For the Record

Straight talk about antibiotic use in food-animal production

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INSIGHTS ON THE ISSUE

In the environmental back door

"We are taking unprecedented action against the factory hog industry. These are outlaws and bullies who have…shattered the lives of tens of thousands of rural Americans."

—Robert F. Kennedy, Jr., 2001

"…What is dangerous about extremists, is not that they are extreme, but that they are intolerant. The evil is not what they say about their cause, but what they say about their opponents."

—Robert F. Kennedy, Sr., 1964

When the Junior Kennedy, an attorney for the Natural Resources Defense Council and president of the Waterkeeper Alliance, repeats his well-worn contention that today's hogs are fed so many antibiotics and "growth hormones" that their legs sometimes break under their own weight, it might leave the curious "factory-farmer" wondering: Just why is a guy who cut his legal teeth by suing EPA to clean up polluted rivers talking about hog-farm antibiotics? Kennedy echoes an emerging strategy from the movement to ban antibiotics:

a) Modern confined animal feeding operations are a hazard to the environment.

b) They can only exist through continued use of antibiotics.

c) Therefore, eliminate antibiotics and by default you eliminate "the nation's largest source of water pollution."

Kennedy's accidental honesty reveals an underlying motive harbored by most groups on the front lines of the movement—groups that bundle

together their aim to ban antibiotics with an overall anti-confinement farming environmentalism. Although sweetened by the language of guarding children's health, the high-profile movement laid bare is often less about hospital patients and more about controlling farmers' ability to succeed using modern animal management.

Frustrated by the public's 30-year-long unwillingness to believe agriculture is to blame for an increasing failure of drugs in humans, advocates of a ban continue looking for an around-the-barn route to bring a larger share of that public to their side. Kennedy-Junior environmentalism could in the near future become that back door.

MYTH BUSTERS AMMUNITION TO FIGHT BACK

Where would it stop?

Advocates of ending antibiotic use in farming recognize that calling for an all-out ban tempts opponents to unite and dig in their heels. Most thus claim desire to ban only "medically important antibiotics."

Yet, current research defining antibiotic resistance as an environmental issue suggests that once you concede that animal antibiotic use significantly contributes to resistance, such a distinction becomes irrelevant–and easy to be dismissed.

Harvard microbiologist Thomas O'Brien expresses it plainly in a 2002 *Clinical Infectious Diseases* article. O'Brien theorizes that antibiotic-resistance genes—easily swapped by individual bacteria— confer on those bacteria a unique "overwhelming advantage" that increases their survivability regardless of the environmental niche they inhabit, whether animal or human. The broad sweep is summarized by the journal article's title: "How Use of an Antimicrobial Anywhere Can Increase Resistance to Any Antimicrobial Anywhere Else."

Also in this issue:

For the record

When scare tactics regarding human health fail, opponents of farm-animal antibiotic use turn to an environmentalist message, striving for public acceptance by linking the two issues.

For the record

New research demonstrating that the genes causing antibiotic resistance can move between bacteria has been latched onto by opponents of livestock antibiotic use as an environmental threat.

For the record

Opponents of using antibiotics to produce meat, milk and eggs hope that pinning their message to the environmentalists' aims will earn them consumer attention and, ultimately, action. *For the Record*, sponsored by a grant from ALPHARMA, is designed to help unite the industry and provide a unified, rational message on behalf of producers facing this threat to their freedom to use safe, effective, economical production methods. Working together, we can set the record straight on antibiotics. Questions or comments? Contact Steve Kopperud, at skopperud@poldir.com. Want to read past issues or link to more information on this issue? Visit us online at www.alpharma.com/ahd/For_The_Record

The ecology of antibiotic resistance

Up until the last decade, microbiologists assumed antibiotic resistance increased in a population of bacteria—whether inside humans or animals—much the same way any trait worked its way into a population of higher-level organisms. Occasional, random mutations in the genetic code of individuals naturally produce immunity to antibiotics. If those resistant individuals are then given a reproductive advantage when the antibiotic kills off competing, susceptible organisms, those resistant individuals can thrive. That "natural selection" then rapidly populates the host with succeeding generations of resistant germs.

