RS Policy Document 14/08

Innovative mechanisms for tackling antibacterial resistance

Summary

On 7 March 2008 the Royal Society hosted an international symposium on recent advances in research and development in antibacterial resistance and how these may be used to develop policy in this area.

There were 74 participants including leading academics, representatives from industry, policy makers and other stakeholders from the UK and other European countries, USA and Canada.

The symposium examined the scale of the problem of antibacterial resistance and the challenges faced by policy makers. Presentations and discussion focussed on recent scientific and technological advances, including in our understanding of fundamental biology of resistance, in addition to mechanisms for prevention and treatment. The symposium also discussed barriers to the development of novel antibacterial agents. Behavioural and environmental aspects of antibacterial resistance, such as antibiotic prescribing practices and hospital cleanliness, were not addressed.

This report summarises key issues raised in presentations and discussion sessions and does not necessarily represent the views of the Royal Society. The programme of the symposium and list of participants are provided in Appendices A and B respectively. A glossary of terms is provided at Appendix C.

Key points arising from the workshop were as follows:

- An escalating number of pathogenic (disease-causing) bacteria are becoming resistant to available drugs rendering these treatments ineffective, and for some of these pathogens we are in danger of returning to a 'pre-antibiotic era'.
- The prudent use of existing antibacterial agents must continue in order to slow down the development of resistance.
- Resistant bacteria and resistance genes can transfer between animals and humans. Use of antibacterial agents in animals needs close scrutiny whilst ensuring animal welfare.
- More efficient diagnostic tools must be developed to enhance the rapid identification of species of bacteria causing an infection as well as their resistance profile. This will enable appropriate and effective treatment to be given. Sustained funding commitment towards the development of novel diagnostics is also needed.
- The potential for development of traditional antibiotics has not been exhausted. However, the development of antibacterial agents acting on/in bacteria in novel ways is vital. There are numerous scientific approaches that are promising and require investigation. These include targeting bacterial virulence, inhibiting efflux pumps and destroying bacterial cell walls (eg phage lytic enzymes).
- The reluctance amongst funders to support work on novel approaches for development of antibacterial agents must be overcome.
- Venture capitalists, biotechnology companies and pharmaceutical companies need conditions that will

encourage them to invest in antibacterial agents. This can be done by simplifying regulatory hurdles and enhancing financial returns of antibacterial agents, for example by pricing to reflect the fact that they are life saving drugs.

- Collaborations between companies and building public-private partnerships might enable the risks associated with expensive and lengthy research and development processes to be shared.
- Centres of excellence should be set up to promote the wide range of expertise needed throughout the expensive and lengthy research and development process and to train a new generation of experts in antimicrobial therapeutics.

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1 Background

1.1 The problem of resistance

Antibacterial resistance is the process by which bacteria develop properties that render drugs used against them ineffective. Traditionally, antibiotics (for example penicillin) have been used to treat bacterial infections and hence this problem is often referred to as 'antibiotic resistance'. Currently used antibiotics tend to be broad spectrum (ie they kill many different types of bacteria). Broad spectrum antibacterial agents are desirable to pharmaceutical companies for economic reasons, since they only need to develop a single agent, and to physicians because no specific microbiological diagnostic tests are required before the drugs can be administered.

An increasing number of pathogenic (disease-causing) bacteria are becoming resistant to available drugs and, for some pathogens, we are in danger of returning to a 'pre-antibiotic era', with bacterial diseases becoming more difficult and expensive to treat. Antibacterial resistance includes, but is not limited to, some healthcare-associated infections such as Methicillin-resistant *Staphylococcus aureus (*MRSA) which kills more people per year in the USA than HIV (Bancroft 2007).

Incidence of resistance is increasing both in hospitals (in species such as *Staphylococcus aureus (S. aureus), enterococci, Escherichia coli (E. coli) and klebsiella*) and in the community (in species such as *Streptococcus pneumoniae (S. pneumonia), Haemophilus influenza (H. influenzae), S. aureus, enterococci and Mycobacterium tuberculosis (M. tuberculosis))*. It is also important to note that many bacteria have now developed resistance to varying numbers of different antibacterial drugs (referred to as multiple-resistant bacteria).

Antibacterial resistance has been raised as an important issue several times over the last fifty years by several bodies including the House of Lords Science and Technology Committee (House of Lords Science and Technology Committee 1998), the Chief Medical Officer (Donaldson L 2002), the European Parliament (European Technologies Assessment Group 2006), the European Academies Science Advisory Council (EASAC) (EASAC 2007) and the World Health Organisation (Kaplan W and Laing R 2004), yet the problem continues to worsen.

1.2 Drivers of resistance

The use, and misuse, of antibiotics in both humans and other animals, for example livestock, is a significant driver of antibiotic resistance. Data from the European Surveillance of Antimicrobial Consumption (ESAC), has shown good correlation between the extent and duration of use of antibacterial agents and resistance levels. Higher use rates of antibacterial products increase the selective pressure for resistance development.

1.3 Controlling resistance

National policies, such as antibiotic prescription and hospital cleanliness, are important in controlling resistance. However there are other factors involved. In Europe, higher levels of bacterial resistance are found in the south than north, although there are large variations in resistance between hospitals in the same country. Potential factors affecting this variation may include the age of the hospital and the characteristics of the patients (such as age and reason for hospitalisation), as well as the range of antibiotics used and duration of use.

2 Policy setting and strategies

2.1 European Union (EU) policy

The views of EU policy makers were initially detailed by a 2001 European Council Recommendation on prudent use of antimicrobial agents in human medicine (European Council 2001), which recommended improving surveillance of antimicrobial resistance; enforcing control measures on the prudent use of antimicrobials; educating health professionals in the appropriate use of antimicrobial agents; and undertaking research on mechanisms of emergence and spread of antimicrobial resistance, new means of preventing and treating infections and alternatives to antimicrobial agents.

An intergovernmental conference on resistance was held during the UK's presidency of the European Council in 2005. This event recommended decreasing the use of some antimicrobials; improving technology such as IT systems so that surveillance data can be better used to inform clinical practice; incentives to encourage large pharmaceutical companies to work with small biotechnology companies; modifying the international drug licensing regulations; and encouraging the development of rapid, sensitive and specific diagnostics (Finch R and Hunter PA 2006).

In 2006, the European Parliament produced a report on scientific technology options for antibiotic resistance (European Technology Assessment Group 2006). This report focussed on short term measures including the need for increasing general awareness of the problem, improving surveillance of resistance rates, more prudent use of antibiotics to contain the spread of resistance, and increasing the role of the European Centre for Disease Control (ECDC) to enable better co-ordination of antimicrobial resistance strategy between member states. However, in 2007, EASAC '*…disagreed strongly with the conclusion in the European Parliament report that sustained investment in R&D to deliver new antibiotics has less priority than the short-term objective of containing resistance. Containment will not be enough and a longer term vision is vital*' (EASAC 2007). EASAC also highlighted the need for sustained commitment to research and development in order to strengthen the science base, develop novel diagnostics and support industry innovation in drug development. It is imperative that the development of novel drugs is not neglected because the average time taken from inception of the project to market is over 13 years.

