated. Herds were visited once between June and August 2012. Two organic herds were visited later in October and November. Furthermore, some of the conventional herds were larger than the organic herds despite best efforts to enroll predominately grass based herds of similar size to the organic herds. Therefore,

the conventional herds were split into small (<200 mature cows, SC) and large (≥200 mature cows, LC) conventional herds. Appropriate statistics were used to compare management practices and reported disease incidence and measure parameters among the 3 herd types.
The median organic herd size was 68 milking cows (interquartile range: 42-110). Organic dairy herds tended to have higher proportion of 3+lactation and more cross-bred cows than conventional herds, but the average age of the oldest cow did not differ between organic and conventional herds. The average milk production was significantly lower and the latest bulk tank SCC tended to be higher in organic herds, but the average annual bulk tank SCC, number of cows with <4 functioning quarters and the bacterial burden of the collected bulk tank sample were comparable among farm types. The proportion of lame cows (~25%) as well as the hygiene scores also did not differ between herd types, but organic herds had lower hock lesion scores than conventional herds. The SC and organic herds (47% and 43%, respectively) were less likely to test positive for MAP than the LC herds (92%). The average number of parasite eggs per gram (epg) was overall low and only 4 of over 1,100 heifers had more than 500 epg. However, organic herds had, on average, higher fecal egg counts than conventional herds. Most diseases as well as the percent of died cows were reported at a slightly lower rate on organic farms than conventional farms.

Although there were many similarities, several differences between organic and conventionally managed herds were noted in this pilot study and future studies need to investigate further which management practices are most useful to ensure animal health on organic dairy farms.

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