

Antimicrobial Resistance

Evidence from the Society for Applied Microbiology to the House of Commons Science and Technology Select Committee

October 2013

The Society for Applied Microbiology (SfAM) is the oldest microbiology society in the UK.

SfAM envisages a future where applied microbiology research and development is strong in the UK and beyond, and the applications of microbiology contribute significantly to all global challenges facing humanity, including infectious diseases; the changing environment; sustainability of energy, food, water, and land resources; and economic growth.

This response is in addition to SfAM's endorsement of the Society of Biology submission. SfAM is a member organization of the Society of Biology.

Q. How has antimicrobial resistance developed in the past decade?

- a. Widespread emergence of resistance to third-generation cephalosporins in both pathogens and non-pathogens, resulting in community outbreaks of *Escherichia coli* exhibiting resistance to such antibiotics, with numerous fatalities.
- b. Increasing incidence of commensal *E. coli* with such resistance in poultry in several European countries, resulting in the spread of cephalosporin-encoding resistance genes to pathogens, with fatal consequences in some cases.
- c. Emergence of resistance to carbapenem antibiotics in already multiple drug-resistant pathogenic bacteria, predominantly in countries in the Indian sub-continent, thus making infections with such strains almost untreatable.
- d. Worldwide spread of such strains as a result of international travel, resulting in untreatable infections in developed countries such as those in Europe and North America.
- e. Recent appearance of resistance to carbapenem antibiotics in *Acinetobacter* spp, *Salmonella enterica* and *E. coli* in food animals in some European countries.
- f. Emergence of extensively drug resistant tuberculosis (XDR-TB).
- g. Detection of MRSA strains with varying levels of resistance to vancomycin (from vancomycin intermediate to vancomycin resistant).
- h. Increase in essentially untreatable gonorrhoea.

Q. What are the gaps in our knowledge about antimicrobial resistance?

- a. There is a severe lack of understanding of exchange of genes in the wider environment and what drives this.

It will also be important to understand what resistance reservoir exists in normal human and animal commensal microbiota (even prior to any antibiotic exposure).

We need to know:

- What is the composition of resistance genes and/or resistant organisms in gut, skin, oral cavity etc. and how does this contribute to the emergence of resistant pathogens? How does antibiotic exposure alter this in the short and long term?
 - This could tell us the distribution of resistance genes, particularly those encoding resistance to critically-important antibiotics (CIAs), or antibiotics of last resort, in human and food animal ecosystems in non-pathogenic and pathogenic bacteria.
 - Extent of transmission of resistance genes from bacteria from humans (both pathogens and non-pathogens) to animals, and particularly animals bred for food.
 - Extent of transmission of resistance genes from bacteria from animals, particularly food production animals, to bacteria in humans.
- b. Contribution of foods imported into the country to the spread of resistant bacteria to humans.
- c. Effects of 'off-label' use of antibiotics in both human and veterinary medicine in the development and spread of resistance.
- d. Can the burden of resistance be reduced by removing the selective pressure (e.g. by reducing prescription of antibiotics or reducing use in animal foods)? This would require a large scale carefully controlled study.
- e. The potential for metal resistance, particularly silver, as used in wound dressings.
- Resistance in clinical isolates is seldom seen but exposure around silver mines and in other non-clinical settings is documented to confer resistance. We know that a number of metal resistances are co-transmitted with antibiotic resistances on plasmids/transposons (genetic material) so the use of silver as an antimicrobial treatment in many different environments has the potential to start to select for resistant strains and could indirectly drive antibiotic resistance – this requires further investigation.
 - Silver is synergistic with a number of antibiotics and therefore has the potential to be extremely useful if we can understand how to use it appropriately.

Q. Is there sufficient research and investment into new antibiotics or other treatments and methods to ensure continued protection against infection? If not, how could this be rectified?

- a. In the past, pharmaceutical companies have been prepared to invest to find formulations that are both effective antibiotics and also discourage/minimise the evolution of resistance. That isn't the case at present and there is relatively little R&D going on in this area. The reason appears to be the greater financial rewards available in developing other classes of drugs. This puts the onus on the UK government to fund antimicrobial drug development outside of the pharmaceutical companies and/or incentivise this work within the industry.
- b. It is also vital to first understand the drivers selecting for resistance, which may include as yet unknown factors. A quantitative risk assessment of the effects of different control measures in human and animal populations would provide the basis from which to develop new drugs that have the potential for greater longevity. There

will always be a degree of selection pressure and as such bacteria remain 'one step ahead' but opportunities surely exist to minimise selection pressure and slow the development of resistance.

