35 years of resistance

The misuse of antibiotics is not only a medical problem, but also a major agricultural one. The US Food and Drug Administration has recently shifted its focus to voluntary oversight.

In April 2012 the US Food and Drug Administration (FDA) published its long-awaited guidelines on the judicious use of medically important antibiotics in agriculture. The guidelines call on drug companies, veterinarians, farmers and food producers alike to voluntarily change their habits in order to help preserve the clinical utility of antibiotics.

The use of antibiotics in the production of livestock and poultry for non-medical purposes has been a widespread practice for more than 50 years. In the late 1940s and early 1950s, very soon after the first antibiotics became available commercially, it was discovered that oral administration of antibiotics at subtherapeutic levels allowed animals to extract more energy from food and gain weight more quickly. As antibiotic resistance came to prominence in the clinic, campaigners for the more judicious use of antibiotics did not focus solely on medical usage but also turned their attention to agricultural use. That such use can promote the development and selection of resistant bacteria is well documented, and there is evidence that resistance determinants can transfer from animals to humans and vice versa. In an interesting recent example, a whole-genome sequencing study[1] revealed that a livestock-associated methicillin-resistant *Staphylococcus aureus* (MRSA) clone, CC398, which causes infections in individuals who have close contact with pigs, actually originated as a methicillin-sensitive clone in humans, and the genetic cassette that confers resistance to methicillin was acquired in pigs, presumably in response to antibiotic use.

In the European Union (EU), the overuse of prescribed antibiotics in medicine is still a major problem, and the inappropriate use of antibiotics in agriculture has in fact been easier to tackle. In 1986 Sweden banned the use of antibiotics as growth promoters. Denmark banned the use of avoparcin in 1995, and this was extended to the EU as a whole in 1997. Four more antibiotics belonging to classes that were in clinical use were banned in 1999. Finally, on 1 January 2006 a comprehensive ban on the use of all antibiotics for growth promotion was implemented across the EU. The prophylactic use of antibiotics — that is, using antibiotics on a herd- or flock-wide basis to prevent, rather than treat, infection — is still permitted, but there are signs that the political tide could be turning against this practice, and in October 2011, in a statement on the public health threat of antimicrobial resistance, the European Parliament called for the practice to cease.

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The situation in Europe is in stark contrast to that in the United States. In 1977 the FDA began a process which could have resulted in a similar ban to that seen in the EU, by issuing notice of their intention to hold hearings into the withdrawal of approval for the use of penicillin and tetracycline in animals. However, these hearings never took place, and in December 2011 the agency announced that these notices had been formally withdrawn. Instead, the focus has shifted almost entirely towards voluntary regulation. The new guidelines for industry establish “the framework for phasing out production uses of antimicrobials that are important in treating humans and phasing in veterinary consultation or oversight of the remaining therapeutic uses of such drugs”. These guidelines are accompanied by two other draft publications, one recommending that drug companies voluntarily change their product labels to avoid mentioning non-medical uses and one proposing veterinarian oversight for the use of drugs in animal feed. Defending the switch to voluntary control, FDA Associate Commissioner for Foods Michael Taylor said that instigating a voluntary oversight programme would produce benefits much faster than going through the protracted legal process that is required to implement a full ban. In an interesting development, the legality of the FDA’s decision not to hold the hearings has been challenged by campaign groups, and a federal judge recently found in the campaigners’ favour, ordering the FDA to hold the hearings in order to allow drug companies the chance to prove that such use of antibiotics is safe.

Fortunately, one important piece of legislation did make it through, and on 5 April 2012 the FDA enacted tougher rules on the use of cephalosporins, meaning that only those that are specifically approved for use in food-producing animals can be used in animals and then only to treat specific infections. Given the current crisis regarding antibiotic resistance, however, it is clear that this is not enough.

1. Price, L. B. *et al. mBio* **3**, e00305-11 (2012).

FURTHER INFORMATION

FDA’s April 2012 guidelines: http://www.fda.gov/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/ucm216939.htm

EU’s October 2011 statement: http://www.europarl.europa.eu/sides/getDoc.do?pubRef=-//EP//TEXT+TA+P7-TA-2011-0473+0+DOC+XML+V0//EN

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