However, a recent trend has emerged toward viewing antibiotic resistance not so much as a problem brought about by generational shifts in individual populations. Instead, this new approach views it as an overall ecological problem. Here's how it works: Scientists now speculate that bacteria don't always have to wait for those genes that cause antibiotic resistance to be handed down from generation to generation. Instead bacteria living in a common environment readily swap pieces of floating genetic material between individuals. If those pieces of independent DNA, or "plasmids," contain the particular genetic code that causes the organism to become resistant to one or more antibiotics, it can pass that resistance between individuals of different bacterial species for different antibiotics.

With that model in mind, much recent research has focused on the questions that logically follow: How many of these plasmids are in the environment? How easily do they pass back and forth between different bacteria species? Most importantly, is it possible for a harmless bacterium that possesses a gene making it resistant to an antibiotic to pass that resistance coding to a germ capable of causing disease, thus creating a "super bug?"

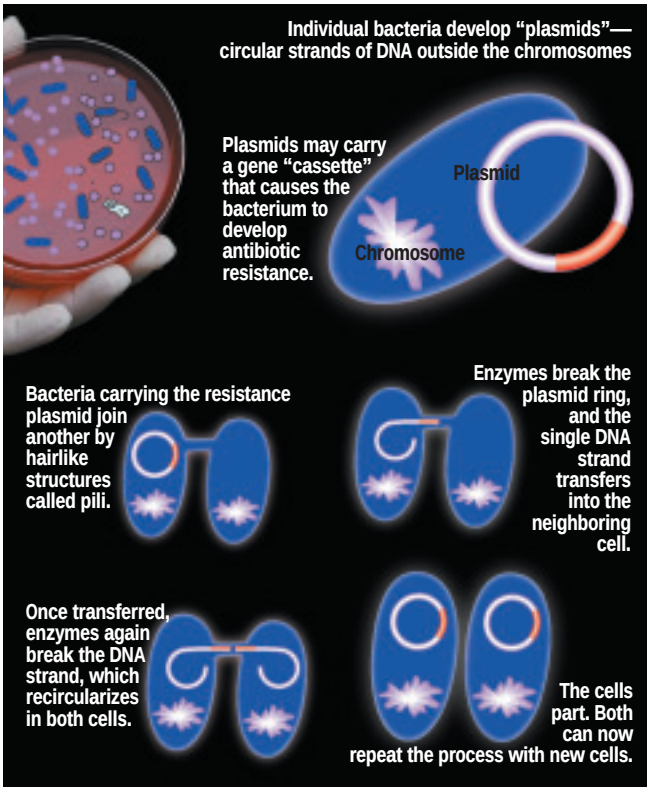
Activists on both the environmental-protection and the antibiotic-resistance fronts have adopted the theories to further their argument that we can no longer depend on antibiotic resistance to stay corralled within the previous safe-bounds—say, within individual farms, species or hospitals—where normal environmental barriers prevented them from escaping their defined niche. Instead, they believe, that roving genetic code provides a constant "reservoir" of antibiotic resistance that disease-causing organisms can borrow from. They also contend that reservoir is somehow maintained or enlarged by on-farm antibiotic use. Thus they claim, by extension, eliminating that use of antibiotics will eliminate the source of resistance genes.

HOW THE THEORY WORKS

Resistance plasmids are short circles of DNA molecules that, unlike longer DNA strands, carry only a few specific genes. Those genes can cause bacteria to express any number of traits in their development–in this case, resistance to specific antibiotics.

Plasmids are free to move from one bacterium to another nearby, spreading the traits throughout a bacterial population.

Such "horizontal gene transfer," is still not well understood in its origin. Resistant plasmids have been found in bacteria isolated from wild animal populations never exposed to antibiotics and from as long ago as 1888–more than a half century before antibiotics' discovery.



