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HEAD TO HEAD

Does adding routine antibiotics to animal feed pose a serious risk to human health?

As fears rise over resistance, some countries have banned routine use of antibiotics in animal feed. **David Wallinga** says a ban is possible without damaging food productivity, but **David G S Burch** argues that the drugs used in agriculture are not those causing problems with resistance in humans

David Wallinga *physician member of steering committee*[1], David G S Burch *veterinarian*[2]

[1]Keep Antibiotics Working: the Campaign to End Antibiotic Overuse in Animal Agriculture, 305 Brimhall Street, St Paul, MN 55105, USA; [2]Octagon Services, Old Windsor, Berkshire SL4 2NR, UK

Yes—David Wallinga

You cannot dispute the warning of England's chief medical officer, Sally Davies, that antibiotic resistance is one of modern health's greatest threats. Also beyond dispute is her analysis of its causes—the lack of new drugs combined with massive overuse of existing antibiotics. What physicians and policy makers generally overlook, however, is the critical role played by the ongoing overuse of antibiotics in livestock and poultry production. Enforceable measures to reduce this overuse must be core to any effort to avert the coming catastrophe. Because meat production is global in nature, these measures must be implemented nationally and supranationally.

Cost of resistance

Resistant infections generally cause more morbidity, mortality, and longer periods in hospital. In the United States alone, associated treatment costs add as much as $26bn (£17bn; €20bn) to the nation's annual hospital bill; in 2012 dollars, the figure could be nearly $35bn, closer to $70bn if lost work and other societal costs are included.[1 2]

It will get worse. Ten times more cases of meticillin resistant *Staphylococcus aureus* occurred in US children's hospitals in 2008 than a decade earlier.[3] From 2000 to 2009, admissions to hospital associated with *Clostridium difficile* doubled to 336 000,[4] while deaths have tripled. Infections by deadly extended spectrum β-lactamase producing Enterobacteriaceae (especially Escherichia coli) are on the rise, in hospital and in communities.[5] The World Health Organization states that bacteria – including antimicrobial resistant bacteria—commonly transferring from food animals to people comprise Salmonella, Campylobacter, *E coli,* and *Enterococcus* species. Emerging evidence shows that *S aureas*, including MRSA and *C difficile,* "also occur in food animals [those we eat] and can later be found in food products and environments shared with humans."[6]

Interest in creating a pipeline of new antibiotics is understandable. But we cannot be sure that drug companies will succeed, regardless of the size of the financial incentives extended to them. Even if they do, some bacteria are likely to acquire resistance to the new drugs in a fraction of the time spent developing them. Meanwhile, how affordable will these new patented drugs be?

Ecological challenge

An ecological approach frames the problem of antibiotic resistance differently. Like Darwin, an ecologist asks what characteristics of the microbial ecosystem drive bacteria to evolve, acquire, and then expend the fitness cost to retain resistance genes in the first place. The answer is the selection pressure provided by our enormous use of antibiotics. This use creates environmental reservoirs of resistance genes (other genetic "determinants" of resistance, like plasmids) and resistant bacteria. These reservoirs now exist throughout the bacterial ecosystem: in the gut flora of human and food animals; in sewage plants, rivers, and farms; as well as in households and hospitals. By itself the development and use of new antibiotics will only add to this selection pressure. To decrease that pressure, overall reductions in antibiotic use—which is unpopular with drug companies—should come first.

That is where antibiotic overuse in animal agriculture becomes relevant. Data for drugs sold in the US in 2009-11, collected by the US Food and Drug Administration, show that antimicrobials added to animal feed or drinking water comprise 72% of all US sales of antimicrobials, over 13 000 tonnes a year.[7] Most, though not all, antimicrobials routinely fed to US animals are medically important, including penicillins, tetracyclines, aminoglycosides, streptogramins, macrolides, and sulfas.

These are not single injections for sick animals. They are additives in feed given routinely, without a prescription, at lower than therapeutic concentrations, for purposes such as growth

Correspondence to: D Wallinga dwallinga@gmail.com, D G S Burch d.burch@octagon-services.co.uk

promotion and controlling disease in otherwise healthy animals being raised in crowded and often unhygienic conditions that can promote disease.

