Guidance on the Use of Antibiotics in the Production of Animals for Food

Jared Rhoads

The Dartmouth Institute for Health Policy and Clinical Practice

March 16, 2015

Executive Summary

Antibiotics have been called the "wonder drugs" of the twentieth century for their ability to treat illnesses and bring about better health in both humans and animals. In the U.S. today, between 3.1 million pounds and 25 million pounds of sub-therapeutic antibiotics are used annually in raising animals for food production—e.g., cattle, poultry, and hogs. Therapeutic-level doses of antibiotics are given to animals who are sick, and lower, non-therapeutic-level doses are often added to animal feed as prophylaxis and to promote general health. Concerns, however, have been raised that the use of these antibiotics may result in the transfer of antibiotic resistance or other undesired health effects to humans via the food chain.

Residual amounts of antibiotics have been found in the meat and animal products that consumers purchase in grocery stores. It has been posited that, when consumed by humans, these residual antibiotics could interfere with prescription drugs, cause allergic reactions, interfere with natural gut flora, or contribute to the further evolution of antibiotic-resistant bacteria. Unfortunately, there is little understanding and scientific consensus on exactly how this transmission mechanism might work, and few (if any) cases in which specific harms can be proven.

Still, scientists generally agree that a cautious, judicious use of antibiotics in both veterinary and human medicine is likely to reduce certain risks associated with residues and resistant bacteria. It is on this basis that in 2013 the U.S. Food and Drug Administration (FDA) took action to encourage antibiotics manufacturers to label their products in such a way as to discourage use for non-therapeutic growth purposes. To date, almost all of the manufacturers have complied. However, the FDA's guidelines, which are voluntary, did not satisfy many consumer advocates, who called for—and continue to call for—stricter mandatory regulations limiting antibiotic use in animal production to medically necessary uses.

In light of the scientific evidence surrounding antibiotic resistance, the vague and unspecific nature of the hazard, and the willingness of industry stakeholders to comply with the FDA's current voluntary guidelines, it is the recommendation of this report to maintain the FDA's 2013 guidelines and impose no new regulatory requirements at this time. This gives researchers and stakeholders (including the FDA) additional time to collect and study evidence about potential or alleged harms, and if necessary, develop new guidance that is better informed and more likely to be effective.

Problem Statement

Concerns have been raised that the use of antibiotics in animals for food production may result in the transfer of antibiotic resistance or other harmful effects to humans via the food chain. The U.S. Food and Drug Administration (FDA) has taken initial action, but many advocates believe the agency's guidelines do not go far enough. Should the FDA make mandatory its currently-voluntary guidelines limiting antibiotic use in animal production to medically necessary uses?

Background

For more than seventy years, antibiotics have enabled doctors to treat a wide range illnesses, saving hundreds of millions of lives and raising life expectancy across the globe.[1] When penicillin—the first antibiotic—was first manufactured in large quantities around the time of World War II, it was called a wonder drug for its ability to fight infection. Soon other antibacterial compounds were developed and also put into use, including prontosil and tyrothricin, and later ampicillin, flucloxacillin, methicillin, and others.

Also in the 1940s, many farmers adopted the practice of using antibiotics to promote growth in their animals. Animals were fed small, less-than-therapeutic doses of dried mycelia of *Streptomyces* containing chlortetracycline residues.[2] Farmers noted that the use of this and other antibiotics significantly improved animal growth and animal health, and lowered animal mortality.[1] The average improvement in growth has been estimated to be 4% to 8% (by animal weight).[3] The precise mechanism by which low-dose antibiotics in animal feed promote growth is still not known[3], although it is believed to be related to interactions with intestinal microbes.[4]

The practice of feeding antibiotics to animals intended for food production (e.g., cattle, poultry, and hogs) started to spread more rapidly starting around the late 1960s.[3] Researchers estimate that today in the U.S., somewhere between 3.1 million pounds and 25 million pounds of sub-therapeutic antibiotics are used annually.[5] Many observers believe that the motivating reason to use antibiotics was to increase the productivity of farms[1], although there is disagreement in this area. Some economic analyses have found that while feeding antibiotics to animals does make the animals healthier, it does not lower the total cost of production or increase production yields.[1,5]

Food producer associations argue that restricting the use of antibiotics will lead to sicker animals and more waste, which could result in higher prices for consumers.

The main human health concern related to the practice of using antibiotics in industrial animal production is that residual amounts of antibiotics may inadvertently show up in the meat and animal products that consumers purchase in grocery stores. When consumed, these residual antibiotics may interfere with prescription drugs, cause allergic reactions, interfere with natural gut flora, or contribute to the further evolution of antibiotic-resistant bacteria.[1,6] Antibiotic resistance is of particular concern, as illnesses caused by drug-resistant strains of bacteria could be fatal if the drugs used to treat those illnesses are no longer effective.

The question at hand is whether the above-described concerns warrant stronger regulatory action on the part of the FDA.