Participants at this symposium supported the view of EASAC that further action is needed to reverse the situation since it was felt that the implementation of the measures detailed by the European Parliament alone would at best slow down the escalation of resistance. It was questioned by participants whether the European Parliament might have a role in providing guidance to restrict the use of antibiotics. However, it was felt that this is unlikely to work at the hospital level as physicians make drug choices according to their judgement of the individual circumstances.

2.1.2 EU research funding

There has been commitment to funding of research into antibacterial resistance at the European level. For example, 20 million Euros will be awarded under the European Commission-funded Seventh Framework Programme to support research on Gram-negative bacteria (bacteria are classified as either Gram-negative or Gram-positive according to their cell wall structure as demonstrated by the colour they are dyed in Gram's stain, and resistance can develop in both), new sources of antibiotics and new diagnostics. A Technology Platform on Global Animal Health has potential to create a coherent research strategy, allowing for the pooling of resources and avoidance of duplication between the human and animal sectors. However, these

sums represent only a tiny fraction of the total EU science budget and are almost insignificant in the face of the problem.

2.2 UK policy: human health

Measures undertaken by the UK Government to address antibacterial resistance centre on surveillance of resistant bacteria (undertaken by the Health Protection Agency); prudent antibacterial use (including an awareness campaign run by the Department of Health); and infection control measures (determined by the National Health Service Executive).

Public health concerns over antibacterial resistance were first raised in the UK by a report of the Joint Committee on the Use of Antibiotics in Animal Husbandry and Veterinary Medicine (Swann *et al* 1969), which concluded that the administration of traditional antibiotics to livestock posed a hazard to human health as it resulted in resistance in bacteria found in humans. The report recommended the formation of an advisory Committee with overall responsibility for the field of antibacterial agents. The 1998 House of Lords Science and Technology Committee report *Resistance to antibiotics and other antimicrobial agents* (House of Lords Science and Technology Committee 1998) recommended the development of a strategy to safeguard the effectiveness of antimicrobials. In 2001, the Department of Health formed the Specialist Advisory Committee on Antimicrobial Resistance (SACAR) to develop expert recommendations on resistance, including animal, human, hospital and community aspects. This Committee was succeeded in 2007 by the Advisory Committee on Antimicrobial Resistance and Healthcare Associated Infection (ARHAI), which has the remit to advise Government on strategies to minimise the incidence of healthcare associated infections and to maintain the effectiveness of antimicrobial agents.

The UK strategy for tackling antibacterial resistance is led by the Department of Health and focuses on preserving the efficacy of existing antibacterial agents through prudent use, surveillance and infection control, rather than encouraging new drug innovation. Current priorities include professional and public education and stewardship guidance for prudent use of antibacterial agents. In support, the Health Act 2006 code of practice for the prevention and control of healthcare associated infections requires audited formulary and prescribing policies accompanied by staff training. However, surveillance of prescription is often difficult as the stop dates for medications and the reason for prescription are not always entered on the patient notes. Data on secondary (hospital) care prescribing is only available from financial management and stock control, and the limited sources of data skew the available information. Participants at the symposium felt that more research is needed into the prescribing habits of physicians and demand by patients for antibacterials, which in conjunction with increased surveillance of prescription would help to formulate better guidelines on the prescription of antibacterial agents.

2.2.1 Department of Health research funding

The Department of Health Policy Research Programme commissions research to provide evidence for policy making. From 2004-2008, 14 research projects were funded in areas including mechanisms of resistance, infection control, surveillance, public education and one project on laboratory testing. Participants felt that the overall balance of projects needs to reflect the areas of greatest need. Further research on targets and modes of action of antibacterial agents; mechanisms of resistance; surveillance of resistance; antibacterial usage and clinical outcome; and alternatives and adjuncts to existing antibacterials would be of value for informing the UK public health response to antibacterial resistance.

2.3 UK policy: animal health

Although antibacterial resistance is not as frequently observed in non-human animals as in humans, it is still a significant problem, affecting both animal health and the cost of treatment and creating a risk for human health. The Department for Environment Food and Rural Affairs (Defra)'s Antimicrobial Resistance Co-ordination Group is responsible for advising Defra on antimicrobial resistance issues arising from antimicrobial usage in animals, including human-animal aspects, surveillance, research and international issues such as the antimicrobial resistance risk from imported meat or animal feed. Antibacterials are used both therapeutically (for example, to treat infection in domestic animals) and as prophylactics (preventative measures), for example to prevent infection in livestock kept close together. Low, sub-therapeutic doses of antibacterials have also previously been used to promote growth, as the presence of infectious agents has been shown to reduce yield of food animals. However such low doses encourage the development of resistance to agents used in human medicine as they do not quickly kill all of the bacteria. This practice was banned in the EU in 2006.

Around half of antibacterial active ingredients authorised for use in animals are also used in humans, and it is possible for resistant bacteria and genes for resistance to transfer between species (including animal to animal, animal to human and human to animal). Sometimes slightly different versions of antibacterial medicines are used in animals and humans. Bacteria that develop resistance to the animal version may also be resistant to the human version. It is therefore important that there is close scrutiny of resistance and prudent use of antibacterial agents without compromising animal welfare. Antibacterial use should not replace good animal husbandry as safe food comes from healthy animals.

All veterinary antibacterial agents are vet prescribed. Defra's annual sales data report gives a good indication of the quantities of antibacterials used in animals. The risk-benefit analysis that must be performed for new veterinary medicines is more difficult than for medicines for humans, as it must take into account the effects on the animal, the person who administers the medicine, those living around the animal, the effects on the environment and consumers (where appropriate). Where antibacterials are used in animals destined for consumption, the withdrawal period for the antibacterial must also be determined. This is the time taken for residues of the active ingredient to reduce to a safe concentration in the edible produce for consumers after use of the medicine has been stopped. Major residue surveillance is carried out to ensure that farmers are adhering to withdrawal guidelines and animal produce for sale does not contain unacceptable residues.

The UK market for veterinary medicines is much smaller than that for human medicines, so there is relatively little incentive to develop new drugs for animals. It was previously common for pharmaceutical companies to develop both human and animal medicines. However, many companies now concentrate on the more profitable area of human pharmaceuticals, and the once strong links between human and veterinary pharmaceutical companies have deteriorated. This causes difficulty in drug development in the animal sector, and there is often a time lag before new substances developed for use in human pharmaceuticals are used in animal medicines.

