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Agricultural livestock, such as these factory-farmed pigs, consume most of the antibiotics around the world, reducing the effectiveness of the drugs.

PUBLIC HEALTH

The politics of antibiotics

Policy-makers and medical experts need to think globally if we are to prevent an antibiotic ‘tragedy of the commons’.

BY MEGAN CULLY

In the early nineteenth century, demand for wool in England skyrocketed, and shepherds expanded their flocks accordingly. At that time, many sheep grazed on communal fields known as the commons. But the large flocks overgrazed the commons, so there was not enough food for other sheep or for cows, which became small and stunted. Inevitably, all the users of the commons suffered because there simply wasn't enough grass to go around. This ‘tragedy of the commons’ is a classic example of how individuals — acting rationally and according to self-interest — can damage or destroy communal property. The idea is often used to frame environmental issues, but it also has resonance for bacterial resistance. Individuals who overuse antibiotics are like the shepherds with large flocks, and the resulting tragedy is the rise of resistance to antibiotics.

Repeated exposure of microorganisms to antimicrobial agents — in humans, animals or the environment — increases the selection pressure for antibiotic resistance. In many

developed nations, livestock consume an estimated 50–80% of antibiotics. Humans consume most of the rest, with crops, pets and aquaculture collectively accounting for about 5%.

To curtail the antibiotics tragedy, a wide range of people and governments must make changes. Antibiotics must be used wisely and sparingly, and farmers, physicians and the general public must all recognize the importance of this valuable resource.

PUTTING MEAT ON THE BONES

Antibiotics have many uses in livestock. They are used to treat active infections, prophylactically to prevent infections, or even as growth promoters. It was shown in the 1940s that treating pigs and chickens with broad-spectrum antibiotics increased their size and the amount of meat produced. Antibiotics then became widely used as growth promoters, despite evidence as early as 1951 of antibiotic resistance in farm animals. In countries that still allow this type of use, including the United States, more than half of the antibiotics given to animals are for the purpose of increasing growth.

The use of antibiotics as growth promoters is most common in pigs. China produces almost 30% of the world's pork, and its farmers use four times more antibiotics than their US counterparts to produce the same amount of meat. Yong-Guan Zhu from the Institute of Urban Environment in Xiamen, China, has found that antibiotic resistance genes are enriched by up to 28,000-fold in manure and soil on Chinese pig farms¹. These antibiotic resistance genes are easily transferred from bacteria that infect animals to those that infect humans. Zhu fears that overusing antibiotics in livestock could make a large contribution to antibiotic resistance. “We are increasingly developing good sewage treatment plants [for human waste] and they help mitigate the problem,” says Zhu. “But the animal industry is less developed in coping with manure and waste water” (see ‘Detection drives defence’, page S14). Indeed, Stuart B. Levy, president of the Alliance for the Prudent Use of Antibiotics, a US organization that works to decrease antibiotic misuse, says that “some of the more unusual [mechanisms of resistance] have emerged among the Chinese.”

Changes have already been made in Denmark. In 1995, the Danish minister for agriculture and fishing banned avoparcin — one of the 11 antibiotics used for growth promotion — because it was seen to increase antibiotic resistance. Where the Danes led, others followed, and the use of antibiotics for growth promotion was banned entirely in the European Union (EU) in 2000. The use of antibiotics in Denmark has fallen by half since the early 1990s, despite an increase of more than 60% in the number of pigs. The use of antibiotics in animals still varies widely among EU members, however, with Nordic and Baltic states using about 10% of that used by Spain and Italy for a given amount of meat² (see ‘EU countries cutting back on antibiotics in farm animals’).

“Originally, everybody in Denmark expected that this would have a negative influence on Danish pig production,” explains Frank Aarestrup, a microbiologist at the Technical University of Denmark in Copenhagen who was instrumental in reducing the country’s use of antibiotics. But the high productivity achieved in the early 1990s continued when antibiotics were banned³ — and resistance to many of the 11 banned antibiotics more than halved in bacteria obtained from animals and humans.

The United States, where antibiotics are still widely used as growth promoters, uses about 1.5 times as many antibiotics as Spain, one of the heaviest European users. In December 2013, the US Food and Drug Administration encouraged the agricultural industry to stop using antibiotics as growth promoters, but Levy doesn’t expect such a light touch to have much effect. He thinks that outlawing these drugs for growth promotion is inevitable, but he accepts it will take time. In Europe, it was possible to simply outlaw the use of antibiotics as growth promoters. “In the United States, you’re going to have a recommendation that will probably

have to go through a judge. It’s a whole different process — much lengthier and more expensive and time-consuming,” he explains.