In 1951, the FDA approved the use of antibiotics as additives in animal feed.[4] Under those original guidelines, farmers were not required to obtain a veterinary prescription to engage in the practice. Over time, however, opinion of the potential dangers of antibiotic use in livestock changed. In 1969 in the United Kingdom, the influential Swann report on the use of Antibiotics in Animal Husbandry and Veterinary Medicine was published, which recommended that the only antibiotics that should be permitted in animals are those that are not used in, or needed for, human therapies.[2]

Other regulatory actions ensued. In 1986, Sweden banned all antibiotics for growth promotion.[3] Denmark banned avoparcin in 1995 and virginiamycin in 1998. Most noteworthy, between 1997 and 2006, the European Union (EU) rolled out bans on some of the most commonly-used antibiotics, including avoparcin, bacitracin, spiramycin, tylosin, and virginiamycin.[7]

In 2013, the FDA released a voluntary set of guidelines aimed at addressing the issue of non-therapeutic use of antibiotics in animals. The FDA asked antibiotics manufacturers to remove indications for growth enhancement on the labels of their products, and change the availability of certain antibiotics from over-the-counter to requiring veterinary approval. Watchdogs and advocacy groups voiced their disapproval of the FDA's approach, arguing that the guidelines do not do enough and that the voluntary nature of the action provides a loophole for commercial interests to take no meaningful action (e.g., producers could still use the antibiotics, but claim that they are using them to keep their animals healthy, not to promote their growth).

As of March 2014, the FDA reported that 26 of the 27 involved companies had voluntarily agreed to adhere by the guidelines. No evidence, however, is currently available as to whether that has succeeded in limiting or reducing the presence of residual antibiotics in meat purchased by consumers.

Exposure Assessment

The exposure of interest is the ingestion, by retail consumers, of meat containing either antibiotic-resistant bacteria or residual antibiotics from the animal production process. Meat products include beef, chicken, pork, and turkey. Farm-raised fish can also be a source of exposure, but the production practices and the body of research evidence differ enough that they have not been made part of this analysis.

Meat consumption has increased substantially in the modern era. According to data from the United States Department of Agriculture (USDA), meat consumption has roughly doubled from 1909 to 2007.[8] Across the U.S. and most of Europe, meat accounts for more than 15 percent of the average person's daily energy intake, 40 percent of daily protein intake, and 20 percent of daily fat intake.[8] Meat consumption has climbed steadily, with only occasional economic-related dips interrupting the pattern (see **Figure 1**).

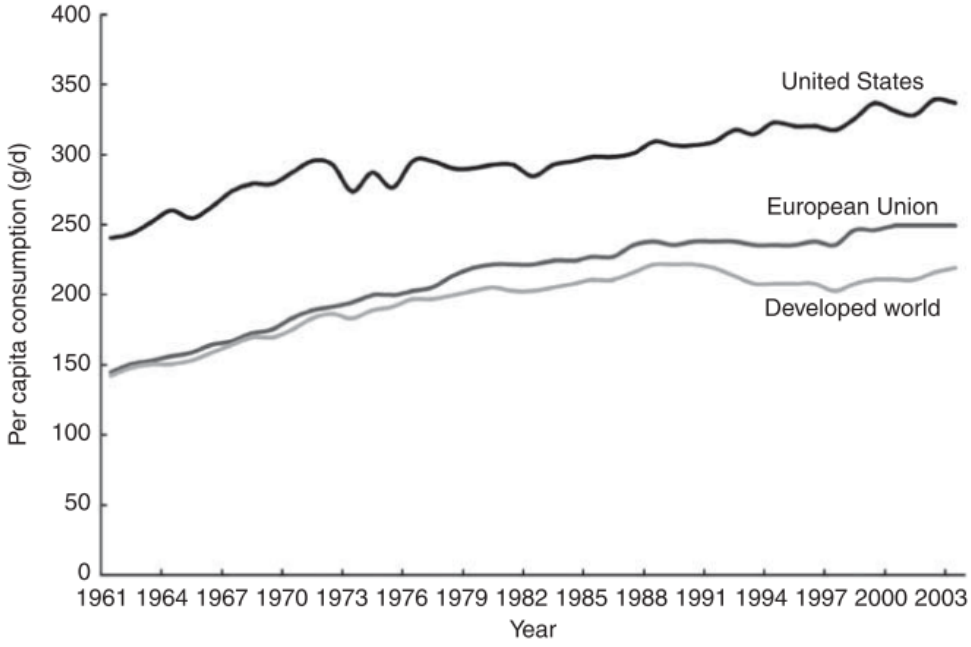

Figure 1. Total meat consumption in the U.S., European Union, and developed world, 1961–2003. *Data from the Food and Agriculture Organization of the United Nations (2008) FAO Statistical Databases (FAOSTAT). Graphic from Daniel CR, Cross AJ, Koebnick C, Sinha R. Trends in meat consumption in the USA. Public health nutrition 2011;14:575-83.*

Exposure may differ by factors such as sex, age, and race for the simple reason that these groups differ in their consumption of meat. On average, men consume 87.6 grams of red meat and 48.8 grams of poultry per day over the course of a year, compared to 52.8 grams of red meat and 38.1 grams of poultry per day over the course of a year for women. By age, those who are 20-49 years old consume the most meat, at 80.3 grams of red meat per day and 51.7 grams of poultry per day. There is no major difference between racial groups, as whites, blacks, and Hispanics all consume roughly equal amounts of meat, with the exception that blacks consume a slightly higher amount of poultry. As for socioeconomic factors, total average daily meat intake (all types of meat and meat products) does differ by education level. Those with less than a high school education consume a total of 115.7 grams per day, compared to 139.4 grams per day for high school graduates and 138.8 grams per day for those with more than a high school education.[8]