2.3.1 Defra research funding

Defra currently funds research on the emergence, prevention and spread of resistance. Defra has expanded its research activity beyond food-producing animals, for example to evaluate MRSA in companion animals, and to understand, prevent and reduce the incidence of resistance. However, participants also heard that more research is needed on the ecological impact of veterinary products, such as the potential for resistance

to develop in cattle as a result of re-ingestion of antibacterial agents excreted into fields. More evidence is also needed to determine whether it is realistic to choose different antibacterials in human and veterinary medicine, as has been attempted in some EU countries. It is also unclear whether there should be continued animal use of an agent if resistance has become a problem in humans because it is not known if animal use is a significant contributory factor to the problem in humans.

3 Predicting and preventing resistance

Understanding the factors that control the emergence of resistance can help its prediction and prevention. Factors that can be controlled include the extent to which a specific antibacterial product is used and its dosing regimen (the amount of antibacterial given in a particular time and the duration over which it is administered). There has been little research on dosing regimens, but there may be much to learn in this area, for example on the optimum amount of drug and timings of doses needed to kill the bacteria whilst minimising resistance. There are also factors related specifically to the host which affect whether resistance will develop in a patient, such as proximity of infected patients, pre-existing immunity to the specific bacteria and general hygiene standards.

Certain resistance variables are specific to bacteria. Although these factors cannot be controlled they can be used to predict the likelihood of resistance development. For example:

- *Mutation rates.* The term mutation rate describes the chance of a mutation occurring in each successive generation of bacteria. A high mutation rate makes it more likely that a mutation which confers resistance will occur. A mutation which leads to resistance might not be entirely beneficial, and whilst it may allow the bacteria to survive in the presence of an antibacterial agent it may have a detrimental effect on another essential function, due to the diversion of resources such as energy to the resistance mechanism. Mutation rates are often used to predict the development of resistance, but for most infections this does not actually determine the number of resistant mutants.
- *Fitness cost of resistance.* This describes the net effect that resistance development will have on the ability of the bacteria to survive, and may be a more relevant means than mutation rate of predicting resistance. A high fitness cost of resistance means that resistance development will have an effect on the bacterium's viability in the absence of the antibacterial, and so will result in a slower rate of resistance development and also faster reversibility of resistance.

A concept often used to determine whether resistance has developed is minimum inhibitory concentration (MIC). This is the lowest concentration of an antibacterial needed to inhibit the growth of bacteria after overnight incubation. After the MIC reaches a threshold, or biological breakpoint value, it is assumed that resistance has developed and the antibacterial in question is no longer used. However, it is possible that the antibacterial may still be effective at much higher concentrations and so care should be taken to ensure that a strict implementation of breakpoint values does not exclude the use of antibacterials which may still be effective.

4 Tackling antibacterial resistance

Conventional methods for treating bacterial infections involve the use of traditional antibiotics such as penicillin. There is an urgent need for development of new treatments as alternatives as resistance is developing to these long-established drugs. There is some evidence that some potential remains to develop novel antibiotics of the conventional kind, targeting essential functions that are present in a broad spectrum of bacteria (for example, the gyrase and FtsZ inhibitors being developed by the company Prolysis). This symposium featured presentations and discussion on promising areas for the application of basic research in development of novel antimicrobials.

4.1 Targeting bacterial virulence

Much interest focused on targeting bacterial virulence. The term 'virulence' refers to the ability of bacteria to cause disease, and involves the processes by which they attach to and colonise the host, and avoid host defence mechanisms. When drugs are designed to kill bacteria, there will always be a selective pressure for the development of resistance to survive. If, instead, bacteria could be modified to stop them causing disease without actually being killed, this selective pressure may be reduced. Preventing infection without killing the pathogen can be viewed as a form of 'acute vaccine'. This approach may be beneficial to high risk patients, for example after surgery, particularly for preventing respiratory, intestinal and urinary tract infections.

Targeting bacterial virulence might be a viable option for circumventing the problem of resistance, although it is still possible that some resistance may develop. As long as developing resistance confers an advantage to the bacteria, resistant bacteria will be more likely to survive and reproduce than non-resistant bacteria and so widespread resistance will develop. Anti-virulence measures are non-bactericidal, which mean that the bacteria are not killed and they will stay in the body unless they are flushed out by the immune system. Although the bacteria would not cause any harm in this attenuated state there is, at present, reluctance by funders to support strategies that do not kill the pathogen. Reasons for such reluctance may include that, where bacteria are not removed from the body, long term treatment may be required to keep them in a non-pathogenic state. This issue is also problematic in future use of such treatments since it would presumably make anti-virulence treatments more expensive than conventional antibiotics as drugs would need to be prescribed for longer.

Anti-virulence strategies are often more specific (to certain types of bacteria) than conventional antibacterial agents. It is first necessary to know which species a patient is infected with so that the right drug can be used. In situations such as a primary care setting this detailed knowledge of the patient's microbiological status is not always possible as the diagnostic tools are not available. Narrow spectrum products (which act against a small range of bacteria) would need to be accompanied by faster, more effective diagnostics, and training of physicians in how to use them. There would be an increased cost for improved tests at the bedside. Products requiring expensive diagnostic tools may be of little use in developing countries as hospitals would not be able to afford the necessary equipment. Experience in different EU Member States suggests that clinicians do not necessarily use new diagnostic tests when they are available. Education programmes to guide the correct use of new diagnostic tools need to be informed by research into the use of diagnostic tools by physicians. However, broad spectrum products often also kill commensal bacteria (non-harmful bacteria such as those in the human gut which aid in digestion) as well as the bacteria causing the infection. This has led to an increase in the incidence of resistance, as the genes for resistance may spread between different populations of bacteria.

4.1.1 Targeting Multiple Adaptation Response (MAR) proteins

Bacterial virulence is primarily regulated at the transcriptional level. Multiple Adaptation Response (MAR) proteins are transcriptional regulators (proteins that control whether a particular gene or genes are transcribed and therefore whether the resulting protein can be made) found in all bacteria that control the infection process, and might be appropriate targets for anti-virulence approaches. It may be possible to develop inhibitors to these proteins which would stop them functioning and therefore prevent the bacteria from causing infection. As MAR inhibitors would not interfere with the growth of bacterial populations, this approach may reduce the incidence of resistance, as explained above. Although it is theoretically possible that resistance to the drug may still develop, this would require a mutation in the region of the protein which the inhibitor binds to. However, as this is also the region of the MAR protein which binds to the bacterial DNA, such a mutation may in itself reduce the viability of the bacteria as the protein would no longer be able to control transcription.

In *E.coli*, MAR-A (a type of multiple adaptation response protein) affects the transcription of more than 80 genes, many of which are involved in the development of drug resistance. Analysis of *E.coli* MAR-A proteins has identified several classes of potential MAR inhibitor. Proof of concept for the role of MAR-A like proteins as regulators of virulence has been obtained in animal experiments. For example in research presented at the symposium, mice treated with one MAR inhibitor (hydroxybenzimidazole P5631 MAR inhibitor) demonstrated increased survival when infected with *Pseudomonas aeruginosa* (*P.aeruginosa).* This approach is now being investigated in primates. Further work will have to be carried out on the pharmacokinetics of the MAR inhibitor (determined by factors such as its rate of absorption, metabolism and excretion) before its effects can be tested in humans.

