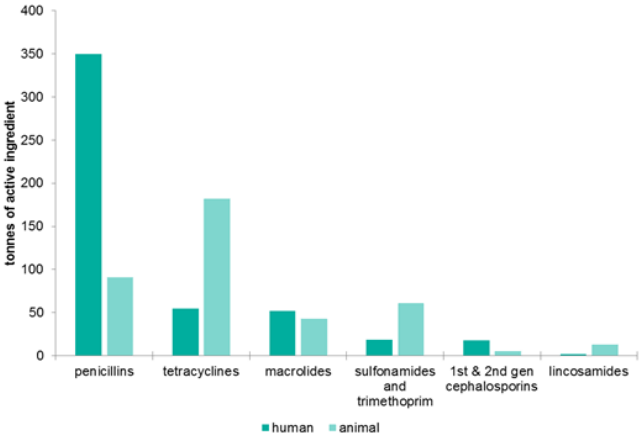
Medicated Feed, Antibiotics and Global Concern

PEER REVIEWED

For a physician, scientist and advocate of a 'one health' policy for both humans and animals, all medicines must be used judiciously. Physicians in training within the UK are receiving guidance on best prescribing practice, especially the use of antibiotics in primary care. Veterinarians are similarly charged with a responsible prescribing policy, and medicines cannot be added to animal feed without the written authorisation of a veterinary surgeon. Stringent regulations apply to the medication of feed[1] with correct dosing and mixing to avoid carry-over of a medicated feed to a batch o non-target feed. This is where the prescription of a medicine for a group of animals differs significantly from the more usual prescribing practice in human bacterial infections. Very rarely in human medicine is the whole local community treated for disease or prophylaxis. Most humans do not live in very close proximity, (perhaps only in very large family groups in some communities, or nursing homes and university residences), but farm animals very commonly live in herds or flocks and will have close contact with their fellows, both day and night. Such close contact may be less in free-range animals but this is often the exception in most developed countries including the UK.

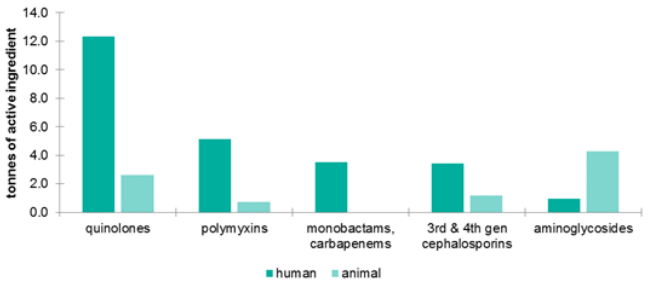
Treating the whole herd can therefore make welfare, economic and efficiency sense, and if one animal is unwell in a herd situation and the disease has been diagnosed as infectious, then treating the whole group may be the best course of action and the veterinarian will advise. The problem here is that the best treatment for the sick animal may be an antibiotic and treating the whole herd will significantly increase the use of that antibiotic, perhaps setting the scene for emergence of antimicrobial resistance. This practice is usually called metaphylaxis and there may be strategies for avoiding this practice (metaphylaxis is defined as the treatment of a group of animals after the diagnosis of infection and/or clinical disease in part of the group, with the aim of preventing the spread of infectious disease to animals in close contact who are at considerable risk and may already be sub-clinically infected), but this may involve much more accurate and faster methods of diagnosis of an animal in a sub-clinical phase of infection. This practice, though, would ensure that only the infected, but presently well animals have the benefit of treatment and thereby reduce the more widespread use of antimicrobials. Such sub-clinical testing methods do exist but they often require validated individual animal laboratory tests where there is little time for decision-making and, presently, significant cost implications.

A brief article in the June 2016 issue of '*Commentary*', the membership magazine of the Royal College of Physicians of London[2], discusses antibiotic overuse in farming and Emma Rose of the Alliance to Save our Antibiotics and Paul Belcher, Principal EU Advisor to the Royal College argue that the medical community must call for EU-wide measures to combat the problem. They write of systemic overuse of antibiotics in farming and state that two-thirds of all antibiotics used in 26 European countries, and around 45 % of total antibiotic usage in the UK, is for animals. This was not referenced and does depend on the number and weight of animals potentially available for treatment. A 600kg cow would receive considerably more antibiotic than a 60kg human, (consider metaphylaxis), but the critical question is whether this antibiotic use has led to significant antimicrobial resistance, and if so, is there good published evidence for this. David Birch, veterinarian, in a letter published in the *Veterinary Record*[3] considers that the Prime Minister-commissioned O' Neill report[4] and government have overestimated the role that antimicrobial use in animals is having on human antimicrobial resistance in the UK, and gives good evidence for this assertion. Equally important is the difference in antibiotic class use between animals and man. In human use, 44 % of prescriptions and sales are for penicillin whereas in animals, 41 % are for tetracycline, according to the US Food and Drug Administration (FDA)[5], although penicillin is occasionally used in animal medicine (6 %), and tetracycline is used in human medicine (4 %), (FDA figures). The following bar charts taken from the UK Government 'One Health Report' of 2013[6] gives good indication of the differences in use of commonly used and critically important antibiotics in disease control.