A key question for policy guidance is how much antibiotic-resistant bacteria or residual antibiotics from the animal production process is actually consumed by people purchasing and eating meat from standard retail establishments. (Note: antibiotic-resistant organisms have also been found among workers at industrial-sized animal production facilities that administer antibiotics to animals. Rinsky, et al, describe an occupational exposure of this type occurring in the state of North Carolina.[9])

The use of sub-therapeutic antibiotics in animal feed is very common. It is a practice that is approved and regulated by the FDA.[10] It is not isolated to a small number of animal production facilities, nor is it limited to particular states or regions. According to estimates, at least 70 percent of U.S. beef feedlots use antibiotics to control disease, promote health, or promote growth.[11] The types of antibiotics, feed recipes, and feed mixtures vary greatly from one farm to the next, but unfortunately there does not exist a reliable data collection system for monitoring which antibiotics and how much of them are being used.[1] Together, these factors make it difficult to establish links between specific antibiotics and their effects.

Researchers are just beginning to understand the extent to which antibiotic use in animals can have effects that are transferred through the food chain. A seminal work comes from a 2001 paper published in the *New England Journal of Medicine* in which the isolation of antibiotic-resistant salmonella from retail ground meats was described. The authors of that paper wrote, "The routine practice of giving antimicrobial agents to domestic livestock as a means of preventing and treating diseases, as well as promoting growth, is an important factor in the emergence of antibiotic-resistant bacteria that are subsequently transferred to humans through the food chain. Most infections with antimicrobial-resistant salmonella are acquired by eating contaminated foods of animal origin."[12]

Unlike some exposures, there is no reliable way for consumers to know in advance whether the meat they are consuming contains residual antibiotics or antibiotic-resistant strains of bacteria. Labels do not currently include this information. Practicing good hygiene, heat treatment, and various food preparation methods do not necessarily eliminate the residues, causing consumers to feel as though they are not able to mitigate the risk."[13]

As an immediate response, concerned individuals can limit their exposure by choosing to abstain from eating meat altogether. Individuals could choose to avoid certain high-risk meat products, although this would achieve limited benefit, as the highest-risk meat products are generally not the ones that are most widely consumed. A study from Japan that compared retail chicken meat and offal products (products that can various organ parts) found a significantly higher level of antibiotic-resistant isolated in offal products than in standard chicken products, however those products are considered delicacies, not mainstream fare.[14] A final way to limit exposure is to purchase and consume meat only from meat producers who advertise that they do not use antibiotics to promote growth in animals. This is a viable option for some people, depending on location, cost, and availability, but it is not an option for many people who live in urban or suburban areas.

Hazard Identification

Historically, the study of the hazards of meat consumption has centered on the effects of food components such as cholesterol, saturated fats, and total fat. Recently, researchers began to find

correlations between high meat consumption and higher rate of chronic disease.[8] However, new hazards related to residual antibiotics and antibiotic resistance are not nearly as well-understood.

According to the Centers for Disease Control and Prevention (CDC), approximately 2 million people are infected with antibiotic-resistant bacteria each year. Of those, roughly 23,000 people will die each year as a result of those infections.[15] Estimates, however, as to how many of these cases can be fully or partly attributable to meat production practices are not available. Evidence exists that resistant bacterial strains of *Salmonella*, *Campylobacter*, and *methicillin-resistant Staphylococcus aureus* (MRSA) can be transferred from animals to people through the food vector[16] (see **Table 1**). For example, in 1983 researchers identified 18 persons living in the Midwest who were infected with an antibiotic-resistant strain of *Salmonella Newport*. The patients had all consumed cooked hamburger from a farm in South Dakota that had used sub-therapeutic chlortetracycline to promote animal growth. The study clearly showed that antibiotic-resistant bacteria originating in animal production could cause acute human illness.[3,17]

Despite reports of specific incidents, it is challenging to obtain an accurate broad-based assessment of the hazard. It is believed that long-term effects of exposure to antibiotic residues can include carcinogenicity, reproductive effects, and teratogenicity, but there are few reports of harm from this specific hazard available in the scientific literature.[13,18] Some independent reviews have concluded that the "actual risk is extremely small and may be zero."[19] As researchers have pointed out, many of the antibiotics that are used are not well-understood in the human model, and many are neither clinically available to humans nor important in human medicine.[3] Antibiotic resistant bacteria have been found in wildlife that have not had contact with domestic livestock, therapeutics, or humans, suggesting that some level of resistance is a naturally occurring phenomenon.[2,20] Further, some scientific sources argue that the risk from antibiotics in edible tissues generating toxic or allergic reactions is negligible, because the types of antibiotics that are capable of producing that effect are not used as growth promoters.[4]

