Antimicrobial resistance: we need better stewardship in all sectors

Pressure is increasing for better stewardship of antibiotics in health care. Most recently, a report by the Select Committee on Science and Technology concluded that: 'All levels of the NHS must be given clear responsibilities for stewardship of antibiotics and better monitoring and reporting put in place to bear down on unnecessary use of antibiotics' (House of Commons Science and Technology Committee, 2014). The Chief Medical Officer, Professor Dame Sally Davies, continues to warn about the drastic medical consequences of antimicrobial resistance: that achievements in modern medicine, such as major surgery, organ transplantation, treatment of preterm babies and cancer chemotherapy will not be possible without access to effective treatment for bacterial infections.

The issue is likely to rise even further up the political agenda with the forthcoming publication by Public Health England of a first set of national mortality data from improved surveillance of antimicrobial resistance. The EU estimates that at least 25 000 people die in Europe each year from an antibiotic-resistant infection (European Centre for Disease Prevention and Control and European Medicines Agency, 2009). In England alone, resistant *Escherichia coli* bloodstream infections are implicated in the causation of 5000 deaths per year, and there are warnings that a large proportion of the infections may be derived from food sources (Vieira et al, 2011).

Antibiotic use in animals

Although resistance in human infections is mainly caused by human antibiotic use, this is not the entire picture. For a range of bacteria, evidence increasingly suggests that use of antibiotics in the care of farm animals contributes significantly, and for some infections it may be the main source of resistance. These allegations are supported by decades of research and are acknowledged by the World Health Organization and the European Food Safety Authority. It is estimated that over 40% of all antibiotics used in the UK are given to farm animals (UK Government Agencies, 2007). This is only an estimate, because although farm antibiotic use – as in medicine – is prescription-only, no prescription records are collected. To summarize the broad scientific consensus:

- For some bacterial infections, such as Campylobacter and Salmonella, farm antibiotic use is the principal cause of resistance in human infections
- For other infections, like *E. coli*, farm antibiotic use is likely to have contributed significantly to the human resistance problem
- The emergence of resistance to critically important antibiotics, in particular extended-spectrum beta lactamase resistance in *E. coli* and Salmonella, is a major development which has occurred in recent years. This has been driven by inappropriate use of these antibiotics in both human and veterinary medicine
- Livestock-associated strains of meticillin-resistant *Staphylococcus aureus* infecting humans are also a developing problem, resulting from the high use of certain antibiotics in farm animals. The spread of meticillin-resistant *S. aureus* in farm animals is very unwelcome, as the large reservoir of resistant bacteria could threaten the progress that has been made in reducing meticillin-resistant *S. aureus* infections in medicine.

It is vitally important that momentum building up in the health-care sector to improve antimicrobial stewardship is not undermined by delay in the farming and veterinary sectors. The Alliance to Save Our Antibiotics – an alliance of health, medical, environmental and animal welfare groups working to stop the over-use of antibiotics in animal farming – is warning of this outcome.

Need for government intervention

According to data collated by the Alliance – whose campaign is supported by Professor Sir Liam Donaldson – there has been a history of government failure to reduce farm antibiotic use. Simply banning growth promoters (achieved across Europe by 2006), but allowing routine preventative use to continue, has failed to reduce overall use of antibiotics. Penicillin and tetracycline were banned as growth promoters after the Swann Report in 1969, but since then the total veterinary use of tetracyclines has increased nearly tenfold, and that of penicillin-type antibiotics has increased nearly fivefold (Veterinary Medicines Directorate, 2013).

Antibiotic use in the British pig and poultry industry is three to five times higher than it is in Denmark, Finland, Iceland, Norway and Sweden (European Medicines Agency, 2013; House of Commons Science and Technology Committee, 2014), and those countries generally have much lower antibiotic resistance in bacteria causing food poisoning (House of Commons Science and Technology Committee, 2014).

The European Food Safety Authority says that most antibiotic-resistant Campylobacter involved in human disease are spread through food, but the two classes of antibiotics that are most important for treating human Campylobacter infection, the macrolides and the fluoroquinolones, continue to be widely overused in farming. In 2012, the total veterinary use of macrolides increased by 11% and the veterinary use of the fluoroquinolones increased by 17% (European Food Safety Authority, 2008; Veterinary Medicines Directorate, 2013).

Modern cephalosporins (3rd and 4th generation cephalosporins) and fluoroquinolones are two of the most important classes of antibiotics used in human medicine, and have been classified by the World

Health Organization as critically important in human medicine. The increasing use of these antibiotics in agriculture, in many European countries over the past decade, is widely recognized to have contributed to the emergence of a range of highly resistant bacteria in farm animals, such as extended-spectrum beta lactamase *E. coli*, extended-spectrum beta lactamase Salmonella, fluoroquinolone-resistant Campylobacter and meticillin-resistant *S. aureus*.

