ANTIMICROBIAL RESIDUES AND RESISTANCE: UNDERSTANDING AND MANAGING DRUG USAGE ON DAIRY FARMS

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Introduction

In modern dairy cattle operations, most antimicrobials are administered for therapeutic purposes but some antimicrobials are used to prevent disease during periods of increased susceptibility. While mastitis is the most common disease of adult dairy cows and accounts for most cases of antibiotics (Pol and Ruegg, 2007, Saini, 2012) lactating cows are also treated for other infectious diseases, including respiratory and uterine infections and infectious foot disease. The use of antimicrobials to treat food animals has the potential to affect human health through 2 mechanisms: 1) increasing the risk of antimicrobial residues, and 2) influencing the generation or selection of antimicrobial resistant foodborne pathogens. The risk of antimicrobial residues in meat and milk is well known and if the focus of intensive regulatory processes. However, there is increasing public concern about the impact of antimicrobial usage in food animals on the development of antimicrobial resistance. The purpose of this paper is to review important data about how antimicrobials can be safely and judiciously used on dairy farms.

Antibiotic Residues and Risks to Human Health

The occurrence of antibiotic residues in milk intended for human consumption is undesirable for a number of reasons. As recently as 30 years ago, the presence of antibiotic residues in milk was considered primarily a manufacturing problem related to inhibition of cheese and yogurt starters (Cogan, 1972). More recently, the presence of antibiotics in milk has been prohibited because of concerns about public health. Initially, public health officials desired to protect hypersensitive individuals from exposure to specific antibiotics but recent concern has focused on the potential for antibiotic residues in milk to contribute to the development and/or transmission of resistant bacteria (Mitchell et al., 1988).

Allergic reactions to antibiotics are well recognized and hypersensitivity to β-lactam compounds is especially prevalence. The literature regarding allergic responses of humans after exposure to drug residues found in milk is sparse and focused primarily on risks associated with exposure to β-lactams (Dewdney and Edwards, 1984; Ormerod, et al., 1987; Wicher et al., 1969). The immunological characteristics of most other drug classes (including macrolides, tetracyclines and aminoglycosides) makes the development of allergic responses to minute residues unlikely, although it is considered theoretically possible that exposure could result in clinically relevant immunological events (Dewdney and Edwards, 1984). Oral administration of antibiotics does not stimulate as strong of an immunological response as compared to systemic administration and there is no scientific evidence that β-lactam residues present in milk have ever induced primary sensitization in humans (Dewdney and Edwards, 1984). Allergic reactions of pre-sensitized individuals caused by β-lactam residues in milk have been documented for a small number of people (Dewdney and Edwards, 1984). Exposure to penicillin residues in milk has been reported as a cause of chronic urticaria (Ormerod, et al., 1987). Verified case reports after 1987 are apparently non-existent.

At this point, the relationship between antibiotic residues in milk and the development or transfer of resistant pathogens appears to be hypothetical. The direct transfer of resistant organisms to humans through consumption of milk is unlikely because most dairy products are made from pasteurized milk (Teuber and Perreten, 2000). Traditional methods of pasteurization reduce the quantity of bacteria present in milk to negligible levels but will not appreciably reduce the level of antibiotic residues (Moats, 1999). Milk can be contaminated with fecal pathogens that exhibit resistance to antibiotics and raw milk products have been implicated as mechanisms for transferring fecal pathogens from farm environments to humans (Villar et al., 1999). There is some indication that exposure of dairy cattle to some antimicrobials may be associated with increased proportion of resistance of some organisms but the associations are not uniform (Pol and Ruegg, 2007, Saini et al, 2012). However, mastitis pathogens in general do not appear to be becoming more resistant to commonly used antimicrobials (Erskine, et al., 2004, Makovec and Ruegg, 2003).

