APUA NEWSLETTER
ALLIANCE FOR THE PRUDENT USE OF ANTIBIOTICS

December 15, 2010 *Vol. 28 No. 2*

Antibiotics in food animal production: *A forty year debate*

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Happy holidays to APUA colleagues throughout the world.

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SITUATION ANALYSIS OF ANTIBIOTIC MISUSE IN U.S. FOOD ANIMALS : APUA BACKGROUND PAPER

EXECUTIVE SUMMARY

Antibiotics are widely used in food animal production for therapy and prevention of bacterial infections and for growth promotion. Food animals are raised in confined conditions that promote the spread of infectious diseases. Antibiotics are often used over alternatives, because of low cost and ready availability, often without prescription. Most of the antibiotics used in food animals are the same as those used in humans. Some antibiotic growth promoters (AGPs) used in food animals in the United States are drugs classified by the World Health Organization (WHO) as critically important antibiotics for use in human medicine.

Resistance has developed to virtually all antibiotics used in food animals. The most important driver of resistance selection and spread is antibiotic use [1, 2]. To slow the pace of resistance, the use of antibiotics for growth promotion should be terminated. In addition, it is recommended that antibiotic use data for animals be made available to aid in assessing the public health impacts of antibiotic use in animals and policy changes on antibiotic consumption.

INTRODUCTION

Since the 1950s antibiotics have been widely used in food animal production in the United States. They are used for many purposes, including the therapeutic treatment of clinically sick animals, for disease prophylaxis during periods of high risk of infection, and for promotion of growth and feed efficiency [3]. Food animals are raised in groups or herds, often in confined conditions that promote the spread of infectious diseases [4]. Antibiotics are frequently used to compensate for poor production practices. Most of the antibiotics used in food animals are the same as or belong to the same classes as those used in humans.

Nearly all of the classes of antibiotics used in humans have also been approved for use in animals, including most of the antibiotics classified as critically important for use in humans [5, 6]. Antibiotics are used in all of the major (cattle, pigs, poultry) and minor (e.g. sheep, goats) land-based species and in aquaculture (e.g. salmon, trout) and are administered for therapy, prophylaxis (prevention) and growth promotion / increased feed efficiency [3, 4].

In the U.S., antibiotics must be approved for use in food animals by the Food and Drug Administration (FDA), before they can legally be administered to food animals [6]. However, the vast majority of antibiotics were approved without consideration of the human health impacts due to antibiotic resistance. Therefore, the approved conditions for use are not necessarily safe for humans from the antibiotic resistance standpoint. It is only in the last decade that procedures to evaluate these impacts have been developed and adopted by FDA and similar agencies in other countries [7].

For therapy of clinical bacterial infections, animals are treated with therapeutic doses of antibiotic for a period of time that is specified on the product label. Therapeutic treatment of individual animals is common practice in dairy cattle production (e.g. treatment of pneumonia or mastitis) but occurs in other species only when it is economically or logistically feasible to handle and treat individual animals (e.g. beef claves in a feedlot, sows, breeding animals) [3]. In many cases (e.g. flocks or broiler chickens or pens of salmon), it is impractical to capture, handle and treat individual animals. In these instances, the entire group is treated, including clinically sick animals, those that may be incubating the disease, and those not infected [3].

Group-level use of antibiotics

Group-level prophylactic use of antibiotics is also very common. In some cases, for example, beef calves on arrival at the feedlot, may be administered by injection, but in most cases, prophylactic antimicrobials are administered in feed or water [8, 9]. Prophylactic treatments may be given at therapeutic or sub-therapeutic doses and the duration of treatment is frequently longer than for therapy. Most commonly, prophylactic treatments are administered to all animals in a group considered to be at risk of infection due to their age or stage of production [3, 6, 8]. Examples of prophylactic treatments include: administration of ceftiofur by injection of hatching eggs or day-old turkey poults to prevent *E.coli* infection; administration of chlortetracycline to feed to beef calves to prevent liver abscess; and, administration of tylosin in feed to weaned piglets to prevent diarrhea [10, 11, 12].

Antibiotics used for growth promotion

Antibiotics are also used for growth promotion, which is also sometimes called increased feed efficiency [3, 4, 6, 10]. Most AGP is used in production of pigs, broiler chickens, turkeys, and feedlot beef cattle. The specific physiological basis of the growth promoting effects of antibiotics is unknown, but is hypothesized to involve a nutrient sparing effect in the gut and selective suppression of species of bacteria and clinical expression of infection, i.e., disease prophylaxis [3, 6]. AGPs are typically administered in sub-therapeutic doses for long periods of time (usually greater than 2 weeks), and sometimes for the entire duration of the production cycle. At one time, it was thought that AGPs improved production by 2-10%.

Recent national-level data from Denmark, however, showed that AGPs were of negligible benefit in broiler production, and only of benefit in pork production for prevention of diarrhea in weaned pigs [6]; an effect that in light of more recent data is now in some doubt [13]. Some researchers have claimed that certain AGPs may improve food safety by reducing the incidence of carriage of foodborne infections in animals, but this claim is based on limited evidence [14].

The quantity of antibiotics used in food animal production is thought to be very large, by some estimates comparable to quantities used in human medicine [4]. Unfortunately, few publicly available data on quantities of specific antibiotics used in specific species of food animals are available in the United States. This is a serious information gap that is largely attributable to the lack of a national antibiotic use monitoring system. Such data that are available are derived from targeted surveys and very limited aggregate data provided by the pharmaceutical industry [6, 15].

Selection and spread of resistance in agriculture

Use of a given antibiotic in food animals (or any other sector) selects for resistance to that particular antibiotic (direct selection), but also to related drugs in the same antibiotic class (cross-selection) and even to unrelated drugs (co-selection), when resistance genes to both drugs are present within bacteria [2]. Bacteria may be exposed to these drugs within the intestines, lungs or other locations within food animals, or in the farm environment after drugs are excreted in urine and feces.

Resistance has developed to virtually all antibiotics used in food animals

For some antibiotics, resistance is somewhat slow to emerge, but in other cases, for example, among *Campylobacter* to the fluoroquinolones, it occurs very quickly [16]. Resistance is acquired both by disease-causing (pathogenic) and harmless (commensal) bacteria found within animals and the environment. Resistant bacteria spread among groups of animals or fish, to the local environment (inside of pens, barns) and to the wider environment (adjacent soil, air and water) through spreading of manure and dissemination by in-contact wildlife, insects, and rodents [3, 17, 18, 19].

These bacteria also spread to humans, primarily through contaminated meat, but also through direct contact between food animals and humans (e.g. farmers, farm visitors) [4, 6, 20]. Moreover, resistance genes readily spread among bacteria of the same or different species [4]. Nationally, food animals are a very large reservoir of resistant bacteria. Millions of livestock are produced annually in the United States [15], and these produce millions of tons of manure, each of which contains billions of bacteria that are readily available to contaminate the environment and food chain. Once selected in food animal populations, these resistant bacteria cannot be contained on the farm. Some "biosecurity" measures are used on certain types of farms (e.g. poultry or swine) to restrict the entry and further transmission of selected infectious diseases of animal health significance, but these are not designed for preventing the introduction of further dissemination of *Campylobacter, E. coli* or many other bacteria of human health significance, nor the spread of these resistant bacteria off the farm and into food and the environment.

Antibiotic use – the most important driver of resistance

The most important driver of resistance selection and spread is antibiotic use [1, 2]. AGPs are particularly potent in this regard, because they are administered in low doses (that provide sublethal injury and selective advantage to resistant mutants) for long periods of time (resistance spread is time-dependent) and in large numbers of animals (increasing the odds that resistant strains will emerge and spread) [4]. Other drivers of spread include animal density, housing and hygiene [4].

In the United States, most food animals are reared intensively in large groups that are housed in conditions of close confinement and high stocking density [6]. Examples include the rearing of tens of thousands of broiler chickens within single barns, hundreds or thousands of cattle in feedlots, and hundreds or thousands of pigs in confined swine operations. High stocking density and close confinement encourage the rapid spread of bacteria between animals, including important human pathogens such as *Salmonella*, *Campylobacter* and *E. coli*. Huge quantities of manure are produced on these facilities, which if not composted properly, is an important source of these and other bacteria and resistance determinants for environmental contamination of soil and water.

