Antibiotics in agriculture: When is it time to close the barn door?

Commentary

Antibiotics in agriculture: When is it time to close the barn door?

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Everybody knows that bacterial resistance to antibiotics is a bad thing, at least for humans and animals, if not for bacteria. Drugs that were effective for treating community- and hospital-acquired infections are no longer so because the target bacteria are resistant to their action. To be sure, it may be some time before we really enter the predicted "postantibiotic era" in which common infections are frequently untreatable. Even now, however, the consequences of resistance in some bacteria can be measured as increases in the term and magnitude of morbidity, higher rates of mortality, and greater costs of hospitalization for patients infected with resistant bacteria relative to those infected with sensitive strains (1). Dozens of new antimicrobial compounds have been licensed in the U.S. during the last half century, but almost all "new antibiotics" introduced in the last 40 years have been relatively minor chemical variants of compounds to which bacteria have already developed resistance. As a result, bacteria have rapidly adapted existing resistance mechanisms to evade the new compounds. Indeed, only a single chemically novel class of antibacterial agents, the oxazolidinones, has been introduced into clinical use since the 1970s.

There is no question that the resistance problem is of our own making, a direct consequence of the appropriate as well as the inappropriate use of these "wonder drugs" by humans. The abundant calls for the more prudent use of antibiotics (http://www.healthsci.tufts.edu/apua/apua.html) are well justified, if seemingly unnecessary. Who would admit to being against the prudent use of anything? Although it is not clear that by reducing our use of these drugs alone we will be able to reverse the growing tide of resistance (2–5), we can certainly slow and maybe even stop that tide. But how do we reduce antibiotic use? Although many antibiotic-prescribing decisions in human medicine may be black or white (clearly medically necessary or clearly not indicated), there is a large gray area in which they provide a small but significant clinical benefit to the individual (for example, more rapid cure of acute otitis media) or psychological benefit to the patient (for example, a placebo effect) and/or the physician (for example, to facilitate the closure of a consultation). These gray-area applications of antibiotics must be weighed against the incremental harm to the population as a whole caused by the additional selective pressure for antimicrobial resistance. In such contexts, determining what is an appropriate use of an antibiotic is a judgment call in which cultural, social, psychological, and economic factors play at least as great a role as clinical and epidemiological considerations.

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The article in this issue by Smith *et al.* (6) focuses on the theater of antibiotic use that for more than three decades (7) has been the major target of those campaigning to reduce antibiotic use: their use for growth promotion and treatment of food animals. Over half of the antibiotics that are produced in the U.S. are used for agricultural purposes, according to a recent estimate (8), and there is no question that this application of these drugs has contributed to the generally high frequency of resistant bacteria in the gut flora of chickens, swine, and other food animals. However, regulation of agricultural uses of antibiotics has been controversial, largely because policymakers have been urged to weigh the clear benefits to animal health as well as the economic benefits of antibiotic use to food producers, pharmaceutical companies, and possibly also to consumers against a threat to human health that is often difficult to quantify precisely. Antibiotic use in animals has at least four potential effects on human health, each of which presents separate challenges to unambiguous documentation and quantitative measurement.

The most readily demonstrable and quantifiable effect of antibiotic use in animals and resistance in animal flora on human health is through zoonotic infections that are rarely transmitted between humans. By ingesting contaminated meat (or other foods that have been cross-contaminated by animal manure or by meat-borne bacteria during preparation), people can become infected by bacteria that can be pathogenic to humans and are resistant to one or more of the drugs that could be used to treat these infections. An example that has engendered much recent discussion is gastroenteritis (food poisoning) caused by *Campylobacter jejuni* resistant to fluoroquinolones (ciprofloxacin and related compounds). Among their many uses, fluoroquinolones are used to treat chickens for bacterial infections, and fluoroquinolone-resistant *Campylobacter* have been found in raw chicken. Thus, it would seem that consumption of chickens would be a risk factor for the acquisition of a fluoroquinolone-resistant *Campylobacter* infection, and some studies, although not all, have supported this proposition. A recent risk assessment study commissioned by the U.S. Food and Drug Administration (FDA) has estimated that about 8,000–10,000 persons in the U.S. each year acquire fluoroquinolone-resistant *Campylobacter* infections from chicken and attempt to treat those infections with a fluoroquinolone (9). Molecular epidemiological studies provide further support for the causal link between chicken consumption and fluoroquinolone-resistant *Campylobacter* infections. The strains of *Campylobacter* found in the meat of chickens seem to be identical to those responsible for human infections (10).

