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Calf Note 162 – Feeding antibiotics to calves and its effect on antimicrobial resistance

Introduction

Increasing attention is being paid to the use of antimicrobials (antibiotics) in animal agriculture. The issue of antimicrobial use is fraught with political overtones. Passionate debates are underway on both sides of the political spectrum – those who espouse outlawing the use of antimicrobials in animal agriculture for almost any purpose and those who accept the status quo (in the U.S., at least) of allowing use of antimicrobials for treatment of disease as well as to promote growth.

The objective of this Calf Note is to evaluate recent (as of November, 2011) research related to the use of antimicrobials in dairy calf raising and evaluate the potential for increasing antimicrobial resistance on the farm.

Antimicrobial resistance

Is antimicrobial resistance a big deal? The short answer is, yes. Certain bacteria may develop resistance to a class of antibiotics **(Ab)** when those Ab are used for a period of time. Improper dosage or extended use of Ab can increase the development of resistance.

Resistance to Ab occur when bacteria mutate and are no longer susceptible to the Ab. It's a matter of genetic selection and "survival of the fittest". Once a bacterium becomes resistant, it can flourish, as other, susceptible bacteria are inhibited. Thus, Ab resistance can occur quickly and the antibiotics that previously were effective on the farm are no longer effective.

There are many reviews of how any why Ab resistance occurs on the web. Some good examples are:

1. Nature Reviews dedicated an entire issue in 2010 to the issue. Very technical stuff.
2. The World Health Organization published the report of a working group on the issue. Lots of detail, particularly appropriate for developing countries.
3. The Food and Drug Administration has a website dedicated to antimicrobial resistance. Good background information.
4. A terrific review of the issue from the National Institute for Animal Agriculture is available. You can read background info, watch and listen to presentations from a symposium on antimicrobial resistance.

5. And from the "other side" of the argument, here's what some advocates for banning use of antimicrobials in farming are saying. Caution – if you read this article, you'll be entering a "logic free" zone.

So, what's all this have to do with calf raising? Well, the issue of antimicrobial resistance is important to calf raisers, as they frequently deal with sick animals.

Let's set the stage…

Here's an example to consider. Mel is owner / manager of M&J Farms, located in New Mexico. Mel and his staff feed about 2,000 milk-fed calves at on operation working at the same location since 1991. Calves arrive at the ranch at 1-2 days of age from about ten different dairies. Calves return to the home dairy when confirmed pregnant at 14-16 months of age. Serum total proteins of calves arriving at the ranch average about 5.0 g/dl and range from 4.0 to 7.0 g/dl. Four of the dairies consistently do a good job with colostrum and serum proteins are usually around 5.7 g/dl. The other six dairies struggle with colostrum, even though Mel sends people to the dairies to train them on colostrum feeding practices from time to time. Calves from these farms are frequently sick – more than half develop diarrhea in the first two weeks after arrival. Mel feeds waste milk collected from the dairies that is pasteurized prior to feeding. Milk is fed twice per day to weaning at 70 days. A high quality textured starter and water are available at all times.

Mel's normal protocol is to treat diarrhea with electrolytes (fed between milk feedings) for at least 3 days. Calves are also treated with Ab using a protocol worked out with his veterinarian. They use one antibiotic as the first treatment, then switch to another if the first appears ineffective after the second treatment. He generally doesn't culture feces to determine the source of diarrhea – after all, it's very common (especially around 7-10 days) and the bout of diarrhea generally doesn't last long (3-7 days). Culturing all calves would be very expensive, time consuming and inefficient. Most calves have uncomplicated diarrhea and recover well. Others, though some have a tough time – high fever, severe, watery scours, dehydration and depression. Mortality is acceptable (<3% on the four good dairies and about 15% on the others) but morbidity is quite high.

It's increasingly common for Mel's workers to use two or three different Ab during the course of a treatment. It seems tougher and tougher to find an Ab that works consistently. Treatments are becoming more expensive, time consuming and the calf health is affected.

Recently, fecal samples collected during a necropsy were evaluated for Ab resistance. The report indicated that *E. coli* isolated from the feces was resistant to nearly all Ab tested.

Some insight from research

To understand what's happening on M&J, let's take a look at some research findings. The results of these studies may provide some insight on why Mel is having more trouble dealing with outbreaks of disease on his operation

Calf ranch milk feeding study. A study conducted by Berge et al. (2006) used 120 newborn bull calves at a calf ranch in the Central Valley of California. Calves arrived on the ranch at 1 day of age and were monitored for 28 days. Calves were obtained from area dairies, comingled and transported together to the ranch and were housed in wooden hutches with three calves per hutch. Calves were fed 2 quarts (1.9 L) of milk replacer twice per day. A commercial calf starter and water were available at all times. The treatments in the study were (1) no Ab feedings in milk or treatment with Ab when sick and housing in clean hutches previously uninhabited by other calves; (2) no Ab in milk or Ab treatments when sick and housing in hutches previously inhabited by other calves; (3) no Ab in milk, but Ab (primarily ceftiofur) used if calves became clinically sick; and (4) Ab in milk (neomycin/tetracycline combination) and treatment with Ab when calves became sick. Calves non fed Ab when they became sick (treatments 1 and 2) were treated with bismuth salts, kaolin-pectin, electrolytes and/or flunixin meglumine (Banamine). On day 1, 14 and 28, fecal samples were collected from each calf and a strain of *E. coli* was grown from the sample. The *E. coli* was then tested to determine the degree of resistance to various Ab.