Whilst MAR inhibitors have potential in the fight against resistance, any drug used must target pathogenic bacteria and not harmless commensal bacteria as there is currently little information available on the role for MAR proteins in these bacteria.

4.1.2 Quorum sensing as a target to attenuate virulence

Another option for tackling bacterial virulence is altering the behaviour of groups of bacteria. Bacteria need to recognise self from non-self, when to mobilise their defence mechanisms and when to move. They are capable of complex patterns of behaviour resulting from the co-operation of individual cells, such as the formation of biofilms (complex aggregations of bacteria). This behaviour is mainly achieved through the release of small, diffusible signal molecules by the bacteria. The higher the density of bacteria, the more signal molecules they produce. This is regulated by modules incorporating an amplification system, which enables the presence of signal molecule to stimulate the production of more signal molecule. When a critical threshold (quorum) of bacteria is present, the level of signal molecule affects the regulation of certain genes, resulting in collective behaviour. The size of the quorum needed to reach this critical threshold depends on the rate of production and loss of the signal molecule.

Research presented using *P.aeruginosa* as a model organism showed that quorum sensing functions regulate virulence, biofilm maturation, sensitivity to antibacterials and to host defences. Studies in models of cystic fibrosis have shown that *P.aeruginosa* does indeed deploy quorum sensing during infections in humans. This is demonstrated by the increase of signal molecules during acute exacerbation of infection. Disrupting quorum sensing might be a means of tackling bacterial virulence.

Therapeutic means of disrupting quorum sensing include the targeting and inactivation of signal molecules or interrupting the process by which the signal molecule is produced. The latter approach involves screening combinatorial chemistry libraries to select compounds that are chemically similar to signal molecules. These compounds might act as receptor antagonists, binding to the receptors and blocking the action of the bacterial signal molecules. Most of the work in this area has been performed *in vitro* but some *in vivo* work is progressing, using natural products such as furanones (chemicals produced naturally by marine algae) which have been screened as quorum sensing inhibitors in mouse lung infection models. Proof of principle of alternative products is also now being sought in the clinic using herbal preparations such as the 'garlic oil quorum sensing inhibitor'. This is currently going through randomised clinical trials in cystic fibrosis patients with chronic *P.aeruginosa* infection.

Quorum sensing inhibitors compared to conventional antibacterial agents may lessen the problem of resistance and do not harm commensal organisms. However, potential obstacles to commercial application include their non-bactericidal nature (as pharmaceutical companies are unwilling to invest in strategies which do not kill the bacteria), a narrow therapeutic spectrum (a particular inhibitor will only work against a narrow range of bacteria), uncertainty on their use as prophylactic or therapeutic (whether they can be used to treat as well as prevent infections) agents and on whether efficacy will be obtained in immunocompromised patients (patients whose immune system is not fully able to fight infectious diseases such as those undergoing chemotherapy or taking immunosuppressive drugs). More selective inhibitors may be needed, for instance to target *S.aureus* that often infects wounds but exclude other species of harmless staphylococci found on the skin. This approach might prevent the formation of new biofilms but could be less effective at breaking up existing biofilms. Interrupting quorum sensing will stop bacteria aggregating and forming biofilms, but once a biofilm has been formed the interruption of quorum sensing is not sufficient to break it up. However, interrupting quorum sensing might make an existing biofilm more susceptible to antibacterials as it might affect their ability to co-ordinate defence mechanisms.

4.1.3 Interfering with pilus biogenesis

Uropathogenic *E.coli* (UPEC) are the main cause of urinary tract infections (UTIs), which account for an estimated 8 million physician-office visits and 100,000 hospital admissions every year in Europe and the United States. It has been estimated that 1 in 2 women will contract a UTI during their lives, and that 20-40% of these will suffer from more than one infection.

Gram-negative bacterial pathogens such as UPEC possess cell surface fibres known as pili. The pili are virulence factors which are essential for the onset of bacterial infection by allowing the bacteria to recognise and attach to the epithelium (lining) of the host kidney (P pili) and bladder (type 1 pili). P and type 1 pili are assembled by the same fibre assembly mechanism used to manufacture surface organelles in many other bacterial pathogens, including enterotoxigenic *E. coli. Klebsiella pneumonia (K.pneumonia)*, *H.influenzae*, *P.aeruginosa*, *Bordetella pertussis (B.pertussis)*, *Proteus mirabilis (P.mirabilis)*, and *Salmonella* and *Yersinia* species including the potential bioterrorism agent *Yersinia pestis (Y.pestis)*.

Pilus biogenesis proceeds by what is known as a 'chaperone/usher pathway'. This involves a chaperone transporting pilus subunits through the periplasm (the space between the inner and outer membranes of the bacteria) and an usher which is a pore in the outer membrane which forms the site of assembly of the pili. The chaperone assists subunits in folding and prevents subunits from aggregating and assembling prematurely. Another important role for periplasmic chaperones is to prime subunits for future assembly at

the usher. Structural biology studies were described that showed the molecular basis of chaperone function and subunit assembly at the usher. Chaperones stabilise pilus subunits *via* a mechanism termed 'donor-strand complementation' (which allows the folded subunit to bind to the chaperone) and pilus assembly at the usher occurs via a mechanism termed "donor-strand exchange" (whereby the subunit is incorporated into the pilus fibre upon release from the chaperone). The usher itself has a twinned-pored structure with two subunits, and acts as a catalyst for donor-strand exchange through a zipping mechanism.

Host recognition and attachment occurs early on in a bacterial infection, so the mechanisms described above may form the basis of developing novel anti-virulence drugs. Following the detailed structural characterisation of the P and type 1 pilus systems, specific 'pilicides' have been designed that are small molecule compounds that prevent pilus biogenesis and therefore render the bacterium harmless. As the chaperone-usher pathway is responsible for pilus assembly in a number of pathogens, this approach may be used in many bacteria other than UPEC. The pilicide approach relies on inactivating virulence factors (the pili), so evidence is needed to show that the immune system would be able to flush out the disarmed pathogen. If this is not possible long term treatment may be needed to keep the bacteria in an attenuated state.

4.2 Targeting efflux inhibitors

Efflux pumps are found in the bacterial cell membrane and are responsible for removing substances toxic to bacteria, including antibacterials, from the cell. This can result in antibacterial resistance if the pumps are able to remove the antibacterial agent before it is able to act. Some pumps are able to transport several different substances. A pump may be able to export more than one class of antibacterial which results in multiple drug resistance. Efflux pumps may also be involved in the disease causing process. They may do this by either export of a quorum sensing molecule to enable communication between bacteria; export of a virulence factor (a molecule which enables the bacteria to cause disease); or by enhancing the production of virulence factors. Inhibiting efflux pumps would prevent resistance by stopping the bacteria expelling antibacterials.

