Antimicrobial Use in Agriculture: How Risky?

Food Fight: Debating Animal Antibiotics

This special issue of the newsletter focuses on an increasingly contentious question in public health: Do antimicrobials in animal food production threaten human health?

APUA founder and president Stuart B. Levy, M.D. revealed the urgency of that question more than three decades ago. He led the first prospective study linking subtherapeutic antibiotics in feed to the carriage of antibiotic-resistant bacteria among farm animals and farm families. This landmark study, published in the New England Journal of Medicine in 1976, showed that the introduction of the growth promoter oxytetracycline in chicken feed led to colonization in the flocks of singly resistant, then multiply resistant, E. coli, as well as to the development of multidrug-resistant intestinal flora among the birds’ human handlers.

Today, the animal-to-human transfer of drug-resistant bacteria is no longer an obscure scientific finding, but headline news. Of course, no one disputes the use of antibiotics to cure animal disease. Rather, at issue is the use of such drugs for purely economic purposes. In 2002, APUA released its landmark report “Facts about Antibiotic Use in Animals and its Impact on Resistance” (FAAIR), which recommended the elimination of antibiotics for growth promotion and limiting farm use of critically important drugs for human infections, such as fluoroquinolones and third-generation cephalosporins. A forthcoming FAAIR II report focuses on the need for sound scientific data on antibiotic use in meat and poultry production, in order to pinpoint risks and guide public policy. (For more information on the FAAIR reports, contact APUA consulting scientist Bonnie Marshall: bonnie.marshall@tufts.edu.) In keeping with this trend, fast food giant McDonald’s last year announced that its meat and chicken suppliers must stop using low-level antibiotics to make animals grow faster.

Still, as this issue of the newsletter makes clear, the science behind the human health risks of antimicrobial use in food animal production remains enormously complex — and the political debate as fierce as ever.

Antimicrobial Resistance in Foodborne Pathogens from Mexico


Background

The emergence and global dissemination of multidrug resistance in foodborne pathogens is considered a threat to human public health worldwide. Resistance to broad-spectrum antibiotics, such as ciprofloxacin and ceftiraxone, is of particular con-
**Point/Counterpoint**

**Does Misuse of Antibiotics in Food Animals Threaten Human Health?**

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**NO**

By Dr. Richard Carnevale

**YES**

By David Wellingo, M.D., M.P.A

**Vice President of Scientific, Regulatory and International Affairs**

Animal Health Institute

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After 50 years and a mountain of published research, it is clear that the use of antibiotics to keep food animals healthy presents an extremely small risk to humans. In fact, recent data suggest that the greater risk to food safety is making decisions to ban antibiotics without sufficient scientific basis.

Antibiotics are used in food animals to treat disease, prevent disease, and control disease, and to maintain health and promote growth. Less than 10% of the antibiotics used in animals fall into the last category. The use of other terms and estimates to describe antibiotic use are simply mechanisms of obfuscation.

The evidence documenting the very small risk to humans is strong and growing.

Overwhelmingly, the major problems with antimicrobial resistance in human medicine, as documented by physicians, have little if anything to do with animals or food. MRSA, by all accounts the biggest resistance concern, is not the result of antibiotic use in animals.

Clear and dramatic reductions in foodborne pathogens in our meat supply, and the reduced incidence of foodborne infections as reported by USDA and the Centers for Disease Control and Prevention, cut the already small risk of resistance determinants, including “infections that would not have otherwise occurred, increased frequency of treatment failures (in some cases death) and increased severity of infections.” In 2003, the National Academy of Sciences likewise stated, “Clearly, a decrease in antimicrobial use in human medicine alone will have little effect on the current situation. Substantial efforts must be made to decrease inappropriate overuse in animals and agriculture as well.”

Although some quantitative risk assessments purport to show low human health risks from antibiotic use in food animals, those assessments ignore key aspects of the issue — notably the transferability of resistance determinants. Indeed, methods to quantify this critical attribute of bacteria do not now exist.