The US is not exceptional. Frank Aarestrup, head of the World Health Organization's collaborating centre for antimicrobial resistance in foodborne pathogens and of Denmark's National Food Institute, found that before Denmark phased out antibiotics for growth promotion, which it completed in 2000, about two thirds of antimicrobial use in pork and 90% in poultry production was for promoting growth and most of these were human antibiotics.[8]

Selection for resistant bacteria can occur at antibiotic concentrations hundreds of times lower than those previously thought[9]; the lower concentrations of antibiotics put into animal feed compared with injections for sick animals therefore offer little basis for complacency. New research also indicates that antibiotics in feed can spur the spread of resistance by promoting new genetic mutations[10] as well as by promoting the transfer among gut bacteria of resistance genes (including, potentially, antibiotic resistance genes) through phages.[11] Transfer of resistance between pathogenic and commensal bacteria, Gram negative and Gram positive bacteria species, and between bacteria in farm and human settings have all been observed, not surprisingly. All inhabit the same microbial ecosystem.

An essential and typically overlooked point is that antibiotic resistance, often including resistance to a dozen or more antimicrobials of different classes, is often physically linked on single strands of DNA. The physical linkage means that cross selection can and does occur. In other words, exposure to just one of the antimicrobial agents represented on that genetic "cassette" can provide the selection pressure for a previously susceptible bacteria to acquire resistance to all the antimicrobials physically linked on that cassette. The fact of cross selection means that regulatory agencies' typical approach of assessing the risk of single bug-drug combinations is at odds with the actual threat of resistance that exists in the microbial ecosystem.

Routine antibiotics are not necessary

Contrary to claims by some in the livestock and drug industries, routine antibiotics are not necessary for animal health. Pasture based production was the norm before antibiotics. Industrial style meat production, in which animals are confined in close quarters and fattened on soy and maize based feeds, also is possible without routine antibiotics, as Denmark has shown. Writing last year in *Nature*, Aarestrup compared Denmark, where antibiotic use is now 50 mg/kg of meat produced, with the US, where it is 300 mg/kg.[8] Denmark has reduced antimicrobial use in livestock production by 60% while increasing pork production by half since 1994.

Almost every European and North American public health authority agrees: routine antibiotic use in animal food production likely worsens the epidemic of resistance. Hundreds of studies, recently summarised, comprise the ever growing body of evidence.[12] Less certain is the political will to act on that information.

No—David G S Burch

When antibiotics are used, whether in humans or animals, there is a risk of selection for resistance. This applies not only to the target bacteria but also to commensal bacteria such as *Escherichia coli* and *Enterococcus* species that exist in the gut and may also be exposed to the antibiotic. Resistant infections have become increasingly problematic in hospitals and care homes, hence the concern about the extent of antibiotic use. However, adding antimicrobial products to the feed of animals in the European Union is unlikely to affect development of critical drug resistance in humans and pose a serious risk to human health.

How resistance develops

Treatment with oral antibiotics exposes the gut microflora to the drug and even some injectable products are excreted through bile into the gut. The drugs may kill susceptible bacteria and leave resistant ones, or resistant mutants may develop through a natural competitive response, with genes for resistance then passed from one bacterium to another, often by plasmids. Resistant strains are therefore just as likely to occur from human treatment as from adding an antimicrobial substance to the feed of an animal.

