Agricultural Uses of Antibiotics Escalate Bacterial Resistance

ORGANIC LEADS IN PROHIBITING ANTIBIOTIC USE

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With the explosion of antibiotic resistance in the U.S. and worldwide, antibiotic use in crop and livestock production is a major public health issue. Regulation of the use of antibiotics in chemical-intensive agriculture is weak, allowing residues of antibiotics and antibiotic-resistant bacteria to emerge on agricultural lands, move through the environment, contaminate waterways, and ultimately reach consumers in food. The human gut and contaminated land and waterways provide incubators for antibiotic resistance. The main health impacts of antibiotic residues in food are the promotion of antibiotic resistance and disruption of the microbiota in the human gut.

Antibiotic use has been prohibited in organic animal agriculture since the promulgation of the organic rule in 2000. The use for control of fire blight (whose name is derived from the black shoots and leaves caused by a bacterial infection) in apples and pears was removed from the allowed list of materials by decisions of the National Organic Standards Board (NOSB) in 2013 and 2014. Although consumers can avoid antibiotic residues in their food supply by buying organic, more stringent regulation is needed to eliminate antibiotic use in agriculture and the breeding of antibiotic resistance in the environment.

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Antibiotic Use in Animal Agriculture

The use of antibiotics in animal agriculture has received a great deal of attention—and rightly so. Most traditional antibiotic use occurs in the production of livestock and animal products. Because the antibiotics pass through the animal and end up in poorly-managed manure, animal agriculture is a major source of environmental contamination with antibiotics and antibiotic-resistant bacteria. According to Physicians for Social Responsibility, in 2011, 29.9 million pounds of antibiotics were sold for cattle and poultry production, compared to 7.7 million pounds of antibiotics for sick humans. Of the antibiotics used in animal production, 90% were administered at low levels to animals through feed and water to prevent disease and promote growth in order to compensate for overcrowded and unsanitary living conditions in concentrated animal feeding operations (CAFOs), used by the industry to fatten livestock quickly on their way to market. Although the U.S. Food and Drug Administration's (FDA) Veterinary Feed Directive, which took effect in January 2017, will now limit the use of medically important antibiotics for humans to therapeutic use only with the oversight of a veterinarian, significant loopholes for continued antibiotic use remain. (The regulatory section provides details.) Antibiotic use is prohibited in all organic production. While organic standards require that sick animals be treated, meat and other products from animals treated with antibiotics cannot be sold as organic.

Treated Animals Contaminate Manure

Antibiotic residues are carried over into manure, which is then applied to crops that would otherwise not be exposed to antibiotics, including organic crops. Such residues may be taken up by crops. While conventional agriculture has no restriction on the use of manure, organic standards require that, if used on crops for human consumption, it must be either composted or incorporated into the soil 90–120 days before harvest, which may reduce concentrations of some antibiotics and populations of antibiotic-resistant microbes. More research on this is needed.

While the use of antibiotics in animal agriculture is widely acknowledged as harmful, the use of antibiotics in chemical-intensive crop production also poses unnecessary risks. Glyphosate, while marketed as a weed killer, is patented by its manufacturer, Monsanto, as an antibiotic. It is the most widely used antibiotic in agriculture—attacking the shikimate pathway, part of the mechanism for producing certain amino acids in both plants and microbes.