THE RIGHT PRESCRIPTION

Antibiotics use in humans also varies by region. “The average Greek or Frenchman consumes about three times as much antibiotics as the average Dutchman or Swede,” says David Livermore, a microbiologist at the University of East Anglia in Norwich, UK, who leads on antibiotic resistance at Public Health England (PHE), an executive agency of the UK Department of Health. The Department of Health’s five-year strategy outlined seven key areas to address antibiotic resistance; PHE is charged with improving surveillance, optimizing prescribing practices, and educating doctors and the public about the risks of antibiotic misuse.

Anthony Kessel, director of strategy at PHE, was particularly concerned by a 2011 survey of prescribing practices at English hospitals, in which meropenem — a drug that can kill a broad range of bacteria — was the ninth most commonly prescribed antibiotic. Such broad-spectrum antibiotics are exceptionally useful because they can treat so many different types of infection. But their overuse could leave physicians with no useful drugs to target bacteria with multidrug resistance. “These drugs should really be held for use as a last resort, when everything else has failed,” says Kessel.

Many patients, particularly children with sore throats in the United States, are given antibiotics they don’t need. Viruses cause about 90% of sore throats — and antibiotics don’t kill viruses. Levy thinks it is possible to cut US community-based antibiotic use by up to 50% by identifying which sore throats are caused by bacteria. The key to this is better diagnostics.

“We must also get better at optimizing the duration of antibiotic treatment,” says

Livermore. Courses of antibiotics could be tailored to individual patients, particularly in hospitals. Livermore thinks that some courses of antibiotics, which often last 7–14 days in the United States, could be shortened by 2–3 days if biological markers were used to determine whether an infection is still present.

For physicians, handing out prescriptions is easier than explaining antibiotic resistance during a five-minute consultation. But educating doctors and parents with sick kids on the risks of overusing antibiotics might just spark the enlightened self-interest shown by Danish farmers in the 1990s, who voluntarily gave up using all 11 of their antibiotics long before being mandated to do so.

WORKING TOGETHER

Education is also a central theme of Antibiotic Action, a UK-based organization headed by Laura Piddock. She and her colleagues have worked with UK and EU parliamentarians and the UK Department of Health, and the organization’s ‘antibiotic action champions’ around the world are educating people about the importance of tackling antibiotic resistance. One of their key target groups is the public. Exposure to chemicals such as triclosan, the active ingredient in many antimicrobial cleaning agents, can select for mutations in genes that encode bacterial efflux pumps, which can eject antibiotics. Antibiotic Action targets women’s magazines and lifestyle TV programmes to educate users of antimicrobial products about their potential harm. “Soap and water is enough,” says Piddock.

There are many diverse approaches to reducing the use of antibiotics. For example, Aidan Hollis, an economist at the University of Calgary in Canada, suggests imposing a fee for the non-human use of antibiotics⁴. He says this would deter the low-value use of antibiotics, would be easy to administer, and would be easy to replicate in other countries. The fees would also generate revenue that could help to further our understanding of antibiotic resistance, discover new antibiotics, and educate more stakeholders.

Farmers, physicians and patients need to recognize the value of antibiotics and protect this vulnerable resource. In the absence of enlightened self-interest, more effective policies are required because the current ones are insufficient. A global, multidisciplinary effort is needed to slow the development of antibiotic resistance — it will take more than one shepherd to prevent our commons from being overgrazed. ■

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1. Zhu, Y.-G. *et al. Proc. Natl Acad. Sci. USA* **110**, 3435–3440 (2013).
2. European Medicines Agency. *Sales of Veterinary Antimicrobial Agents in 25 EU/EEA Countries in 2011* (2013).
3. Aarestrup, F. M. *et al. Am. J. Vet. Res.* **71**, 726–733 (2010).
4. Holis, A. & Ahmed, Z. *N. Engl. J. Med.* **369**, 2474–2476 (2013).

EU COUNTRIES CUTTING BACK ON ANTIBIOTICS IN FARM ANIMALS

The amount of antibiotics used — adjusted here for different population sizes — varies widely from one EU country to another. Most importantly, every country on this list, except Spain, reduced its agricultural use of antibiotics from 2010 to 2011.