Veterinary medicine often involves treating large numbers of animals. Medicated feed is a common approach in the United Kingdom and other countries such as the US, especially in pigs, but less so in poultry where water medication is often preferred. More than half of antimicrobial use in the UK is in feed.[13] Some countries want to reduce antibiotic use in animals because of fears about resistance, and the Netherlands has stopped the routine use of these drugs in feed. The main concerns in the Netherlands were an increase in meticillin resistant *Staphylococcus aureus* (MRSA), which had spread throughout the European Union pig herd, but not in the UK; increasing identification of extended spectrum β-lactamase producing bacteria, especially in poultry; and increasing fluoroquinolone resistance in *E coli*, again, especially in poultry.[14]

Different antibiotics

So was use of antibiotics in feed associated with this increased resistance? It was not. No meticillin or related products (which directly select for MRSA), third or fourth generation cephalosporins (which select for extended spectrum β-lactamase producing bacteria), or fluoroquinolones are approved for use in feed in the EU. In the UK the antibiotics licensed for use in feed under veterinary prescription only are mainly older classes such as tetracyclines, macrolides (tylosin, tilmicosin, and tylvalosin), lincosamides (lincomycin), pleuromutilins (tiamulin, valnemulin), diaminopyrimidine-sulfonamide combinations (trimethoprim-sulfadiazine), β-lactams (penicillin V, amoxicillin), aminoglycoside-aminocyclitols (neomycin, apramycin, and spectinomycin), and amphenicols (florfenicol).

Since the complete ban of antibiotic growth promoters in the EU, completed in 2006, the glycopeptide, avoparcin (human use: vancomycin, teicoplanin) and the streptogramin, virginiamycin (human use: quinupristin, dalfopristin) are no longer used in feed, although virginiamycin is still used in the US. Oxazolidinones (linezolid), carbapenems (meropenem, imipenem), and glycylcyclines (tigecycline) are not used at all in feed or licensed for veterinary use. A current controversy is colistin, which is approved for use in feed in some EU countries but not in the UK and is being considered for use in humans as a last resort, despite its toxicity.

Low risk of transmission to humans

How bacteria that might carry resistance genes are transmitted to humans must be considered. Farmers and workers in close contact with animals are likely to be exposed to infections from animals. The transmission of MRSA from infected pigs to farmers is common,[15] but transmission to the general public is rare, reported at 0.003% of the population in Denmark.[16]

The main potential route of transmission to the public is through contaminated food products. Zoonotic infections, such as *Salmonella enterica* Enteritidis has been shown to be transmitted through eggs and poultry meat. The reported incidence of *S* Enteritidis infection in the EU fell by 41% between 2006 and 2009 because of the vaccination of laying and breeder flocks.[17] Campylobacter is still a major contaminant of chicken carcasses, and the EU needs to tackle this. Pig meat and beef seem to be very low campylobacter carriers in comparison, but they are associated with *S* Typhimurium, with reported cases affecting 0.0045% of the UK human population.[18] It is difficult to quantify *Escherichia coli* and enterococci carriage and spread by food to humans, but if campylobacter and salmonella are used as models, their contamination rate and survival after consumption are also likely to be relatively low. If the meat is cooked properly and there is good hygiene in the kitchen, the risk is extremely low—almost zero.

Environmental transmission is another possible route, through faecal and slurry spreading on fields, but normal mains water processing seems to be highly effective in managing this risk. Regulatory authorities assess the environmental risk of manure and the safety of antimicrobial residues in edible tissues before use is approved, unlike in human medicine.

Given that the critical antimicrobials in human medicine are not used in animal feed, that regulatory authorities conduct thorough assessments of the risk of resistance from use of antimicrobial substances, and that the environmental effect and the effects of residues in edible tissues are also assessed, it is highly unlikely that adding antibiotics to feed poses a serious risk to humans, especially compared with the extensive use of antibiotics directly in humans.

Competing interests: The authors have read the BMJ Group policy on declaration of interests and declare the following interests: DW works as an advocate for public health and founded Healthy Food Action, a network of health professionals voicing the need for healthier food and agriculture. DGSB runs a consultancy company for the animal health and pharmaceutical industries and has worked for many companies. He has been involved in successfully registering two veterinary medicated feed premixes and oral powders including pleuromutilin and macrolide antibiotics in the European Union's centralised regulatory system through the European Medicines Agency (EMA). He has worked on registration of several other antimicrobial substances, primarily through writing expert efficacy reports that review the pharmacology, pharmacodynamics, and clinical efficacy in artificial challenge trials and field trials but also benefit-risk assessments for their safety both in the target species of animal and humans.

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