Antibiotic Use in Food-Animal Production in Denmark

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Modern food animal production depends in large part on the use of antibiotics for disease control and growth promotion. This practice has left many in Denmark concerned about its potential effect on the efficacy of these important drugs. In 1969, the Swann committee recommended that those antibiotics used for the treatment of infections in animals and humans not be used as growth promoters, a policy that was partly adopted by the European Union as a whole. Still, during the early 1990s more antibiotics were used to promote growth than to treat infections in Denmark. During this same time, researchers at the Danish Veterinary Laboratory noticed an increase in the occurrence of antimicrobial resistance among bacteria causing infections in animals. Following this, and the discovery in 1994 and 1995 that the use of the glycopeptide avoparcin for growth promotion was associated with the occurrence of vancomycin-resistant enterococci (VRE), Danish authorities implemented a number of initiatives.

Among them has been the establishment of an integrated surveillance program, including an effort to monitor the use of antimicrobials in food animal production. The Danish Integrated Antimicrobial Resistance Monitoring Program (DANMAP) for surveillance was established in 1995. Information gathered has formed the basis of practical recommendations for veterinary use of antimicrobial agents, and the use of selected drugs for growth promotion has been banned. As mandated by Danish law, all veterinary medicines are available by prescription only.

Use in Growth Promotion

In 1995, as Danish authorities observed an increase in the use of antibiotics for the treatment of animals, their use for growth promotion came under increased scrutiny. Avoparcin was banned in Denmark because of its selection of VRE and the potential to spread through the food chain, and in 1997, all EU countries banned its use. Since then, the occurrence of vancomycin resistance has decreased significantly among enterococcal isolates from broilers, and to a lesser extent, among isolates from pigs. The consumption of avilamycin decreased between 1997 and 1998, and was followed by a significant decrease in the occurrence of resistance among E. faecium from broilers. In January 1998, virginiamycin was banned in Denmark because of cross-resistance to Synercid, a streptogramin of potential value in human treatment. That year also saw a decrease in the consumption of the macrolide tylosin, a drug used in large quantities for growth promotion in pigs, though it is too early to detect any decrease in resistance. In December 1998, the European Commission banned the use of bacitracin, spiramycin, tylosin and virginiamycin for growth

Antimicrobial Agents in Aquaculture: Potential Impact on Public Health

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Antimicrobial agents have been widely used in aquaculture to treat infections by a variety of bacterial pathogens of fish, including A. salmonicida, A. hydrophila, A. salmonicida, Edwardsiella tarda, Pasteurella piscicida, Vibrio anguillarum, and Y. ruckeri. As this industry expands, questions arise concerning the consequences of this practice. Because these drugs are administered by mixing them with feed that is dispersed in the water, they directly dose the environment, resulting in selective pressures in the exposed ecosystem. The emergence of antimicrobial resistance following use of antimicrobial agents in aquaculture has been identified both in bacteria that are fish pathogens and those that are not.

A. salmonicida is an example of a fish pathogen which, in many countries, is frequently resistant to multiple drugs commonly used in aquaculture. These include sulfonamides, tetracycline, amoxicillin, trimethoprim-sulfadimethoxine and quinolones. Often the first isolation of A. salmonicida resistant to a specific antimicrobial agent has been reported shortly after the introduction of the agent into aquaculture. Similar correlations have been observed with other fish pathogens.
FOOD-ANIMAL continued from page 1

promotion, effective July 1, 1999.

In addition to mandated changes in consumption, food animal industries in Denmark have made voluntarily efforts to end all use of antimicrobials as growth promoters by the close of 1999. Consequently, the use of subtherapeutic agents decreased significantly during 1998 (Fig. 1), and the numbers for 1999 are expected to show further reduction. The Danish Veterinary Laboratory and local agricultural organizations have provided extensive information to farmers and veterinarians on how to treat diarrhea or other diseases as a result of the cessation of these drugs.

The gradual elimination of antibiotics as growth promoters has so far proven to be without an increase in the use of these drugs for therapy. Furthermore, no decreased productivity or increase in overall morbidity has been detected. With proper care and good management of animals, especially young ones, the value of antibiotics for growth promotion may prove to be greatly overestimated.

Denmark has a very low consumption rate of antimicrobial agents...as compared to most other countries.