Statistics in the UK from the Veterinary Medicines Directorate (2013) show that, after fluoroquinolone use was cut significantly in 2000 following warnings in a report by the House of Lords Committee on Science and Technology in 1998 and a report by the Advisory Committee on the Microbiological Safety of Food in 1999, farm use of both fluoroquinolones and modern cephalosporins has increased in most years since then.

In 2009, the British Veterinary Association issued an eight-point plan for limiting the development of antibiotic resistance in farm animals (British Veterinary Association, 2009). One of its recommendations was that vets should keep the fluoroquinolones and modern cephalosporins in reserve and only use them in very limited situations. The Summary of Product Characteristics of many of these antibiotic products have also been amended to discourage overuse. Unfortunately, the government has not yet introduced more restrictive legislation, as has been done in some other countries, and use continues to rise.

In contrast, in human medicine the use of these antibiotics has fallen sharply in recent years. This has occurred in part as a result of the Health Act 2006 which introduced a requirement for all NHS trusts to have antibiotic-prescribing policies. The Act put a particular emphasis on reducing the use of certain antibiotics, including the fluoroquinolones and modern cephalosporins, which are implicated in promoting and exacerbating *Clostridium difficile* infections. The focus on better antibiotic prescribing as a means of reducing these infections was re-enforced in the Health and Social Care Act 2008.

The Alliance to Save Our Antibiotics is not the only new group which has sprung up to tackle the problem: in Germany a new organization of health-care professionals – doctors, nurses and pharmacists – has formed to challenge farm practice. Arzteinitiative gegen Massentierhaltung (www.aerzte-gegen-massentierhaltung.de) warns that in areas such as Lower Saxony, where there is a high density of intensively reared livestock, 30% of meticillin-resistant *S. aureus* in high-risk patients is transmitted from farm animals. According to the group, around 42% of thawed retail chicken and turkey carries antimicrobial-resistant bacteria. They highlight the practice of keeping over three-quarters of pigs and poultry on antibiotics routinely during their life – the approximate equivalent of 20 years of permanent medication in a human.

Conclusions

We are reaching a crisis point at which the costs to the health service of increasing antibiotic resistance are unaffordable. The difficulty of developing new antibiotics means that it has become ever more important that we exercise stewardship over the antibiotics that we have. Profligate farm antibiotic use can no longer be afforded, and must be challenged. Supporting the work of the Alliance to Save Our Antibiotics is one way of doing so. **BJHM**

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British Veterinary Association (2009) Responsible use of antimicrobials in veterinary practice: the 8-point plan. www.bva.co.uk/uploadedFiles/Content/News,_campaigns_and_policies/Policies/Medicines/BVA_Antimicrobials_Poster.PDF (accessed 10 September 2014)

European Centre for Disease Prevention and Control and European Medicines Agency (2009) The bacterial challenge: time to react - a call to narrow the gap between multidrug-resistant bacteria in the EU and the development of new antibacterial agents. www.ecdc.europa.eu/en/publications/Publications/0909_TER_The_Bacterial_Challenge_Time_to_React.pdf (accessed 10 September 2014)

European Food Safety Authority (2008) Foodborne antimicrobial resistance as a biological hazard. Scientific Opinion of the Panel on Biological Hazards, adopted on 9 July 2008. *The EFSA Journal* **765**: 1–87

European Medicines Agency (2013) Sales of veterinary antimicrobial agents in 25 EU/EEA countries in 2011. www.ema.europa.eu/docs/en_GB/document_library/Report/2013/10/WC500152311.pdf (accessed 10 September 2014)

House of Commons Science and Technology Committee (2014) Ensuring access to working antimicrobials. First Report of Session 2014–15. The Stationery Office, London (www.publications.parliament.uk/pa/cm201415/cmselect/cmsctech/509/509.pdf accessed 10 September 2014)

UK Government Agencies (2007) Overview of Antimicrobial Usage and Bacterial Resistance in Selected Human and Animal Pathogens in the UK, 2007. www.vmd.defra.gov.uk/pdf/AMR_overview07.pdf (accessed 10 September 2014))

Veterinary Medicine Directorate (2013) UK Veterinary Antibiotic Resistance and Sales Surveillance UK-VARSS 2012. www.vmd.defra.gov.uk/pdf/varss.pdf (accessed 10 September 2014)

Vieira AR, Collignon P, Aarestrup FM, McEwen SA, Hendriksen RS, Hald T, Wegener HC (2011) Association between antimicrobial resistance in Escherichia coli isolates from food animals and blood stream isolates from humans in Europe: An Ecological Study. *Foodborne Pathogens and Disease* **8**: 1295–301

KEY POINTS

- Over 40% of all antibiotics used in the UK are given to farm animals.
- A recent report from the Select Committee on Science and Technology advocated urgent action to reduce use of antibiotics in medicine, but such reduction is not yet being required from agriculture.
- Profligate farm use of antibiotics can no longer be afforded and must be challenged.