White Paper on Antibiotic Use in Food Systems: Critical Findings For Registered Dietitians

Hunger and Environmental Nutrition
Dietetic Practice Group of the
American Dietetic Association
www.HENdpg.org

Mission: **Empowers members to be leaders in sustainable and accessible food & water systems.**

Vision: **HEN members optimize the nation's health by promoting access to nutritious food and clean water from a secure and sustainable food system.**

February 2011

This information is provided as discussion points for HEN DPG members and is not an official position of the American Dietetic Association. An ADA workgroup has been formed to address this issue. This document was prepared by an Ad Hoc task force of members from the Hunger and Environmental Nutrition DPG#15:

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Introduction
Concern regarding the consequences of subtherapeutic antibiotic use in animal production is receiving more attention as resistant infections become more common both in the hospital and community settings. Registered Dietitians are receiving more questions from clients, the media, and other professionals, about the role subtherapeutic antibiotic use in animals has on the incidence of these infections.

The purpose of this document is to provide HEN DPG Members and other food and nutrition professionals information that they can utilize to speak knowledgeably about the impact of subtherapeutic antibiotic use in animal production when interacting with clients, other professionals, and the media.

The FDA 2009 Summary report on the distribution of antibiotic use in the United States revealed that 80% of all antibiotics are reserved for use in animals. (Congresswomen Slaughter, 2011) As in humans, antibiotics may be used to treat infection in animals. Still, the majority of these antibiotics are currently used at low, subtherapeutic levels, in animal production to promote rapid growth and to prevent diseases that may otherwise occur in confined, unsanitary living conditions often found within Concentrated Animal Feeding Operations (CAFOs) (Swann, 1969).

While the potential for antibiotic residues on food products is a food safety concern, antibiotic use may impact human health in the absence of residues. It is generally accepted by the scientific community that the subtherapeutic use of antibiotics leads to the emergence of antibiotic resistant bacteria that can then be transmitted to humans through direct contact, contact with contaminated animal products, and through the contamination of the environment with animal waste (Van der Bogaard, 2000; Campagnolo, 2002).

As experts on food and nutrition and key members of the healthcare team, Registered Dietitians need to understand and be able to educate the public on the use of subtherapeutic antibiotic use in animal production and its impact on health and the environment.

Philosophy and definitions around topic
Antibiotic resistant infections occur too often and with increasing frequency, interfering with the effective treatment of people and animals. Although antibiotics and antibiotic resistance are natural phenomena, the population of resistant bacteria has increased by the introduction of antibiotics into an environment. (CDC, 2008) To preserve the effectiveness of antibiotics, it is critical to examine the uses of these drugs, in both humans and animals. This series of talking points developed for use by dietetic and nutrition professionals will provide a background on the use of subtherapeutic antibiotics in animals.

“Antimicrobial drugs that are Food and Drug Administration (FDA)-approved for use in food-producing animals are normally used to: treat or control an on-going infectious disease; prevent an infectious disease before an outbreak occurs; or to ensure rates of production by making food animals gain weight faster. In latter case, disease does not have to be present and no outbreak is anticipated to occur. This is commonly called subtherapeutic use. The FDA states that using medically important antimicrobial drugs to increase production in food-producing animals is not a judicious use. (FDA, 2010) Furthermore, a majority of the antibiotics approved by the FDA were done so before resistance was a consideration.

To decrease antibiotic use, livestock farmers have implemented approaches to keep animals healthy and reduce the need for antibiotics such as the manipulation of animal spacing, rigorous biosecurity measures to keep diseases out of farms, intense sanitation, and vaccination. (FASS, 2010)

Definitions[1,2]

- Antimicrobial drugs: includes all drugs that work against a variety of microorganisms, such as bacteria, viruses, fungi, and parasites. Antimicrobial drugs that work specifically against bacteria are called antibacterial drugs or antibiotics. The broader term "antimicrobial drugs" is used interchangeably with the terms "antibacterial drugs" and "antibiotics" in this document .
- Medically important antimicrobial drugs are antimicrobial drugs that are important for treating infectious diseases in people, particularly infections caused by bacteria.
- Subtherapeutic use or Non-therapeutic use (of antibiotics in animals): any use provided as a feed or water additive in the absence of any clinical sign of disease in the animal for growth promotion, feed efficiency, weight gain, routine disease prevention, or other routine purpose.
- Antibiotic-resistant bacteria: New emerging strains of bacteria that have been found to survive traditional antibiotic treatments.
- Antimicrobial resistance or Antibiotic-resistant infection : is when bacteria are no longer susceptible to an antimicrobial drug, meaning that the drug, and similar drugs, will no longer work against those bacteria. Antimicrobial resistance occurs after bacteria are exposed to an antimicrobial drug and continue to survive in the drug's presence. Once bacteria become resistant to a drug, the continued use of that drug may increase the number of resistant bacteria. Public health may be affected if resistant bacteria enter the food supply.