There is a variety of classes of efflux pump, and the relative numbers of each class vary from species to species of bacterium. The drug resistance due to efflux pumps depends on the species of bacteria, the drug being administered and the type of infection. Some efflux pumps confer resistance to natural substances produced by the host, for example, bile and hormones, as well as conferring resistance to antibacterials. Some resistance nodulation division (RND) family efflux pumps have also been shown to have a role in the colonisation and persistence of bacteria in the host, so are essential for their survival even in the absence of antibacterial agents. Research has confirmed that efflux pumps are important in the survival and therefore the natural selection of resistant bacteria.

Efflux pump inhibitors should restore the activity of the antibacterial and prevent the selection of resistant bacteria, as the bacteria (resistant and sensitive) can no longer survive without functioning efflux pumps. Inhibitors might work by binding to the efflux pump protein; acting on the energy source of the pump so that it can no longer function; or by preventing the production of the pump, either by stopping the component proteins being made according to information in the DNA or by preventing the assembly of the components to make the pump. Inhibitors should also stop both resistant and wild-type bacteria from causing disease to begin with when the efflux pumps play a role in pathogenicity. Bacteria sometimes possess multiple efflux pumps with complementary activity, so if one type of pump stops working another may be able to carry out the same function. Therefore an inhibitor that works on one pump alone might not prevent resistance or restore antibacterial activity. However, experimental work has shown that inhibiting RND family

pumps prevents bacteria from colonising the host. It may be possible to design inhibitors which act on more than one class of pump by targeting regions which they share in common.

4.3 Use of phage lytic enzymes

Some pathogenic bacteria that regularly colonise humans can be triggered to cause disease at some point after colonisation when the immune system is weakened after an operation. Targeting these bacteria in their asymptomatic carrier state might be beneficial to prevent them causing disease in patients about to undergo an operation. Such species include *Streptococcus pneumoniae (S.pneumoniae)* and *Streptococcus pyogenes (S.pyogenes)* in the nasopharynx (the upper portion of the nasal passage), and *S.aureus* in the anterior nares (the external portion of the nostrils).

Some viruses produce bacteriophage lytic enzymes (lysins) that punch holes in the cell wall of the bacteria. These enzymes are bacterial strain specific. Recombinant (genetically engineered) phage enzymes could be used to decolonise bacteria in the carrier state, and thereby prevent them going on to cause disease.

Lysins have been characterised that are effective against *S.pneumoniae, Bacillus anthracis (B.anthracis), Enterococcus faecalis (E.faecalis), S.aureus* and group B *streptococci*. The enzymes contain a catalytic domain which is constant, and a recognition domain, which determines the specificity of the enzyme for the bacterium it acts against. Purified lysins have been shown to kill bacteria very quickly *in vitro*. Studies on lysins have also examined whether they might have activity against infections, for example, acute otitis media, pneumonia and septicaemia. Studies have shown that lysins worked better than conventional antibiotics, and that the effect is greater with increasing doses. The lysins leave the circulation quickly in the mouse models used, which means that multiple doses may be needed to keep the circulating concentration up in order to kill all of the bacteria. However, it is possible that in humans the lysins may not leave the circulation as quickly as in mice.

Lysins have several advantages over traditional antibiotics. Resistance to lysins has not been observed so they may be useful in chronic situations, for example, in treating resistant bacteria in hospital and care settings. Lysins might also be used in combination with other antibacterial agents, meaning that any bacteria that developed resistance could be killed before the trait could be passed on. The specificity of lysins means that they would not harm the commensal bacteria. There are possible drawbacks to the use of lysins. They could stimulate an immune response that would destoy them and render them ineffective, or that a patient may already have circulating antibodies which may neutralise the effect of the enzyme (which may be the case if they have previously been infected with the virus from which the lysins were isolated). Cell lysis may have inflammatory or other clinical consequences and this needs further investigation. Resistance genes may transfer from the bacteria being treated to other species of bacteria when the cells are lysed, thus unintentionally creating new resistant strains. However, the risk of sections of DNA containing the resistance genes being released and picked up by other organisms is reduced since lysins make holes in the cells rather than completely chopping them up.

4.4 Genomics

Disappointment was expressed about the contribution of genomics as a tool to identify new pathogen targets. It was felt that there had been, at least initially, too much hype surrounding this whole area. Understanding of pathogen genomes should lead to the development of new tools longer term. Genomics has an important role to play in characterising organisms which produce antibacterials (including natural

products), and therefore predicting their efficacy. There remains much information in the private domain of pharmaceutical companies which has not been fully assessed and, with the demise of antimicrobial drug development, this is unlikely to be exploited.

4.5 Vaccines

The potential of vaccines to reduce antibacterial use and spread of resistance was discussed. Some companies have become active in this area, despite earlier reservations about the scientific and commercial opportunities for vaccines. The EU intergovernmental conference on antibacterial resistance held in 2005 concluded that vaccine technology is underused for bacterial infections, particularly for resistant bacteria (Finch R and Hunter PA 2006).

5 Barriers to the development of novel antibacterial agents

5.1 Investment in antibacterials

In November 2004, a report from the World Health Organisation (WHO) (Kaplan W and Laing R, 2004) identified infections from bacteria resistant to antimicrobials as the largest, worldwide, pharmaceutical gap. Several factors would appear to make antibacterial research an attractive area for investment:

- the effectiveness of currently available drugs is decreasing due to resistance and hence there is an increasing market for new drugs;
- there remain many conventional targets for antibiotics (of essential functions present in a broad spectrum of bacteria) that remain unexploited or poorly exploited;
- there are a large number of possible targets for new antibacterial agents, for example efflux pumps, MAR proteins and quorum sensing, which have been shown to be important in the disease process;
- there are good, representative, *in vitro* tests and animal models for antibacterial compounds; and
- there is a long history of clinical studies in this therapeutic area that may ease the process of clinical trial design and approval.

The pharmaceutical sector is experiencing significant economic problems at the moment, so there are few new drugs currently in development that will impact on future sales and hence profit. There are also many blockbuster drug patents that are due to expire shortly, resulting in a significant loss of revenue for the patent holders. There is an escalating amount of money being spent on research and development processes for the number of resulting drug approvals due to the current clinical regulatory environment, which is discussed further in section 5.3. These problems mean that companies are cautious about new investments into research and development.

Antibacterial research must compete with other therapeutic areas for prioritisation and consequently the number of antibacterial agents in clinical development is currently on the decrease. Reasons for the decline in the development of antibacterial agents include:

- Time required to move from initial discovery to the market place: the research and development phase for a new antibacterial takes on average 13 years. This long time period makes it difficult to predict which clinical treatments will be most needed by the time the drug reaches market, and hence whether the new drug will be commercially successful.