Intensive rearing is also conducive to spread and expression of clinical diseases in animals that require antibiotic therapy. These diseases provide a rationale for widespread and often unnecessary use of prophylactic antibiotics, some of which are of critical importance to human health. Beef and veal calves are usually sourced from different locations and transported long distances prior to confinement in barns and feedlots. These conditions are stressful and lead to a host of infectious diseases for which AGPs and prophylactic antibiotics are used [6, 21]. Similarly, piglets are weaned at an early age and litters are mixed, causing stresses that precipitate diarrhea and other diseases for which AGPs are widely used [10, 9].

Animals of various species are routinely fed AGPs throughout the fattening period in order to enhance feed efficiency, promote growth and prevent clinical disease. Many of these AGPs are also used in human medicine (e.g., penicillin, tetracycline) or are members of important classes of human drugs (e.g. tylosin, a macrolide related to erythromycin, and virginiamycin, a streptogrammin) [4, 6].

Time for Some Changes

AGP use in the United States should be terminated to protect public health [22]. European data suggest that AGPs have little actual benefit in terms of growth promotion or increased feed efficiency [22]. AGP termination should be accompanied by appropriate steps to ensure that animal health and welfare are maintained in ways that do not result in significant increases in the use of therapeutic or prophylactic antibiotics that offset the benefits to public health from reduction in AGP use [22]. This is possible through greater implementation of non-antibiotic strategies for animal health maintenance, and where necessary, more targeted use of therapeutic antimicrobials that are less likely than AGPs to select for resistance of public health importance.

Monitor antimicrobial use and antimicrobial resistance

A major barrier to better understanding of the public health impacts of antibiotic use in animals is a lack of publicly available data on antibiotic consumption in the agricultural sector. The limited information currently available on antibiotic use in food animals in the United States is pieced together from special research studies, regional surveys and indirect estimates [23].

Good quality national-level data are essential to risk assessment, interpretation of resistance trends, and assessment of the impact of policy changes on consumption [22]. In countries (e.g. northern Europe) where antibiotic use monitoring data are publicly available, it is much more feasible to evaluate the relative contributions of veterinary and human antibiotic use on resistance in bacterial populations [10].

This policy brief is made possible with the support of The Pew Charitable Trusts.

References

1. Aarestrup, F.M., H.C. Wegener, and P. Collignon, Resistance in bacteria of the food chain: epidemiology and control strategies. Expert Rev Anti Infect Ther, 2008. 6(5): p. 733-50.
2. O'Brien, T.F., Emergence, spread, and environmental effect of antimicrobial resistance: how use of an antimicrobial anywhere can increase resistance to any antimicrobial anywhere else. Clin Infect Dis, 2002. 34 Suppl 3: p. S78-84.
3. McEwen, S.A. and P.J. Fedorka-Cray, Antimicrobial use and resistance in animals. Clin Infect Dis, 2002. 34 Suppl 3: p. S93-S106.
4. World Health Organization. Division of Emerging and other Communicable Diseases Surveillance and Control., The Medical impact of the use of antimicrobials in food animals : report of a WHO meeting, Berlin, Germany, 13-17 October. 1997, Geneva: World Health Organization. 24 p.
5. Collignon, P., et al., World Health Organization ranking of antimicrobials according to their importance in human medicine: A critical step for developing risk management strategies for the use of antimicrobials in food production animals. Clin Infect Dis, 2009. 49(1): p. 132-41.
6. National Academy of Sciences. The use of drugs in food animals, benefits and risks. in Committee on Drug Use in Food Animals 1999. Washington, D.C.: National Academy Press.
7. Tollefson, L., Developing new regulatory approaches to antimicrobial safety. J Vet Med B Infect Dis Vet Public Health, 2004. 51(8-9): p. 415-8.
8. Duff, G.C. and M.L. Galyean, Board-invited review: recent advances in management of highly stressed, newly received feedlot cattle. J Anim Sci, 2007. 85(3): p. 823-40.
9. Rajic, A., et al., Reported antibiotic use in 90 swine farms in Alberta. Can Vet J, 2006. 47(5): p. 446- 52.
10. World Health Organization. Dept. of Communicable Disease Prevention Control and Eradication, Danish Veterinary Institute., and Danmarks jordbrugsforskning, Impacts of antimicrobial growth promoter termination in Denmark : the WHO international review panel' s evaluation ∗ For more information and detailed policy recommendations, see the FAAIR Report, edited by Michael Barza, MD and Sherwood L. Gorbach, MD. 6 of the termination of the use of antimicrobial growth promoters in Denmark : Foulum, Denmark 6-9 November 2002. 2003, Geneva: World Health Organization. 57 p.
11. Dutil, L., et al., Ceftiofur resistance in *Salmonella enterica* serovar Heidelberg from chicken meat and humans, Canada. Emerg Infect Dis, 2010. 16(1): p. 48-54.
12. Nagaraja, T.G. and M.M. Chengappa, Liver abscesses in feedlot cattle: a review. J Anim Sci, 1998. 76(1): p. 287-98.
13. Aarestrup, F.M., et al., Changes in the use of antimicrobials and the effects on

productivity of swine farms in Denmark. Am J Vet Res, 2010. 71(7): p. 726-33.
14. Cox, L.A., Jr. and D.A. Popken, Quantifying potential human health impacts of animal antibiotic use: enrofloxacin and macrolides in chickens. Risk Anal, 2006. 26(1): p. 135-46.
15. Mellon M, B.C., Benbrook K., Hogging it! Estimates of antimicrobial abuse in livestock. 2001, UCS Publications: Cambridge, MA.
16. Zhang, Q., J. Lin, and S. Pereira, Fluoroquinolone-resistant *Campylobacter* in animal reservoirs: dynamics of development, resistance mechanisms and ecological fitness. Anim Health Res Rev, 2003. 4(2): p. 63-71.
17. Chee-Sanford, J.C., et al., Occurrence and diversity of tetracycline resistance genes in lagoons and groundwater underlying two swine production facilities. Appl Environ Microbiol, 2001. 67(4): p. 1494- 502.
18. Kozak, G.K., et al., Antimicrobial resistance in *Escherichia coli* isolates from swine and wild small mammals in the proximity of swine farms and in natural environments in Ontario, Canada. Appl Environ Microbiol, 2009. 75(3): p. 559-66.
19. Heuer, O.E., et al., Human health consequences of use of antimicrobial agents in aquaculture. Clin Infect Dis, 2009. 49(8): p. 1248-53.
20. Fey, P.D., et al., Ceftriaxone-resistant salmonella infection acquired by a child from cattle. N Engl J Med, 2000. 342(17): p. 1242-9.
21. FAO/WHO/OIE. in Joint FAO/WHO/OIE Expert Workshop on Non-Human Antimicrobial Usage and Antimicrobial Resistance: Scientific Assessment. 2003. Geneva, Switzerland.
22. FAAIR, Policy recommendations. Clin Infect Dis, 2002. 34 Suppl 3: p. S76-7.
23. Viola, C. and S.J. DeVincent, Overview of issues pertaining to the manufacture, distribution, and use of antimicrobials in animals and other information relevant to animal antimicrobial use data collection in the United States. Prev Vet Med, 2006. 73(2-3): p. 111-31.

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CONSEQUENCES OF ANTIBIOTIC MISUSE IN FOOD ANIMALS AND INTERVENTIONS: APUA BACKGROUND PAPER

EXECUTIVE SUMMARY

Antibiotic growth promoters (AGPs) are particularly problematic from the resistance perspective because they are used without veterinary prescription, administered for long periods of time at subtherapeutic concentrations, and to entire groups or herds of animals. These conditions favor the selection and spread of antibiotic resistant bacteria among animals, to the environment and eventually to humans, where they cause infections that are more difficult to treat, longer lasting or more severe than antibiotic sensitive infections.