Where theory still doesn't quite meet reality

Although the idea of transferring antibiotic resistance via plasmid exchange is very real, the link that connects human disease to such on-farm "ecological" antibiotic resistance caused by plasmid exchange is still a long, uncertain leap. Consider:

■ A common assumption by some is that the transfer of resistance plasmids between organisms is initiated or encouraged by using antibiotics in a population of bacteria. However, new research reported by Alpharma scientists demonstrates that using some antibiotics may also actually reduce the level of resistance by limiting that movement of plasmids between bacteria. Researchers demonstrated that ionophores, bacitracin and broader-spectrum chlortetracycline, when used at levels that would mimic the levels typically used in feed on the farm, actually significantly reduced the transfer of the plasmids between *E. coli*.

■ Although plasmid exchange that could transfer resistance from animals to humans has been suggested by several recent studies, it is yet to be directly proven. Exceptions exist to make such cross-species transfer an arguable issue. For instance, a study in the 2001 *Lancet* genetically typed 165 isolates from humans of *Enterococcus* bacteria that were resistant to the drug vancomycin. They conducted similar genetic "mapping" on 98 similarly resistant *Enterococcus* bacteria from animals. The researchers then looked for the specific gene that caused that particular resistance—a DNA fragment they call "esp." They found that sick hospital patients were infected by their own genetically distinct species of the bacterium, which differed both from the isolates found in animals and in healthy humans. That distinct species infecting sick humans contained a variant of the esp gene that could not be found in any of the animal isolates, nor in any humans that were healthy.

That finding shouldn't come as a surprise. Advocates of banning antibiotics in Europe typically lump any *Enterococcus* strain possessing a resistance gene into the group that is resistant to vancomycin, thus labeling them a human threat. The truth is most are harmless. In fact, as many as 10 strains are actually approved for use as probiotics.

■ In a similar vein, North Carolina State researchers matched 843 isolates of *Salmonella typhimurium* from humans against 1,314 swine isolates in the state over a period of three years. They found that although antibiotic resistance was present in both sets of *Salmonella*, the patterns of resistance were different between pigs and humans: The most common swine *Salmonella* resistant to several drugs was uncommon to find in humans, human strains tended to be resistant to a wider spectrum of drugs than the swine ones, and the predominant serotype of *Salmonella* in pigs was genetically different from human isolates. These results came even as another study estimating that at least 240 of the state's large swine operations' lagoons had been flooded during Hurricane Floyd. If the contention that farm wastewater serves as a reservoir of antibiotic-resistance genetic material that can be transferred to humans, such contamination of human drinking water sources with organisms from the farms should have led to the opposite effect of that found by the research.

For the record

Direct transfer of resistance factors into bacteria through plasmid exchange can happen whether antibiotics are applied or not. Yet, over 40 years of farm use has not resulted in 'super bugs' that pose serious risks to humans.

For the record

Traces of farm antibiotics show up in streams far less frequently and at far lower concentrations than other significant pollutants.

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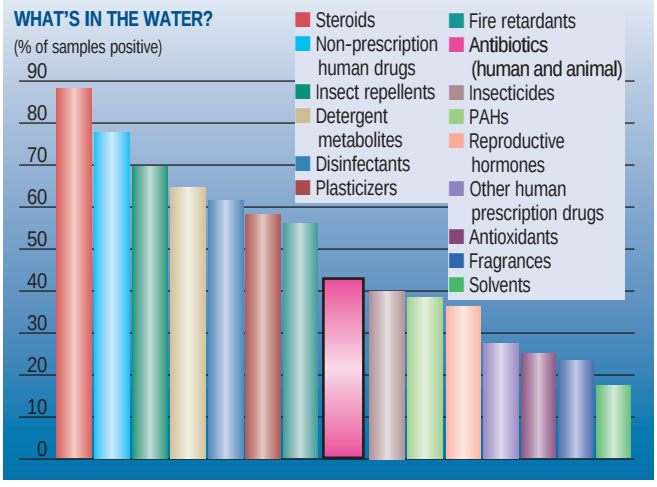
Antibiotic pollution in context

The U.S. Geologic Survey analyzed water samples from a network of 139 streams, purposely selecting waters most likely to be contaminated by organic pollutants from cities or farms. Although trace levels of some veterinary drugs were found, a long list of other human, animal and natural pollutants were detected in more samples and at higher concentrations. The concentrations of any of the animal drugs detected were below FDA's Acceptable Daily Intake levels.