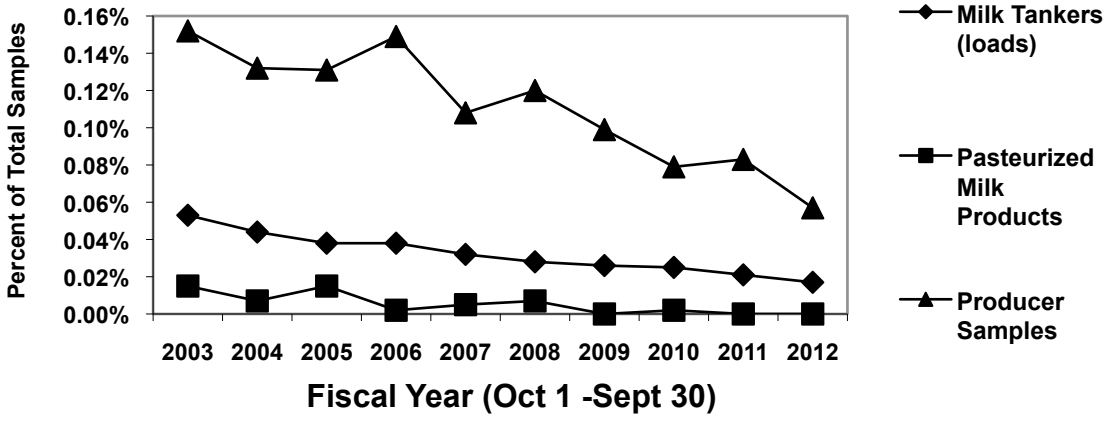
Administration of Antimicrobials on Dairy Farms

Most usage of antimicrobials is related to the occurrence of infectious diseases and thus most antimicoribal usage on dairy farms is associated with treatment and prevention of mastitis. Almost all conventional dairy farms report some regular usage of antibiotics (Zwald et al., 2004; Ruegg and Oliveira, 2013). However, the most comprehensive data about antimicrobial usage occurring on dairy farms in the U.S. comes from the National Animal Health Monitoring System (NAHMS) (USDA, 2005). Virtually all dairy farmers report the occurrence of mastitis but surveys indicate wide variation in the occurrence of other diseases. About 40-50% of dairy farms reported treatment of adult cows for foot infections, pneumonia or metritis (USDA, 2005). However not all of the affected animals received antimicrobials. For example, most cases of pneumonia received antimicrobial treatment but only two thirds of the animals with metritis and foot infections received antimicrobials. Dairy farmers must focus on prevention to remain profitable and on many farms preventive health programs are effective. On most farms, the relatively low incidence of many diseases, results in a small proportion of the adult cows receiving antimicrobial treatments (< 14% of animals were treated for pneumonia, metritis or foot infections). When antimicrobial treatments are quantified, recent research in the US and Canada was demonstrated that each adult cow receives about 5 defined daily doses per year (Pol and Ruegg, 2007, Saini et al., 2012). Data collected from dairy farms consistently demonstrates that ß-lactam compounds (primarily penicillin and cephalosporins) are the most commonly administered classes of antimicrobials used on dairy farms. While tetracyclines and sulfonamides are commonly used, many drug classes that are important for treatment of human infections (such as florquinolones) have no approved usages in adult dairy cows and are rarely used on dairy farms.

Antimicrobial Residues in Milk & Meat

Antibiotic residues occur in milk supplies throughout the world. In the US, public health is protected by regulations that prohibit the presence of antibiotics in milk intended for human consumption (www.fda.gov/downloads/Food/.../UCM291757.pdf) and the dairy industry bears the primary responsibility for ensuring the safety of milk and milk products. The FDA is responsible for verifying that the industry is complying with regulations and initiates regulatory action when necessary. Appendix N of the Grade A Pasteurized Milk Ordinance requires that every tanker of milk must be screened for β-lactam residues prior to unloading. Individual bulk milk samples from every farm are tested once monthly 4 times in every 6 month period. Additional random testing for other drug classes is also performed and individual state regulatory agencies or individual milk processors may test more frequently. Results of official drug testing are compiled annually in the National Milk Drug Residue Database (http://www.kandc-sbcc.com/nmdrd/). The prevalence of positive antibiotic test results for bulk milk tankers has been steadily declining (Fig 1) and about 70% less milk was discarded because of the presence of antibiotic residues in fiscal year 2012 as compared to FY 2002 (23,717,000 lbs in 2012 as compared to 85,703,000 lbs in 2002).

Figure 1. Prevalence of Positive Antibiotic Test Results



As context, it is important to note that the US dairy industry produced 198.9 billion pounds of milk in 2012 and the cost of the discarded milk is about $3.5 million USD (at $15.00 per cwt). The FDA also tests

pasteurized fluid milk and milk products for antimicrobial residues and no tests of these products have been positive since 2010. ß-lactams are the most common class of drug that is tested for and are the most common residue that is detected. Results of expanded testing for residues in milk samples anonymously collected from 1,800 dairy farms is expected to be released in 2013.