Nevertheless, even in this seemingly straightforward situation, unequivocally documenting and quantifying the effects

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of antibiotic use in food animals on human health has caveats. First, the presence of identical strains of fluoroquinolone-resistant *Campylobacter* in chickens and in humans does not causally link the use of fluoroquinolones in the chickens to the resistant strains. There is ample evidence to suggest that bacteria, including resistant strains, enter the poultry environment from many different sources (11), and that transmission of resistant bacteria on a farm may occur in the absence of antibiotic-mediated selection (12). Thus, humans may acquire resistant infections from food animals even if antibiotics are not used by those animals. Second, epidemiological studies have identified other risk factors for *Campylobacter* infection in humans, including contact with companion animals, like dogs and cats. These animals may be treated with fluoroquinolones but are rarely tested as potential sources of the human infection.

Unfortunately, the other three ways in which antibiotic use and resistance in food animals can impinge on human health are even more difficult to document unambiguously, much less to quantify. The first of these possible contributions is as a breeding ground for resistance genes and operons, for the accumulation of these genes on integrons and their movement to plasmids and other accessory elements. That is, animal use could in principle be a selective force responsible for the assembly of resistance gene clusters [like that postulated for the vancomycin-resistance operons in *Enterococcus* or the multiple-resistance island in *Salmonella* DT104 (13)] and movement of those genes and clusters from their ancestral bacteria into the commensal and pathogenic bacteria of mammals. Second, once the genetic machinery for resistance or multiple resistance is assembled, commensal bacteria inhabiting food animals may serve as a reservoir for resistance-encoding plasmids and other accessory elements, and the size of this reservoir will be enhanced by antibiotic use in agriculture. When humans ingest these animal commensals, they may transfer their resistance elements to other strains or species that are pathogenic to humans. In this case, bacteria from zoonotic sources serve as vectors that transmit resistance genes to the human bacterial flora. Finally, there is the contribution of antibiotic use in food animals to resistance in bacteria that are shared by food animals and humans and infectiously transmitted among humans. Among the more notorious of these examples are vancomycin-resistant strains of *Enterococcus* that plague the intensive care units of hospitals. In this situation, it is clear that resistant organisms can enter human flora from contact with farm animals, but the majority of human exposure occurs through transmission from one human to another (largely in hospitals), rather than from direct exposure to animal sources and is amplified by the extensive use of vancomycin in these settings.

Although these last three contributions of antibiotic use in food animals to human health are hard to directly document and quantify empirically, the Smith *et al.* (6) article in this issue of PNAS offers a way to quantitatively evaluate the last of these possible contributions (and to some extent the penultimate). They address and provide answers to questions that should be of considerable interest to policymakers formulating regulations for the use of antibiotics in food animals: If human exposure to antibiotic-resistant commensal bacteria from food animals could be limited or prevented, how much difference would it make to the impact of these bacteria (and resistance-encoding accessory elements) on human health, and what factors affect the magnitude of this difference?

Smith *et al.* (6) use a simple but realistic mathematical model in which there is a constant influx of resistant bacteria via food to the human population. Based on the analysis of the properties of this model, they conclude that for bacteria like *Enterococci* that are frequently transmitted among humans, "input" of resistant strains from the food chain will make only a small difference in the eventual equilibrium prevalence of resistant strains in the human population. The reason for this conclusion is intuitively appealing; the rate of input of resistant bacteria from animal sources is small relative to the amplification achieved by the human use of antibiotics and the transmission of resistant strains among humans. More colloquially, their theoretical results support the adage that once the horse has fled the barn, it is too late to close the door. On the other side, their results also point to the role antibiotic use in food animals may have had in unlocking if not fully opening that door. The use of antibiotics in food animals may have little effect on the eventual prevalence of resistance in human commensals, but if extensive animal use precedes extensive human use of drugs, the animal use may well shorten the time before resistance becomes problematic in the human flora.

