

Antibiotic use in livestock production in the USA

Antibiotics are arguably the most important medical technology ever developed, and save thousands of human lives every day. But their biggest consumers in the USA are no longer people, but livestock and poultry. And animals are not getting antibiotics just when they are sick; many of them are fed the drugs to get fat.

To some, this practice is the basis for a healthy animal population, efficient food production, and cheap meat. For others, it is propelling the evolution of infectious microbes that are no longer susceptible to antibiotics, and compromising the effectiveness of medical treatment for everything from strep throat to bubonic plague. Lost in the cacophony are the regulatory agencies who are responsible for defining the judicious use of antibiotics and balancing the wellbeing of food producers and public health, but who seem without the determination to act.

A few facts are indisputable. The USA is awash in antibiotics, and livestock and poultry are the biggest consumers, taking more than 13 million kg of antibiotics in 2010—four times more than people—as reported by the US Food and Drug Administration (FDA). The evolutionary processes that are set in motion are also well understood; antibiotics kill susceptible bacteria and thus select for new resistant strains. Finally, the toll that resistant pathogens have on human health is increasingly clear. Patients with multidrug-resistant infections have become a permanent fixture in the modern hospital; they are quarantined from others, reliant on second-line or third-line treatments that can be costly or hazardous, and run a high risk of complications. Annually, tens of thousands of deaths in the USA are attributed to drug-resistant pathogens.

But if there is agreement about these facts, there is little consensus about how to connect them.

Advocates for a reduction of use of antibiotics in livestock have been particularly critical of so-called growth promotion—the non-therapeutic application of antibiotics to manipulate the commensal bacteria in an animal's digestive tract and accelerate weight-gain. The process helps food producers to prepare animals quickly for slaughter, reducing the cost of meat, but is not essential for animal health. Moreover, the subtherapeutic doses used might exert evolutionary pressure on microbes without eliminating them, thereby accelerating the development of resistance.

The Animal Health Institute—a trade association for companies that make medicines for animals and a frequent defender of antibiotic use in food animal production—disputes these criticisms. Richard Carnevale, their Vice President for Regulatory and Scientific Affairs, says that their member companies report that only 13% of the antibiotics they sell are used for growth promotion, and these drugs are older and therefore less essential to health care than are other antibiotics. “From a safety standpoint”, he says, “if I were the head of FDA, I wouldn't see any particular safety concern to restrict those products for growth.”

Admittedly, establishing the relation between antibiotic use in animals and resistance in human pathogens has proved complicated. Even Denmark's 2000 ban on the use of antibiotics for growth promotion, which created a natural experiment for measuring the effect of the policy, has had mixed results. There, the decline in overall use of antibiotics was moderated by a rise in therapeutic use, and while the prevalence of resistant bacteria in food animals and meat products declined, no measurable effect on rates of resistant infection in the human population was recorded. The European Union as a whole banned

antibiotic use for growth promotion in 2006.

Mary Torrence, National Program Leader for Food Safety and Health at the US Department of Agriculture (USDA), is not surprised that causality has been hard to establish. “The problem is that it's such a long production chain that you literally can't start with one point and follow it all the way through”, she told *TLID*. Researchers focus on every step individually—from the administration of antibiotics to animals, to the emergence of resistant pathogens, to their transmission to people—but each poses its own challenges. Accessing farms to identify resistant bacteria is particularly difficult for investigators, because animal producers have little to gain and much to lose from divulging such information.

One of the few researchers to collect data on-site is Tara Smith, who “grew up downwind from a pig farm” and is now an assistant professor of epidemiology at the University of Iowa. Her present work examines variation in the prevalence of methicillin-resistant *Staphylococcus aureus* on farms with different protocols for antibiotic use. She explains that farms have strong incentives to remain ignorant of the risks that resistant infections pose to their workers. “If they know

For more on FDA data from 2010 see <http://www.fda.gov/downloads/ForIndustry/UserFees/AnimalDrugUserFeeActADUFA/UCM277657.pdf>



Antibiotics are given to livestock to help them gain weight quickly



Some fear contamination of food with drug-resistant bacteria

For more on **Price and colleagues' work on *S aureus*** CC398 see <http://mbio.asm.org/content/3/1/e00305-11>

For more on **FDA data from 2009** see <http://www.fda.gov/downloads/ForIndustry/UserFees/AnimalDrugUserFeeActADUFA/UCM231851.pdf>

about something, then it's just like any other exposure", she says. "So it becomes a legal issue for them if they know about it—how do they inform their workers, and how do they protect them?"