To date, quantitative assessments have focused solely on potential treatment failures for traditional foodborne pathogens. Moreover, those assessments have ignored nonfood pathways for transmitting resistant pathogens or resistance determinants, including...
ments show very small risks. For example, a study of the use of two macrolide products concluded their use is accompanied by a very low risk to public health. As one of the scientists said, “People would be more likely to die from a bee sting than for their antibiotic treatment to fail because of macrolide-resistant bacteria in meat or poultry.”

Other studies have also demonstrated the danger of making decisions about antibiotic use without a scientific risk assessment. A risk assessment on the use of fluoroquinolones to treat sick chickens showed that withdrawal of the product would increase the incidence of foodborne illness by more than 100 cases for each incidence of antibiotic-resistant disease avoided, due to more foodborne pathogens contaminating slaughter plants.

Any serious discussion of risk and risk management options must be done on the basis of specific drug/pathogen combinations. A common mistake is to make reference to the risks associated with broad antibiotic use and to confuse potential hazards with risks. Critics like to cite numerous published studies where resistance to antimicrobials in enteric bacteria has been reported and then conclude that human health is being compromised. Yet the evidence that those bacteria actually arose due to animal use and then led to untreatable human infections is rarely if ever available.

Another common mistake is to confuse risk with the amounts of antibiotics used. Clearly, those who wish to attribute risk based on overall quantities used in animals have an agenda outside of scientific risk assessment. The amount of use of a particular drug may be an important data point in an accurate risk assessment of the compound, but it is not a substitute for quantitative risk assessment.

The European experience in banning antibiotics safeguard public health while allowing for the use of these products to reduce disease in animals. The veterinary community has written and follows principles of proper use for antibiotics in animals. Monitoring and surveillance systems to watch for the rise of resistant bacteria are in place, and can be strengthened. As many experts have pointed out, the best protection against the foodborne spread of resistant bacteria is improvement in food hygiene, and data show large gains have been made in that arena. Finally, science-based, data-driven risk assessments on both new and existing antibiotic products should be the basis for policy decisions about their use.

Data and experience show that non-science based decisions about antibiotic use are likely to have unintended, negative consequences for animal health and food safety.

Current protections built into the use of antibiotics safeguard public health while allowing for the use of these products to preserve animal health. The veterinary community has written and follows principles of proper use for antibiotics in animals. Monitoring and surveillance systems to watch for the rise of resistant bacteria are in place, and can be strengthened. As many experts have pointed out, the best protection against the foodborne spread of resistant bacteria is improvement in food hygiene, and data show large gains have been made in that arena. Finally, science-based, data-driven risk assessments on both new and existing antibiotic products should be the basis for policy decisions about their use.

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Ample evidence thus supports restrictions on agricultural use of antibiotics—particularly the long-term, relatively low-dose use of antibiotics as feed additives, a practice particularly likely to stimulate spread of resistance determinants. These additives are used not to treat sick animals, but rather for non-therapeutic purposes, i.e., to promote growth and to prevent disease more likely to result from crowded, often stressful conditions. APUA’s own exhaustive report in 2002 reviewed 500 studies and concluded, “The elimination of non-therapeutic use of antimicrobials in food animals and agriculture will lower the burden of antimicrobial resistance... with consequent benefits to human and animal health.” The Union of Concerned Scientists estimates that this use constitutes 70% of total antimicrobial use in the U.S. By contrast, the Animal Health Institute cites the deceptively low figure of “less than 10%” of antibiotics being used in animals for growth promotion, an estimate that disregards the widespread and routine use of antibiotics for disease prophylaxis.

The FDA acknowledges that its cumbersome process for withdrawing agricultural drugs takes six to 20 years to complete per drug or drug class. Bipartisan legislation has been introduced to more expeditiously phase out use of feed additives of antibiotics that belong to classes of drugs also used in human medicine. The American Medical Association and dozens of other health organizations endorse the legislation.