AGP use in the United States should be terminated to protect public health. European data suggest that AGPs have little actual benefit in terms of growth promotion or increased feed efficiency. In some cases, however, they may have disease prophylaxis benefits. Therefore, AGP termination should be accompanied by appropriate steps to ensure that animal health and welfare is maintained in ways that do not result in significant increases in the use of therapeutic or prophylactic antibiotics that offset the benefits to public health from reduction in AGP use. This is possible though greater implementation of non-antibiotic strategies for animal health maintenance, and where necessary, more targeted use of therapeutic antimicrobials that are less likely than AGPs to select for resistance of public health importance.

INTRODUCTION

Antibiotics are widely used for growth promotion in food animal production in the United States. Some of the antibiotics used for growth promotion in pigs, poultry and/or cattle are classified by the World Health Organization (WHO) as critically important antibiotics for use in human medicine [1]. Antibiotic growth promoters (AGP) are particularly problematic for resistance, because they are used without veterinary prescription and are administered for long periods of time at sub-therapeutic concentrations to entire groups or herds of animals.

These conditions favor the selection and spread of antibiotic resistant bacteria among animals, to the environment and eventually to humans, where they cause infections that are more difficult to treat, last longer or are more severe than antibiotic sensitive infections [2].

Options to address the resistance problems of AGP use include doing nothing, restricting use to those that do not select for antibiotic resistance of importance to human or veterinary medicine, or to stop using them altogether in food animal production [3]. The United States has essentially followed the first option. European countries initially adopted the second option, but in recent years banned the use of all AGPs in food animal production [4]. The purpose of this brief is to describe the public health consequences of using AGP in food animals and options for reducing these consequences.

Public health consequences of growth promoter use

Recent research implicates food animals as an important reservoir for urinary tract and blood stream infections in people

Food animals are an important reservoir of non-typhoidal *Salmonella*, as well as *Campylobacter* and some types of *E. coli* infections of humans [5, 6, 7, 8]. Recent research suggests that food animals (particularly pigs) may also be a reservoir of some strains of methicillin resistant *Staphylococcus aureus* (MRSA) for humans, although it appears that people are the major reservoir for most epidemiologically important strains of MRSA [9]. While the major public health impact from food animals is normally attributed to foodborne *Salmonella* and *Campylobacter*, recent research is making it increasingly apparent that food animals are also an important reservoir of antibiotic resistant *E. coli* urinary tract and probably bloodstream infections of humans [8, 10].

AGPs used in the United States include members of important classes of antibiotics used in humans, including penicillins (beta-lactams), macrolides, tetracyclines, streptogramins, sulfonamides and others. Fortuitously, avoparcin, a member of the glycopeptide class that includes vancomycin, was never approved for AGP or therapeutic use in the United States as it was in Europe and elsewhere. This was not because of resistance concerns, but because of evidence that residues of the drug in edible tissues from treated animals would be toxic to humans [11]. As a consequence of decades of widespread use in the United States, resistance to the AGPs is very common in pathogenic and commensal bacteria from food animals.

For example, the prevalence of resistance to tetracyclines, sulfonamides and beta-lactams among fecal *E. coli* from pigs and poultry is typically greater than 20%, and in some cases greater than 90% [12, 13]. Importantly, AGPs also exert selective pressure to other antimicrobials of great importance to human medicine through the process of co-selection [3, 5]. These resistant bacteria may colonize or cause infections in people exposed through contaminated food, by direct contact with infected animals, or indirectly through contaminated water or other environmental sources. Importantly, some of these bacteria that acquire resistance determinants in animals (e.g. *Enterococcus faecium*, *E. coli*) may colonize humans and share these genes with other human pathogens. In some cases, these altered pathogens may spread to other people in hospitals or other settings, in the face of additional antibiotic selection pressures in people [2, 5].

Antibiotic resistance increases the human burden of illness

Antibiotic resistance among enteric pathogens of humans increases the burden of illness in humans by increasing the total number of infections that occur (through altered colonization resistance), and increasing the severity and duration of infection [2, 14]. The precise burden of illness attributable to AGP use and antimicrobial resistance selection is unknown, due to lack of comprehensive epidemiological studies and risk assessments that account for the tremendous complexity of the farm animal / environment / human ecosystem. Various risk assessments of limited scope have been conducted to estimate the magnitude of public health impact of antimicrobial use in animals on certain types of antibiotic resistance. The results vary from minimal impact in the case of certain macrolides and selection of resistance in enterococci [15] to many thousands of additional cases of fluoroquinolone resistant *Campylobacter* infections annually in the United States [16].

Antibiotic use in food animals selects for antibiotic resistant infections in humans

Research in the United States and Europe has shown that the risk of death and hospitalization is greater in resistance than sensitive *Salmonella* infections [17, 18, 19]. Many studies have shown that people taking antibiotics are at increased risk of acquiring antibiotic resistant infections [20, 21]. Since person-to-person spread of non-typhoidal *Salmonella* is rare in the United States, resistance to these *Salmonella* is most likely to have been selected by antibiotic use in animals.

Options for containment of resistance – agriculture

It is well recognized that resistance is a problem in food animal production, but there is a lack of consensus on what to do about it. The main options available to improve antibiotic use on farms are to maintain the status quo (i.e. do nothing), ban or restrict the use of specific antibiotics, limit their use to specific situations or conditions through altered licensing, attempt to modify behavior in order to improve "prudent use" practices among veterinarians and farmers, remove incentives to excessive use, and reduce the need for antibiotics by improving vaccines, non-antibiotic growth enhancers, and improved hygiene and health management on farms [3].

Doing nothing is not a viable option because resistance continues to increase and is an unacceptable public health burden. Banning or otherwise withdrawing the use of antibiotics in specific situations has been successful in reducing antibiotic use and resistance. For example, the ban on use of avoparcin and other AGPs in Denmark resulted in the dramatic decline in glycopeptide use and resistance among enterococci (Figure 1) [4]. In Canada, the voluntary (but temporary) withdrawal of the use of ceftiofur for injection of hatching eggs or day-old chicks dramatically reduced resistance to 3rd generation cephalosporins in *Salmonella* from humans and chickens [22]. Unfortunately, the industry has at least partially resumed ceftiofur use, and resistance has increased accordingly (figure 2).

Improved licensing has potential for reducing resistance impacts, particularly for new classes of antibiotics that are not yet approved for use in animals. Unfortunately, most of the antibiotics now on the market were licensed without prior consideration of antibiotic resistance risks to humans. Once on the market, it has proven to be extremely difficult to remove those that pose risks to human health. For example, several years ago the FDA proposed to revoke the approvals for penicillin and tetracycline as growth promoters, but was unsuccessful [23]. Moreover, once approved for use in at least one type of food animals, veterinarians have considerable latitude in prescribing extra-label use in other food animal species.

There are many advocates for the voluntary "prudent use" approach to antibiotic stewardship, which involves adherence to general principles of antibiotic use that maximize therapeutic efficacy but minimize resistance risks [5]. Unfortunately, there is little evidence that this approach has actually changed prescribing or use behavior in the veterinary sector, or has had any impact on antibiotic use or resistance in food animal production. Furthermore, there is no real incentive for veterinarians or farmers to improve their antibiotic use practices, since they receive no financial benefit from producing animals shedding fewer resistant human pathogens or commensals. If anything, there are important financial incentives that drive increased use in food animals.

Alternatives for decreasing use of antibiotics in agriculture

Because antibiotics are generally effective in preventing and treating clinical bacterial infections of animals (the vast majority of which are not human pathogens), farmers realize fewer losses through morbidity and mortality, when antibiotics are used for these purposes. Another incentive to increased use is the financial remuneration received by some veterinarians, who supply antibiotics to farmers. While antibiotics for humans in the United States are normally dispensed through pharmacies and hospitals, veterinarians frequently both prescribe and dispense these drugs and in some cases, may realize considerable profit from doing so. In some European countries, veterinarians are no longer allowed to profit from antibiotic sales, and there is good evidence that this reduces antibiotic use on farms [4].

There are many alternatives to antibiotics. Many of these (e.g. vaccines, health management programs) are already used on good quality farms and probably reduce the need for antibiotic use. Unfortunately, some veterinarians and farmers seem willing to rely on antibiotics to treat bacterial infections rather than prevent them in the first place, or to use antibiotics as cheap and effective options for prophylaxis of bacterial infections. Widespread introduction of health management practices can improve animal health, and, therefore, the need for treatment or prophylaxis. For example, introduction and routine use of a vaccine for farmed salmon in Norway dramatically reduced the quantity of antibiotics used in production (figure 3) [24, 25]. There can be little doubt that the continued ready access to cheap in-feed antibiotics is an important disincentive to development and widespread uptake of additional vaccines and other alternatives to antibiotics.