Risk Characterization

U.S. consumers who purchase and eat meat from retail establishments have almost certainly been exposed to trace doses of residual antibiotics in their food at one time or another. Myriad food tests performed in many countries, not just the U.S., have demonstrated that in almost any cross-

sectional population of retail chicken, beef, pork, and turkey, some small-to-moderate percentage is likely to contain antibiotic residues, antibiotic-resistant microbes, or both. But despite our strong understanding of the exposure, the degree to which a lack of evidence of measurable harm persists. While antibiotic use in food animals may represent a risk to human health, the degree to which this might occur has not well characterized.[21]

The two main risks or concern are that 1) antibiotic use in the production of food animals could contribute generally to antibiotic resistance, and 2) a consumer could have an acute allergic reaction to residual foodborne antibiotics. These two concerns are raised frequently in the scientific literature as hypothetical concerns, but a body of compelling, quantitative evidence still has yet to be compiled.

Antibiotic resistance is challenging to attribute to food chain dynamics in large part because it is a phenomenon that occurs naturally and predates modern use of clinical antibiotics.[22,23] Theoretical mechanisms for transmission of antibiotic resistance from animal to human have been proposed but not proven.[21] Most antibiotic resistance in the human population is thought to be the result of antibiotic use in humans, not due to the human-animal connection in the food chain.[20] Many examples of resistance—including some of the most dangerous ones such as methicillin-resistant Staphylococcus aureus (MRSA)—do not involve an animal connection at all.[24]

A scientific survey of recognized experts in antimicrobial microbiology found that among those scientists, the perceived contribution of animals to antibiotic resistance in humans is "very low" and limited primarily to three: *Salmonella*, *Enterococci*, and a particular type of *E. coli* (see **Figure 2**).[24] Moreover, in places where use of antibiotics in animals has ceased (either voluntarily or by law), there is little evidence of a clinical benefit to humans.[20] Overall, the evidence is insufficient to establish in a reliable way that antibiotic use in animals is a meaningful contributor to the spread of antibiotic-resistant pathogens in humans.[20]

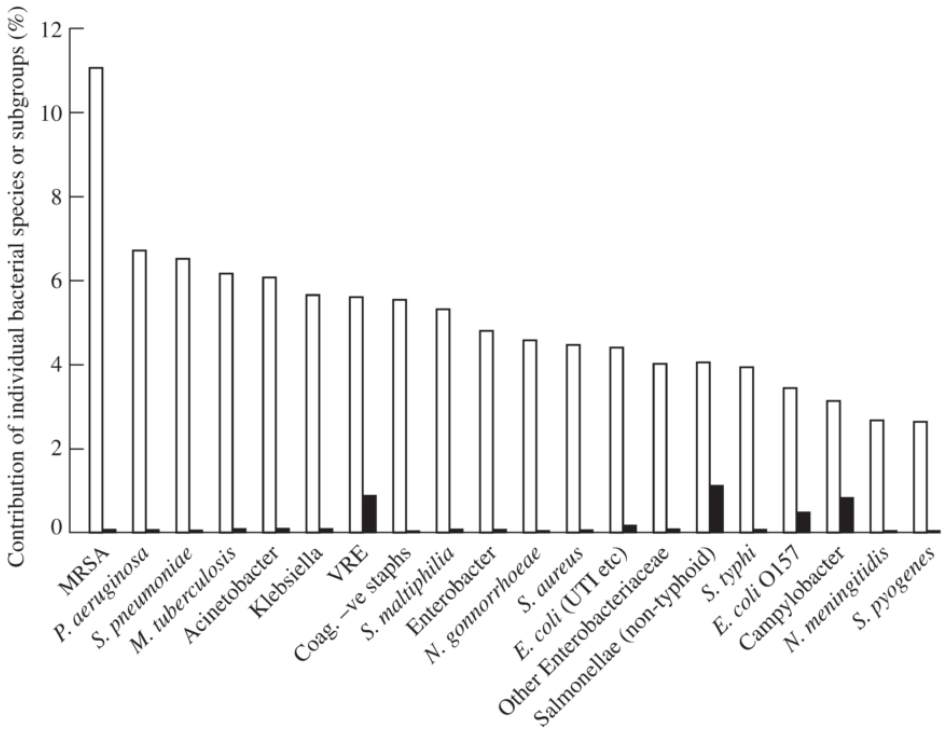

Figure 2. Perceived contribution of individual bacterial species (white bars) and of possible animal sources (black bars), to antibiotic resistance in humans. *Graphic from Bywater RJ, Casewell MW. An assessment of the impact of antibiotic resistance in different bacterial species and of the contribution of animal sources to resistance in human infections. The Journal of antimicrobial chemotherapy 2000;46:643-5.*

With regard to the risk of an acute and potentially fatal allergic reaction to residual foodborne antibiotics, again the evidence that there exists a significant risk is weak.