It’s already clear that industry can meet this challenge. Both McDonald’s Corporation and the major food-service company Bon Appétit have developed meat procurement policies aimed at reducing agricultural use of antibiotics. However, we ultimately need legislation to level the playing field and to fully address this problem. WHO-selected experts have
reviewed the phase-out of antimicrobial feed additives as growth promoters by Denmark — the world’s largest pork exporter — and found a 54% reduction in antimicrobial use in food animals. The phase-out had “no serious negative effects” on efficiency of food animal production, animal health, food safety and consumer prices, but was “very beneficial in reducing antimicrobial resistance in important food animal reservoirs,” thereby reducing the threat of resistance to public health.8

To paraphrase the title of a 2001 guest editorial from the New England Journal of Medicine: “Antibiotic use in animal feed — time to stop.”9

References
7. Letter from Dr. Steven Sundlof, Director of Center for Veterinary Medicine to Michael Jacobsen, Center for Science in the Public Interest, February 28, 2001.

ANTIMICROBIAL RESISTANCE continued from page 1
cern, since severe foodborne disease (FBD) cannot be effectively treated and may result in therapeutic failure and death.1 Scientific evidence from industrialized nations points to antimicrobial agents used for livestock and poultry as the main risk factor for the development of resistance in foodborne pathogens (FBP).1,2

While most industrialized countries established foodborne antimicrobial resistance monitoring programs during the last decade, very few, if any, Latin American countries have established such surveillance systems. Moreover, there is very little information on how food animal production contributes to FBP resistance in countries where diarrheal diseases are endemic.

In response to the need to generate information on FBP antimicrobial resistance in Mexico, the Fundación Mexicana para la Salud, Capítulo Peninsular (Mexico) and the U.S. Food and Drug Administration (FDA) Center for Veterinary Medicine initiated the Resistvet Project, a surveillance program in four agricultural states. Prior to the establishment of the official network in 2002 with a three-year cooperative agreement awarded by the FDA, participating laboratories received a series of training courses to ensure standardization of methods and a minimum standard of performance.

Network Capacities

Each participating center conducts statewide active surveillance in slaughterhouses, retail meats, and ill and asymptomatic humans. The slaughterhouse and meat surveillance is closely integrated with the state government program and is jointly conducted with official inspectors. Each laboratory has capacity for the isolation and identification of Salmonella, Campylobacter and Esherichia coli. Susceptibility testing is performed by disk diffusion and agar dilution using NCCLS standards. Serotyping and molecular analysis of isolates are performed at the coordinating laboratories. This paper presents the most relevant findings of the network to date and discusses their implications for regulatory policy and intervention strategies.

Salmonella and Campylobacter Surveillance

Salmonella Enteritidis and Salmonella Typhimurium are the two top serotypes isolated from ill humans. In 2002, they represented 22% and 12%, respectively, of all serotypes from this source. In addition, S. Typhimurium is the most multidrug resistant serotype isolated. The number of resistance determinants in S. Typhimurium has progressively increased in the last four years. In 2002, a strain resistant to ten antibiotics, including third-generation cephalosporins, was detected in Yucatan. This has now become the predominant strain of S. Typhimurium in humans and retail meats in that state.

The prevalence of Salmonella in humans and retail meat varies considerably by geographic location and season. During the summer, up to 45% of diarrheal samples and 33% of fecal samples from healthy kindergarten children have Salmonella. Similarly, Salmonella can be isolated in up to 90-100% of retail meat. Molecular analysis of Salmonella strains of human and food animal origin has shown that many of these are genetically identical.3 The high prevalence of Salmonella in humans and retail meats, and the genetic similarity between these strains suggests that in Mexico considerable transfer from food animals to humans occurs via the food chain.

Quinolone-resistant Salmonella and fluoroquinolone-resistant Campylobacter are emerging problems, with the prevalence of these resistant organisms higher than in industrialized countries such as the U.S. and Denmark. In Mexico, nalidixic acid-resistant Salmonella is highest in samples of poultry origin, particularly in S. Meleagridis, S. Enteritidis, and S. Albany.1 Ciprofloxacin resistance is highly prevalent in Campylobacter jejuni in human and poultry origin, and over half of the isolates are non-susceptible to erythromycin. Multidrug resistance to ciprofloxacin, erythromycin and gentamicin is highest in C. coli from pork.3 These results strongly suggest heavy use of fluoroquinolones and tylosin by poultry and swine producers in Mexico.
Epidemiology of Endemic FBD