Terminate use of antibiotics for growth promotion

U.S. public policy on the misuse of antibiotics in agriculture is severely lagging. AGP use in the United States should be terminated [5, 26]. This widespread use of antibiotics at low doses for long periods of time selects for resistance to antibiotics of importance to human medicine [26]. Such resistance increases the frequency, severity and duration of important human infections, such as *Salmonella*, *Campylobacter* and *E. coli*. European data suggest that benefits to animal production from AGP use are limited or negligible. To the extent that AGPs are preventing some bacterial infections of animals, termination may have some adverse effects. Most of these effects can be anticipated, and may include increased incidence of necrotic enteritis in poultry and diarrhea in piglets. Suitable alternatives that can be put in place include vaccines and where necessary, more targeted use of antibiotics that do not select for resistance to critically important antibiotics for humans [26]. Steps will have to be taken, however, to ensure that veterinarians and farmers do not simply compensate for decreased AGP use by directly increasing use of prophylactic antimicrobials. Quantitative data on antimicrobial use in agriculture should be made available to make assessments to inform animal and public health policy [26].

This policy brief is made possible with the support of The Pew Charitable Trusts.

Figure 1: Trend in avoparcin resistance among Enterococci faecium from broilers and broiler meat and the usage of the growth promoter avoparcin, Denmark; from reference 6

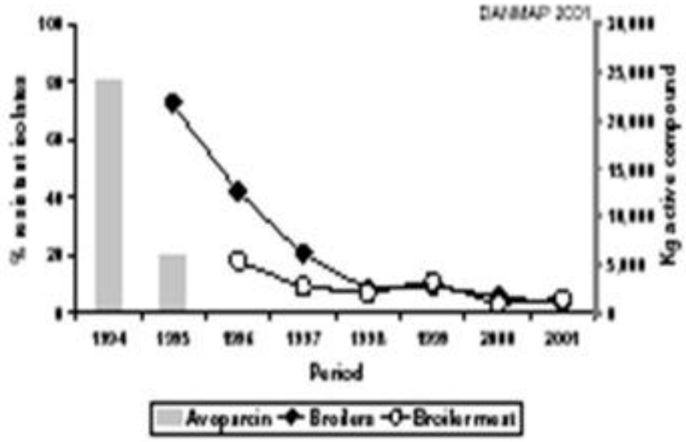


Figure 2: Proportion (moving average of previous three quarters) of isolates resistant to ceftiofur among retail chicken *E. coli*, and retail chicken and human clinical *S. Heidelberg* isolates from 2003 to 2008 (preliminary) in Québec and Ontario.* (Reprinted from reference below)

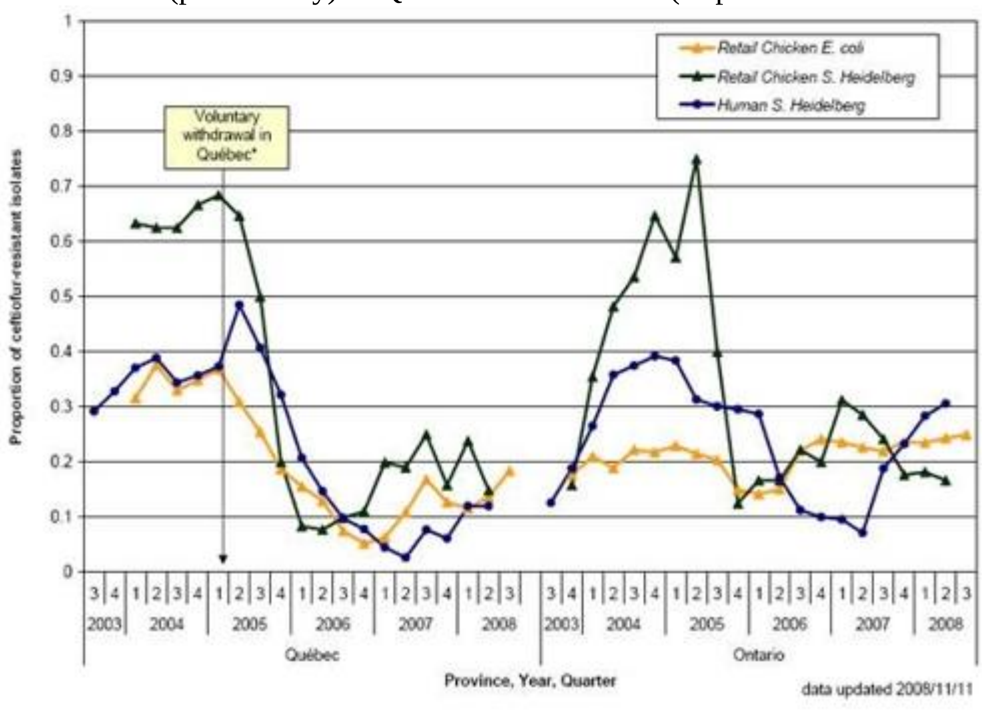
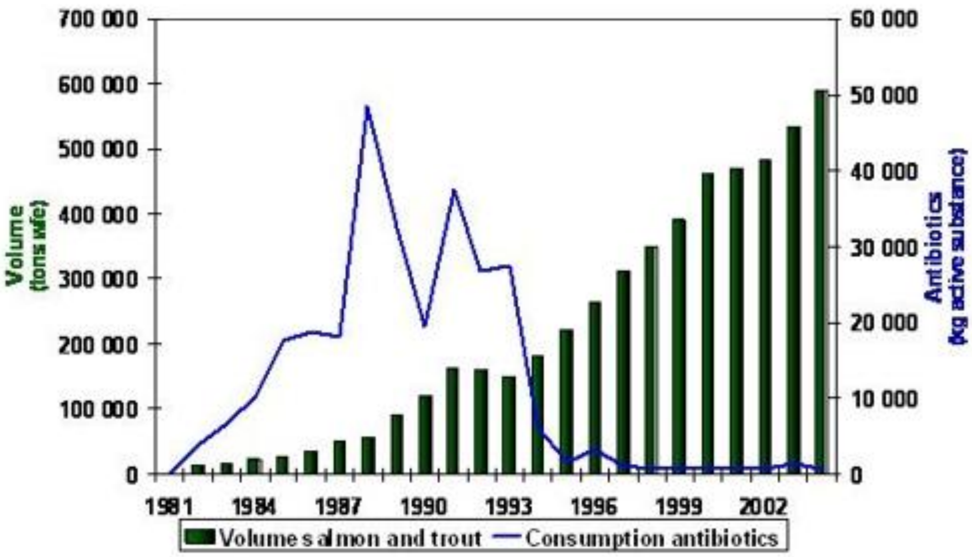


Figure 3: Antimicrobial Usage in relation to Production of Salmon and Trout Production in Norway (from Report FAO/OIE/WHO Expert Consultation on Antimicrobial Use in Aquaculture and Antimicrobial Resistance, 2006)



References

1. Collignon, P., et al., World Health Organization ranking of antimicrobials according to their importance in human medicine: A critical step for developing risk management strategies for the use of antimicrobials in food production animals. Clin Infect Dis, 2009. 49(1): p. 132-41.
2. Barza, M., Potential mechanisms of increased disease in humans from antimicrobial resistance in food animals. Clin Infect Dis, 2002. 34 Suppl 3: p. S123-5.
3. Aarestrup, F.M., H.C. Wegener, and P. Collignon, Resistance in bacteria of the food chain: epidemiology and control strategies. Expert Rev Anti Infect Ther, 2008. 6(5): p. 733-50.
4. World Health Organization. Dept. of Communicable Disease Prevention Control and Eradication., Danish Veterinary Institute., and Danmarks jordbrugsforskning, Impacts of antimicrobial growth promoter termination in Denmark : the WHO international review panel' s evaluation of the termination of the use of antimicrobial growth promoters in Denmark : Foulum, Denmark 6-9 November 2002. 2003, Geneva: World Health Organization. 57 p.
5. World Health Organization. Division of Emerging and other Communicable Diseases Surveillance and Control., The Medical impact of the use of antimicrobials in food animals : report of a WHO meeting, Berlin, Germany, 13-17 October 1997. 1997, Geneva: World Health Organization. 24 p.
6. National Academy of Sciences. The use of drugs in food animals, benefits and risks. in Committee on Drug Use in Food Animals 1999. Washington, D.C.: National Academy Press.
7. FAO/WHO/OIE. in Joint FAO/WHO/OIE Expert Workshop on Non-Human Antimicrobial Usage and Antimicrobial Resistance: Scientific Assessment. 2003. Geneva, Switzerland.
8. Collignon, P., Resistant *Escherichia coli*--we are what we eat. Clin Infect Dis, 2009. 49(2): p. 202-4.
9. Weese, J.S. and E. van Duijkeren, Methicillin-resistant *Staphylococcus aureus* and *Staphylococcus pseudintermedius* in veterinary medicine. Vet Microbiol, 2010. 140(3-4): p. 418-29.