- Value placed on antibacterials: new antibacterial agents were felt (by those present at the symposium) to be undervalued and underpriced, compared to other drugs.
- Current use of antibiotics: the problem of resistance to antibacterial agents and consequent pressure to reduce their use means that prescription rates and associated sales are low. Antibacterial agents are generally given for short periods of time, so do not make as much money as drugs that are given for longer durations.
- Uncertainty of use: uncertainty over how new antibacterial agents might be used in the future. For instance, new drugs stockpiled by hospitals might only be used in the event that resistance developed to an existing product, making returns on the new drug would be smaller. In the US Medicare (a federal government programme for health coverage) may no longer pay out for healthcare associated infections if these are considered to be due to medical malpractice. It is unclear whether this would further affect the market for antibacterial agents.

There are additional problems associated with bringing more novel approaches such as anti-virulence measures, to market. Many companies are less likely to invest in approaches based on relatively new advances in the understanding of the fundamental biology of resistance. There is both a higher risk and higher cost for generating proof of concept for approaches that have not yet been clinically validated. The regulatory pathway is also more uncertain for very new approaches. Some of the approaches described earlier (sections 4 and 5) would target specific bacteria rather than working across a range. Such drugs would have a smaller market as they could only be used to tackle a smaller spectrum of bacteria. However, this does not seem to be a barrier to the market for anti-cancer drugs, which are also very specific.

Many of the overarching approaches taken, for example in tackling virulence, are not necessarily new although the research discussed in this symposium highlighted recent and exciting developments. Research addressing aspects such as quorum sensing, MAR inhibitors and phage lytic enzymes has not yet resulted in treatments for infection, potentially because these approaches are extremely challenging from a commercial and end user point of view (for the reasons discussed above). The actual problems associated with developing novel antimicrobials are not necessarily in establishing potential targets and mechanisms for addressing them, but in translating this research into the market place. The view was also expressed that researchers should focus on more immediately translatable research instead of focussing on fundamental biology as the basis for identifying and developing mechanisms for tackling antibacterial resistance. This shift of focus may increase chances of success for research into antibacterial resistance and improve economic and societal impact of researchers' effort, expertise and financial support.

5.2 Technical challenges of antibacterial discovery

Antibacterial discovery is technically difficult. One of the key challenges is in finding a lead compound, a substance that has the potential to act as an antibacterial agent. Lead compounds can be generated in a number of ways: by screening naturally-produced compounds for antibacterial properties; by screening synthetic compounds against isolated cellular targets; or by using new methods to modify older molecular targets. Over the last decade, most of the work undertaken has been on identifying novel molecular targets using pathogen genomics. This involves comparing the genome sequences of different pathogenic species to identify genes that are highly conserved among them (genes that most of the species have in common). Knockouts of these genes are then made to confirm the dependence of viability (the ability of the pathogen to survive) on the gene.

Once the lead compounds have been identified, the lead has to be optimised. This involves further testing and refining down to a smaller number of compounds to identify candidate drugs. In some of the work described using a pathogen genomics approach, a starting point was used of 360 pathogen genes thought to be essential for pathogen survival. This led to 160 validated targets, 26 hits from high throughput screening (a technique used for screening a library of candidate compounds for specific activity) and 5 leads from combinatorial chemistry (a technique used for rapidly creating a library of structurally similar compounds). However, no compound suitable for further development emerged from the lead optimisation process. Historical data for antibacterial drug candidates indicates that on average it takes 20 development candidates to yield one marketed product.

The pharmaceutical industry's experience was that screening more antibacterial targets did not solve the lead discovery problem. The precise reason for this failure is not clear, although it is probably related to the composition of the industry's synthetic chemical screening libraries, which are biased in favour of molecules that are targeted to mammalian rather than bacterial, targets. Even when a promising lead compound is found, it must be optimised against potency (a measure of the effectiveness of the drug), microbial spectrum (the range of bacteria against which it acts), pharmacokinetic and physicochemical properties (such as solubility). This process is arduous and has a low success rate. In addition, an antibiotic must have an exceptionally good safety profile.

Additional areas were identified where further focus would be beneficial. Compounds previously discarded for development may be reconsidered, but this would require re-analysis of the literature and compilation of new databases. Further research into natural products may also yield good results.

5.3 Clinical regulatory environment

There are currently several challenges to conducting effective clinical trials of antibacterial agents. Clinical trials do not effectively discriminate between good and bad antibacterial products. For instance, it has been suggested that in acute otitis media (an infection of the middle ear) clinical trials exaggerate the apparent effectiveness of poor antibacterials and placebos (inactive substances which investigational drugs are compared to) and decrease the measured effectiveness of good antibacterials. This is because some patients with an infection will get better spontaneously, in which case little difference will be seen between the test product and the control. Whilst the clinical outcome may be the same for two drugs, the patient's microbiological status may be different. Clinical trials fail to show such differences between symptomatic and bacteriological efficacy. In the example of acute otitis media, re-examination of patients that relapsed three to six months after initial treatment showed that these patients were those treated with the drug which resulted in the less improved microbiological status. Another problem is that resistance is not seen in clinical trials, both due to the short duration of the trial and because few patients are recruited with antibacterial resistance. The standard objective of a clinical trial is to prove equivalence to a comparator drug, but this provides very little guidance to real life prescribing conditions. It has also been suggested that new antibacterial agents should be shown to be as safe as currently used antibacterials, rather than as safe as new 'lifestyle drugs' (for example, Viagra) for non life-threatening indications.

Clinical trials are very costly and complex to run. It is thought that the regulatory hurdles for antibacterial drug development are too high. The US Food and Drug Administration (FDA) has started to demand superiority trials (to show whether a drug is better than a comparator) rather than non-inferiority trials (which assess whether a new drug is as good as or better than a comparator). This makes it harder still to show the

effectiveness of a new antibacterial agent. There is currently a low success rate in research and development for both pharmaceutical and biotechnology companies. This suggests that unless the framework in place for clinical validation is changed it will not meet the needs of industry, physicians, microbiologists or patients.

5.4 Incentivising research and development

Antibacterials are low-cost and hence low-return drugs and it is important to acknowledge that the market value of antibacterial products currently reflects the duration of the infection rather than the value of the life saved. Greater incentives are required for antibacterial drug development if we are to meet the demand for new products. Participants at the symposium highlighted concern from the research community that decline in interest in research by the pharmaceutical industry is a disincentive for training or remaining in the area of science and development.

5.4.1 Market pull mechanisms

Antibacterial research and development can be incentivised through market pull mechanisms, which improve the return on investment. A market of greater than $1 billion for a new product is needed to show an attractive return on investment for both venture capitalists and pharmaceutical companies. This requires more realistic market valuation of antibacterial agents. Another suggested option is to give antibacterial agents orphan drug status and to reserve their use for when existing drugs fail. However, companies are unlikely to invest in a drug that will be kept as a reserve. Other possibilities are the extension of patent life for antibacterial agents and transferrable drug certificates (where companies undertaking antibacterial research would be able to transfer a patent extension onto another product). In addition, simplifying regulatory requirements would reduce the cost of drug development. There is also currently much regulatory inconsistency between different countries and this is something that needs to be addressed.