Therapeutic Use

Therapeutic use of antibiotics in animals saw a marked increase between 1990 and 1994 (Fig. 2), correlating with a simultaneous increase in the production of pigs in Denmark. However, increased pork production alone could not explain the rise. In the mid 1990s, large amounts of tetracycline were used for prophylaxis. But in 1995, the regulations governing the sale and delivery of therapeutic antibiotics to farmers were changed, removing the economic incentive for veterinarians to sell these drugs. Consequently, consumption decreased, and while 1996 and 1997 saw an overall increase in total consumption, it correlates with the simultaneous increase in food-animal production.

Figure 1. Consumption of antibiotics* for growth promotion in animals in Denmark 1990-1998

*Antibiotics include: avilamycin, avoparcin, bacitracin, carboxal, flavomycin, monensin, olaquindox, salinomycin, tylosin and virginiamycin.

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Education and Guidelines

Using antimicrobial agents prudently is a way to extend the life span of these drugs. However, the definition of prudent varies widely. In Denmark, using any antimicrobial agent for growth promotion that is also used for therapy in humans – including avoparcin, spiramycin and tylosin in Europe, and tetracycline and penicillin in the US – is discouraged. Guidelines for antibiotic use in human therapy have been in place for more than 30 years in Denmark and other Scandinavian countries. They recommend that antimicrobial therapy only be initiated after a causative agent has been identified, and preferably only after susceptibility testing has been conducted. Furthermore, preference should be given to narrow spectrum drugs. These simple guidelines have proven their value over time, and today Denmark has a very low consumption rate of antimicrobial agents, as well as a low occurrence of resistance among isolates from humans, as compared to most other countries around the world.

In 1996 the Danish Veterinary Laboratory issued a set of guidelines for veterinary practitioners. These include both some overall principles for a veterinary antibiotic policy and some specific guidelines for selecting antimicrobial agents. Priorities are based on a general knowledge of the susceptibility of common disease-causing bacterial pathogens in food animals, and whether or not the antibiotic is important to human medicine. It has, however, been difficult to gauge how effective these guidelines have been, and the monitoring of antibiotic consumption at herd level will soon be undertaken in Denmark.

Mandated and voluntary changes in the consumption of antibiotics in the food-animal industry have lead to some positive results. Furthermore, the establishment of the DANMAP surveillance program has provided a valuable tool for determining the occurrence of resistance among different food-animals and for following trends over time. Such efforts will prove to be worthwhile and important steps toward curtailing drug resistance in Denmark.

References


Figure 2. Consumption of antibiotics* for therapeutic use in animals in Denmark 1986-1998

*Antibiotics include: aminoglycosides, macrolides, penicillins, semisynthetic penicillins, sulfonamides, sulfa/TMP, tetracyclines and others.

Note: APUA is interested in bringing scientific evidence to the current debate over the human health impact of antibiotic use in food animals. An upcoming issue of the APUA Newsletter will carry industry and trade group perspectives on the use of these drugs in agriculture and aquaculture. See related Letter to the Editor, page 6, and APUA’s FAAIR project, page 7.

Colombia is Newest Chapter

We welcome Colombia as the newest addition to APUA’s global network of chapters, led by Jaime Robledo, M.D., Chief of Bacteriology and Mycobacteria at the Corporation for Biological Research in Medellin. Dr. Robledo will be meeting with other founding members of APUA-Columbia to elect a Board of Directors and plan future activities.
Transfer of Resistance

Resistant bacteria that emerge as a result of antibiotic use in aquaculture can transfer their resistance to other bacteria. Many resistance determinants in fish pathogens are carried on transferable R plasmids. Horizontal spread of plasmids from fish pathogens may therefore transfer resistance genes to other bacteria, including those that are pathogenic to humans. This has been demonstrated in bacteria in the water of fish ponds and in marine sediments. Plasmids carrying resistance determinants have also been transferred in vitro from fish pathogens to human pathogens, such as Vibrio cholerae and V. parahaemolyticus, and to potential human pathogens, including Escherichia coli. Furthermore, plasmids carrying multiple antimicrobial resistance determinants have been transferred in simulated natural microenvironments between bacterial pathogens of fish, humans, and other animals. Transfer of multidrug resistance occurred in Ecuador during the cholera epidemic that began in Latin America in 1991. Although the original epidemic strain of V. cholerae O1 was susceptible to the 12 antimicrobial agents tested, in coastal Ecuador it became multidrug resistant. This epidemic began among persons working on shrimp farms, where multidrug resistance was present in noncholera vibrios that were pathogenic to the shrimp. The resistance may have been transferred to V. cholerae O1 from other vibrios and may have conferred a selective advantage because of the local policy of chemoprophylaxis.