10. Manges, A.R., et al., Retail meat consumption and the acquisition of antimicrobial resistant *Escherichia coli* causing urinary tract infections: a case-control study. Foodborne Pathog Dis, 2007. 4(4): p. 419- 31.
11. McDonald, L.C., et al., Vancomycin-resistant enterococci outside the health-care setting: prevalence, sources, and public health implications. Emerg Infect Dis, 1997. 3(3): p. 311-7.
∗ For more information and detailed policy recommendations, see the FAAIR Report edited by Michael Barza, MD and Sherwood L. Gorbach, MD.
12. Alali, W.Q., et al., Longitudinal study of antimicrobial resistance among *Escherichia coli* isolates from integrated multisite cohorts of humans and swine. Appl Environ Microbiol, 2008. 74(12): p. 3672-81.
13. Smith, J.L., et al., Impact of antimicrobial usage on antimicrobial resistance in commensal *Escherichia coli* strains colonizing broiler chickens. Appl Environ Microbiol, 2007. 73(5): p. 1404-14.
14. Heuer, O.E., et al., Human health consequences of use of antimicrobial agents in aquaculture. Clin Infect Dis, 2009. 49(8): p. 1248-53.
15. Hurd, H.S., et al., Public health consequences of macrolide use in food animals: a deterministic risk assessment. J Food Prot, 2004. 67(5): p. 980-92.
16. Nelson, J.M., et al., Fluoroquinolone-resistant *Campylobacter* species and the withdrawal of fluoroquinolones from use in poultry: a public health success story. Clin Infect Dis, 2007. 44(7): p. 977- 80.
17. Holmberg, S.D., J.G. Wells, and M.L. Cohen, Animal-to-man transmission of antimicrobial-resistant *Salmonella*: investigations of U.S. outbreaks, 1971-1983. Science, 1984. 225(4664): p. 833-5.
18. Varma, J.K., et al., Hospitalization and antimicrobial resistance in *Salmonella* outbreaks, 1984-2002. Emerg Infect Dis, 2005. 11(6): p. 943-6.
19. Helms, M., J. Simonsen, and K. Molbak, Quinolone resistance is associated with increased risk of invasive illness or death during infection with *Salmonella* serotype Typhimurium. J Infect Dis, 2004. 190(9): p. 1652-4.
20. Glynn, M.K., et al., Prior antimicrobial agent use increases the risk of sporadic infections with multidrugresistant *Salmonella enterica* serotype Typhimurium: a FoodNet case-control study, 1996-1997. Clin Infect Dis, 2004. 38 Suppl 3: p. S227-36.
21. Koningstein, M., et al., The interaction between prior antimicrobial drug exposure and resistance in human *Salmonella* infections. J Antimicrob Chemother, 2010. 65(8): p. 1819-25.
22. Dutil, L., et al., Ceftiofur resistance in *Salmonella enterica* serovar Heidelberg from chicken meat and humans, Canada. Emerg Infect Dis, 2010. 16(1): p. 48-54.
23. Institute of Medicine. Human health risks with the subtherapeutic use of penicillin or tetracyclines in animal feed. 1989. Washington, D.C.: National Academy Press.
24. Sorum, H., Farming of Atlantic salmon--an experience from Norway. Acta Vet Scand Suppl, 2000. 93: p. 129-34, discussion 149-57.
25. FAO/WHO/OIE. in Expert Consultation on Antimicrobial Use in Aquaculture and Antimicrobial Resistance. 2006.
26. FAAIR, Policy recommendations. Clin Infect Dis, 2002. 34 Suppl 3: p. S76-7.

RAISING AWARENESS AMONG EU POLICY MAKERS ON ANTIBIOTICS IN ANIMALS : APUA POSITION PAPER FOR WHO

Prepared by APUA staff and Mary Wilson, M.D.

This APUA position paper on "Raising awareness for prudent use of antibiotics in animals" was presented by APUA board member Dr. Mary Wilson at the WHO Expert meeting in Rome during November 11-12, 2010. The purpose of this meeting was to develop a policy-oriented guidance booklet for the European countries on antimicrobial resistance from a food safety perspective. In addition to raising awareness, the booklet is intended to advise on and promote best policies and practices to control antimicrobial resistance. Publication of the booklet is expected on World Health Day, April 7, 2011, when WHO will launch a worldwide campaign in collaboration with APUA, Center for Global Development, Gates Foundation, The Global Fund, INRUD, ReAct and others to prevent antimicrobial resistance.

The Ecological Impact of Antibiotic Use in Food Animals

Antibiotics are widely used in food animal production for various purposes including the therapeutic treatment of clinically sick animals, disease prophylaxis during periods of high risk of infection, and promotion of growth. They are routinely placed in livestock feed and water to increase feed efficiency and prevent diseases that may otherwise result from the unsanitary and crowded conditions in which animals are raised. The administration of antibiotics in low doses over long periods of time is one of the strongest selective pressures leading to emergence of resistant bacteria. Under those conditions, antibiotic resistant bacteria emerge and rapidly proliferate, and can then transfer to humans through contact with food animals, food consumption, and contaminated water and soil. Once resistant bacteria emerge in the environment, it is difficult to reverse the process. Resistance genes spread readily between bacteria of the same or different species. Because many of the antibiotics used in food animal production are of the same classes as medically important antibiotics used in humans, this leads to greater human vulnerability to antibiotic-resistant infectious diseases.

The Need for Prudent Use of Antibiotics

Antibiotic use drives the emergence, spread and evolution of resistance genes. Because antibiotic-sensitive strains are suppressed or eliminated, resistant strains are amplified and made more available to recombinant events. Both pathogenic and commensal bacteria can acquire resistance and propagate among groups of animals or fish, to local environments (barns), and to the wider environment (air, soil, water).[1,4] Food animals are a very large reservoir of non-typhoidal *Salmonella, Campylobacter*, some strains of methicillin resistant *Staphylococcus aureus* (MRSA) for humans, and *E.coli* urinary tract and probably bloodstream infections of humans.[3] Millions of livestock are produced every year[2] and their manure contains millions of bacteria that can spread through the environment and the food chain[4]. After a half century of antibiotic use, antibiotic resistance genes have been spread to more than a quarter of the world's infectious bacterial species. In addition, studies have shown that countries with higher rates of antibiotic use also have more antibiotic resistant bacteria. Limiting the use of antibiotics to only circumstances that require them is one of the most important controls on the emergence and spread of resistance. It is a public health imperative to eliminate misuse of antibiotics in human medicine and agriculture to prolong the lifespan of critically important antibiotics.