FIGURE 1: **Traditional Antibiotic Uses* in 2011–U.S.**
(pounds of active ingredients)

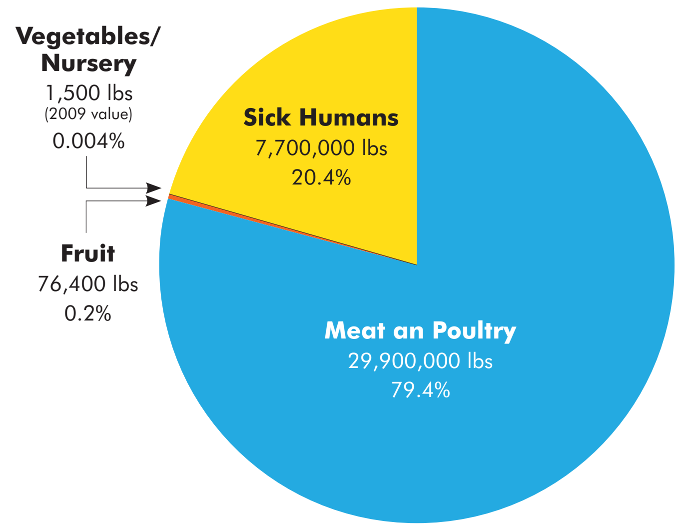
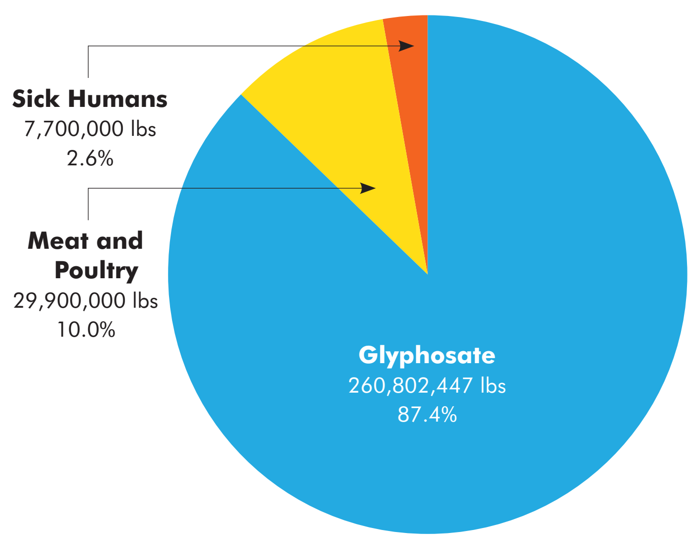


FIGURE 2: **All Antibiotic Uses* in 2011–U.S.**
(pounds of active ingredients)



Sources: IMS Health Inc., U.S. FDA, and USDA NASS.

* "Traditional antibiotic use" is used in this report to refer to uses in animal agriculture and the antimicrobial pesticide uses, while "all antibiotics" includes glyphosate.

Note: Aquaculture not included because such use has not been monitored.

In addition to the promotion of weed resistance by widespread application of glyphosate and use of glyphosate-resistant genes in agriculture, there is evidence that glyphosate at environmentally relevant levels increases bacterial resistance to antibiotics important in fighting human pathogens and bacterial infections (Kurenbach et al., 2015).

Additionally, fungicide use and labeling overlap with antibacterial use. It is not clear to what extent these fungicides are effective as antibiotics and contribute to the problem of antibiotic resistance.

Antibiotics in Fruit and Vegetable Production

Use of traditional antibiotics in fruit and vegetable production is limited in the U.S. to the antibiotics oxytetracycline and streptomycin. Allowed residues, or tolerances, for the antibiotics are set at 0.35 ppm oxytetracycline in or on apples, pears, and peaches (including nectarines), and 0.25 ppm streptomycin in apples and pears in the finished fruit that is purchased in grocery stores. (See Table 2.) Although fruit production only accounts for 0.2% of total domestic traditional antibiotic use, the majority of conventional apple and pear producers use antibiotics, as fruit growers have moved to varieties less resistant to fire blight, a highly contagious and destructive bacterium. In 2011 in California, 45% of apple acres were treated with streptomycin and 29% were treated with oxytetracycline. In the same year in California, 65% of pears were treated with streptomycin and 80% were treated with oxytetracycline (USDA NASS, 2012). A smaller proportion of peach and nectarine trees are treated with oxytetracycline for bacterial spot.