A study in India characterized the risk of anaphylaxis from ingesting antibiotic residues in pork as "very low."[13] The researchers noted that they were not able to find a strong set of case descriptions when searching the literature, although in the interest of precaution, they acknowledged that the potential severity of such an incident—death—is very high. Similarly, a study of anaphylaxis-related deaths in Ontario, Canada, found that from 1986 to 2011, 40 deaths were food-related (43 percent) but none was linked to any of the meats or meat products that are the subject of this analysis.[25]

Interestingly, based upon searches of the literature, descriptions of cases in which anaphylaxis was associated with the ingestion of antibiotic residues on fruits and vegetables appear

to be more common than cases involving meat. In 2014, Graham, et al, described the case of a young girl who experienced an anaphylactic reaction after eating blueberry pie.[26] Testing confirmed that the residue was connected with the use of a pesticide that was used on the fruit, not any of the animal-product ingredients contained in the pie (i.e., milk or eggs).

The doses at which these potential risks might emerge has not been definitively established. The Codex Committees of the Food and Agriculture Organization and World Health Organization (WHO) have created a maximum residue level (MRL) to serve as a quantitative guide for residues of veterinary drugs on food, but the system is neither fully standardized nor is it widely accepted. The WHO in particular has lamented the lack of suitable methods for isolating and measuring the residues in food animal tissues.[27]

To the extent that there is a risk, the risk burden in the population is distributed roughly evenly. As has been discussed, meat consumption is consistent across various demographic groups, including age, race, and sex. Children as a group do not consume particularly large quantities of meat, and the very youngest and most susceptible of children—infants—consume practically no meat at all.

The lack of reversibility of these potential risks, however, is noteworthy. Once a pathogen becomes antibiotic resistant, it becomes very dangerous and difficult to treat. The mutation cannot be undone except to be contained and possibly eradicated before it has the opportunity to spread. In this specific sense, the risk of antibiotic use in animal food products could be characterized as substantial. Likewise, anaphylactic reaction is an extremely dangerous medical event which is capable of causing death quickly and unexpectedly. Such an allergic reaction is "reversible" only in the sense that it can be, and usually is, treatable if the right drugs are present (e.g., epinephrine).

The Landscape

A variety of groups can be described as important stakeholders in the issue of antibiotic use in food animals. Divergent interests and a lack of consensus in research, however, have made the issue landscape contentious in recent years.[21] Consumers, food producers, regulatory agencies and others are all eager to influence public policy, including the following:

1. *Consumers*, who are the main group at risk for the potentially detrimental effects of exposure (to the extent that their individual diets include meat and meat products).
2. *Farmers and farm workers*, whose livelihood depends on there being demand for the meat and meat products that they produce.
3. *Restaurants and other sellers and distributors of meat and meat products*, who depend on there being wholesale and retail markets for meat and meat products.
4. *Antibiotics manufacturers and retailers*, including Merck & Co., Eli Lily & Co., Pfizer, Zoetis, and Elanco, who depend on there being an agricultural-based market for the antibiotics that they produce and sell.
5. *Veterinarians*, who play a role in supplying antibiotics to farmers and in administering certain antibiotics to animals, and who could be called upon to enforce regulations if more restrictive measures are adopted.
6. *Pro-antibiotic advocacy groups*, such as the Animal Health Institute and the American Meat Institute, who support the use of antibiotics in food animals by publishing educational materials, distributing brochures, and commenting on regulation through press releases and speeches.
7. *Anti-antibiotic advocacy groups*, including Meat Without Drugs, the Union of Concerned Scientists, and Moms for Antibiotic Awareness, who oppose the use of antibiotics in food animals by producing videos, publishing articles and commentaries in the popular press, and organizing petitions against companies involved in antibiotic use.
8. *Industry associations and groups*, including the National Pork Producers Council, the National Chicken Council, and the National Turkey Federation, who warn that restrictions on antibiotics will result in sicker animals and higher meat costs for consumers.
9. *United States Department of Agriculture* (USDA), which regulates and inspects meat and poultry products to test for and identify contaminant residues, and administers the National Residue Program (NRP) to collect data on chemical residues in food.
10. *Food and Drug Administration* (FDA), which monitors veterinary drug, pesticide, and environmental contaminant residues in meat and meat products, and collects data on residues in cooperation with the USDA.

11. *Centers for Disease Control and Prevention* (CDC), which studies and tracks this issue through its Interagency Task Force on Antibiotic Resistance (ITFAR) and its National Antimicrobial Resistance Monitoring System, operated in collaboration with the USDA.
12. *Infectious Diseases Society of America* (IDSA), which represents physicians and scientists who study infectious diseases, and advocates for the elimination of inappropriate uses of antibiotics in food animals.
13. *Environmental Protection Agency* (EPA), which works with other agencies to evaluate residues, and studies the long-term effects of antibiotics, pesticides, and hormones on the ecosystem.

The main economic factors in this issue pertain to the effects of enhanced restrictions on the productivity of the farms, and on the risk to the economic outlook of farmers and farm workers, sellers and distributors of meat and meat products, and antibiotics manufacturers and retailers. As already described, some economic reviews have found that the primary benefit of using antibiotics on farms is healthier animals, not increased production yields, but industry stakeholders have also argued that restricting antibiotics would raise production costs. The estimates offered by these groups (e.g., an increase of $1 billion in costs over ten years) have not been verified independently, but a 1999 report from the National Research Council Committee on Drug Use in Food estimates that a ban on nontherapeutic use of antibiotics would cost each consumer approximately $5 to $10 per year in increased food costs.[28] More restrictive action against antibiotic could also lead to sicker animals making their way into meat and meat products, which could also affect consumer demand in the form of lower perceived quality. Finally, a direct economic effect would be felt by the makers and sellers of antibiotics, who would with certainty see a decrease in the demand for their drugs. Again, however, no reliable dollar estimates exist by which to evaluate this effect.