Defining Prudent Use

Because animals far outnumber humans worldwide, the misuse and overuse of antibiotics in food animal production has a broad impact on the environment. The human health consequences of the dissemination of resistance genes from food animal production include increased numbers of infections, increased severity of illness, and increased likelihood of treatment failure. The World Health Organization defines appropriate use as "the cost-effective use of antimicrobials which maximizes clinical therapeutic effect while minimizing both drug-related toxicity and the development of antimicrobial resistance." Any unnecessary use in human medicine should be minimized to reduce selective pressure in the environment. In the context of food animal production, prudent use means eliminating nontherapeutic uses, including growth promotion and feed efficiency. Another definition of prudent antibiotic use is: the right drug for the right condition for the right amount of time. Antibiotics should only be administered for treatment of diseased animals, with veterinary oversight. Decisions about the amount of antibiotics being delivered, how they are delivered and how they are distributed need to be made judiciously to prevent unwanted consequences of antibiotic use.[1]

To minimize infection in food animal production and decrease the volume of antibiotics used, alternative infection prevention methods should be instituted wherever possible to improve animal health and eliminate or reduce the need for antibiotics for treatment or prophylaxis. Alternatives include: improved hygiene and health management on farms, use of probiotics or competitive exclusion products, and vaccination.[18] The introduction and use of vaccines in farmed salmon in Norway was successful in dramatically reducing the use of antibiotics in 2006. Similar interventions should be made in all food animal farms.

Ensuring Prudent Use: Policy Recommendations

A strong prudent antibiotics use policy at the national level is a necessary first step to minimize misuse of antibiotics in food animals. A national policy should require surveillance of antibiotic use and resistance on the farm and establishment of specific antibiotic use guidelines for each type of animal. In 2001, the Alliance for the Prudent Use of Antibiotics (APUA) convened a Scientific Advisory Group meeting as part of its Facts about Antimicrobials in

Animals and the Impact on Resistance (FAAIR) project. After extensively reviewing the scientific evidence, key policy recommendations were suggested.[18] Similar recommendations were identified by the World Health Organization in its 2001 Global Strategy for Containment of Antimicrobial Resistance.[17] These experts all agree that the following prudent use principles should be part of national public health policy. Associated guidelines, surveillance and compliance regulations should be instituted to protect public health.

<u>APUA Principles for Prudent Use of Antibiotics in Food Animals</u>

- Antimicrobials should only be used in agriculture for treatment of diseased animals. Antimicrobial growth promoters and other non-therapeutic uses should be eliminated; AGP restrictions should not be compensated for by simply increasing use of prophylactic antimicrobials [17,18].
- Antimicrobials should be administered to animals only when prescribed by a veterinarian. Professional societies of veterinarians should establish guidelines about recommended dosage, interval, and duration of antibiotic treatment. Economic incentives that promote the inappropriate prescription of antibiotics should be eliminated [17,18].
- National-level quantitative data on antimicrobial use in agriculture should be made available to support risk assessment, interpretation of resistance trends, and assessment of the impact of policy changes on consumption. Pharmaceutical manufacturers should be required to report the quantities of antimicrobials produced, imported and sold. End-user surveys should be conducted to monitor use of antimicrobials in agriculture [18].
- The ecology of antimicrobial resistance should be considered by regulatory agencies in assessing human health risk associated with antimicrobial use in agriculture. Regulatory agencies should work with research organizations to conduct risk assessment studies. When not enough data are available, regulators should follow the "precautionary principle" [18].
- National surveillance programs for antimicrobial resistance should be improved and expanded to monitor antimicrobial usage in food animals. Programs should be linked to allow for joint analysis of human and animal data. They should include standardization of sampling, culture, identification, and susceptibility testing methods. Results should be published frequently [17,18].
- Alternatives to antimicrobials, and new risk-assessment models should be instituted as well as research to improve understanding of the effects of antibiotic use [18].
- Introduce pre-licensing safety evaluation of antimicrobials with consideration of potential resistance to human drugs [17].
- Monitor resistance to identify emerging health problems and take timely corrective actions to protect human health [17].

APUA also advises policymakers to separately categorize antibiotics from other drugs because they are "societal drugs." Antibiotics not only affect the individual using them, but the larger community and the environment as well. A separate class would allow for implementation of incentives to industry for developing new antibiotics, post-marketing surveillance to curb resistance, and efforts by producers and consumers to preserve their efficacy.

Conclusion

Antibiotic resistant infections are increasing in healthcare settings and the community. Antibiotic overuse is the main driver. There is an urgent need for action on the issue of antibiotic resistance. The misuse and overuse of antibiotics in food animals is a major source of the problem. Improved surveillance and national regulation is needed to ensure that antibiotics are used prudently and are not routinely fed to animals for nontherapeutic purposes. Maintaining the status quo and continuing to misuse antibiotics as we have been doing will jeopardize our ability to effectively treat infectious diseases in the future. National authorities, veterinarians, physicians, and farmers all have a role in "preserving the power of antibiotics®."

References

[1] McEwen, S.A. & Fedorka-Cray, P.J. (2002). "Antimicrobial use and resistance in animals." Clin Infect Dis 34(Supplement 3): S93-S106
[2] Mellon, M., Benbrook, C., & Benbrook, K.L. (2001). Hogging It!: Estimates of Antimicrobial Abuse in Livestock. Cambridge, MA: Union of Concerned Scientists.
[3] World Health Organization. Division of Emerging and Other Communicable Diseases Surveillance and Control. (1997). "The Medical Impact of the use of antimicrobials in food animals: report of a WHO meeting, Berlin, Germany, 13-17 October 1997." Geneva: World Health Organization. P. 24.
[4] Alliance for the Prudent Use of Antibiotics. (2010). Misuse of Antibiotics in Food Animal Production, Policy Brief and Recommendations #4: Antibiotic Misuse in Food Animals-Time For Change. Submitted for publication.
[5] O'Brien, T.F. (2010). Misuse of Antibiotics in Food Animal Production, Policy Brief and Recommendations #3: Reduce Antibiotic Use to Delay Antibiotic Resistance. Alliance for the Prudent Use of Antibiotics. Submitted for publication.
[6] Chee-Sanford, J.C., et al. (2001). "Occurrence and diversity of tetracycline resistance genes in lagoons and groundwater underlying two swine production facilities." Appl Environ Microbiol 67(4): 1494-1502.
[7] Kozak, G.K., et al. (2009). "Antimicrobial resistance in *Escherichia coli* isolates from swine and wild small mammals in the proximity of swine farms and in natural environments in Ontario, Canada." Appl Environ Microbiol 75(3):559-566.
[8] Heuer, O.E., et al. (2009). "Human health consequences of use of antimicrobial agents in aquaculture." Clin Infect Dis 49(8): 1248-53.
[9] National Academy of Sciences. (1999). The use of drugs in food animals, benefits, and risks. Committee on Drug Use in Food Animals. Washington, D.C.: National Academy Press.
[10] FAO/WHO/OIE. (2003). Joint FAO/WHO/OIE Expert Workshop on Non-Human Antimicrobial Usage and Antimicrobial Resistance: Scientific Assessment, Geneva, Switzerland.
[11] Collignon, P. (2009). "Resistant *Escherichia coli*-we are what we eat." Clin Infect Dis 49(2): 202-4.
[12] Weese, J.S. & van Duijkeren, E. (2010). "Methicillin-resistant *Staphylococcus aureus* and *Staphylococcus pseudintermedius* in veterinary medicine." Vet Microbiol 140(3-4): 418-29.
[13] Manges, A.R., et al. (2007). "Retail meat consumption and the acquisition of antimicrobial

resistant *Escherichia coli* causing urinary tract infections: a case-control study." Foodborne Pathog Dis 4(4): 419-31.
[14] Lester, S.C., et al. (1990). "The carriage of *Escherichia coli* resistant to antimicrobial agents by healthy children in Boston, in Caracas, Venezuela, and in Qin Pu, China." N Engl J Med 323(5): 285-9.
[15] Goossens, H. (2009). "Antibiotic consumption and link to resistance." Clin Microbiol Infect 15 (Supplement 3): 12-5.
[16] Barza, M. (2002). "Potential Mechanisms of Increased Disease in Humans from Antimicrobial Resistance in Food Animals." Clin Infect Dis 34(Supplement 3): S123-S125
[17] World Health Organization. (2001). WHO Global Health Strategy for Containment of Antimicrobial Resistance.
[18] APUA FAAIR Scientific Advisory Panel (2002). "Policy Recommendations." Clin Infect Dis 34(Supplement 3): S76-S77.
[19] Sorum, H. (2000). "Farming of Atlantic salmon-an experience from Norway." Acta Vet Scand Suppl 93:129-34, discussion 149-57.
[20] FAO/WHO/OIE. (2006). Expert Consultation on Antimicrobial Use in Aquaculture and Antimicrobial Resistance.
[21] Levy, S.B. (2010). "Antibiotics Should Be Assigned to a Special Drug Class to Preserve Their Power, Says Alliance for the Prudent Use of Antibiotics." [Press Release].