Humans who are exposed to aquaculture settings may become infected with bacteria in several ways. For example, Vibrio spp., part of the normal warm marine flora, can cause wound infections in persons with open cuts or abrasions exposed to seawater or marine life. Bacteria from the aquaculture ecosystem may also be transmitted directly to humans through handling of fish. Recently, the fish pathogen Streptococcus iniae caused invasive infections in persons who handled store-bought aquacultured tilapia. The organism was isolated from the aquaculture ecosystem and on fish in grocery stores. Similarly, a new biotype of V. vulnificus caused hundreds of serious infections among persons handling live tilapia produced by aquaculture in Israel. Bacteria on fish may also be transmitted to humans when the aquacultured fish, or other foods that have been cross-contaminated, are eaten. V. parahaemolyticus, for example, is a common foodborne disease in Japan linked to the consumption of aquacultured fin fish. Furthermore, Salmonella, a typical cause of foodborne disease, has been isolated from aquacultured fish and shrimp ponds.

S. typhimurium DT104

Newly available molecular characterizations of antimicrobial resistance determinants provide further evidence of the transmission of resistance between aquaculture ecosystems and humans. Some of the antimicrobial resistance determinants in Salmonella serotype typhimurium definitive type 104 (DT104), for example, may have originated in aquaculture. S. typhimurium DT104, which is typically resistant to ampicillin, chloramphenicol, florfenicol, streptomycin, sulfonamides, and tetracycline, was first isolated from an ill person in 1985 and emerged during the 1990s as a leading cause of human Salmonella infections. Tetracycline resistance in S. typhimurium DT104 is due to a class G resistance gene. The class G resistance determinant is rare and had not previously been reported from Salmonella isolates. It was first identified in 1981 in tetracycline-resistant isolates of V. anguillarum, a pathogen of fish. Furthermore, the recently described novel florfenicol resistance gene, floR, in S. typhimurium DT104, which also confers resistance to chloramphenicol, is almost identical by molecular sequence to the florfenicol resistance gene first described in Photobacterium damselae, another bacterium found in fish. Again, this resistance gene is rare and has not previously been found in Salmonella isolates. Finally, all the antimicrobial resistance determinants in S. typhimurium DT104 are grouped on the chromosome within two distinct integrons and an intervening plasmid-derived sequence. The class G and floR determinants are located within the intervening plasmid-derived sequence. By molecular sequence, the plasmid-derived sequence is closely related (94% identity) to a plasmid identified in Pasteurella piscidia, a pathogen of fish. These molecular characterizations strengthen the evidence that antimicrobial resistance determinants selected for in aquaculture ecosystems can be transmitted to bacteria that cause illness in humans, perhaps at a greater frequency than previously suggested.

These data demonstrate that use of antimicrobial agents in aquaculture has selected for resistance among bacteria in the exposed ecosystems. This resistance can disseminate through the environment and can be transmitted to a variety of bacterial species, including bacteria that can infect humans.
A virtual upper respiratory infection can lead not only to a blocked and runny nose, but also to obstructed sinus cavities which rapidly become filled with fluid. Although it is difficult for a cold to obstruct the passages for very long, prolonged blockage of the small (2-3 mm) sinus ostia can occur more easily. When this process prevents drainage, the result is often a closed-space, purulent infection with more prolonged or pronounced illness than one would expect from an uncomplicated viral cold. Such secondary infections complicate from between 5% to 10% of colds in children and, on the basis of studies correlating signs and symptoms with sinus aspiration and culture, can be diagnosed solely on clinical criteria.

Bacterial rhinosinusitis presents most often in a “persistent” form with nasal discharge of any quality (thick, thin, clear, cloudy, purulent) and/or daytime cough (which may be worse at night) lasting longer than 10-14 days. Less frequently, it occurs in a “severe” form, characterized by temperatures of 102°F or more, with a thick colored nasal discharge for 3-4 days in a sick-appearing child. Both forms may be accompanied by facial pain, bad breath and periorbital edema. The distinguishing features differentiating the mucopurulent rhinitis integral to a common cold from an acute bacterial sinus infections are: 1) the duration of the nasal discharge or cough, or 2) the severity of the accompanying signs and symptoms. Plain sinus radiographs are no longer considered necessary to confirm the diagnosis and are, in fact, discouraged by the American College of Radiology. They add little in terms of accuracy in diagnosis in children under 6 years of age, are difficult to perform, and tend to both over and underestimate the presence of abnormalities within the sinuses.