[1] Food and Drug Administration (FDA). Questions and Answers on FDA's Draft Guidance on the Judicious Use of Medically Important Antimicrobial Drugs in Food-Producing Animals. Available at: http://www.fda.gov/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/ucm216939.htm

[2] Center for Disease Control(CDC). Get Smart: Know When Antibiotics Work. September 2010. Available at: http://www.cdc.gov/getsmart/antibiotic-use/anitbiotic-resistance-faqs.html#f

Antibiotics in Agriculture Regulation

Federal Agencies

Antibiotics cannot be marketed for use in animals in the U.S. without prior approval by the Food and Drug Administration (FDA). Within FDA, the Center for Veterinary Medicine oversees the use of animal antibiotics. FDA has statutory authority to withdraw approval for an agriculturally used antibiotic if there is evidence showing that the drug "is not shown to be safe"

On January 6, 1999 the FDA releases "Proposed Framework for Evaluating and Assuring the Human Safety of the Microbial Effects of Antimicrobial New Animal Drugs Intended for Use in Food Producing Animals" (64 Fed. Reg. 887, Jan. 6, 1999). This document proposed that new agricultural antibiotics could be approved and used until resistance to them exceeded a particular threshold level. Several public-interest groups submitted comments challenging the effectiveness of the proposed approach, which failed to address the problem of antibiotics with existing approval for use in agriculture.

In December, 2000 the FDA releases a document, titled "An Approach for Establishing Thresholds in Association with the Use of Antimicrobial Drugs in Food-Producing Animals," This document described a system under which FDA will consider the potential effect new uses of antibiotics in animal agriculture could have on the problem of antibiotic resistance in human pathogens. It also outlined requirements for post-approval studies and monitoring of resistance levels for new uses of antibiotics in animal agriculture. This document failed to address the problem of antibiotics already approved for use in animal agriculture.

On September 6, 2002 the FDA issued a draft guidance document #152 describing a methodology for evaluating how agricultural use of antibiotics may impact human health via antibiotic resistance.

On October 23, 2002 the FDA issued the FINAL Draft Guidance # 152: Guidance for Industry: Evaluating the Safety of Antimicrobial New Animal Drugs with Regard to their Microbiological Effects on Bacteria of Human Health Concern.
http://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/UCM052519.pdf

On September 12, 2005, the FDA banned Fluoroquinolones (Cipro-like drug) used in treating sick poultry**.** This action is the first time that FDA has ever withdrawn an agricultural antibiotic from the market because of concerns about antibiotic resistance affecting human health
http://www.fda.gov/AnimalVeterinary/SafetyHealth/RecallsWithdrawals/ucm042004.htm

On June 28, 2010 the FDA released Draft Guidance #209 The Judicious Use of Medically Important Antimicrobial Drugs in Food-Producing Animals.
http://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/UCM216936.pdf

The Centers for Disease Control (CDC) also administers the National Antimicrobial Resistance Monitoring System (NARMS), a monitoring program that gathers data on the incidence of antibiotic resistance

among a handful of different bacteria. NARMS collects bacteria both from human samples as well as from food-animal samples. This data is not used to regulate the usage of antibiotics in feed.