What did they learn? Basically, there were three notable findings. First, adding Ab to milk replacer selected for *E. coli* that were highly resistant to Ab. Indeed, the *E. coli* developed resistance not only to neomycin and tetracycline, but to other Ab that weren't used on the farm. It should be noted that the FDA has changed the regulations on feeding of Ab in calf milk replacers. However, on farm addition of Ab still occurs frequently, as Ab packs can be purchased from many feed companies and veterinary suppliers.

The second finding was that calves treated with ceftiofur when clinically sick (but without Ab added to milk) shed *E. coli* that were more resistant to Ab. This resistance was not only to ceftiofur but other Ab as well. Interestingly, however, this resistance appeared to be transient – i.e., if calves weren't treated within 5 days of sampling, the degree of resistance was lower than if calves were sampled within 5 days of treatment. Thus, treating calves with ceftiofur prompted development of Ab resistance shortly after treatment, but then this resistance appeared to *decline within a few days of treatment*.

The third finding was that *E. coli* from calves at 14 and 28 days had more Ab resistance than *E. coli* from calves on day 1, regardless of treatment regime or housing. This suggests that development of at least some Ab resistance may be independent of any type of Ab therapy.

These researchers concluded that using Ab, but especially Ab in milk replacer promotes highly Ab resistant *E. coli* (and likely other types of bacteria) in the intestine of young calves.

With and without milk Ab. The second study compared feeding Ab in milk on three farms in NY. Two of three dairy farms (800 and 3,000 cows) fed calves without added Ab. The third farm (4,500 cows) fed calves sulfamethazine (1.56 ml/L milk) and chlortetracycline (1.04 mg/L) along with amprolium and a commercial mannanoligosaccharide product. The study was designed as a case – control; i.e., calves that developed diarrhea between 2 and 8 days of age were sampled and a healthy calf of similar age was also sampled to be the positive "non-ill" control.

Results from this study are in Table 1. Clearly, feeding Ab on farm C resulted in a dramatic increase in Ab resistance. Note that the larger the zone of inhibition (the numbers in Table 1), the more effective the Ab inhibited growth of the *E. coli*. Larger numbers mean that the Ab was more effective in controlling bacterial growth. In Table 1, calves fed without Ab had consistently larger zones of inhibition compared to calves fed Ab; suggesting that Ab in milk increased development of Ab resistance in several different classes of Ab.

An interesting observation was that there was no effect of calf health on the degree of resistance in the *E. coli*. Calves with diarrhea and healthy calves were equally likely to have resistance to Ab as long as they were fed Ab in the milk.

One problem with this study is that there were no true "controls" on any farm – farms A and B didn't use Ab and farm C had no calves not fed Ab. Thus, the location of the farm and the feeding of Ab are confounded in this study.

Type	*No Ab*	*Ab*	*P*
Tetracycline	8.1	1.4	0.0001
Ampicillin	12.0	4.6	0.0002
Streptomycin	11.6	7.3	0.0002
Sulfamethoxazole / trimethoprim	20.7	1.6	0.0001
Amoxicillin	23.0	17.0	0.0001
Neomycin	15.3	19.6	0.0001
Ceftiofur	28.6	22.4	0.0001
Gentamycin	23.9	25.5	0.044
Nalidixic acid	27.9	31.4	0.447
Enrofloxacin	34.8	34.2	0.265
Ciprofloxacin	41.5	41.2	0.436
Cefepime	36.8	35.1	0.0005

Table 1. Inhibition zone diameters for E. coli isolates from dairy calves 2-8 days of age (from: Pereira et al., (2011).

Multiple reasons for Ab resistance. The final study we'll evaluate was a review of several geographic, management and other factors associated with Ab resistance in the Western U.S. In this study (Berge et al., 2010), fecal samples were collected from calves (2 to 4 weeks old) housed on different types of farms – dairies, beef cow-calf farms, beef feedlots and calf ranches. Farms were located in California, Oregon or Washington. On dairies, samples were also collected from fresh cows and cattle on feedlots had arrived within 10 days of testing.

The researchers isolated *E. coli* from fecal samples and tested it for Ab resistance to various drugs. Based on these findings, the researchers conducted an analysis to determine what factors are most likely to increase the risk of Ab resistance.