Alternatives to antibiotics to combat fire blight in apples and pears were examined in depth by the NOSB, when it rejected the use of tetracycline and streptomycin in organic fruit production. The first line of defense for fire blight is choosing resistant varieties and rootstocks. Highly resistant apple varieties include Jonafree, Melrose, Prima, and Quinte. Fire blight resistant pear varieties include the Atlantic Queen, Ayers, and Seckel varieties. Other practices for avoiding fire blight in apples include balancing nutrients and avoiding over-application of nitrogen fertilizers, avoidance of over-pruning in the dormant season, use of copper materials on the trees between delayed dormant and tight cluster stages as preventive measures against overwintering of disease, and use of lime sulfur during bloom, with some slight differences for pears. In addition to these methods, considering how changes in the orchard environment have contributed to epidemics of fire blight is important for orchard managers. In response, fruit producers can increase species diversity and decrease tree density, use resistant cultivars and rootstocks, and plant a variety of cultivars on a variety of rootstocks (Steiner, 2000). The elimination of antibiotic use in organic apple and pear production demonstrates that antibiotics are not needed for fruit production.

There are several registered uses for streptomycin in vegetable and seedling production, but there are no registered uses for oxytetracycline in vegetable production domestically. In addition to these uses for food crops, streptomycin is used in nursery and floriculture production, according to the U.S. Department of Agriculture's (USDA) National Agricultural Statistics Service (NASS), with 1,400 pounds applied in 2009.

TABLE 1: **Use of Antibiotics on Fruit in the U.S. in 2015 according to USDA NASS** (www.nass.usda.gov)

	Streptomycin				Oxytetracycline			
Crop	Percentage of Acres Treated	Acres Treated	Pounds per Acre per year	Total Active Ingredient Per year (lb)	Percentage of Acres Treated	Acres Treated	Pounds per Acre Per Year	Total Active Ingredient Per year (lb)
Apple	26	68,581	0.49	33,600	11	30,000	0.27	8,100
Pear	16	7,346	0.39	2,900	30	14,200	0.5	7,100
Peaches					5	4,103	0.39	1,600
Total				**36,500**				**16,800**

TABLE 2: **Tolerances for Residues on Foods in U.S.** (parts per million)

	Apples, Peaches, Pears	Beans	Celery	Pepper	Tomato	Potato
Streptomycin	0.25	0.5	0.25	0.25	0.25	0.25
Oxytetracycline	0.35	–	–	–	–	–

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Fungicides Used as Antibiotics

The universe of "traditional antibiotics" used to manage bacterial plant diseases is larger than generally recognized. Bacterial diseases on tree fruit include fire blight, bacterial spots, and bacterial cankers, for which tetracycline and streptomycin are registered as fungicides or bactericides, as controls. Vegetable crops, such as potatoes, tomatoes, peppers, and beans, are also vulnerable to bacterial diseases, including but not limited to bacterial canker, soft rot, and bacterial wilt. Although the only product generally called an "antibiotic" that is registered for bacterial diseases in U.S. vegetable production is streptomycin, several "fungicides" are registered for managing bacterial diseases in fruits, vegetables, grains, and other food crops. These fungicides include biologics, a number of copper compounds, inorganic oxidizers, growth regulators, and fungicides from several chemical classes. The use data is not available to separate the antibiotic uses of these materials from the fungicidal uses, but their inclusion in the totals would increase considerably the total antibiotic use in fruit and vegetable production shown in Figures 1 and 2.

The labeling of these "fungicides" to control bacterial diseases raises a number of questions that remain unanswered. First, are these materials effective in controlling bacteria? Plant pathologists recommend their use only in an integrated pest management (IPM) system that also includes disease-resistant varieties, pathogen-free seeds and transplants, crop rotation, field sanitation, and spacing. Or, are chemical manufacturers simply adding additional pests to products used to control fungal diseases? If the materials are effective antibiotics, does their agricultural use adversely affect their ability—or the use of related chemicals—to control human pathogens? Since at least three of these materials (Agri-Phene, Decon Phase, and Mar-V-Cide II Germicidal Cleaner) are labeled for control of HIV and tuberculosis, it can be assumed that the potential exists to promote resistance in human disease organisms.

