

Antibiotics: precaution vs. proof Part 3 of 4

Part 1 of 4: Scrutiny of livestock antibiotic use pressures veterinary profession

Part 2 of 4: FDA: Food-animal antibiotic consumption dwarfs human medical use

Part 3 of 4: Antibiotics: precaution vs. proof

Part 4 of 4: Antibiotics: spinning the data from Denmark

Editor's Note: This is the third installment of a four-part series that explores the use of antibiotics in the livestock industry, the threat of antibiotic-resistant pathogens and the veterinary profession's role in safeguarding animal and public health. Today's story investigates how two sides in the debate evaluate the human health risks of livestock antibiotic use.

It's a fact of evolutionary biology that feeding antibiotics to livestock generates drug-resistant bacteria. Whether society ought to do anything about it is another question.

The [American Medical Association](#), the [American Public Health Association](#) and other health and environmental advocates cite dozens of studies as evidence that feeding medically important antibiotics to poultry, pigs and cattle is generating drug-resistant pathogens that pose a significant threat to human health.

While these groups concede that the magnitude of the threat is difficult to quantify, they argue that current science provides more than enough justification to stop routinely feeding antibiotics to livestock. On that basis, a coalition of environmental groups [sued](#) the U.S. Food and Drug Administration (FDA) Wednesday, seeking to force the agency to ban the use of penicillin and tetracyclines for growth promotion and disease prevention.

[Drug makers](#), the [meat industry](#) and the American Veterinary Medical Association (AVMA) [counter](#) with [analyses](#) indicating that the human-health risk posed by current livestock antibiotic practices is extremely small. While they do not contest the fact that antibiotic use generates drug-resistant pathogens, these groups argue that the public-health impact of such pathogens is extremely small. They contend that animals fed antibiotics are more likely to remain healthy, which helps to cut pathogen loads on meat and protect public health.

The FDA is at the debate's center. The agency first expressed reservations about routine antibiotic use in livestock more than 40 years ago. But it has never withdrawn an antibiotic labeled for growth promotion or disease prevention, the two categories targeted by critics. While the FDA recently indicated that it intends to increase its scrutiny of such uses, regulators are moving cautiously.

Experts in the veterinary profession are divided on the issue, as last year's report of the 15-member [AVMA task force](#) on antibiotic use showed. Some task force

members agreed with the AVMA's official position that current antibiotic practices pose a negligible threat to public health. Others pointed to studies that suggest the risk is serious enough to warrant some restrictions on uses of antibiotics.

"There's science on both sides," said Dr. Mark Starr, who represented the National Association of State Public Health Veterinarians on the AVMA task force. "While some people would say there is no science showing that there is a risk, from the perspective of many folks, there's plenty of evidence."

Public health community makes its case

In [testimony to Congress](#), [reports](#), [journal articles](#) and now a [legal complaint](#) against the FDA, the public health community points to serious risk associated with the use of antibiotics to promote growth and prevent disease in livestock. Public health advocates maintain that the use of an antibiotic in livestock selects for strains of bacteria resistant to that antibiotic. And this resistance involves [genetic changes](#) that can be passed to other types of bacteria, generating a "reservoir" of antibiotic resistance in the environment.

The research behind their arguments spans temporal, food and environmental impacts as well as animal-to-human infection:

- Several cases have linked the introduction of an antibiotic for use in food animals to an increased incidence of pathogens resistant to that drug in humans. For instance, after fluoroquinolones were licensed to treat respiratory diseases in poultry in 1995, a [study](#) in Minnesota found an increase in quinolone-resistant *Campylobacter* infections acquired from poultry. Conversely, following the withdrawal of the antibiotic avoparcin from animal use in Europe, the prevalence of resistant bacteria [declined](#) in retail poultry meat and human fecal samples.
- The [National Antimicrobial Resistance Monitoring System](#) consistently has found that contamination of retail meat and poultry products with antibiotic-resistant bacteria is common. In addition, [several studies have found](#) that food animals raised on antibiotic-free farms are less likely to carry resistant bacteria than those raised in conventional operations.
- Farmers and others working or living near livestock have been [infected](#) with the same antibiotic-resistant microbes carried by their animals. Livestock workers also are known to host pathogens [resistant to commonly used food-animal antibiotics](#).
- Antibiotic-resistant bacteria have been found in [air samples](#) in and near food-animal operations, as well as in fields fertilized with manure, showing that antibiotic resistance may pass into the environment through routes other than meat or infected humans. [Birds](#), [flies](#) and rodents also may carry the bacteria off the farm.

This evidence, taken together, constitutes “strong scientific evidence of a link between antibiotic use in food animals and antibiotic resistance in humans,” according to a recent [letter to Congress](#) from Dr. Thomas R. Frieden, director of the Centers for Disease Control and Prevention.

Furthermore, public health groups argue, many uses of antibiotics for growth promotion and disease prevention are dispensable. [Several studies](#) show little or no benefit to animal health or farmers’ profits from common uses of growth-promoting antibiotics. The increasing production of organic and antibiotic-free meat shows that it is possible to raise healthy animals without using antibiotics to prevent disease.