Risk Management Options

The purpose of this analysis is to evaluate the issue of antibiotic use in the production of animals for food, in order to offer guidance to the FDA with regard to its policies. In light of the evidence published on this topic, potential options for managing the associated risks are as follows:

1. Make no changes to current regulations

   Under this action, the FDA's current request that antibiotics manufacturers voluntarily remove indications for growth enhancement on product labels would stand, and certain antibiotics would only be available for purchase with veterinary approval. Farmers would be allowed to continue current practices in accordance with their own judgment. This option imposes no new compliance or enforcement costs for the time being.

2. Change the current guidelines from voluntary to mandatory

   Under this action, the FDA's current request striking indications for growth enhancement on product labels would be made mandatory, and certain antibiotics would only be available for purchase with veterinary approval. The FDA would enforce the new labeling rules, but farmers still would be allowed to continue their current practices as they see fit. New enforcement costs would be small for federal agencies but moderate for industry.

3. Cease FDA oversight by eliminating the guidelines and veterinary approval altogether

   Under this action, the FDA's current request regarding product labeling would be halted, and antibiotics manufacturers would not receive any guidance on how to label their products. Veterinary approval would not be required for the use of any antibiotics for any reason, including therapeutics, growth, and general health. This would be arguably the most favorable option for industry, but could potentially hinder epidemiological efforts to understand and mitigate potential problems that might arise. This option would be extremely unpopular with many consumer-led advocacy groups.

4. Require veterinary approval for all antibiotics

   Under this action, veterinary approval would be required for all antibiotics by farmers for the purposes of food animal production, regardless of the particular antibiotic being purchased and its intended use. This would complicate the practice of antibiotic use without

providing a certain benefit. It would be unfavorable to farmers and industry, and would pose enforcement challenges. Veterinary groups may feel empowered by their increased involvement, but more likely overwhelmed by it.

5. Ban all uses of antibiotics in food animals

Under this action, no antibiotics whatsoever would be allowed in the production of food animals. Farmers would not be allowed to purchase antibiotics from manufacturers for any use, whether therapeutic, growth, general health, or otherwise. This policy would be enforced at the farm and farm supplier level by a designated federal agency. This would be highly unfavorable to farmers and industry stakeholders. Unintended consequences would likely include sicker animals, and realistically, such a ban would like drive the practice underground rather than eliminate it, resulting in the emergence of a culture of illicit, unreported antibiotic use.

6. Increase data collection activities and study specific concerns scientifically

Under this action, the sales data that the FDA collects on antibiotics would be enhanced to include voluntary reporting of retail outlet-level sales. The Animal Drug User Fee Act of 2008 (ADUFA) already authorizes the FDA to collect this information, but current data collection practices are insufficiently detailed to offer much benefit. Better data could help relevant stakeholder agencies interpret trends in rates of resistance and track regional variation, while continuing to study the underlying science surrounding the use of antibiotics, the biology of the animal-human pathway, the types and levels of antibiotic residues found in food, and whether they pose actual danger. This would give agencies an opportunity to accumulate epidemiological evidence, monitor industry practices, and revisit potential policy changes after more is known.

7. Launch an FDA-reviewed public consumer awareness and education campaign

Under this action, the FDA would pursue a public campaign of educating consumers about the risks of antibiotic residues appearing in the foods they eat, and the potential for adverse

effects. This could sensitize consumers to concerns, but could also result in unwarranted hysteria, overreaction, and unjustified backlash against food producers who are acting in good faith and are in full compliance with the law. A government-sponsored awareness campaign gives the impression that the dangers are well-known and understood when in fact they are far from settled.

Some of these options can be combined to address multiple concerns and achieve multiple goals.

Recommendations

The concerns over antibiotic use in the production of food animals are not unreasonable, but there are many factors that make it difficult to recommend an aggressive change of course with regard to FDA policy. Overall, the current state of scientific understanding of animal-to-human resistance transmission is weak,[29] with many isolated findings of multidrug-resistant pathogens in the food supply but little cohesive theory to help us understand the nature of the transmission. Relatively little is known about the extent to which use of antibiotics on farms contributes to antibiotic resistance in general,[20] and what actual harm to end consumers can be justly attributed to the practice.