- c. There is a recent Journal of Antimicrobial Chemotherapy article that provides detailed analysis of the proportion of total infection research spend dedicated to research into antimicrobial resistance (<http://jac.oxfordjournals.org/content/early/2013/09/13/jac.dkt349.full.pdf+html>). The paper also outlines some recommendations for future direction of R&D. In summary: despite the rapid emergence of antimicrobial resistance, the proportion of UK infection-research spend targeting this critical area remains small (3.9%; £102 million of £2.6 billion total spend). Mean annual funding ranged from £1.9 million in 1997 to £22.1 million in 2009. The study concluded that, whilst this is an encouraging indication of increased emphasis and investment in this important area of research, the UK government must continue to fund antimicrobial resistance research in a sustained, targeted manner.
- d. In October 2012 a conference entitled "Antimicrobial Resistance in Human and Veterinary Medicine – one medicine, one problem?" was held in the UK. The conclusions of the symposium, which was organised by the Royal College of Veterinary Surgeons, the Royal College of Pathologists, and the Royal College of Physicians in association with the Health Protection Agency and the Veterinary Medicines Directorate, were as follows:
- Veterinary and medical professionals must work together under the banner of 'One Health, One Medicine' to tackle antimicrobial resistance in a social context
 - The issue of acquisition, evolution and transmission of AMR is complex and involves human and domestic animal populations (both food animal species and non-food companion animal species), but also wildlife and the environment. It is important to understand how these factors interact, particularly with increasing international movement of people, food and animals.
 - In an increasingly connected world, it is evident that any measures need to tackle global use. The probability that selection for resistance will occur where antimicrobial usage is highest and least controlled, coupled with unprecedented mobility of humans, means that, whether AMR originates from animal use or human use, the threats in Britain and in Europe will often emanate from outside.

Q. What measures (including behavioural change) have been most effective in controlling the spread of resistant pathogens, and could such measures be used to control other pathogens?

- a. The continued promotion of responsible use of medicines in agriculture, as carried out by the responsible use of Medicines in Agriculture Alliance (RUMA) in the UK, the European Platform for the Responsible use of Medicines in Agriculture (EPRUMA) and the OIE (World Organisation for Animal Health).
- b. In food animals, the withdrawal of antibiotics as growth promoters in the EU has been a highly effective measure in controlling the appearance and spread of some, mainly gram positive, organisms in food animals and thence their spread to humans through the food chain.

- c. Similar controls for the prophylactic use of certain antibiotics in food production may have some effect, but such measures need to be balanced against possible effects on animal health and on food production. A typical example is weaner pigs where antibiotic treatment is seen as a crucial preventative measure. Parallel controls on the use of prophylactic use of antibiotics in humans should also be considered.
- d. For food animals, EU-wide legislative controls to reduce the occurrence of pathogenic bacteria such as *Salmonella* Enteritidis and *Salmonella* Typhimurium in poultry have been highly effective in reducing the occurrence such bacteria, including antibiotic-resistant strains of these serovars, as these bacteria are frequently resistant to commonly-used antibiotics as a consequence of antibiotic use in certain food production animals.
- e. Of fundamental importance in controlling the occurrence and spread of antibiotic-resistant organisms is education. Many medical doctors prescribe antibiotics unnecessarily; veterinarians also often use antibiotics as a substitute for poor husbandry, thereby perpetuating the occurrence of antibiotic-resistant strains in the food chain.
- f. Many of the antibiotic resistant strains (gram positive and gram negative) are isolated from chronic wounds so careful management of these patients are important so they do not become a source of infection. Frequent debridement of the wound using non-invasive techniques (care here because aerosols can be produced) then topical application of antiseptic dressings until bacterial numbers are reduced, is effective. The wound then slowly heals.
- g. The prevention of infectious disease through appropriate hygiene and biosecurity, through the use of vaccines where available, and by appropriate nutrition and housing of animals, reduces the need for antibiotic use on farms.
- h. High hygiene standards during slaughter, processing and preparation of animal products (including dairy and eggs) is vital. This means education of food industry workers on compliance with legislation and enforcement where breaches have occurred is effective to reduce the spread of food borne pathogens. Food hygiene campaigns aimed at the general population are also effective to reduce the transmission of bacteria through the food chain.