AVMA and industry: Antibiotic resistance exists, but there's little risk

Livestock groups, the pharmaceutical industry and the AVMA counter that there is little evidence that the risk associated with antibiotic use is large enough to be a concern.

“If you look at how many deaths are caused by treatment failures of foodborne illnesses and what fraction of those might be averted by banning certain uses of antibiotics in food animals — those numbers are tremendously small,” said Tony Cox, Ph.D., a Denver-based risk assessment consultant and clinical professor of preventive medicine and biometrics at the University of Colorado Health Sciences Center.

Cox’s work is central to the [AVMA’s position](#) on the issue. Of the seven peer-reviewed papers the group cites on its website in support of the idea that “the risk to people of becoming infected with resistant organisms by consuming animal products (meat, milk, eggs) is extremely low,” four are lead-authored by Cox and one is co-authored by him. Between 2000 to 2005, Cox’s firm worked for several drug companies and the Animal Health Institute, a pharmaceutical-industry advocacy group, to develop quantitative estimates of the human health risks associated with the use of various antibiotics in livestock. Previously, Cox worked as a consultant for the FDA and the U.S. Department of Agriculture (USDA) on similar issues.

[Table 1](#) lists the human health risks associated with livestock antibiotic use, as calculated in peer-reviewed journal articles by Cox and others.

These studies start with epidemiological figures on the incidence of serious food-borne illnesses caused by a particular pathogen. The authors then estimate the fraction of those illnesses — and the associated days of illness and/or mortalities — that could be prevented by discontinuing the use of the antibiotic in livestock. The result is based on a series of estimates: the fraction of illnesses caused by the pathogen that can be attributed to meat or poultry; the fraction of illnesses known to be caused by resistant pathogens; the fraction of illnesses that are

treated with the resisted food-animal antibiotic or a related human-medicine antibiotic; and the health consequences, such as prolonged illness and potential complications, that result when treatment with a resisted antibiotic fails.

As the [table](#) shows, the calculated burden to the U.S. population ranges from small (57 additional illness-days per year) to negligible (one additional treatment failure every 200 years) for the various antibiotics evaluated.

This sort of risk assessment is criticized by many in the public health community for being overly narrow. The approach, for instance, ignores potential — but poorly quantified — risks associated with antibiotic resistance spreading across multiple pathogens, and with non-food modes of transmission. In addition, the risk assessments have been criticized for using biased assumptions.

“There's never enough data to fill all the data gaps, so you're always left having to make certain assumptions and a lot of that is what ends up driving your risk assessment,” said Dr. William Flynn, deputy director for science policy at the FDA's Center for Veterinary Medicine (CVM).

The FDA has performed two analyses that can be compared directly with Cox's estimates. One differs sharply from Cox's; the other closely matches his result.

For enrofloxacin — a fluoroquinolone — the [FDA in 2001 estimated](#) that 9,000 people annually in the United States contract a fluoroquinolone-resistant *Campylobacter* infection from chicken and are treated with a fluoroquinolone (and thus are potentially hurt by the use of enrofloxacin in chickens). Cox's estimate for that same scenario was 28. Differences in estimates for three key figures account for most of the 300-fold difference in the results ([Table 2](#)). Other estimates for these figures ([Table 2](#), third column) suggest the real answer may lie somewhere between Cox's result and the FDA's.

A second FDA analysis, this time focusing on virginiamycin, reached conclusions that were in general agreement with Cox's published figures. In a 2004 draft risk assessment, the FDA CVM used three different modeling approaches to estimate that the use of virginiamycin in livestock likely contributed to an additional two to 39 drug-resistant infections annually among U.S. hospital patients. Cox estimated the same figure at roughly five such infections annually. Industry applauded the FDA's analysis, which was prepared in response to concerns about the risk to human health posed by the use of virginiamycin in poultry, pigs and cattle. The FDA has not released a final version of the risk assessment and has not proposed restricting the use of the drug.

Two of Cox's papers ([Table 3](#)) also estimate the number of human illnesses that might be caused by the withdrawal of a particular antibiotic used in poultry. These estimates are based on the assumption that if antibiotics are not used to promote growth or prevent disease, more animals would enter the meat

processing system with subclinical infections and would tend to be carrying more pathogens. (Research on this point, however, is inconclusive; some studies have found that animals raised without antibiotics carry no more pathogens than those fed antibiotics for growth promotion and disease prevention.) An increased pathogen load at slaughter would lead to higher pathogen levels at every stage of meat processing and distribution, producing more illnesses among consumers. While the pathogens causing these illnesses would be less likely to be antibiotic resistant, the people they infect would get sick.

As calculated by Cox, the human health risk associated with stopping the use of certain antibiotics swamps the risk tied to antibiotic resistance.

“There may be a higher risk from changing things” than from staying with status quo antibiotic practices, said Dr. Scott Hurd, a professor at the Iowa State University College of Veterinary Medicine and the former deputy undersecretary for food safety at USDA. Hurd also was a member of the 2010 AVMA task force on the issue.