While the epidemiology of FBD and FBP resistance in Mexico and industrialized nations share common elements, there are also fundamental differences. Underlying these differences is a complex combination of social, economic and political factors that create a greater potential for the emergence and dissemination of FBP resistance. A major contributing factor is the infrastructure for sanitation. In 2000, 46% of all households in Mexico did not have potable running water, 14% lacked toilets or latrines, and 21% had no sewage systems or septic tanks. In the poorer southeastern states, an even greater proportion of the population lack these basic services. Heavy fecal-oral contamination means greater human-to-human transmission of FBP; as a result, humans constitute a more important reservoir of FBP than in industrialized nations — a notion supported by the high prevalence of Salmonella in our healthy asymptomatic children. Likewise, Calva et al found a high incidence of persistent asymptomatic Campylobacter infections during the first years of life in children from periurban Mexico City. In such a setting, it is likely that the usage of antimicrobials in clinical medicine is an important contributor to FBP drug resistance.

Other fundamental differences can be found in local food production processes and government regulation of antimicrobials. Current slaughtering practices lead to considerable carcass contamination, and the distribution of meat in open air markets facilitates the dissemination of FBP through the food chain and environment. In addition, weak legislation, unenforced regulation and an absence of prescription requirements lead to uncontrolled over-the-counter sales of both human and veterinary antibiotics. This trend, in turn, results in improper selection of antimicrobial compounds and more frequent administration of subtherapeutic doses. In combination, all these factors create a greater potential for the emergence and dissemination of FBP antimicrobial resistance.

Future Direction

In the first phase of the network, efforts were focused on strengthening laboratory capacities and obtaining baseline data. In the second phase, our goal is to consolidate effective and sustainable food-animal and human surveillance programs. Moreover, we must involve our producers and decision-makers in the network activities and jointly address the issues that can lead to informed policy changes. Some of the questions we need to answer are:

- How prevalent is resistance to therapeutically important antimicrobials and how fast is it spreading?
- How much does FBP resistance add to the burden of disease in countries where immunity is acquired at an early age?
- What is the impact of high FBP resistance rates on tourism and exportation of food?
- How can we quantify and regulate the total usage of antimicrobials at the human, veterinary and agricultural level?

By gathering all available data, policy makers will be able to understand the nature and implications of FBP resistance. Control measures and regulations must respond to the epidemiology of FBD in Mexico and should form part of a comprehensive health policy that provides the basis for sustainable health and agricultural development.

Notes:

6. XII Censo General de Población y Vivienda 2000. Tomo III. INEGI, México, D.F.

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Table 1. Antimicrobial-resistant Salmonella in ill humans and retail meats from Mexico and U.S.A. 2001-2002*

<table>
<thead>
<tr>
<th>Country</th>
<th>NA-resistant Salmonella–Ill humans</th>
<th>NA-resistant Salmonella–Chicken</th>
<th>NA-resistant Salmonella–Pork</th>
<th>NA-resistant Salmonella–Beef</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mexico</td>
<td>10.3 (113)</td>
<td>40.7 (108)</td>
<td>27.2 (268)</td>
<td>27.8 (191)</td>
</tr>
<tr>
<td>U.S.A</td>
<td>3 (1419)</td>
<td>0.0 (75)</td>
<td>0.0 (5)</td>
<td>0.0 (14)</td>
</tr>
</tbody>
</table>

NA: Halidixic acid

*Data from Mexico and retail meats from USA are for 2002; data from humans in USA is 2001.
In this country, the reduction in total antibiotic usage in farm animals, and how much did antibiotic resistance in the animals decrease as a result?

A: In this country, the reduction in total antibiotic use was 54%. In terms of reducing resistance, it depends on what you look at. In poultry, it’s striking how marked the effect has been. When you look at vancomycin-resistant enterococci that had been selected for by the use of avoparcin as a growth promoter, we came from a situation where 70-80% of the flocks had VRE; all of the live birds in those flocks more or less carried vancomycin-resistant enterococci. Today, we are down to just a few percent. When avoparcin use went down, another drug, virginiamycin — which is closely related to Synercid and promotes resistance — was used instead. Synercid-resistant enterococci peaked at about the same level, but now they’re coming down too, a 75-80% reduction.