Other Resources

Levy, S.B. (2002). The Antibiotic Paradox. Cambridge, Perseus Publishing Services.

Anthony, F., Acar, J., Franklin, A., Gupta, R., Nicholls, T., Tamura, Y., et al. (2001). Antimicrobial resistance: responsible and prudent use of antimicrobial agents in veterinary medicine. Rev. sci. tech. Off. int. Epiz. 20(3): 829-839.

Food and Drug Administration. Judicious Use of Antimicrobials. http://www.fda.gov/AnimalVeterinary/SafetyHealth/AntimicrobialResistance/JudiciousUseofAntimicrobials/default.htm

The Pew Commission on Industrial Farm Animal Production. Putting Meat on the Table: Industrial Farm Animal Production in America. http://www.pewtrusts.org/uploadedFiles/wwwpewtrustsorg/Reports/Industrial_Agriculture/PCIFAP_FINAL.pdf

Roundtable of Experts Review EU Ban on Antimicrobial Use in Food Animals

APUA convened a Roundtable of Experts, co-chaired by Herman Goossens, MD, PhD and Christina Greko, PhD, on May 29, 2010 in Paris. Experts in molecular biology, veterinary and clinical medicine reviewed scientific evidence and their experiences with the withdrawal of antimicrobials for non-therapeutic use in food animal production in the European Union (EU) and specific EU countries.

Among the topics addressed were:
"Resistance gene transfer induced by low concentrations of antibiotics" (Patrice Courvalin), "Antibiotics in agriculture and farming as ecotoxic agents favoring antibiotic resistance in different environments" (Fernando Baquero, MD, PhD), "Scientific arguments for and against the ban" (Wolfgang Witte, PhD, Jacques Acar, MD), and "The human health consequences of antimicrobial use in animals." (Frank Aaerstrup, DVM, PhD, Denmark), (Christina Greko, PhD, Sweden, Dik Mevius, DVM, PhD, The Netherlands and Christopher Teale, DVM, United Kingdom) reported on country experiences and their perspectives regarding the withdrawal of antibiotics for non-therapeutic use in food animal production.

EU policy on the issue of judicious use of antimicrobials in food animal production is in contrast to that of United States, where antimicrobials continue to be used for growth promotion and other non-therapeutic purposes. One of the experts stated that the world is on the verge of a global epidemic of multi-resistant *salmonellas* and *E. coli* resistant to ESBLs, and the United States is still "burying its head in the sand" with respect to antibiotic usage. The time for action is now. Publication of a report highlighting select proceedings, lessons learned and recommendations is forthcoming. The entire program is accessible on the APUA website *www.apua.org*. The APUA Roundtable was made possible with the support of The Pew Charitable Trusts.

Policy Updates

PAMTA

APUA continues to support passage of the Preservation of Antibiotics for Medical Treatment Act (PAMTA), introduced by Rep. Louise M. Slaughter and the late Sen. Ted Kennedy on March 17, 2009. Passage of PAMTA would require the "phased elimination of nontherapeutic use in animals of critical antimicrobial animal drugs important for human health." Critical drugs include any kind of penicillin, tetracycline, macrolide, lincosamide, streptogramin, aminoglycoside, sulfonamide, or any other drug used to treat or prevent diseases in humans caused by microorganisms.

On April 28, 2010, Rep. Slaughter submitted testimony to the Committee on Energy and Commerce describing the need for passage of PAMTA. On July 13, 2010, she chaired a Rules Committee hearing on the legislation. Another hearing followed on "Antibiotic Resistance and the Use of Antibiotics in Animal Agriculture," held by the Committee on Energy and Commerce. Stuart B. Levy, M.D. was amongst a group of experts who presented testimonies in support of Congressional action on this issue and advocating for the passage of PAMTA.

As of December 6, 2010, PAMTA is endorsed by 377 organizations representing various interests (health, consumer, agricultural, environmental, and humane). The legislation has 125 co-sponsors in the House and 17 in the Senate. Although this is twice the amount of co-sponsors PAMTA had in the previous four Congresses, it needs 218 to pass. Since the 111th Congress is coming to a close, PAMTA, or similar legislation, will need to be introduced again in the next Congress.

FDA Draft Guidance

On June 28, 2010, the FDA issued a draft guidance, "The Judicious Use of Medically Important Antimicrobial Drugs in Food-Producing Animals," concluding that the unnecessary or inappropriate use of medically important antimicrobials in food animal production is not beneficial to public health. In agreement with APUA, the FDA recommends that antibiotics be used with veterinary oversight. The FDA does not consider use for growth promotion or improvement of feed efficiency to be judicious. However, it does consider antimicrobial use for treatment, control, and prevention of disease to be "necessary for assuring the health of food-producing animals." APUA believes that prevention should not fall under this category because it provides a loophole that may be taken advantage of by food producers.

The FDA will work with various stakeholders such as drug companies and members of the veterinary, public health, and animal agriculture communities to implement these recommendations. APUA founder, Dr. Stuart B. Levy, APUA vice president, Dr. Thomas F. O'Brien, and APUA Executive Director, Kathleen Young, submitted comments applauding this step forward. Furthermore, they stressed the limitations of these guidelines and the need for termination of all non-therapeutic use of antibiotics in food animal production and establishment of a system to monitor compliance. Nearly 100,000 additional comments were sent to the FDA.

Food Safety Bill

Following several food-related outbreaks in the past few years, the Senate recently passed the Food Safety Modernization Act on November 30, 2010 by a vote of 73 to 25. This bill would allow the government to increase inspections of food processing facilities, recall tainted foods, enforce stricter standards for imported foods, create new safety regulations for high-risk produce, and require large food processors and manufacturers to register with the FDA and establish new food safety plans. This shift in focus to prevention will help the FDA to stop outbreaks before they occur. In response to concerns over the impact this bill would have on small farms, senators agreed to exempt some of them from costly food safety plans. They have also eliminated fees and reduced the amount of money spent on FDA inspectors, which differentiates this bill from a House version passed in July 2009.

The likelihood of this bill's passage is not clear. Due to a parliamentary mistake, the bill has to be approved by the House of Representatives, then sent back to the Senate to be approved again before reaching President Obama. Many Senate Republicans have stated that they will not address any legislation until the debate over expiring tax cuts is settled.

If passed, this bill will help protect consumers from dangerous food pathogens and show the government's commitment to improving food safety and the health of its people.

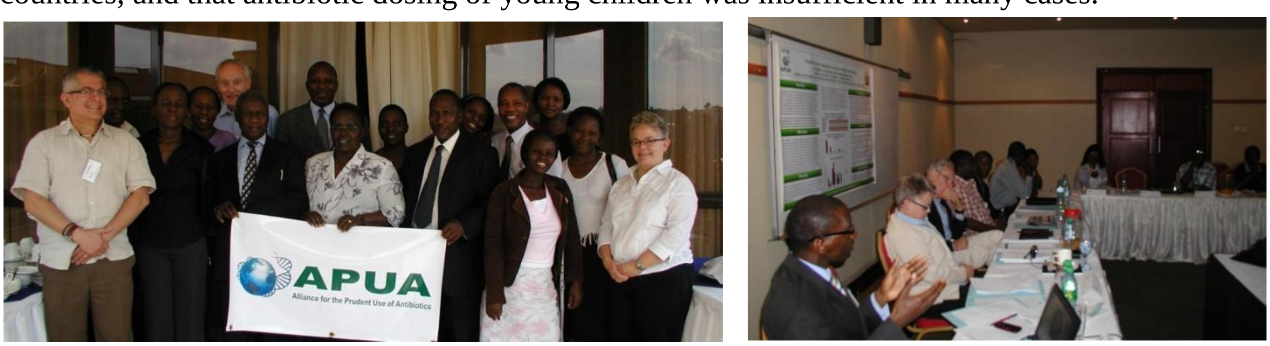
Organizational News

APUA joins IDSA's 10 x '20 initiative

APUA endorsed IDSA's advocacy campaign, the 10x'20 initiative to address the dry antibiotic pipeline and call for 10 new antibiotics by 2020. 10 x '20 encourages the development of antibiotics and the improvement of diagnostic tests for priority resistant infections, as well as the creation of incentives that stimulate new antibacterial research and development.