It is generally accepted that more judicious use of antibiotics in both veterinary and human medicine would reduce numbers of resistant bacteria,[29] but a call for stringent, mandatory restrictions in food production does not necessarily follow. Adherence to current voluntary guidelines is already high. Of the 27 antibiotics manufacturers who are subject to the FDA's guidelines, 26 are already complying voluntarily (>96%), including the two largest producers, Eli Lilly & Co. and Zoetis Inc. Moreover, secular trends and market changes are already reaching the mainstream and could prove to be more effective than enhanced regulation. For example, on March 4, 2015, the McDonald's Corporation announced that, in response to changing consumer preferences, it would begin sourcing only chicken raised without antibiotics that are relevant to human medicine (using a WHO definition).[30] As part of its initiative, McDonald's will verify antimicrobial use in its supply chains, and require suppliers to maintain records of antimicrobial use and compliance for review by third party auditors. The company's vision statement for antimicrobial stewardship suggests that similar company standards for sourced beef and pork may

not be far behind. McDonald's has the market clout to bring about substantial change in this area, and the infrastructure to accomplish it. (Mid-scale food chains such as Chipotle Mexican Grill Inc. and Panera Bread Co have already switched to antibiotic-free meats, although given their sizes, they influence a far smaller portion of the nation's food environment.)

All things considered, it is the recommendation of this report to take actions #1 and #6, keeping the current voluntary guidelines put into place by the FDA in 2013 but making no modifications to those guidelines, and in the meantime encouraging the medical and scientific community to continue studying the issue, as well as track and monitor for specific risks. This collaborative approach relieves the agency of potentially having to undertake an enormous (and possibly unrealistic) inspection and enforcement effort—an effort that would be highly resource intensive, potentially disruptive to farmers and industry, and that would risk unintended consequences.

Table 1: Summary of Evidence Surrounding Presence and Harms from Antibiotics in Meat

Study (Year)	Food(s)	Study Design	Findings	Strengths & Weaknesses
Bengtsson and Greko (2014)	All meats	Review	Healthy animals do not need antibiotics.	Strengths: synthesizes a wide range of studies. Weaknesses: not a controlled trial.
Butaye, et al (2003)	All meats	Review	Few antibiotics used in animal production have been well-investigated.	Strengths: a comprehensive review of a large number of antibiotics. Weaknesses: not a controlled trial.
Casewell, et al (2003)	Beef, chicken, and pork	Review	Bans on growth promoting antibiotics have reduced overall antibiotic use.	Strengths: evaluates the issue at the policy level. Weaknesses: not a controlled trial.
Castanon (2007)	Chicken	Review	Sweden's ban on growth-promoting antibiotics has led to an increase in infections and thus an increase in the use of therapeutic antibiotics.	Strengths: Examines the Swedish ban closely, with detailed data. Weaknesses: not a controlled trial.
Diarra and Malouin (2014)	Chicken	Review	Use of non-therapeutic antibiotics is inappropriate. Alternatives are needed that will give the same health benefit without the risk.	Strengths: Examines the Canadian experience closely. Weaknesses: not a controlled trial.
Fahrion, et al (2013)	Pork	Cross-sectional	Antibiotic residues were present in 4.5% of pork samples in one city in India.	Strengths: Documents multiple foodborne hazards in India. Weaknesses: small sample.
Graham, et al (2007)	Chicken	Non-randomized controlled trial	Growth-promoting antibiotics do not lower the cost of animal production.	Strengths: it is a large scale analysis. Weaknesses: It is an economic analysis, not an epidemiological analysis.
Hidano (2014)	Chicken	Cross-sectional	Antibiotic-resistant Campylobacter was found in retail chicken meat in Japan.	Strengths: helps to quantify a specific exposure in a specific setting. Weaknesses: limited generalizability.
Johnson, et al (2012)	Chicken	Cross-sectional	Antibiotic resistance is now widespread in E. coli of poultry origin in the U.S.	Strengths: a detailed examination of E. coli. Weaknesses: authors admit a bias in the dataset analyzed.
Landers, et al (2012)	All meats	Review	Research is insufficient to establish the role of antibiotic use in food animals.	Strengths: a comprehensive systematic review. Weaknesses: focused on reports from agencies.
Philips, et al (2004)	Chicken, beef, pork	Review	Risks associated with resistant Salmonella and campylobacter are concerning, but resistance acquired in animals likely add very little to human disease burden. Bans may cause harm.	Strengths: An independent review that is extremely comprehensive. Weaknesses: not a controlled trial.
Soulsby (2007)	Chicken, beef, and pork	Review	Given the lack of knowledge about antibiotic resistance,	Strengths: studies the effect of multiple bans. Weaknesses: not a controlled trial.

			private consortia in the UK are responding appropriately.	
White, et al (2001)	Ground beef, turkey, chicken, and pork	Cross-sectional	Salmonella was isolated from samples of meat purchased at three supermarkets. Resistant strains of salmonella are common in ground meats.	Strengths: showed that antibiotic-resistant organisms are present in retail meat. Weaknesses: small sample.