Although the clinical diagnosis of acute bacterial sinusitis is based upon clearly defined criteria, they are often modified to suit the needs of the practitioner. If/one perceives that parents want antibiotics for their child’s cold, the criterion for persistence of symptoms will be ignored and a diagnosis of sinusitis will be rendered despite a history of only two or three days of cough and snotty nose, particularly if it is yellow-green in color. A brief episode of low-grade fever, headache and runny nose is, likewise, labeled as sinusitis, disregarding the criterion for severity of symptoms. The myth of “recurrent sinusitis” becomes fixed in the parents’ minds, with future expectations of antibiotic therapy for what is, in most instances, a viral cold. In 9 out of 10 cases, taking a few minutes to educate parents, to explain why antibiotics are not being given, and why they are unlikely to be helpful, would not only suffice for the visit under consideration, but for future episodes of upper respiratory infection as well.

References
**APUA News**

**Promoting Prudent Antibiotic Use Around the World**

APUA-International has organized several upcoming CME-accredited programs to improve the understanding of antibiotic resistance:

**April 13, 2000:** In conjunction with the 9th International Congress on Infectious Diseases, Buenos Aires, the Sheraton Hotel and Convention Center, 5:30-7:30 p.m., APUA and APUA-Argentina, along with the Pan American Health Organization and the Pan American Society for Infectious Diseases, are sponsoring a symposium, with a reception to follow. The program, made possible through an unrestricted grant from Bayer Pharmaceuticals, will present effective interventions to improve antibiotic use, and methods to design local guidelines for use of these drugs in the developing world.

**May 2, 2000:** the CME-accredited day-long course, *Antibiotic Resistance: Global Challenge with Local Solutions*, presented by 15 US infectious disease experts and representatives from the US Centers for Disease Control and Prevention, and the World Health Organization. This program is geared toward primary care physicians, and is sponsored in conjunction with the Massachusetts Department of Public Health, American Association for World Health and the Massachusetts Medical Society.

For more information, go to [www.apua.org](http://www.apua.org).

**May 24, 2000:** American Society for Microbiology (ASM) symposium: Panel on Reservoirs of Antibiotic Resistance (ROAR), Los Angeles, CA. Presenters include Drs. Julian Davies, Stuart Levy, and Abigail Salyers.

For more information, see [www.asm.org](http://www.asm.org).

Additionally, APUA joins in co-sponsoring or endorsing the following meetings:

**May 4-5, 2000:** Anti-microbial Resistance The Royal Society of Medicine, London, the Westin Fairfax Hotel, Washington, DC.

**May 9, 2000:** APUA interactive session as part of the European Congress for Chemotherapy, Madrid, Spain.

**July 6-7, 2000:** ASM/Interregional Association for Clinical Microbiology and Anti-microbial Chemotherapy, Moscow, Russia.

**July 16-19, 2000:** International Conference on Emerging Infectious Diseases, Centers for Disease Control and Prevention, the Marriott Marquis Hotel, Atlanta, GA.

**May 17-18, 2000:** International Conference on Emerging Infections Diseases, Centers for Disease Control and Prevention, the Sheraton, N eedham, Massachusetts, presented by 15 US infectious disease experts and representatives from the US Centers for Disease Control and Prevention, and the World Health Organization. This program is geared toward primary care physicians, and is sponsored in conjunction with the Massachusetts Department of Public Health, American Association for World Health and the Massachusetts Medical Society.

For more information, go to [www.apua.org](http://www.apua.org).

APUA President Stuart B. Levy will be speaking at the meetings in Washington, Madrid, and in Moscow.

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**APUA Co-Organizes Course on Resistance Surveillance and Drug Policies in Italy**

APUA, the European Society of Microbiology and Infectious Diseases, and the Italian Surveillance Group for Antimicrobial Resistance co-organized a post-graduate interdisciplinary course entitled “The Role of Antimicrobial Resistance Surveillance for Effective Antibiotic Policies,” on December 10 and 11, 1999, held in Verona, Italy. The course was attended by 65 European participants, eight of whom had been awarded scholarships by the Italian chapter of APUA. A plenary meeting, attended by 250 participants, including physicians, microbiologists, pharmacists and public health officers, closed the course. APUA President Stuart B. Levy concluded with a lecture on defining prudent use of antibiotics.

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**In Memory of Dr. María Alicia Rossi**

It is with great sadness that we learned of the passing of Dr. María Alicia Rossi, international scientist and founding member of APUA-Argentina. Dr. Rossi was Chief of the Laboratory of Antimicrobial Agents at the National Institute of Infectious Diseases, in the Ministry of Public Health, Argentina. Recently, she was leading the collaborative effort with APUA-International to host the first Latin American Course on Laboratory Techniques for Antibiotic Resistance Surveillance, in Buenos Aires, Argentina, April 3-7, 2000. To honor the memory of Dr. Rossi, APUA-International plans to sponsor a series of laboratory trainings in lesser-developed countries, to be spearheaded by Dr. Aníbal Sosa, APUA Project Director.