The FDA’s approach to judging the prudence of using a particular antibiotic in food animals does not include weighing, in the way Cox does, the benefits of continuing to use the drug.

“The safety standard that we apply is ‘a reasonable certainty of no harm.’ It’s not a risk-benefit,” said FDA-CVM’s Flynn. “Our focus is still that ... if the use itself is contributing to the emergence of resistance, if it is presenting a public health risk, then we feel that there is a basis to raise safety questions.”

Who's right?

It’s not possible to weigh the arguments of one side directly against the other because they use different lines of reasoning. The public health argument shows the presence of a potentially serious risk. Industry and the AVMA argue that the magnitude of the risk is what matters, and that current evidence has not established that the risk is anything but small.

The job of deciding which side is right, for a given drug, falls to the FDA (though Congress could potentially intervene with legislation). When evaluating the safety of an animal drug, the agency attempts to establish that it is safe, using the “reasonable certainty of no harm” standard described by Flynn. If the agency decides to pursue the withdrawal of an already-approved drug, it must present evidence through a formal hearing process that raises “serious questions” about the safety of using the drug as approved. If the agency raises such questions successfully — in the opinion of a judge — the burden of proof shifts to the drug’s sponsor, which must demonstrate its safety.

To date, FDA has withdrawn approval of only one food-animal antimicrobial drug

on the basis of its risk to human health — enrofloxacin, which was sold by Bayer Corp. under the brand name Baytril. The drug was administered by prescription through poultry-barn watering systems for the mass treatment of respiratory diseases in chickens and turkeys.

The Baytril case

Baytril and a similar drug, sarafloxacin (manufactured by Abbott Laboratories), were approved by the FDA in 1996 and 1995, respectively. The approvals raised antimicrobial-resistance concerns because similar drugs, such as ciprofloxacin (sold by Bayer under the brand name Cipro) are used widely in human medicine. Because of these concerns, during the approval process an FDA advisory committee recommended that a nationwide monitoring system be developed to help evaluate whether the use of the drugs in poultry was causing a serious antibiotic-resistance problem.

By 1999, there was significant evidence that the prevalence of fluoroquinolone-resistant *Campylobacter* species had increased. In 2000, the agency proposed withdrawing sarafloxacin and enrofloxacin for use in poultry. Abbott preemptively withdrew its drug from the market. Bayer requested a formal hearing, touching off a legal battle that was not resolved until 2005, when the FDA commissioner ordered that the drug no longer be used in poultry.

The arguments about the withdrawal of Baytril reflect, in many respects, those that continue today concerning the broad issue of antibiotic resistance. The FDA presented a body of evidence suggesting a variety of potential links between the use of Baytril in poultry and the development of antibiotic-resistant strains of *Campylobacter* that may infect humans. Bayer countered that the agency was overstating the number of illnesses that could fairly be linked to the use of Baytril and ignoring countervailing evidence.

In his [initial decision](#) on the matter, FDA administrative law judge Daniel Davidson found that the weight of the evidence supported withdrawing the drug. He wrote:

“... it appears that while each of the studies and/or analyses relied on by CVM, standing alone, would not support a finding that the use of fluoroquinolones in poultry has resulted in an increase in drug-resistant *Campylobacter*, when the record is viewed in its entirety, there is a substantial body of evidence supporting the conclusion that the increase in fluoroquinolone-resistant *Campylobacter* and resultant campylobacteriosis is a result of the extensive use of enrofloxacin in poultry.”

Bayer appealed the ruling. Sixteen months later, then-FDA Commissioner Dr. Lester Crawford, a veterinarian, [affirmed the judge's decision](#).

Cox was an important expert witness for Bayer in the hearings. But Judge Davidson threw out his testimony after FDA lawyers showed that Cox repeatedly had misquoted published research:

“It seems that Dr. Cox edits referenced material, prefers his edited version to the original, and quotes the edited version in his testimony. Apparently, this is his usual way of presenting cited material,” Davidson wrote. “Under the circumstances, this witness’ credibility is severely compromised and his testimony cannot be relied on.”

In an e-mail exchange, Cox said the alterations he made were trivial.

“It was a line of attack suggested by FDA's consultants and lawyers at the time, which the administrative law judge embraced, that gave him and his employer at the time (the FDA) an excuse to avoid discussing the technical substance of the case.”

It’s not yet clear — and may never be — whether withdrawing Baytril has had a significant impact on public health in America. The use of the drug in chickens was only one of many factors influencing the rates of food-borne illness and antibiotic-resistant infections.

Federal monitoring data show that since 2005, the rate of *Campylobacter* contamination in retail chicken [has fallen](#), and the rate of *Campylobacter* infection among the U.S. population has been [flat](#). These results suggest that stopping the use of the drug has not had the substantially negative impact on food safety that Cox and industry groups warned of.

At the same time, resistance to ciprofloxacin in *Campylobacter* samples taken from humans has [continued to increase](#). While the Baytril ban may have slowed this growth, it has not reversed it.

Next up: What we can learn from Denmark, where the use of antibiotics for growth promotion was banned in the mid-1990s.

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