Most frequent antibiotic groups prescribed for humans in primary and secondary care/sold for use as veterinary medicines in the UK, 2013 (Animal data are taken from data on veterinary antibiotics for all animals [livestock, companion animals and horses])[6]

Prescriptions and sales of key antibiotics used to treat serious human infections in the UK, 2013 (Animal data are taken from data on veterinary antibiotics for all animals [livestock, companion animals and horses])[6]



Some classes of antibiotic (carbapenems) are never used in food producing animals and it is illegal to do so. I take some comfort from these figures as the situation is changing responsibly in the UK from 2013 where there existed a reasonable division between human and animal use, with some antibiotic classes banned from use in animals.

The Responsible Use of Medicines in Agriculture Alliance (RUMA), welcomed Jim O'Neill's latest review on antimicrobial resistance and has set up a task force to look at developing strategies for the replacement, reduction, and refinement of antibiotic use in UK agriculture and particularly supports the report's main finding, which states that the battle to maintain the efficiency of antibiotics requires a global focus combined with local action across both human and animal medicine. Programmes of refined antibiotic use can only be properly undertaken when high-quality surveillance data is considered for specific animal species, including humans, and such data is now being collected for poultry, pigs, cattle and humans. The emerging awareness of this most serious problem is now circulating the globe, but some nations appear less able to control irresponsible use of these most precious medicines. The problem of antibiotic resistance, though, has been present since antibiotics were first discovered; this is a natural phenomenon of nature's survival arrangements and is no more than natural selection and survival of the fittest (microorganisms). All species are effectively in competition with each other and bacteria are very effective competitors, even in the most hostile of situations. What perhaps was not fully understood was the 'transference' of resistance, especially with Gram-negative bacteria, including genes coding for extended-spectrum beta-lactamases (ESBLs) and AmpC beta-lactamases, primarily of concern among members of the Enterobacteriacae (e.g. Escherichia coli, Klebsiella pneumonia, Pseudomonas aeruginosa). Epidemiologically, the pattern is of gene acquisition and clonal expansion, as these genes are located on plasmids and can be spread by lateral gene transfer within, and between, bacterial species and genera. This resistance to Gram-negative bacteria is becoming a serious problem, especially with childhood urinary tract infections with almost 80% resistance to ampicillin globally. If this trend continues there may well be a re-emergence of serious bacterial renal disease and renal impairment in young adults who have never been able to properly rid themselves of recurrent urinary tract infections.

The situation is very serious but certainly not hopeless, yet some of the recent statistics make for gloomy reading, with antimicrobial-resistant infections currently claiming at least 50,000 human lives each year across Europe and the United States (US) alone, with many others dying in other areas of the world[7]. Antibiotics are (quite incredibly) still used for growth promotion, and this practice was banned in all EU countries in January 2006. In the USA, the FDA has released draft guidelines on judicious use of antimicrobials in the rearing of animals for food production. These recommendations aim to reduce the overall use of medically important antimicrobials and include veterinary oversight and consultation. Therefore a 'phasing out' of growth-promoting use is to be expected, but there is no such ban or restriction in many other countries, and this is almost unbelievable in the present situation. It is difficult to interfere with animal production and longstanding custom and practice in other jurisdictions, but this is not a situation that will allow a passive bystander attitude. The World Health Organisation (WHO) are now involved in education and advice, but enforcement is another matter in sovereign states. The only way forward may be an energetic WHO task force working with individual governments, the World Health Organisation for Animal Health (OIE) and the Food and Agriculture Organisation of the United Nations (FAO). The effort must be coordinated and the full facts of the situation understood, encouraging each countries administration to take urgent and effective action to ensure the proper and prescribed use of antibiotics only for the treatment of disease and illness. Even antibiotics that are only used in animals have been associated with resistance transfer to essential human antimicrobials, and that was found to be the case with the glycopeptide avoparcin, which was associated with the selection of vancomycin-resistant enterococci. Effective restrictive antibiotic use in some countries will be swamped by the unrestricted use in the many other countries that rely on the sale of their agricultural livestock for economic existence, and it would be a brave government indeed that imposed a ban on growth promotional use without concomitant education, subsidies and compensation. Yet it has clearly been proven that excellent husbandry and improved environmental conditions may compensate for some of the inadequacies in hygiene and the requirement for growth promoting antibiotics. However, such changes will take time in widely disbursed and isolated rural communities where custom and agricultural practice are firmly entrenched.