5.4.2 Market push mechanisms

Market push mechanisms reduce the cost of research and development. These include the provision of external funding, which is of most use when it bridges the gap between the discovery of an early lead compound and its development into a valuable drug candidate. The Wellcome Trust's *Seeding drug discovery* initiative provides translational research funding along with project management support, which is important to assist small biotechnology companies and academic groups up to the point when they can secure support from venture capitalists or larger pharmaceutical companies. This support is essential for later stage drug development due to the high cost of bringing a drug to market. The Innovative Medicines Initiative in the European Commission funded Framework Programme Seven is a public-private partnership that aims to tackle research and development bottle necks. The first area to be addressed under this programme is chronic diseases, but infection will be addressed in the future. It was felt that it would be beneficial to start forming early the links between academia and industry ready for when infection does come up. Collaborations between companies are also an effective means of sharing risk and expertise. Focussed companies with good links with academia are often able to make rapid progress in drug discovery.

5.5 Centre of excellence

There was considerable support for the development of centres of excellence in antimicrobial therapeutics. Such centres would bring together expertise in target validation, medicinal chemistry, clinical pharmacology and clinical trials. This would enable focussing on more specific targets, as already demonstrated by centres of excellence in the cancer sector such as the Institute of Cancer Research. Patient groups and medical research charities should be involved as partners in the proposed centres that would be physical rather than

virtual and aim to attract and train scientists with disparate skills. Elements that would be needed for a strong antibacterial discovery unit include:

- the identification of specific scientific questions to ensure a targeted approach;
- the generation of a skilled workforce at both graduate and post-graduate level for a range of disciplines; and
- the stimulation of pre-clinical research and development.

6 Conclusion

Antibacterial resistance is an important worldwide issue that is not being adequately addressed at present. There is a real danger of returning to a 'pre-antibiotic era' for some pathogens, and so it is essential that there is a renewed focus on research and development into innovative approaches to tackle the problem. Broad spectrum antibacterial agents have traditionally been more prevalent in clinical development as only a single agent needs to be developed for a range of indications and no specific diagnostic tests are required by clinicians. However, these products also act on commensal bacteria and have been over-used, which are both factors in the spread of resistance in bacterial populations. There should be a focus on more targeted approaches accompanied by faster, more specific diagnostic tools to better identify the precise bacterial cause of infection. Such mechanisms for tackling resistance include anti-virulence approaches, the use of efflux inhibitors and phage lytic enzymes, all of which may present opportunities to create therapies with a lower incidence of resistance than traditional antibiotics. If anti-virulence approaches are to be pursued, the reluctance of funding bodies to support strategies that do not kill the pathogen must be addressed. The development of antibacterial agents encompasses a number of technical challenges. Centres of excellence should be set up to bring together the scientific expertise needed for a comprehensive approach to the problem of resistance. Although antimicrobials are the largest worldwide pharmaceutical gap, the return on investment is low compared with other therapeutic areas. Greater incentives must be given to stimulate product development in this area, for example the pricing structure must be improved to ensure that the cost of products reflects the fact that they are lifesaving drugs.

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Appendix A: Programme

Innovative mechanisms for tackling antibacterial resistance

Friday 07 March 2008

Welcome and introduction

Sir David Read FRS, Biological Secretary and Vice-President, The Royal Society

Session 1. Science and policy (Chair: Sir David Read FRS)

Professor Jos van der Meer, Radboud University Medical Centre, Netherlands
A future without effective antibiotics?

Professor Brian Duerden, Department of Health, UK
Facing the public health challenge of antibacterial resistance

Mr John Fitzgerald, Veterinary Medicines Directive, UK
Antimicrobials and animals

Session 2. Fundamental and applied biology (Chair: Professor Richard Moxon FRS)

Professor Stuart Levy, Tufts University, USA
Sidestepping resistance: targeting virulence not growth

Professor Laura Piddock, University of Birmingham, UK
Multidrug efflux pumps and antibacterial resistance

Professor Paul Williams, University of Nottingham, UK
Quorum sensing as a target for novel antibacterial agents

Discussion

Professor Gabriel Waksman, Birkbeck College and University College London, UK
Interfering with the chaperone-usher pathway of pilus biogenesis

Professor Vincent Fischetti, Rockefeller University, USA
Controlling pathogenic antibiotic resistant bacteria with phage lytic enzymes

Professor Dan Andersson, Uppsala University, Sweden
Predicting and preventing antibiotic resistance: what do we need to know?

Discussion

Session 3. Barriers to the development of novel antibacterial agents (Chair: Professor Jeffery Errington FRS)

Dr David Pompliano, Merck & Co, USA
Drugs for bad bugs: challenges of antibacterial discovery

Dr Lloyd Czaplewski, Prolysis Ltd, UK
Challenges to antibacterial R&D in the UK: a biotech perspective

Dr Richard Bax, ViroPharma Europe, UK
Barriers to the development of novel antibacterial agents

Discussion

Concluding remarks

Sir David Read FRS, Biological Secretary and Vice-President, The Royal Society

Appendix B: List of participants

Professor Dan Andersson	Professor of Medical Bacteriology, Uppsala University
Dr Kathy Bamford	Consultant Microbiologist, Imperial College Healthcare NHS Trust
Dr Richard Bax	Vice President and Director Clinical Development & Medical Affairs Europe, ViroPharma Europe
Professor Clive Beggs	Professor of Medical Technology, Bradford Infection Group
Dr Philippa Bell	Manager Biosciences, Royal Society of Chemistry
Professor Mervyn Bibb	Department of Molecular Microbiology, John Innes Centre
Dr Amanda Brown	Post Doctoral Research Fellow, Queen Mary's, University of London
Professor Stewart Cole FRS	Director, Global Health Institute
Dr Derrick Crook	Consultant Microbiologist, John Radcliffe Hospital
Dr Lloyd Czaplewski	Director of Research, Prolysis Limited
Professor Julian Davies FRS	Professor Emeritus, Dept of Microbiology and Immunology, University of British Columbia
Dr Mike Dawson	Chief Scientific Officer, Novacta Biosystems Limited
Dr Francesca Day	Veterinary Surveillance Team, Defra
Professor Brian Duerden	Inspector of Microbiology and Infection Control, Department of Health
Dr Peter Dukes	Manager, Infections and Immunity Programme, Medical Research Council
Professor Mark Enright	Professor of Molecular Epidemiology, Imperial College London
Professor Jeffery Errington FRS	Director of Institute for Cell and Molecular Biosciences, University of Newcastle Upon Tyne
Dr Simon Evans	Parliamentary Office of Science and Technology
Professor Neil Fairweather	Professor of Microbiology, Imperial College London
Dr Robin Fears	Rapporteur
Lady Finlay of Llandaff	House of Lords Science and Technology Committee
Professor Vincent Fischetti	Co-head of Laboratory of Bacterial Pathogenesis and Immunology, Rockefeller University
John Fitzgerald	Operations Director, Veterinary Medicines Directive
Professor Simon Foster	Professor of Molecular Microbiology, University of Sheffield
Andrew Frost	Veterinary Surveillance Team, Defra
Professor Ruth Gilbert	Professor of Clinical Epidemiology, University College London
Dr Pat Goodwin	Head of Pathogens, Immunology and Population Health Department, Wellcome Trust
Dr Kay Goodyear	Defra Antimicrobial Resistance Co-ordination Group
Dr Ian Gould	Consultant Microbiologist, Aberdeen Royal Infirmary
Dr Felix Greaves	Department of Health
Professor Jorg Hacker	Director, Centre for Infectious Diseases, University of Wurzburg
Dr Sarah Hardy	Business Analyst, The Wellcome Trust
Sir David Hopwood FRS	Emeritus Fellow, John Innes Centre
Professor Colin Hughes	Head of Division of Microbiology and Parasitology, Department of Pathology, University of Cambridge
Dr Rowena Jecock	Infectious Diseases and Blood Policy, Department of Health