Health Impacts of Antibiotics Used in Agriculture

The main health impacts of antibiotic residues in food are the promotion of antibiotic resistance and disruption of the microbiota in the human gut.

Antibiotic resistance turns common infections deadly

The spread of antibiotic resistance is a health care crisis of major proportions. The Centers for Disease Control and Prevention (CDC) calls it "one of the world's most pressing public health problems." Many bacterial infections are becoming resistant to the most commonly prescribed antibiotics, resulting in longer-lasting infections, higher medical expenses, the need for more costly or hazardous medications, and the inability to treat life-threatening infections. The development and spread of antibiotic resistance is the inevitable effect of antibiotic use. Bacteria evolve quickly, and antibiotics provide strong selection pressure for those strains with genes for resistance.

The principal traditional antibiotics used in plant agriculture to fight disease are both important for fighting human disease. Tetracycline is used for many common infections of the respiratory tract, sinuses, middle ear, and urinary tract, as well as for anthrax, plague, cholera, and Legionnaire's disease, though it is used less frequently because of resistance. Streptomycin is used for tuberculosis, tularemia, plague, bacterial endocarditis, brucellosis, and other diseases, but its usefulness is limited by widespread resistance (U.S. National Library of Medicine, 2006).

It may not be widely appreciated that use of antibiotics on fruit trees can contribute to resistance to the antibiotic in human pathogens. The human pathogenic organisms themselves do not need to be sprayed by the antibiotic because movement of genes in bacteria is not solely "vertical," that is from parent to progeny—but can be "horizontal"—from one bacterial species to another. So, a pool of resistant soil bacteria or commensal gut bacteria can provide the genetic material for resistance in human pathogens.

The basic mechanism is as follows. If bacteria on the plants and in the soil are sprayed with an antibiotic, those with genes for resistance to the chemical increase compared to those susceptible to the antibiotic. Resistance genes exist for both streptomycin and tetracycline, and spraying with these chemicals increases the frequency of resistant genotypes by killing those susceptible to the antibiotic and leaving the others. Those genes may be taken up by other bacteria through a number of mechanisms, collectively known as "horizontal gene transfer."

The contribution of antibiotic use in fruit trees to resistance in human pathogens may not be nearly as important as the use of non-therapeutic antibiotics in livestock and farmed fish, but it does have an impact on the pool of antibiotic-resistant bacteria. Furthermore, residues of antibiotics in the soil may be taken up by treated or untreated plants and affect bacteria (Kumar et al., 2005).

Disruption of human gut microbiota

A human being contains more cells in and on the body that belong to microbes—and contain more microbial DNA—than those that originate from human genes. In fact, only 10% of human cells are genetically human, and only 1% of the DNA in the human is "human." The 90% of human cells that are microbial in origin are not (mostly) pathogenic, nor are they (mostly) just along for the ride. They are (mostly) symbionts that help the body function as it should. The human body, rather than being a distinct organism, should be thought of as a biological community, or "superorganism," truly the product of coevolution.

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In addition to interfering with digestion, exposure to antibiotics can disturb the microbiota, contributing to a whole host of "21st century diseases," including diabetes, obesity, food allergies, heart disease, antibiotic-resistant infections, cancer, asthma, autism, irritable bowel syndrome, multiple sclerosis, rheumatoid arthritis, celiac disease, inflammatory bowel disease, and more. The human immune system is largely composed of microbiota. Not all disturbance in the microbiota comes from the conscious use of antibiotics. Researchers have recently documented that the rise in these same diseases is tightly correlated with the use of the herbicide glyphosate (Swanson et al., 2014). They have also shown that glyphosate exposure can result in the inflammation that is at the root of these diseases. The glyphosate results should not be surprising since the pesticide has been patented as an antibiotic, as discussed below.