APUA is seeking sponsors to help support these high-quality trainings throughout Latin America and the developing world. For more information on sponsoring or attending the laboratory training course, please contact Laura Raymond, APUA Project Manager, at 75 Kneeland St., Suite 1512, Boston, MA 02111-1901, or send email to lraymo01@tufts.edu.

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**Dear Editor,**

I wish to point out an error in the article by John Threlfall, et al. in your last issue. It stated that the Swann Committee recommended that feed antibiotics “should not be used for growth promotion.” It did not do so. What the Committee said was, “...If antibiotics are added to animal feed to promote growth (and we have accepted in paragraph 9.6 that there is a case for doing this), the antibiotics should be chosen and used so as to minimize the development and selection of microorganisms resistant to important therapeutic drugs.”

The principles developed by the Swann Committee are still widely supported, so it is important that we remember what they actually are.

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APUA-Moldova Holds Weeklong Training for Physicians and Policy-Makers

Supported by APUA’s small grants program, APUA-Moldova held a weeklong training seminar, entitled “Improving Antibiotic Use in Moldova,” December 20-27, 1999. The conference was organized by chapter leader, Natalia Cebotarenco, and is considered a first step toward the rational use of antibiotics in this country. Presentations were made by leading specialists in pharmacology, infectious diseases, pulmonology and oncology. The initial conference at the national Children’s and Mothers’ Hospital, attended by 75 physicians, pharmacists and medical students, was followed by programs tailored to a variety of audiences. These events included a seminar for pharmacy students, a radio program about the dangers of self-medicating with antibiotics, a training on children and antibiotics, and a seminar for physicians at the Infectious Disease Hospital for Children.

Project FAAIR: Facts about Antibiotics in Animals and Impact on Resistance

APUA has begun a two-year project aimed at increasing public understanding of, and bringing scientific evidence to, the debate over antibiotic use in animals and its potential impact on public health. Meetings with industry representatives, advocacy groups, policy-makers, academia and the veterinary community have been held in an effort to highlight various concerns. The first meeting, held in Toronto in October 1999, took place in conjunction with the conference, Agriculture’s Role in Managing Antibiotic Resistance, cosponsored by APUA-International, the Ontario Ministry of Health, and others. A second meeting, attended by Presidents of the Animal Health Institute, American Pork Producers, American Avian Association and the American Aquaculture Association, was held in conjunction with a related FDA hearing in February, 2000. APUA explored the need for data on antibiotic use in animals and various perspectives concerning prudent use of these important drugs.

APUA Helps Launch Innovative High School Science Curriculum

APUA-International is working with the Cambridge Public Schools Science Department, Tufts University School of Medicine, and the Massachusetts Institute of Technology Public Service Center to implement an innovative science curriculum for high school students on antibiotic resistance. The curriculum, entitled “Frequency and Distribution of Antibiotic Resistant Bacteria on Fruits and Vegetables: Student Research in the High School Classroom,” includes a module on natural selection as it relates to resistance and a component that instructs students on lab methods for its measurement. Students also learn to record and analyze their data. This effort is funded through an unrestricted grant from Bayer’s national “Making Science Make Sense” program.

APUA-PAHO Collaboration

APUA is working with the Pan American Health Organization (PAHO) and their Integrated Management of Childhood Illnesses (IMCI) program to conduct a physician survey of knowledge, attitudes and practices regarding antibiotic use in Latin America. It is hoped this effort will lead to clinical guidelines for common childhood infectious diseases. APUA will coordinate the development of the survey and work with PAHO to develop the guidelines, through a grant from PAHO-IMCI.
If you are concerned about the public health threat of antibiotic resistance, become part of the solution. Make a tax deductible contribution and join our global network of citizens, clinicians, researchers and policy makers.

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The Alliance for the Prudent Use of Antibiotics is a non-profit organization dedicated exclusively to curbing antibiotic resistance and improving the use of antibiotics throughout the world. Founded in 1981, as a global grassroots organization, APUA’s mission is to improve public health through education and research concerning antibiotic use and resistance. With members in over 100 countries and numerous foreign chapters, APUA provides a unique network to support country-based activities and facilitate international communication and planning.

APUA’s resources include an international scientific advisory board with members of national academies of medicine and science, a professional staff with specialized expertise. APUA’s global network of affiliated chapters serves to tailor interventions to local customs and practices.

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