The USDA, FSIS administers a residue testing program for meat, poultry and egg products and reports the results of residue testing on an annual basis (www.fsis.usda.gov/PDF/2010_Red_Book.pdf). The carcass sampling program consists of scheduled sampling using random carcass samples, targeted sampling based on impressions of meat inspectors and targeted sampling of high risk herds. High risk is defined based on a history of previous violations and a list of repeat violators is published on a public website. In general, few violative residues are usually detected in beef cattle and the greatest proportion of violative samples have originated in bob veal and cull dairy cows. The most common residue violations in meat from cull dairy cows are penicillins, flunixin, sulfadimethoxine, desfuroylceftiofur and sulfamethazine. While progress in preventing residues has been made, veterinarians must actively work with dairy clients to ensure that drugs are used properly and that NO animals with the potential for violative residues are shipped to market.

Antibiotic residues usually occur because of mistakes in identification, recording, communication or training and veterinary interventions to reduce residues need to be focused on improvement in these areas. There have been a number of studies looking at reasons for antibiotic residues in milk. The use of intramammary antibiotics and mistakes regarding withholding periods of milk are the most frequently cited reasons for antibiotic residues (McEwen *et al.* 1991, Wilson *et al.*, 1998) and herds that have higher bulk tank SCC (indicating a greater prevalence of infected cows) have been shown to be at greater risk for the occurrence of residues (Ruegg and Tabone, 2000). Surveys have indicated that the vast majority of mastitis treatments are administered by farm personnel, often without veterinary supervision. It is thus very important for veterinarians to be engaged with farmers in the implementation of standard operating protocols that result in judicious usage of antimicrobials on dairy farms.

Types of Antimicrobial Usage

Various types of drug usage are permitted on dairy farms. In farm animals, OTC drugs (such as penicillin) may be used only under the exact label specifications and dosages. A typical label for OTC penicillin would be the treatment of bacterial pneumonia using a dosage of 3,000 IU/lb (1cc/100 lbs) for no more than 4 days and by administration of no more than 10 cc in any one site. Deviation from any of those indications (such as treatment of mastitis, use of a greater dosage or for more than 4 days or administration of >10cc in one site) is not considered OTC. Prescription products cannot be purchased without a veterinary prescription. This type of usage still infers that the product is used exactly as the label specifies. If the product is used outside of label specification a veterinary label for extralabel usage must be applied. The use of a commercially available flunixen product for treatment of acute bovine mastitis is an example of allowed prescription usage. If administration follows the label directions (1-2 ml/100lbs via IV administration), then it is appropriate to follow specified label indications for milk and meat withholding. However, if the product was administered IM, the labeled meat and milk withholding periods are no longer sufficient and the prescribing veterinarian must follow the AMDUCA guidelines for extralabel drug usage. Extra-label usage refers to any use of a drug not specifically listed on the label and it is only legal under the guidance of a veterinarian. The website of the Food Animal Residue Avoidance Database (http://www.farad.org/) is an excellent resource for information about extralabel usage. It is also important for veterinarians to recognize that not all drugs can be used in lactating dairy cows, even as extralabel products, and a list of prohibited products can be found at the FARAD website. For regulatory purposes, lactating dairy cattle are defined as animals >20 months of age regardless of whether they are milking or dry. One of the most confusing issues is the use of sulfonamides in dairy cows. No extralabel usage of sulfonamides is allowed in adult dairy cows and the label for sulfadimethoxine (the only labeled sulfonamide for dairy cattle) specifies that this drug may be used only for treatment of bovine respiratory disease, necrotic pododermatitis and calf diphtheria…. Thus the use of sulfonamides for treatment of other conditions (such as mastitis) is prohibited. Extra-label usage and usage of illegal antimicrobials have been reported among studies. One survey that was administered in 381 herds in Washington State, reported that 23% of dairy farmers used one or more unapproved or

prohibited uses of antimicrobial, of which the most common compounds cited were gentamicin, neomycin, and florfenicol (Raymond et al.,2006).

Conclusion

Veterinarians can play a very large role in promotion of judicious usage of antimicrobials. Veterinarians should work to promote a strong relationship with clients and ensure that that preventive health care programs are focused on surveillance and diagnosis of disease conditions. Farms should have appropriate management structures to limit the number of people who are allowed to treat animals and veterinarians should ensure that accurate identification and recording systems are in place. It is important that veterinarians are familiar with the product labels and that they work to educate their clients about appropriate withholding periods.

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