Federal Food Drug and Cosmetic Act Movement

- August 2004, President Bush signed the **Minor Use/Minor Species Act**, which is intended to facilitate approvals of small-market veterinary drugs expressly clarifies that antibiotic resistance is a key issue for consideration of "safety" under the Food Drug and Cosmetic Act. http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/SignificantAmendmentstotheFDCAct/MinorUseandMinorSpeciesAnimalHealthActof2004/default.htm
- The **Preservation of Antibiotics for Medical Treatment Act (PAMTA) of 2007.** H.R.962, S. 549 was introduced on February 8, 2007 with the goal to amend the Federal Food Drug and Cosmetic Act and require the Secretary of Health and Human Services to withdraw approval of a drug for non-therapeutic uses in food-producing animals two years after the date of enactment of this Act unless certain safety requirements outlined in the bill are met. This would require the manufacturer of such a drug or an animal feed for food-producing animals containing such a drug to report sales information to the Secretary. This bill saw little action and was reintroduced on March 17, 2009 as the **Preservation of Antibiotics for Medical Treatment Act (PAMTA) of 2009** H.R.1549, S.619. The focus of this bill is to improve our food safety system by starting with the healthy maturation of the animal and encourages the proper use of antibiotics. The goal of this piece of legislation is to require the Food and Drug Administration (FDA) to re-review the approvals it previously issued for animal feed uses of the seven classes of antibiotics that are important to human medicine. Any found to be unsafe from a resistance point of view will have their approvals rescinded for use in animal feed and preserved only for use in diagnosed illness. This prevention focused policy aims to decrease the emergence of antibiotic resistant bacteria and preserve the effectiveness of those critical antibiotics used to treat human infection.
    - **H.R.962**
      Latest Major Action: 2/9/2007 Referred to House subcommittee. Status: Referred to the Subcommittee on Health. Died
    - **S.549**
      Latest Major Action: 2/12/2007 Referred to Senate committee. Status: Read twice and referred to the Committee on Health, Education, Labor, and Pensions. Died
    - **H.R.1549**
      House Bill Summary, Status and Cosponsors: http://thomas.loc.gov/cgi-bin/bdquery/z?d111:HR01549:@@@P
    - **S.619**
      Senate Bill Summary, Status and Cosponsors : http://thomas.loc.gov/cgi-bin/bdquery/z?d111:SN00619:@@@P

- The **Animal Drug User Fee Amendments of 2008 (ADUFA)** Section 105 (110 P.L. 316; 122 Stat. 3509) amended section 512 of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 360b) to require that sponsors of applications for new animal drugs containing an antimicrobial active ingredient submit an annual report to the Food and Drug Administration on the amount of each such ingredient in the drug that is sold or distributed for use in food-producing animals
    - 2009 Summary Report on Antimicrobials Sold or Distributed for Use in Food-Producing Animals, Center for Veterinary Medicine, Food and Drug Administration Department of

Health and Human Services. FDA estimates US livestock get 29 million pounds of antibiotics per year http://www.fda.gov/downloads/ForIndustry/UserFees/AnimalDrugUserFeeActADUFA/UCM231851.pdf

Regional Policy Movement

House Bill 2658 proposed in PA 2009-2010: An Act prohibiting the administration of certain antimicrobial agents in agriculture; providing for inspection and testing of agricultural operations, for enforcement, for reporting by agricultural operations and for alternatives to administration of antimicrobial agents to animals; and making related repeals. http://www.legis.state.pa.us/cfdocs/billinfo/billinfo.cfm?syear=2009&sind=0&body=H&type=B&BN=2658

Research Findings

The information in this document is divided into two parts. The first section offers a concise table reference with talking points drawn from the research, organized by the impact antibiotic use has on RDs in different roles. The section following the table offers a more detailed description of the current research.

Concept	Evidence-Based Findings	Requires Additional Research
Subtherapeutic antibiotic use in animals is harmful to humans, animals, and the environment.	• Subtherapeutic levels of antibiotics are used to promote growth and prevent disease in food animals. Resistant bacteria may be transmitted to humans through contact with production animals, animal products, and their waste. • Plants exposed to waste from animals treated with antibiotics become contaminated with the antibiotic	
Antibiotic Use affects the Community RD	• The use of antibiotics in animal production leads to the development of antibiotic resistant bacteria in food animals. • Resistant bacteria may be transmitted to humans and result in resistant infection.	• The primary source of MRSA infections in humans is no longer hospital acquired infection, but an infection that occurs in the community as a result of contact with food animals.

Antibiotic Use affects the Food Service or Culinary RD	• Antibiotic use in production is associated with higher incidence of antibiotic resistant bacteria in milk, poultry, turkey, beef, and pork products. • Foodborne illness caused by resistant bacteria resulting from production practices is increasing. • Foodborne illness caused by resistant bacteria is more difficult to treat than antibiotic susceptible infections. • A food supply contaminated with antibiotic resistant bacteria is especially dangerous for vulnerable populations including the elderly, children, and those with compromised immune systems.	
Antibiotic use affects the Clinical RD	• Patients taking antibiotics are more susceptible to antibiotic resistant bacteria. • Fluoroquinolones, the first treatment choice for the treatment of Campylobacter. When an infection is resistant to it, stronger antibiotics with a greater incidence of side effects are necessary. • Whenever antibiotics are ineffective, side effects ranging from diarrhea and nausea and compromised renal function create a more challenging clinical picture. • As a key member of the health care team, RDs need to visibly support measures that will assure antibiotics and other key tools are available to provide effective interventions for their patients.	
Animal husbandry does not require the use of subtherapeutic antibiotics	• The cost of antibiotics may outweigh the benefits of growth promotion. • The feed conversion ratio of animals will not decline when antibiotics are withdrawn. • Rates of antibiotic resistant infection in humans decline when antibiotic use is restricted in production animals.	