Results are summarized in Table 2. There are several notable observations specifically related to calf raisers. Most notable were the comparisons of farm type. Calves on calf ranches were nearly 114 times more likely to have *E. coli* with multiple Ab resistance. Although this may be due to increased use of Ab to treat calves (that get sick more often than cows) and in the diets of calves, it should also be noted that several studies indicate greater Ab resistance in *E. coli* collected from calves even if they were not treated with Ab (Berge et al., 2010). Also, animals on farms in California were more likely to harbor Ab resistant E. coli compared to farms in Washington or Oregon. The authors of this study could not identify one or

more factors associated with this geographic difference, but suggested that differences by state might reflect differences in farm size, management, weather and many other factors.

Back to M&J

What's going on at the M&J ranch? This common scenario is a classic example of development of antimicrobial resistance. Calves arriving at the ranch with low serum protein are already at a disadvantage – they've not received enough colostrum and have been transported from the dairy to the ranch, which is a stressor that impairs the calf's immune system. They're comingled with other calves and though they're housed separately, they still come into contact with many other calves in transit or on the ranch. Research has shown that calves with failure of passive transfer are much more likely to be treated with antibiotics (i.e., develop an enteric infection) and to die than calves with adequate passive transfer (Berge et al., 2009)

Factor	*Odds ratio*	*P*
State		
WA & OR	--	
CA	2.23	0.01
Farm type		
Beef cow	--	
Dairy	0.69	0.54
Feedlot	6.19	0.01
Calf ranch	113.87	0.01
Age category		
Beef		
Cow	--	
Calf	2.33	0.06
Dairy	--	
Cow	--	
Calf	23.62	0.01

Table 2. Odds ratios of factors that increase multiple antibiotic resistance in fecal E. coli. Adapted from: Berge et al., 2010.

Waste milk – a culprit?

M&J Farms utilizes pasteurized waste milk as a source of feed for calves. This milk comes from dairies can contains milk from treated cows and colostrum. Mel knows that it varies in solids content (he uses a refractometer to evaluate it daily) but is unsure about the levels of Ab that might be present. Thus, the calves – and more importantly, the bacteria in the digestive tracts of the calves – are intermittently exposed to varying doses of different antibiotics. Some research suggests that the antibiotics found in waste milk can contribute to antimicrobial resistance (see Calf Note #35 for more information).

A review from the University of Wisconsin (http://www1.extension.umn.edu/dairy/beef/on-farm-pasteurized-waste-milk-systems.pdf) evaluated the presence of Ab in waste milk from 62 samples collected on dairies. They found that 50% of the samples tested were positive for β-lactam Ab residues. Langford et al. (2003) also reported that Ab resistance appeared to increase and the amount of penicillin G added to milk was increased, suggesting that even low amounts of Ab in waste milk may contribute to increased Ab resistance in calves.

It's difficult to know for sure whether Mel's issues come from the use of waste milk in feeding his calves. It's a reasonable source of nutrients and is inexpensive. However, quality varies (based on the variation he sees in solids content) and the degree of fermentation and plate counts vary also, depending on how long after collection it was pasteurized. But, equally important is the level of Ab contamination and the degree to which those Ab contribute to resistance. Mel hasn't tested the waste milk, but agreed to ask each of the dairies to discard the milk produced from cows in the first day after treatment with Ab of any kind.

What to do?

M&J Farms faces an issue common in calf raising. Calves arriving at his ranch are often at greater risk of disease because of inadequate colostrum management at the dairy. Once these calves get sick, they require greater levels of intervention due to their compromised immune status, which generally means greater Ab use. This increases the risk of developing Ab resistance. Further, the use of waste milk, which contains varying amount of different drugs, may be promoting Ab resistance by exposing bacteria to low levels of Ab – not enough to kill them, but perhaps enough to induce development of Ab resistance.

The solution to Mel's problems are multi-fold. First, he needs to increase the quality of calf he receives from his client dairies. Calves that receive adequate colostrum at birth are healthier and more robust. They'll likely need fewer treatments, which should reduce the continued development of Ab resistance.

Secondly, Mel can look at non-Ab nutritional treatments to control intestinal infections in his calves. Continued feeding of colostrum (Berge et al., 2009) or bovine serum (Hunt et al., 2002) are two sources of antibodies that can reduce the risk of infection and reduce the use of Ab. A commercial product, Gammulin, was recently shown to reduce treatments and death loss in transported calves at the University of Illinois (Pineida et al., 2011).

Thirdly, management on the farm and use of Ab should be evaluated. Scours that occur during the 7-10 day period are often caused by *Cryptosporidium parvum,* a protozoa that is unresponsive to Ab. Viral infections with rotavirus or coronavirus are unaffected by Ab, also. Thus, he may be wasting his time and money by treating the calves, and inducing more Ab resistance. Mel feels that using Ab during this time may help reduce the risk of secondary opportunistic bacterial infections, so it's a balancing act. It's also noteworthy that Ab resistance that occurs in response to Ab treatments appear to be transient, at least in one study (Berge et al., 2006).

Finally, Mel should evaluate the use of waste milk for his calves. The possible increase in Ab resistance derived from the variable exposure to Ab in the waste milk may overwhelm any savings in feed costs compared with a good quality milk replacer. Mel also has to manage the variation in nutrient content and pasteurization. This product may be more problems to Mel than it's worth.

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