Stakeholders in Uganda and Zambia consider APUA findings on antibiotic resistance and pneumonia

In September, the APUA team of Professor Susan Foster, Dr. Anibal Sosa, and Dr. Tom O'Brien, carried out stakeholders' meetings in Zambia and Uganda for the Gates Foundation funded "Antibiotic resistance situation analysis and needs assessment" project. Approximately 25 high-level persons from a variety of disciplines and agencies attended each meeting, at which the findings of the project were presented. The project examined the drivers of antibiotic resistance and their role in causing sub-optimal treatment for severe bacterial respiratory infections and pneumonia. Nearly 1,000 drug samples were collected for quality testing, and over 14,000 outpatient records were collected and analyzed. Some of the findings were of particular interest, especially the findings with regard to issues with quality of amoxicillin samples collected in both countries, and that antibiotic dosing of young children was insufficient in many cases.



Dr. Anibal Sosa, Dr. Tom O'Brien, Dr. Susan Foster, meet with stakeholders in Uganda (left) and in Zambia (right)

APUA introduces new communication vehicles

APUA recently launched several new communication vehicles. The APUA Newsletter, which has been published since 1983, is now distributed electronically and is also available in PDF form. More frequent updates on the actions of APUA can be found in APUA Highlights, which is distributed by email. To receive news from APUA, please sign up via the website www.apua.org. Lastly, APUA's blog, "Superbugs and Drugs"®, promotes discussion about antibiotic resistance issues impacting public policy and patient care around the world. It features the input of APUA's distinguished Expert Panel whose members hold vast global experience and expertise in improving antibacterial treatment and containment of antibiotic resistance. Join the discussion now at http://superbugsanddrugs.blogspot.com!

APUA welcomes newest board member Mary Wilson, MD

Mary E. Wilson, MD, is Associate Clinical Professor of Medicine at Harvard Medical School and Associate Professor, Department of Global Health and Population at the Harvard School of Public Health. Her academic interests include tuberculosis, ecology of infections, emergence of new infections, determinants of disease distribution, travel medicine, and vaccines. She has served on the Advisory Committee for Immunization Practices of the CDC and the Academic Advisory Committee for the National Institute of Public Health in Mexico. Dr. Wilson has been writing for Journal Watch Infectious Diseases since the publication was launched in 1998.

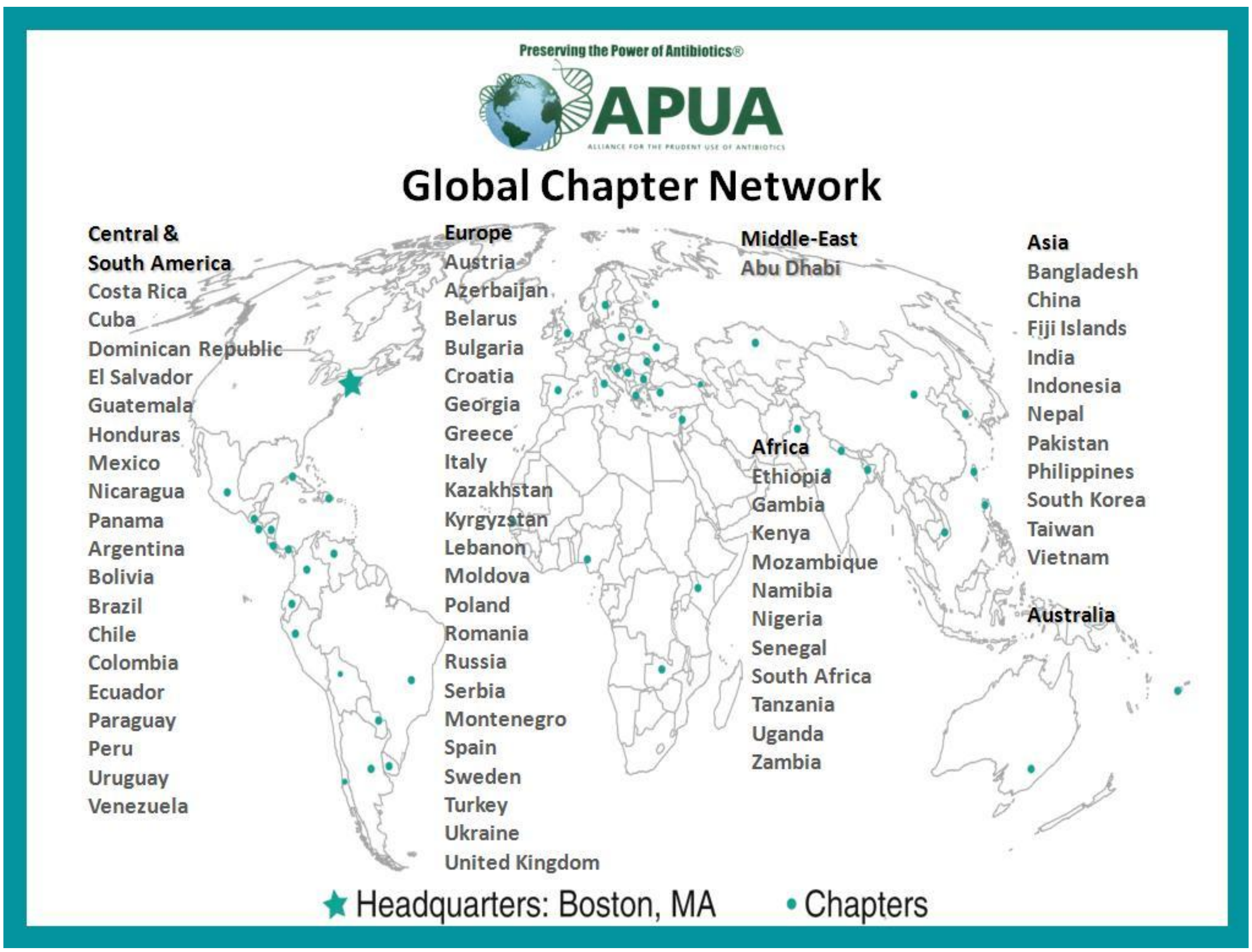
In memoriam

It is with profound regret that APUA announces the passing of Dr. Calil K. Farhat on September 8, 2010. Dr. Farhat was an active member of APUA's Brazilian chapter (APUA-Brazil). As a titular professor in both the Pediatrics Department of Federal University of São Paulo and Infectious Diseases Department of the College of Medicine of Marilia, São Paulo, Brazil, Dr. Farhat was a dynamic and committed figure in the control of pediatric infectious diseases in Latin America. In the 1980's he envisioned convening pediatricians of Latin American countries in order to develop the discipline of Pediatric Infectious Diseases in Africa which aimed to form new generations of specialists equipped with the tools of modern science and a focus on research. In recent years, he was a major force with the Sabin Vaccine Institute's Pneumococcal Awareness Council of Experts (PACE) in advancing the cause for the control of pneumococcal disease. Dr. Farhat received multiple honors in Brazil and abroad, and was distinguished with an Honours Diploma from the American Academy of Pediatrics.

APUA

"Preserving the Power of Antibiotics"®

Since 1981, the Alliance for the Prudent Use of Antibiotics (APUA) has been dedicated to strengthening society's defenses against infectious disease by promoting appropriate antimicrobial access and use and controlling antimicrobial resistance. With a network of affiliated chapters in over 64 countries, more than 33 of which are in the developing world, APUA stands as the world's leading organization conducting focused antimicrobial resistance research, education, and advocacy at the grassroots and global levels. APUA's goal is to improve antimicrobial policy and clinical practice so as to preserve the power of these lifesaving agents and improve treatment for patients with acute bacterial diseases, tuberculosis, AIDS, and malaria.



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