How does antibiotic use affect the RD working in the community setting?

Production animals treated with subtherapeutic antibiotics and their products are a source of antibiotic resistant bacteria that can be transmitted to humans and cause antibiotic resistant infection..

- Cases of human infection with antibiotic resistant organisms originating in production animals treated with antibiotics have been documented since the 1970s (Lyons et al., 1980).
- There is general consensus that antimicrobial resistant bacteria is transmitted from animals to humans (WHO, 2003; IOM, 2010; USDA, 2007)
- Transmission of antibiotic resistant bacteria from production animals to humans is documented in poultry (Levy et al., 1976), swine (Molbak, 1999; Cole, 2000; Chapin, 2005), cattle (Fey et al., 2000), dairy (Lyons et al., 1980), and veal production (Akkina et al., 1999; Wegener et al., 1999).
- Workers in contact with production animals have a higher incidence of colonization with bacteria that is resistant to multiple antimicrobials (Price et al., 2007).

- Use of subtherapeutic antibiotics in swine productions is linked to the transmission of microbial resistant *Salmonella*, (Molbak et al., 1999) MRSA (Huijsdens et al., 2006), H1N1, H2N2 (Myers et al., 2006), and *E Coli* (Akwar et al., 2007) in humans.
- Use of subtherapeutic antibiotics in poultry production is linked to the transmission of microbial resistant *E coli* (Ojenyiyi, 1989; Kuskowski et al., 2006)*, Campylobacter* (Endtz et al., 1991) *, Enterococcus faecium* (van der Bogaard et al., 2001; Kieke et al., 2006), and MRSA (Nemati et al., 2008)
- Resistant strains of *E Coli* are found in workers with close contact with turkey or turkey carcasses (van der Bogaard et al., 2001).

Antibiotic resistant infections are now more commonly of *community* origin than hospital origin – putting the community RD and their clients at increased risk of a variety of antibiotic resistant infections.

- MRSA is now emerging as a pathogen more commonly of community origin, occurring in patients without hospital related risk factors (Springer et al., 2009).

How does antibiotic use affect the RD working in a clinical setting?

Production animals treated with subtherapeutic antibiotics and their products are a source of antibiotic resistant bacteria that can be transmitted to humans and cause antibiotic resistant infection.

- It has been well established that MRSA can be transmitted from production animals provided subtherapeutic levels of antibiotics to humans (Khanna et al., 2008; Lewis et al., van Belkum et al., 2008; Duijkeren et al., 2008; van Rijen, van Keulen, & Kluytmans, 2008; Smith et al., 2009).
- Research models suggest that transmission of antimicrobial resistant bacteria may be more likely to occur from agriculture sources than transmission in hospital settings (Smith, Dushoff, & Morris, 2005).
- 20% of MRSA in the Netherlands is estimated to originate from swine production utilizing tetracycline (van Loo et al., 2007).

Antibiotic resistant infections cost lives and money.

- Data collected in a Chicago hospital in 2000 suggests the medical cost associated with each case of MRSA is between $18, 588 and $29,069 per patient. This translates into a societal cost of $10.7 to $15 million annually (Roberts et al., 2009).
- In 2010 a study published in Pediatrics reports a 10 fold increase in the incidence of children with MRSA between 1999 and 2008 (Herigon et al., 2010).

As antibiotic resistant bacteria become more common in food production, some antibiotics are becoming less effective in treating infections. This results in the greater reliance of alternate antibiotics that may include greater side effects

- Fluoroquinolones may be of limited use in many areas as the overuse of enrofloxacin and other drugs in food animals has resulted in increased incidence of resistance of *Campylobacter* to these antibiotics (Engberg et al., 2001).

Banning the use of subtherapeutic antibiotics in animal production will help safeguard the efficacy of these antimicrobials.

- Banning the use of subthreshold antibiotics in animal production will lower the burden of antimicrobial resistance (Alliance for the Prudent Use of Antibiotics, 2002).

How does antibiotic use affect the RD working in a food service or culinary setting?

While antibiotic withdrawal periods prior to slaughter may help prevent antibiotic residues on animal products, antibiotic resistant bacteria often remain.