Incubators of Antibiotic-Resistant Bacteria

The gut of humans and other animals provides an efficient incubator for antibiotic resistance. Antibiotic resistance increases first in commensal bacteria—the bacteria that naturally live within the human body—and may then be transferred to pathogens. Thus, the position that human pathogens are not present in orchards sprayed with antibiotics is irrelevant to the actual development and spread of bacteria resistant to antibiotics. The number of bacteria in the gut is large—often more than 10 bacteria of several hundred species—with a large gene pool offering many mechanisms of resistance. Every exposure to antibiotics provides new opportunities for selection for resistance (Chee-Sanford et al., 2009).

Antibiotics from use on animals and crops are washed into waterways, where they find another environment perfect for encouraging the growth of antibiotic-resistant bacteria. Aquatic environments are rich in bacteria, and many of those bacteria contain genes for antibiotic resistance (Baquero et al., 2008). Thus, waterways are another place where pathogens can obtain genes for resistance.

GMOs, Glyphosate, and Antibiotic Resistance

The most widely used antibiotic in agriculture is glyphosate. Although it is registered as an herbicide, glyphosate works by attacking the shikimate pathway, part of the mechanism for producing certain amino acids in both plants and microbes. In fact, Monsanto holds a patent for glyphosate as an antibiotic. The patent for glyphosate claims efficacy against the malaria plasmodium and other protozoan parasites. Other research supports this claim and identifies the shikimate pathway as a target for *Mycobacterium tuberculosis,* the cause of tuberculosis (Schönbrunn et al., 2001). Thus, two of the most troublesome human diseases may be susceptible

Antibiotic Use in Fish Farms/Aquaculture

There are over 4,000 aquaculture facilities in the U.S., dominated by catfish farms in the south. The risks posed by antibiotic use are different in the varied systems of aquaculture: ponds, closed/recirculating systems, flow-through, net pens and sea cages. In net pens and sea cages, the release is directly into the ocean, where the chemicals and resistant bacteria can spread more easily. Other facilities may release water into natural waterbodies without treatment to remove antibiotics.

Eighty to 90 percent of total farmed fish production occurs in Asia and is known for overcrowded, unhygienic conditions that act as stressors to the fish and lead to the increased use of prophylactic antibiotics (Marshall & Levy, 2011). Although the use of antibiotics for non-therapeutic purposes in aquaculture is prohibited by law in the U.S., a study assessing the presence of 47 antibiotics in U.S.-purchased salmon, catfish, shrimp, trout, and tilapia originating from 11 different countries found sub-regulatory levels of antibiotics, which can promote antibiotic resistance development (Done & Halden, 2015). Additionally, this study detected the presence of virginiamycin below the regulatory level in salmon marketed as "antibiotic-free.

Entire populations are commonly treated when only a small percentage are sick, but that use is not considered "prophylactic." Such treatment is designed to protect the healthy fish, since the infected fish generally do not consume the medicated feed. The result is use of sub-therapeutic doses that promotes resistance and rarely clears the infection.

Antibiotic use is one of several factors to consider in choosing fish to eat. Other concerns include the contaminants in the fish's environment, sustainability of the feed, types of parasiticides used, and fishing practices for wild-caught fish. Key issues to consider when purchasing fish to eat, include the following: Is it farmed or wild? How is it farmed? What synthetic materials are used in its production? Is it associated with any contaminants?

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to antibiotics using glyphosate's mode of action. The use of glyphosate can thus be a contributor to the spread of resistance to medically important antibiotics.

Broadcasting this antibiotic on grain crops—and spreading genes for resistance through genetically engineered crops dependent on glyphosate—is as problematic as the use of streptomycin and tetracycline on fruit trees.