Her work, and that of other researchers, seems to raise as many questions as it answers. Why antibiotic-resistant bacteria emerge at some farms but not others, by what routes pathogens travel from animals to food products, and at what rate animal-derived bacteria cause human disease are all still poorly understood. Yet a growing number of leaders say the evidence is sufficient to merit further regulatory action. Thomas Frieden, director of the Centers for Disease Control and Prevention, testified to Congress in July, 2010, that the link was clear. 2 months later, the Infectious Diseases Society of America announced that "the use of antibiotics in animal agriculture poses an important threat to human health that warrants urgent action".

The point of contention has ultimately proven to be just what constitutes sufficient proof. It is difficult to observe the emergence of antibiotic resistance and still more challenging to disentangle the effect of antibiotic use in food animals from applications in health care. Ron Phillips, Vice President for Legislative and Public Affairs for the Animal Health Institute, says that

if resistant bacteria are emerging in animal production and causing illness in people, we should be able to watch the process happen; that we cannot readily do so disproves its existence. "If there is a theoretical risk that it is actually happening, it is so minuscule as to be unmeasurable." Tara Smith disagrees: "I think they want more proof than is ever going to be possible from scientists."

Additional evidence could be provided by a national system that carefully monitors where and for what purposes antibiotics are given to animals, and the correspondent evolution of resistant microbes. But the National Antimicrobial Resistance Monitoring System, with a 2011 budget of just US\$7.8 million for all 50 states, does not sample live animals on the farm and does not track the microbes most relevant to human health, such as *S aureus* and the extraintestinal pathogen *Escherichia coli*.

In September, 2010, a report by the US Government Accountability Office established that the FDA and USDA had not implemented a joint plan for the collection of data that had been recommended 7 years earlier, and the information they do gather does not include essential details, such as the species of animal receiving the drugs and the purpose of use. Lance Price at the Translational Genomics Research Institute says, "this is a major threat to public health and we don't have the tools or access necessary to even quantitatively evaluate it." Price and colleagues have identified a strain of *S aureus* that seems to have acquired resistance after passing from people to livestock.

Without up-to-date data for the effects of antibiotics in food animals, regulation has been defined by the status quo. The FDA has expressed concerns about the use of medically important antimicrobials for growth promotion, their availability over the counter without veterinary supervision, and their application

through feed or water without rigorous dose control, but has asked only for voluntary action from producers to reduce injudicious use. Effectively, producers are regulating themselves.

There is little evidence that the FDA's strategy is having much effect. Between 2009 and 2010—the first period in which any measure of total antibiotic use in animals was reported—overall consumption increased by 1.3%. Richard Isaacson, a professor of veterinary science at the University of Minnesota who has had frequent contact with employees of the FDA, believes that the agency is well meaning but under-resourced. "The problem with the FDA is that it takes almost literally an act of Congress to get something out of them", he says.

Indeed, legislation offers the greatest promise of change. Congresswoman Louise Slaughter—herself a former microbiologist—introduced the Preservation of Antibiotics for Medical Treatment Act in March, 2009, which calls for the use of antibiotics only in sick animals with veterinary supervision. The bill was reintroduced in the 112th Congress and has acquired 78 cosponsors so far, but remains in committee.

Nevertheless, restriction of non-therapeutic use of antibiotics in food animal production will only partly reduce their overall use in animals, so new vaccines and further application of preventive medicine will be necessary. And the bill does nothing to alter use of antibiotics in people, which is also an important driver of antibiotic resistance.

The imperative for action, even one step at a time, continues to animate individuals who are studying the issue. Lance Price explains his passion as one of self-preservation: "I don't have kids but if I have them, I'd sure like them to live in a world where antibiotics still work."

Ted Alcorn