- A study of feedlot cattle found that cattle fed subtherapeutic doses of antibiotics developed resistant *E coli*. Despite a 2-month withdrawal period of antibiotics prior to processing, the resistant bacteria were still present (Alexander et al., 2008).
- Antibiotic resistant bacteria is regularly found on retail animal products in countries where antibiotics are used in animal production:
    - In a study conducted in Minnesota, 14% of domestic chicken products sampled contained Quinoline-resistant *Campylobacter jejuni*. (Smith & Besser, 1999).
    - Results from a study conducted in the Greater Washington area found retail meats were commonly contaminated with resistant *E Coli* bacteria (Ayers & Zhao, 2003).
    - A later study, also conducted in Washington, found 20% of samples of ground chicken, pork, beef, and turkey contained *Salmonella*, and of these positive samples, 84% were resistant to at least one antibiotic (White & Zhao 2007).
    - A national study found a reservoir of ciprofloxacin-resistant bacteria on retail chicken over a two and a half year time period (Nannapeneni & Story, 2005).
    - In a study conducted over two years in Spain, 99% of the *Campylobacter jejuni* strains isolated in pigs and broilers were resistant to ciprofloxacin, with high percentages also resistant to ampicillin, erythromycin, gentamicin, and amikacin (Saenz et al., 2000).

The antibiotic resistant bacteria on animal products can be transmitted to humans and result in antibiotic resistant infection.

- Human contact with resistant bacteria on food products of animal origin has been clearly linked to human infection (van der Bogaard et al., 2000b).
- The consumption of antimicrobial residues on food products is responsible for resistant enterobacteria in the human gut (Corpet, 1993).
- Urinary tract infections may be cause by foods contaminated with resistant *E coli* (Mangers & Johnson, 2001; Unicomb & Ferguson, 2003; Ramchandi, 2005; Tartof & Solberg 2005; Manges & Tabor, 2008; Smith & Manges, 2008; Wong & Chow, 2010; Vincent et al., 2010).

Those who develop infections from antibiotic resistant bacteria are more likely to experience a more severe infection – or treatment failure.

- Use of antibiotics in production increases the likelihood of antibiotic resistant Salmonella infections in humans that have treatment failure and more severe disease (Angulo, Nargund & Chiller, 2004).

How does antibiotic use effect the environment?

Antibiotic resistant bacteria originating in animal production may move throughout the environment, contaminating wind, water, land, and other living things.

- Plants exposed to waste from animals treated with antibiotics become contaminated with the antibiotic (Dolliver & Kumar, 2007).
- Antimicrobial residues move through the environment through the spreading of contaminated manure and contamination of wastewater (Campagnoio et al., 2002; Kumar et al. 2005).
- 25% of air samples collected from cars driving behind poultry transport vehicles were resistant to at least 1 antimicrobial (Rule, Evans & Silbergeld, 2008).

What are the impacts of ending subthreshold antibiotic use in production animals?

In the long run, producers will economically benefit from the discontinuation of subthreshold antibiotic use.

- A report in Clinical Infectious Disease found that subtherapeutic antibiotic use could be discontinued without economic detriment and replaced with management techniques including

vaccination, good sanitation, clean water, temperature control and the development and use of probiotics (O'Brien, 2002).

- A study of poultry production based on data from Purdue found that the cost of antibiotics was greater than the economic benefit of their use as growth promoters (Graham, Boland, & Silbergeld, 2007).
- A study in swine production found that removal of Growth Promoting Antibiotics (GPA) decreased return at sale when feed included four or less different rations. When more than 4 different rations were offered, animals without GPA experienced an increase in food conversion rates (Miller et al., 2003).
- GPAs were withdrawn for a study in Maryland and North Carolina poultry cites. Small reductions in body weight (0.03 and 0.04 Lb) were reported, but feed conversion ratios were unchanged and there were no reports of disease outbreaks (Engster, Marvil, & Stewart-Brown, 2002).

The incidence of antibiotic resistant infection will decrease when subtherapeutic antibiotics are removed from animal production.

- Resistance to antibiotics resulting from their overuse in animal production will economically hurt producers in the long run (Catry et al., 2005).
- In 1986 Sweden discontinued the use of avoparcin, an antibiotic similar to vancomycin, in animal production and has not reported any Vancomycin resistant *Enterococci* (VRE) since. (van den Bogaard et al., 2000a).
- Denmark banned the use of Avoparcin in 1995. As a result, poultry isolated cases of VRE fell from 80% in 1995 to 5% in 1998. (van de Bogaard et al., 2000a).

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