Regulation of Antibiotics in Agriculture Fails to Adequately Address Risks

Regulation of the use of antibiotics in agriculture is divided between FDA and EPA, with some oversight by USDA. FDA regulates antibiotics used as animal drugs, EPA regulates those used as pesticides, and USDA is responsible for conducting residue testing on animal products and other food products with established residue tolerance levels.

An application for a new animal drug is approved if FDA "agrees with the sponsor's conclusion that the drug is safe and effective if it is used according to the proposed label." FDA states that one goal is to "minimize the number of antibiotic-resistant bacteria that enter the food supply in or on food products made from treated animals," but has not incorporated in its regulation the assessment and prevention of exposure through waterways and manure, a gaping hole in the animal drug approval process that is unprotective of human health.

In response to widespread criticism of the use of antibiotics in animal production, as of January 1, 2017, FDA's Veterinary Feed Directive will limit to therapeutic use only (with the oversight of a veterinarian) the use of antibiotics that are medically important to humans in feed and water. While this move by FDA is important, it is an incomplete solution to the problem of promotion of antibiotic resistance by animal agriculture. Since any use of antibiotics increases the probability of resistance, the following remain problematic:

- Resistance may develop with the continued use of antibiotics that are not currently medically important to humans. As resistance continues to develop, medical professionals are turning to older classes of antibiotics, which must also be preserved for use in human medicine.
- FDA will still allow the use of antibiotics for disease-prevention, thus providing a loophole for antibiotic use in the absence of disease.
- Of the antibiotics that will no longer be allowed to be administered through feed or water as animal growth promotors, 89 percent can still be given to healthy animals for alternative reasons (Food and Water Watch, 2015).

EPA's assessment of pesticide risks generally addresses risks associated with direct exposure of humans to the pesticide. In order to address the problem of antibiotic resistance by tetracycline and streptomycin, EPA's Health Effects Division adopted a qualitative risk assessment process similar to that of FDA's evaluation of animal drugs. The resulting risk estimate provides a qualitative indication of the potential to human health of the proposed use of an antimicrobial pesticide and is ranked as high, medium, or low. For streptomycin, "The assessment concluded that the possibility of antibiotic resistance resulting in adverse human health consequences was of medium concern following occupational application and was of high concern following application by residential users." For tetracycline, the resistance assessment finds, "The overall risk of the development of antibiotic resistance to oxytetracycline in human health and the environment is medium."

However, EPA's response to the "medium" level of concern is inconsistent with the FDA Guidance 152 on which it is based. If it were following the guidance, EPA would limit use to infected plants for a short period of time, classify antibiotics as restricted use, and monitor for resistance. These steps have not been taken.

The only reassessments of these two antibiotics that EPA has undertaken since 1993 have been tolerance reassessments. Since, as EPA states, if "bacterial resistance to oxytetracycline from pesticidal use occurs, it is most likely that it would be caused by development of resistance from non-pathogenic bacteria in orchards which later transferred their resistance to human bacterial pathogens," the reassessment of tolerances, which looks only at food residues, is inadequate for the assessment and management of the risk of antibiotic resistance. EPA's model for assessing and managing risk associated with pesticides thus proves to be inadequate to address the risk of antibiotic resistance.

Consumer Action Is Needed

Stringent regulations are needed to eliminate use of antibiotics in food production, which leads to antibiotic resistance, residues in manure, and contamination of waterways. The success of the NOSB in eliminating antibiotics in organic fruit production highlights successful alternatives to antibiotics. In order to move away from the dependence on antibiotics in human food production, research on alternatives and methods that have already proven efficacious must be expanded. For apple and pear production, switching to fire blight resistant varieties would reduce the need for intervention for fire-blight control. The push and pull of the marketplace, both by consumers and by producers, must work together to expand the number of food products raised or produced without antibiotics in organic systems.

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