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The finding by Smith *et al.* (6) suggests that once evidence of the medical impact of antimicrobial use is apparent (as measurable frequencies of resistant infections of humans by commensal bacteria resistant to clinically important drugs), regulation of the animal use of those drug classes would have little or no effect. If valid and general, this finding creates a difficulty for regulators. Faced with industry and political pressure to show a "scientific basis" for restrictions on antimicrobial use, the regulations they implement may come too late to do anything to prevent the spread of resistance to that drug in the commensal and pathogenic bacteria of humans. This dilemma is not unique to the use of antibiotics in animals. In designing policies that affect infectious diseases (14), global climate (15), or other systems with their own internal dynamics, waiting until there is evidence of conclusive harm may result in a missed opportunity to prevent damage, because the effects of a policy change once the damage is done may be weak or delayed. In such situations, the desire for a scientific basis for regulatory action must be weighed against the potential risks of inaction. Defining these potential risks, as Smith *et al.* have done, then becomes an important role for scientific studies, alongside more conventional efforts to document existing harms.

The other side of this finding by Smith *et al.* (6) also has the potential for being controversial. In essence, they suggest that regulators should have little concern about the use of drugs in animals for which resistant commensals are already problematic in humans. This suggestion contrasts with the traditional recommendation of permitting animal use only for those drugs that are rarely used in human medicine. As Smith *et al.* conclude, "the agricultural use of antibiotics in new resistance classes should be delayed until the period of maximum medical utility has passed."

Their conclusion could be, and doubtless will be, seen as support for the continued use of antibiotics in food animals. If a drug used to treat or promote the growth of food animals has little or no impact on human health, is beneficial to the health of the animals, and reduces the cost of food production, why not use it? However, as Smith *et al.* (6) caution, there are caveats associated with this interpretation of their findings. One is that their conclusion applies to resistance in bacteria that are transmitted among humans for which most of the human resistance can be attributed to the human use of those drugs. Their conclusion does not apply to purely zoonotic infections of humans where resistance could preclude effective treatment, like the antibiotic-resistant *Campylobacter* or *Salmonella* infections acquired from meat (10, 16). Finally, their model and analysis does not address the problem of associated linkage selection in bacterial strains or plasmids that carry multiple genes for resistance to different antibiotic classes. For example, the use of tetracycline in food animals may

have little or no effect on the utility of tetracycline for human use, because it is rarely used for the treatment of food-borne infections or of commensals acquired from food. However, animal tetracycline use could well increase the frequency of multiple antibiotic-resistance plasmids, which, in addition to tetracycline resistance, carry genes for resistance to antibiotics for which resistance in human pathogens and commensals would be more problematic. The same principles apply to multiply resistant bacterial strains, regardless of whether resistance is plasmid-borne or chromosomal.

The controversy about the contribution of agricultural antibiotic use to clinically important resistance in human medicine is fueled and sustained by the problem of obtaining direct, quantitative information about the magnitude and nature of that contribution. The article by Smith *et al.* (6) offers an alternative way to evaluate this contribution through the use of mathematical models of the processes involved in the spread of resistance from food animals to humans. As Smith *et al.* emphasize, their model should not be taken as a precise risk assessment or a quantitative prediction but rather as an illustration of possible mechanisms. Nonetheless, they have taken pains to make assumptions that are consistent with what is known and that make biological sense. Further investigations are certainly required to document and measure many of these biological processes. More immediately, however, Smith *et al.* make the case that restrictions of antibiotic use in animals cannot always wait for incontrovertible evidence of harm and that, indeed, such delays may result in a lost opportunity to preserve the usefulness of classes of antibiotics in human medicine. They also raise the point that under some conditions, there may be little or no harm to human health if the antibiotics used for animal use are those for which resistance is already common in bacteria that are commensal inhabitants and opportunistic pathogens of humans.

Note Added in Proof. Since this commentary was written, market forces have begun to move the debate over antibiotic use in agriculture in new ways. It was recently reported that several major poultry producers had decided to stop using fluoroquinolones to treat chickens (17). Most recently, Russia banned imports of chicken from the U.S., citing concern about antibiotic residues in the meat (18).

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