Dr Alan Johnson	Health Protection Agency
Dr Jack Kay	Veterinary Medicines Directorate
Professor Vasilis Koronakis	Professor of Molecular Biology, University of Cambridge
Professor Simon Kroll	Professor of Paediatrics and Molecular Infectious Diseases, Imperial College London
Dr Joanne Lawson	Government Office for Science
Tung Le	John Innes Centre
Professor David Leaper	Emeritus Professor, Cardiff University
Professor Stuart Levy	Director of the Center for Adaptation Genetics and Drug Resistance, Tufts University, Boston
Dr Anna Lonnroth	Infectious diseases unit, DG Research
Dr Caroline Low	Drug Discovery Facility, Imperial College
Ruth Lysons	Deputy Director, Food and Farming Group, Defra
Jane Mani-Saada	Health Protection Agency
Dr Michael McArthur	Procarta Biosystems Ltd
Sarah Mee	Policy Officer, Biosciences and Health, Royal Society
Professor Nigel Minton	Head of Clostridia Research Group, University of Nottingham
Dr Ian Morrissey	Director of Anti-Infectives, GR Micro Ltd
Professor Richard Moxon FRS	Action Research Professor and Head of Department of Paediatrics, University of Oxford
Dr Gael O'Neil	Senior Scientific Officer, Food Standards Agency
Kristopher Page	University College London
Dr Andrea Patterson	Defra Antimicrobial Resistance Coordination Group
Ms Pauline Philip	Lead of Patient Safety Programme, World Health Organisation
Professor Laura Piddock	Professor of Microbiology, Division of Immunity and Infection, University of Birmingham
Dr David Pompliano	Vice-President, Worldwide Head of Basic Research, Antibacterials and Antifungals, Merck Research Laboratories
Dr Mair Powell	Medicines and Healthcare products Regulatory Agency
Sir David Read FRS	Vice President and Biological Secretary, Royal Society
Dr Nick Renn	Feed Additives, Enforcement and Research, Veterinary Medicines Directorate
Dr John Rex	Vice President and Medical Director for Infection, Astrazeneca
Professor Tom Rogers	President, Association of Medical Microbiologists
Dr Anne Simpson	Manager, Biosciences and Health, Royal Society
Professor Peter Taylor	School of Pharmacy, University of London
Professor Tanel Tenson	Institute of Technology, University of Tartu
Professor Christopher Thomas	University of Birmingham
Professor Jos van der Meer	Professor of Internal Medicine, Radboud University Medical Centre
Professor Gabriel Waksman	Director, Institute of Structural Molecular Biology, Birkbeck College and University College London
Victoria Webster	Government Office for Science
Dr Martin Welch	Department of Biochemistry, University of Cambridge
Sally Wellsteed	Team Leader Infection Control, Department of Health

Professor Paul Williams	Director, Institute of Infections, Immunity and Inflammation, University of Nottingham
Dr Neil Woodford	Head, Resistance Mechanisms Monitoring Unit, Health Protection Agency
Dr Wilma Ziebuhr	School of Biomedical Sciences, Queen's University Belfast

Appendix C: Glossary of terms

Antibacterial agent	A substance that kills or inhibits the growth of bacteria
Antibiotic	A substance that kills or inhibits the growth of microorganisms
Biofilm	A complex aggregation of bacteria
Commensal	An organism that lives on or in another without causing injury
Dosing regimen	The amount of substance (eg antibacterial agent) given in a particular time and the duration for which it is administered
Efflux pump	A pump found in the bacterial cell membrane which removes toxic substances from the cell
Epithelium	Tissue that forms the lining of the internal and external surfaces of the body
European Technology Platform	A framework for industry-lead stakeholders to define research and development priorities on a number of different issues
Fitness cost of resistance	The net effect that the development of resistance will have on the ability of the bacteria to survive
Furanones	Chemicals produced naturally by marine algae
Gram-positive bacteria	Bacteria that are dyed dark blue or violet by Gram's stain
Gram-negative bacteria	Bacteria that do not retain the dye in a Gram's stain test
Healthcare-associated infections	Infections acquired during the course of receiving treatment for another condition in a healthcare setting
Immunocompromised	Having an impaired immune system
In vitro	Outside a living organism
In vivo	Inside a living organism
Knockout model	A genetically engineered organism in which one or more genes have been turned off
Microbial spectrum	The range of organisms against which an antimicrobial product will act
Minimum inhibitory concentration	The lowest concentration of an antibacterial that is needed to inhibit the growth of a bacterium after overnight incubation
Multiple Adaptation Response (MAR) proteins	Transcriptional regulators found in all bacteria that control the infection process
Multiple-resistant bacteria	Bacteria resistant to more than one antibacterial drug
Mutant	An organism which shows a new characteristic due to a change in its genetic material
Mutation rate	The chance of a mutation occurring in each successive generation of bacteria
Organelle	A structure within a cell which performs a specific function
Pathogenic	Capable of causing disease
Pharmacokinetics	Properties of a substance determined by factors such as rate of absorption, metabolism and excretion
Pilicide	Small molecule compounds that prevent the manufacture of bacterial cell surface fibres
Potency	A measure of the effectiveness of a drug
Proof of concept	Demonstration of feasibility
Prophylactic	A preventative measure

Quorum sensing	A mechanism used by bacteria to detect cell numbers, communicate and co-ordinate behaviour via signal molecules
Receptor antagonist	A substance that binds to a receptor to block the action of other molecules
Seventh Framework Programme for Research and Technological Development (FP7)	An EU instrument for funding research in Europe and runs from 2007 until 2013
Transcription	The process by which information in the cell's DNA is used to create the RNA. This is an important step in protein synthesis.
Uropathogenic	Able to cause infection in the urinary tract
Virulence	The ability of bacteria to cause disease
Withdrawal period	The time taken for residues of an animal medicine to reduce to a safe concentration in the edible produce for consumers after use of the medicine has been stopped