Source: Kolpin D.W., et al. Pharmaceuticals, hormones, and other organic wastewater contaminants in U.S. streams, 1999–2000: A national reconnaissance: Environmental Science & Technology, March 15, 2002.



For the record

Is the risk of antibiotic resistance being transferred to humans a real one? Yes.
Is the solution an immediate crackdown on veterinary drugs? No.

REAL-WORLD PERSPECTIVE ON THE ISSUE

The cure should be in proportion to the risk

Lyle Vogel, DVM
Director of Scientific Activities Division
American Veterinary Medical Association

The American Veterinary Medical Association shares the concerns of the public regarding the potential risk of antibiotic resistance developing in animals and transferring to humans. We acknowledge that a substantial proportion—but not all cases—of human *Salmonella* and *Campylobacter* infections originate in animals and are transferred in foods to humans. Therefore, resistant organisms can be transferred from food animals through food to humans. We also acknowledge that the use of antibiotics by veterinarians could possibly contribute to antibiotic resistance. Because of this possibility, the AVMA developed judicious antibiotic use principles and educational materials for veterinarians and veterinary students.

But one of the problems is that we really don't know the magnitude of the human-health impact of that foodborne transfer of bacteria. We don't know how often that transfer occurs. And just because resistant bacteria may develop in animals and then be transferred to humans, that doesn't necessarily equate to a human health impact. First the bacteria may not colonize the individual and create a foodborne disease. Secondly, if a disease does occur, in the majority of foodborne diseases, antibiotic therapy is not needed. And then, if treatment with antibiotics is needed, the bacteria may not be resistant to the drug of first choice. So we believe—and the National Research Council has agreed—that the use of antibiotics in animals is not creating an immediate emergency that calls for drastic action.

We believe there's adequate time to really take a thorough look at the science, and the science to date doesn't justify removing broad classes of antibiotic use, such as uses to prevent diseases or promote growth, even if they are antibiotics also used in humans. Scientific decisions need to be made while assessing the risks from use of individual drugs under specific use conditions. In fact, we are concerned that inappropriate limitation of animal drugs that is not justified by the actual public-health risk may adversely affect animal health and welfare, and may have unexpected adverse human health consequences. Who knows how many promising antibiotics are not being developed because of it?

Coming in the next issue of For the Record

What really happened when European countries banned key farm antibiotic use

MYTH BUSTERS AMMUNITION TO FIGHT BACK

What the World Health Organization could learn from us

The World Health Organization released a final report in mid August summarizing an investigative panel's conclusions about the impact of banning antibiotic growth promotants in Denmark. Many of the major news outlets were quick to lecture producers that they should "take a lesson" from this experiment in a country only about a third the size of Iowa, and ban such antibiotic use here. The Coalition for Animal Health instead recommends the Europeans take a few lessons from our food-production success story:

- Previous published scientific studies have shown that—despite Denmark's ban—the prevalence of resistant enterococcal infections in humans has not fallen. The WHO report itself recognizes that human disease related to resistance to antimicrobial growth promoters were rare in Denmark both before and after the ban. In stark contrast, resistance in food-borne bacteria has dropped in the United States, according to the Centers for Disease Control, as has the incidence of food borne-illness. Voluntary industry policing of antibiotic use, combined with science-based approaches to food safety—not politically based ones—are responsible.
- A recently published article in the *Journal of Antimicrobial Chemotherapy* documents that the removal of antibiotics for growth promotion in Europe has led to a significant increase in animal disease and the use of antibiotics. Total antibiotic use there rose 22 percent between 1999 and 2001. Danish producers reported weaker and more disease-prone post-nursery pigs, which typically required increased use of more of the drugs important to human medicine to control disease normally controlled by feed additives.
- The WHO report claims only relatively minor and near painless adjustments by Danish producers–despite $250 million in additional capital costs necessary to upgrade facilities. However, a 2003 Iowa State study demonstrated that a ban here modeled upon the Danish one could be expected to cost just the U.S. pork industry $700 million in the first decade. That would likely increase pork prices to consumers even while driving more small producers out of business.
- The track record for safety and effectiveness of antibiotic use in food-animal production here dates back over 40 years.