Q: Industry critics claim there aren’t enough data to prove a link between use of animal antibiotics and human disease — though industry also seems to keep and control that...
We are never willing to accept that you first have to create a lot of dead people before you intervene, in order to see if you have fewer dead people later on. From our perspective, this is first and foremost preventive action. It is not acceptable to sit and wait for the next MRSA, or any other major epidemic of a bad nosocomial clone. When we saw VRE starting to go around the world, and we knew we did not yet have the problem in our hospitals, we intervened by banning growth promoters — and I would say this is actually the right time to intervene. Because once resistant organisms have established themselves in hospitals, they don’t need growth promoters anymore to get established. The growth promoter sows the seeds, and doctors commit their own misuse and abuse of antibiotics, creating a really big problem.

Q: Has Denmark or the European Union — which banned certain growth promoters even earlier — followed up with human data?
A: Germany, the Netherlands, and Belgium have all shown reductions in the human carrier rate in the population after they stopped the use of growth promoters. It’s certainly more than 50%. It has been shown beyond reasonable scientific doubt that carriage of VRE in the gut is a risk factor for VRE infection, if you go to a hospital and undergo treatment and so on.

In Denmark, we have had fewer healthy people in the community who carry VRE in their guts since we stopped using growth promoters. That is my public health endpoint. If we start using a lot of vancomycin — which we are likely to do because MRSA is suddenly on the increase in countries where it had not been very prominent in the past — then those individuals will be at a lower risk of getting a VRE infection.

Q: How replicable is Denmark’s experience, both in rich and poor nations?
A: In most nations, if we look at poultry production, the problems would probably be the same. Whether you look at rich or poor nations, intensive animal production is much more similar than is the quality of life for the populations between those nations. Animal production in Mexico or Africa or Laos adheres to the same industrial philosophy, and uses animals that are genetically similar.

In the U.S., the volume of therapeutic drugs being used alongside growth promoters is many, many times more than it is in Denmark, which does not use growth promoters. I think the U.S. is using more than sufficient quantities of therapeutic drugs to prevent the few small problems that might arise.

Q: Looking at antimicrobials and farm animals, what problems on the horizon worry you?
A: Most of the growth promoter issues here have been about gram positives: vancomycin-resistant and Synercid-resistant enterococci. What worries me are the gram negatives. E. coli and Salmonella are becoming resistant to last-generation cephalosporins and quinolones. What we are trying to put in place — and have put in place for the fluoroquinolones — is a policy that says that there are some therapeutic drugs that are so important for humans, where the link between use in animals and resistant infections in humans is so clear, that we are going to put additional restrictions on the therapeutic use of those drugs in animals. Vets here can only prescribe a fluoroquinolone for a farm animal where there is a documented need — that is, if there are no alternatives, which is extremely rare. As a result, we have found a major reduction in quinolone usage and also a reduction in resistance in E. coli and Campylobacter. We are always acting early. We do not cover the well after the baby has fallen in.

Dr. Wegener spoke with Associate Editor Madeline Drexler.

Reference:
1. World Health Organization “Impacts of antimicrobial growth promoter termination in Denmark” 2002
Alliance for the Prudent Use of Antibiotics
75 Kneeland Street
Boston, MA 02111 U.S.A.

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Founded in 1981 as a nonprofit organization, APUA is the only organization in the world solely dedicated to strengthening society’s defenses against infectious diseases through research and education on antibiotic use and antibiotic resistance. APUA’s mission is to improve infectious disease treatment and control worldwide through promoting appropriate antibiotic access and use and reducing antibiotic resistance. With members in over 100 countries and numerous foreign affiliated chapters, APUA provides a unique network to support country-based activities and facilitate international planning and communication. APUA’s resources include an international scientific advisory board with members of national academies of medicine and science and a professional staff with specialized expertise. APUA’s global network of affiliated chapters serves to tailor interventions to local customs and practices.