Q. What global coordination and action is required to fight antimicrobial resistance and is the UK contributing enough towards cross-border initiatives?

- a. There are many global initiatives underway to combat antibiotic resistance at a global level, particularly in respect of resistance in food animals. Some initiatives are as follows:

UK 1970 - The solution - Swann recommendations:

- Ban on use of penicillin and tetracyclines as growth promoters
- Caution in use of chloramphenicol
- Prescription only use of therapeutic antibiotics in veterinary medicine
- Enhanced surveillance of resistance through food chain

EU 2006. Ban of use of growth promoters in animal feeds

'Regulation 1831/2003/EC on additives for use in animal nutrition'

'This regulation will strengthen the EU's rules on the safety of animal feed and complete the EU ban on the use of antibiotics as growth promoters Both these

objectives are of major importance to the EU's food safety strategy and indeed to wider considerations of animal health' **David Byrne, EU Commissioner for Health and Consumer Protection, 2006**

UK Chief Medical Officer Reports 2009, 2011

'There should be a ban on the use of certain types of antibiotics (quinolones and cephalosporins) in animals, in order to protect their activity in humans' **Sir Liam Donaldson, CMO, 2009**

'National approach to tackling antimicrobial resistance should be managed jointly between DH and Defra to ensure that a comprehensive integrated programme is developed'. **Dame Sally Davies, CMO, 2013**

European Food Safety Authority (EFSA), 2011

Scientific Opinion on the public health risks of bacterial strains producing ESBLs and/or AmpC β -lactamases in food and food-producing animals

'A highly effective control option would be to stop all uses of cephalosporins/systemically active 3rd/4th generation cephalosporins, or to restrict their use (use only to be allowed under specific circumstances)'.

European Parliament October 2011

'European Parliament calls upon the European Commission to make legislative proposals to phase out the prophylactic use of antibiotics in livestock farming in the EU'

European Parliament, 27 October 2011

SANCO strategy on Antimicrobial Resistance

5-year strategy presented on European Antibiotic Awareness Day, 18 November 2011

Holistic approach: public health, food safety, consumer safety, environment, animal health and welfare as well as non-therapeutic use of antimicrobials

- To develop new tools to fight microbial infections
- To promote practices known to reduce antimicrobial resistance
- To reduce practices that may contribute to increase of antimicrobial resistance
- To further elaborate phenomenon of antimicrobial resistance and its sources/causes/consequences
- To improve communication among those involved
- To promote international cooperation in tackling AMR

WHO Europe strategy on antibiotic resistance

Seven action areas:

1. Promote national coordination
2. Strengthen surveillance
3. Promote rational use of antibiotics, including surveillance of antibiotic consumption
4. Improve infection control and stewardship of antibiotic use in health care settings
5. Promote surveillance, prevention and control of antibiotic resistance in the food chain
6. Promote research and innovation on new antibiotics
7. Improve awareness on antibiotic use and risk of increasing resistance

Fighting antibiotic resistance a priority for WHO/Europe European strategy under development **2011 publication suggests actions for tackling antibiotic resistance from a food safety perspective**

Key messages for countries

1. Improve overall coordination
2. Improve regulatory framework
3. Reduce the need for and promote prudent use of antibiotics
4. Improve surveillance
5. Advocate and communicate
6. Build capacity and provide training
7. Address knowledge gaps and research needs

WHO/FAO/OIE achievements on AMR since 1997

- International collaboration established
- Codex Alimentarius, FAO, OIE, WHO
- 15 plus expert meetings and consultations Roles
- Codex and OIE: normative work
- FAO and OIE: practical guidance and capacity building
- WHO: raise public awareness, monitoring, leading the debate

Critically-Important Antimicrobials (CIAs) WHO, 2007, 2009, 2011

e.g. Quinolones / flouoroquinolones 3rd / 4th generation cephalosporins Carbapenams

Codex: ad hoc Intergovernmental Task Force on AMR, 2007-2010

Objectives

1. To assess the risks to human health associated with the presence in food and feed of antimicrobial resistant organisms, antimicrobial resistant genes or residues of antimicrobials
2. To develop risk management advice based on that assessment to reduce such a risk

Outcome: Guidelines for the Risk Analysis of Foodborne Antimicrobial Resistance

Codex Alimentarius: Strategic Plan 2008-2013

Develop guidance for safe and prudent non-human antimicrobial usage for containment of resistance

Description:

Develop guidance within the remit of Codex mandate for safe and prudent antimicrobial usage for containment of resistance in food production which focuses on public health, is based on sound science and follows risk analysis principles, and takes into account the work of other international organizations.