References

1. Diarra MS, Malouin F. Antibiotics in Canadian poultry productions and anticipated alternatives. Frontiers in microbiology 2014;5:282.
2. Soulsby L. Antimicrobials and animal health: a fascinating nexus. The Journal of antimicrobial chemotherapy 2007;60 Suppl 1:i77-8.
3. Butaye P, Devriese LA, Haesebrouck F. Antimicrobial growth promoters used in animal feed: effects of less well known antibiotics on gram-positive bacteria. Clinical microbiology reviews 2003;16:175-88.
4. Castanon JI. History of the use of antibiotic as growth promoters in European poultry feeds. Poultry science 2007;86:2466-71.
5. Graham JP, Boland JJ, Silbergeld E. Growth promoting antibiotics in food animal production: an economic analysis. Public health reports (Washington, DC : 1974) 2007;122:79-87.
6. de Been M, Lanza VF, de Toro M, et al. Dissemination of Cephalosporin Resistance Genes between Escherichia coli Strains from Farm Animals and Humans by Specific Plasmid Lineages. PLoS genetics 2014;10:e1004776.
7. Casewell M, Friis C, Marco E, McMullin P, Phillips I. The European ban on growth-promoting antibiotics and emerging consequences for human and animal health. The Journal of antimicrobial chemotherapy 2003;52:159-61.
8. Daniel CR, Cross AJ, Koebnick C, Sinha R. Trends in meat consumption in the USA. Public health nutrition 2011;14:575-83.
9. Rinsky JL, Nadimpalli M, Wing S, et al. Livestock-associated methicillin and multidrug resistant Staphylococcus aureus is present among industrial, not antibiotic-free livestock operation workers in North Carolina. PloS one 2013;8:e67641.
10. Sapkota AR, Lefferts LY, McKenzie S, Walker P. What Do We Feed to Food-Production Animals? A Review of Animal Feed Ingredients and Their Potential Impacts on Human Health. Environmental Health Perspectives 2007;115:663-70.
11. Cazer CL, Volkova VV, Grohn YT. Use of pharmacokinetic modeling to assess antimicrobial pressure on enteric bacteria of beef cattle fed chlortetracycline for growth promotion, disease control, or treatment. Foodborne pathogens and disease 2014;11:403-11.
12. White DG, Zhao S, Sudler R, et al. The isolation of antibiotic-resistant salmonella from retail ground meats. The New England journal of medicine 2001;345:1147-54.
13. Fahrion AS, Jamir L, Richa K, et al. Food-safety hazards in the pork chain in Nagaland, North East India: implications for human health. International journal of environmental research and public health 2014;11:403-17.
14. Hidano A, Yamamoto T, Hayama Y, et al. Antimicrobial resistance among Campylobacter isolates obtained from retail chicken meat and offal products in Japan. Japanese journal of infectious diseases 2014;67:315-7.
15. CDC. Antibiotic Resistance Threats in the United States. 2013.
16. Bengtsson B, Greko C. Antibiotic resistance--consequences for animal health, welfare, and food production. Upsala journal of medical sciences 2014;119:96-102.
17. Holmberg SD, Osterholm MT, Senger KA, Cohen ML. Drug-resistant Salmonella from animals fed antimicrobials. The New England journal of medicine 1984;311:617-22.

18. Al-Waili N, Salom K, Al-Ghamdi A, Ansari MJ. Antibiotic, Pesticide, and Microbial Contaminants of Honey: Human Health Hazards. The Scientific World Journal 2012;2012:930849.
19. Phillips I, Casewell M, Cox T, et al. Does the use of antibiotics in food animals pose a risk to human health? A critical review of published data. The Journal of antimicrobial chemotherapy 2004;53:28-52.
20. Singer RS, Finch R, Wegener HC, Bywater R, Walters J, Lipsitch M. Antibiotic resistance--the interplay between antibiotic use in animals and human beings. The Lancet Infectious diseases 2003;3:47-51.
21. Landers TF, Cohen B, Wittum TE, Larson EL. A review of antibiotic use in food animals: perspective, policy, and potential. Public health reports (Washington, DC : 1974) 2012;127:4-22.
22. van der Kolk JH. Antibiotic resistance from prehistoric to modern times. The Veterinary quarterly 2015;35:1.
23. D'Costa VM, King CE, Kalan L, et al. Antibiotic resistance is ancient. Nature 2011;477:457-61.
24. Bywater RJ, Casewell MW. An assessment of the impact of antibiotic resistance in different bacterial species and of the contribution of animal sources to resistance in human infections. The Journal of antimicrobial chemotherapy 2000;46:643-5.
25. Xu YS, Kastner M, Harada L, Xu A, Salter J, Waserman S. Anaphylaxis-related deaths in Ontario: a retrospective review of cases from 1986 to 2011. Allergy, Asthma, and Clinical Immunology : Official Journal of the Canadian Society of Allergy and Clinical Immunology 2014;10:38-.
26. Graham F, Paradis L, Begin P, Paradis J, Babin Y, Des Roches A. Risk of allergic reaction and sensitization to antibiotics in foods. Annals of allergy, asthma & immunology : official publication of the American College of Allergy, Asthma, & Immunology 2014;113:329-30.
27. Evaluation of certain veterinary drug residues in food. Sixty-sixth report of the Joint FAO/WHO Expert Committee on Food Additives. World Health Organization technical report series 2006:1-80, backcover.
28. National Research Council Committee on Drug Use in Food A. The Use of Drugs in Food Animals: Benefits and Risks. Washington (DC): National Academies Press 1999.
29. Doyle ME. Multidrug-Resistant Pathogens in the Food Supply. Foodborne pathogens and disease 2015.
30. McDonald's. Global Vision for Antimicrobial Stewardship in Food Animals 2014.