My view at this time, examining much of the data comparing human antimicrobial use with agricultural use is optimism for much of the western rural economy and the USA. Using either animal or human abuse as a scapegoat for bad practice is particularly unhelpful. Understanding the species data in detail, education and some restriction of use between species, combined with better and faster diagnosis of disease, will be the key to saving the efficacy of our antibiotics. Sensible

government-approved plans are already in place in the UK, but they are by their very nature globally local, with local enforcement where necessary. There has been a call for the banning of metaphylaxis but this still remains the best method of disease control in a herd or flock situation, and needs to continue in parallel with the introduction of improved disease diagnostic method development, with sponsored research for fast, accurate, on-farm diagnostic tools. There are a number of candidate methods presently being tested, and a fast non-PCR optofluidic diagnostic technique[8] looks promising, but this will depend on further field testing and cost.

There are few medical scientists with a background in both agricultural science and medicine, and I feel privileged to have had professional training in both disciplines with sympathy for all the species. My postgraduate practice has been in human medicine but I have always advised across the species sectors and recognise our interdependence for survival (although some may argue that the demise of humankind would benefit the planet and have no harmful effects on the other non-human inhabitants). We are very much dependent upon the interwoven relationship with other animals and plants, and yet often with the best of intentions, interfere with the balance of nature, occasionally causing unintended and potentially disastrous consequences. We have though, unravelled some of the wonders of nature and harnessed some of this for good. Antibiotics have always naturally existed but the observations of Alexander Fleming in 1928 and the practical application by Florey and Chain some 13 years later gave indication of the power of this antibacterial chemical; however, these substances will be rendered useless unless global action is taken without delay. The pharmaceutical industry have not developed a new class of antibiotic for years because of massive development, testing and licensing costs and the problem of unlicensed generic copies being illegally manufactured abroad. This often occurs in the Far East and Indian sub-continent, and then the product is sold on the street or Internet for quite inappropriate human disease indications, thereby rendering the bactericidal activity of the antimicrobial less and less competent because of developing resistance. Such activity may also be found in the wholesale treatment or growth promotion of animals for food, especially where regulation and inspection is not enforced. Not only does this create unfair competition for the legitimate regulated producer, but again adds to the burden of increasing resistance, some of which could be imported to the UK.

Because this is a global problem, potentially leading to a global catastrophe, the solution must rest with a global health-related organisation, and WHO is a specialised agency of the United Nations (UN) that has global influence. The action, though, must now be executive rather than advisory, and fully and energetically supported by every member of the UN, giving agents of the WHO executive power and authority. Their resources will need to be increased as will their budget, as this will require both words and action. Member states can protect the animal sector by mandating not to purchase any imported food that has not been produced in accordance with a strict antibiotic use protocol and certified as such. This will ensure that all producers are treated equally and antibiotics are only used for animal welfare and in accordance with agreed guidelines.

This will be a long-term and demanding task for WHO, but the responsibility is clear and the stakes are sky-high. None of us can just sit by and allow one of our most important and life-saving therapeutic agents to disappear and drive human and animal medicine back to the 19th century. As the UK's Chief Medical Officer, Dame Sally Davies, quite rightly said in her 2013 annual report; 'antibiotic resistance is one of the greatest threats to modern medicine and we face a future without cures for infection if antibiotics are not used responsibly'. This affects every person on the earth, whether involved in animal or human health or not, and all those with knowledge of this evolving situation have a duty to support and act. The time for allocating the blame is over, and all of us involved in healthcare must now play our part to ensure that we do not lose this most precious therapeutic gift.

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Dr Ian Brown OBE BSc(Agric) FRCP FFOM DDAM, is a clinician and scientist with a longstanding interest in the relationship between work and health and agriculture and medicine. He has spent the last 8 years of his academic and clinical life at the University of Oxford where he was previously head and director of a clinical service department and now continues as a clinical research fellow and college tutor. Dr Brown originally read agricultural biochemistry and nutrition at the University of Newcastle-upon-Tyne and then subsequently read medicine eventually becoming a specialist in occupational health medicine and toxicology. His background interest and expertise in agriculture continues and he has assisted the government as the chairman of the Pesticides Residues Committee, an office he held for more than 10 years. He now chairs the Advisory Committee on Animal Feedingstuffs and takes a particular interest in matters of the food chain, especially the use of antibiotics in feed and the possible consequences of antimicrobial resistance. Dr Brown was awarded an OBE in 2005 for services to agriculture and food safety.
Email: ian.brown@ouh.nhs.uk