Timeline: Completion by 2011

Responsible parties: Existing relevant Codex Committees, *ad hoc* Intergovernmental Task Force on Antimicrobial Resistance Codex Alimentarius: Strategic Plan 2008-2013

OIE List of Antimicrobials of Veterinary Importance

Defines:

- Veterinary Critically Important Antimicrobials
- Veterinary Highly Important Antimicrobials
- Veterinary Important Antimicrobials:

‘Critically Important’ include:

- Aminoglycosides
- Cephalosporins
- Macrolodes
- Quinolones/ fluoroquinolones

Guidance on pre-approval information for registration of new veterinary medicinal products for food-producing animals with respect to antimicrobial resistance

Harmonized technical guidance in E.U., Japan and the U.S. for registration of antimicrobial veterinary medicinal products intended for use in food-producing animals ,with regard to characterization of potential for a given antimicrobial agent to select for resistant bacteria of human health concern.

Information on:

- Antimicrobial class
- Mechanism and type of antimicrobial action
- Antimicrobial spectrum activity -MICs

European Medicines Agency Press release, 16th April 2013

‘Use of antibiotics in animals - European Medicines Agency to give advice to European Commission on public- and animal-health impact’

- ‘One health’ perspective
- Multidisciplinary working group
- Scientific basis to inform decisions
- First report, June 2013
- Final report, June 2014

October 2011 ‘European Parliament calls upon the European Commission to make legislative proposals to phase out the prophylactic use of antibiotics in livestock farming in the EU’ European Parliament, 27 October 2011

UK, January 2011: Similar proposal made during House of Commons debate on antibiotic use on intensive farms House of Commons, 9 January 2013.

RUMA Press statement 26 March 2013

Preventive treatment (sometimes referred to as Prophylaxis)

‘Treatment with antibiotics of an animal or a group of animals, before clinical signs of infectious disease, in order to prevent the occurrence of disease or infection’.

- Must only be applied to animals diagnosed at high risk of bacterial disease,

- Must only occur under prescription by veterinarian on basis of epidemiological and clinical knowledge,**
- Must not be applied systematically or routinely,**
- Must not be used to compensate for poor hygiene or for inadequate husbandry conditions, or where improvements in animal husbandry could reduce need for antibiotic treatment.**

Food industry perspective

The British Poultry Council have introduced a voluntary ban on the use of fluoroquinolones and 3rd and 4th generation cephalosporins in poultry production from January 2012.

- b. Of note is that the European Medicines Agency (EMA), the European Centre for Disease Prevention and Control (ECDC), and the European Food Safety Authority (EFSA) have all realised the importance afforded to the control of infections caused by antibiotic-resistant bacteria, and many collaborative actions are underway. More pro-active collaborations between appropriate UK agencies and these bodies would be both welcome and desirable.
- c. Of paramount importance is controlling antibiotic usage in countries in the Far East. Antibiotics are used freely in these countries in both human and veterinary medicine, often with formulations that have not been subject to proper regulatory controls. This usage has undoubtedly contributed to the appearance of, and subsequent worldwide spread of organisms resistant to CIAs and last-resort antibiotics.
- d. Environment pollution around factories producing antibiotics has been reported – see *Environmental Toxicology and Chemistry*, Vol.28, No.12, pp. 2522-2527. Global regulation and compliance with respect to groundwater and drinking water is essential.

Q. What are the strengths and weaknesses of the Government's 2013-2018 strategy for tackling antimicrobial resistance? What changes might be made to further strengthen the Government's action plan?

Strengths: realisation that there is a problem and that measure should be undertaken to combat this problem.

The Department of Health 5 year strategy states at Point 2.1, page 8; 'Increasing scientific evidence suggests that the clinical issues with antimicrobial resistance that we face in human medicine are primarily the result of antibiotic use in people, rather than antibiotics in animals'.

Weaknesses: lack of willingness to introduce comprehensive legislation to combat resistance development in both the human and veterinary sectors.