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UK FIVE Year Antimicrobial Resistance Strategy and Action Plan 2013-2018

November 2012

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Policy	Clinical	Estates
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Document Purpose	Gathering INFORMATION
Gateway Reference	18082
Title	UK Five Year AMR Strategy and Action Plan 2013 - 2018
Author	Department of Health
Publication Date	**October 2012**
Target Audience	Healthcare and veterinary professions, patient groups, academics / researchers, throughout the UK with expertise in antimicrobial resistance (AMR).
Circulation List	Individuals with expertise relevant to AMR, Associated Societies and Associations, Advisory Bodies and Patient Groups, Academic Organisations and Devolved Administrations.
Description	This requests input into the new five year UK Antimicrobial Resistance strategy and action plan, which the Department is developing with Defra, the Devolved Administrations and other government departments. We seek views on a number of specific aspects of the strategy, including proposed national outcome measures and their impact.
Cross Ref	UK Antimicrobial Resistance Strategy and Action Plan, Department of Health, 2000.
Superseded Docs	UK Antimicrobial Resistance Strategy and Action Plan, Department of Health, 2000.
Action Required	Views are invited on specific aspects of the strategy and action plan and further relevant information or data.
Timing	**Responses are invited by 23 October 2012.**
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Executive Summary

Antimicrobials (i.e. antibiotics, vaccines) are the cornerstone in modern medical practice for treatment and prophylaxis. The rapid spread of multi-resistant bacteria poses an increasing threat to public and animal health and the lack of new antibiotics have provided a driver for action in this area. Containing the problem and preventing the untreatable illness and premature mortality situation is a clear priority. The need for collective action to ensure antibiotics are used wisely and sparingly has never been more important than now, as evidenced by the increase in antimicrobial resistance in hospitals, the community and the environment.

Modern medical practice relies on the widespread availability of effective antimicrobials to prevent or treat infections. Unless concerted action is taken to prevent the emergence of resistance, we could face a future where routine procedures and operations will become much riskier. By way of illustration it has been estimated that a routine operation such as an elective hip replacement which are predominately infection free at the present time could be subject to increasing infections, by up to as much as 50% without effective antibiotics and could lead to a 30% increase in morbidity.

Antimicrobial resistance (AMR) is not a new problem. Work has focussed on the development and implementation of strategies and action plans since 2000 to help mitigate this risk and conserve these valuable medical resources. Our work to date has sought to minimise the effect of AMR in the UK through a combination of surveillance, responsible antimicrobial prescribing and infection control measures. While this work has helped us to become better custodians of these valuable medicines more action is needed if we are to keep pace with and ahead of the antibiotic resistance developing due to multi-resistant bacteria which are leading to a rise in the number of difficult to treat infections. Recent European data estimates mortality rates of around 30% in patients with multi-resistant *E. coli* septicaemia. Previously we relied on the introduction of new antibiotics to deal with the development of resistance but the dearth of new drugs especially for Gram negative organisms such as *E. coli*. means that we need to find new and alternative approaches to address the issue.

Although a significant amount of work on AMR is already underway, across the UK, this new integrated UK Five Year AMR strategy and action plan seeks to accelerate progress by building on the 2000 UK Strategy and Action Plan as well as developments at EU and international level, including the 2011 EU Strategic Action Plan, and 2012 EU Council Conclusions. It will champion the responsible use of antibiotics, strengthen research and surveillance capability, facilitate behaviour change and work to reposition antibiotics at a societal level from being seen as a “cure all” which are used indiscriminately to a medicine of last resort. In addition it includes challenging outcome measures which will be used to assess the effectiveness and impact of the strategy and monitor progress over the five year period.

We can not undo the harm that has already been done but we can take actions to minimise further harm for the future. Collectively eliminating bad habits and changing custom and practice so antimicrobials are used responsibly and less often will not happen over night. It will require the full commitment and engagement of a range of experts, politicians, researchers, clinicians, veterinarians, farmers and the public as part of a wider movement to change practices that have contributed to the rapid development of antimicrobial resistance which are reducing the effectiveness of some medical treatments.

Draft UK FIVE YEAR AMR STRATEGY (2013-2018)

Introduction

Antimicrobials have a variety of uses from preventing to treating infections and reducing the risk of complications in complex medical interventions, such as hip replacements and cancer chemotherapy which can in some cases be life threatening.

Antimicrobial resistance (AMR) is often described as a war of attrition between humans and resistant micro-organisms, and at the moment the microbes are on the ascendancy. We are faced with a situation where some of the micro-organisms against which we had effective agents, have been able to adapt and acquire resistance more quickly than we have been able to develop new effective drugs or alternative treatments. We are already seeing an increase in antimicrobial resistance in hospitals, the community and the environment. The development and spread of resistant microbes and in particular multi-resistant bacteria is a threat to public and animal health.

An over reliance on antibiotics since the 1980s at a time when there were great advances in the development of new families of antibiotics to replenish our armoury of drugs for fighting bacterial infections, has led to a situation which is untenable for the long term. The complacent and sometimes inappropriate use of antibiotics has depleted our reserves particularly at a time when there is a lack of new families of antibiotics to replenish them. The emergence of a growing number of bacteria responsible for infections that are becoming increasingly resistant to multiple antibiotics of different classes and modes of action has exacerbated the situation. Unless we take concerted action fast, we could face the possibility of a future without effective antibiotics for some infections.

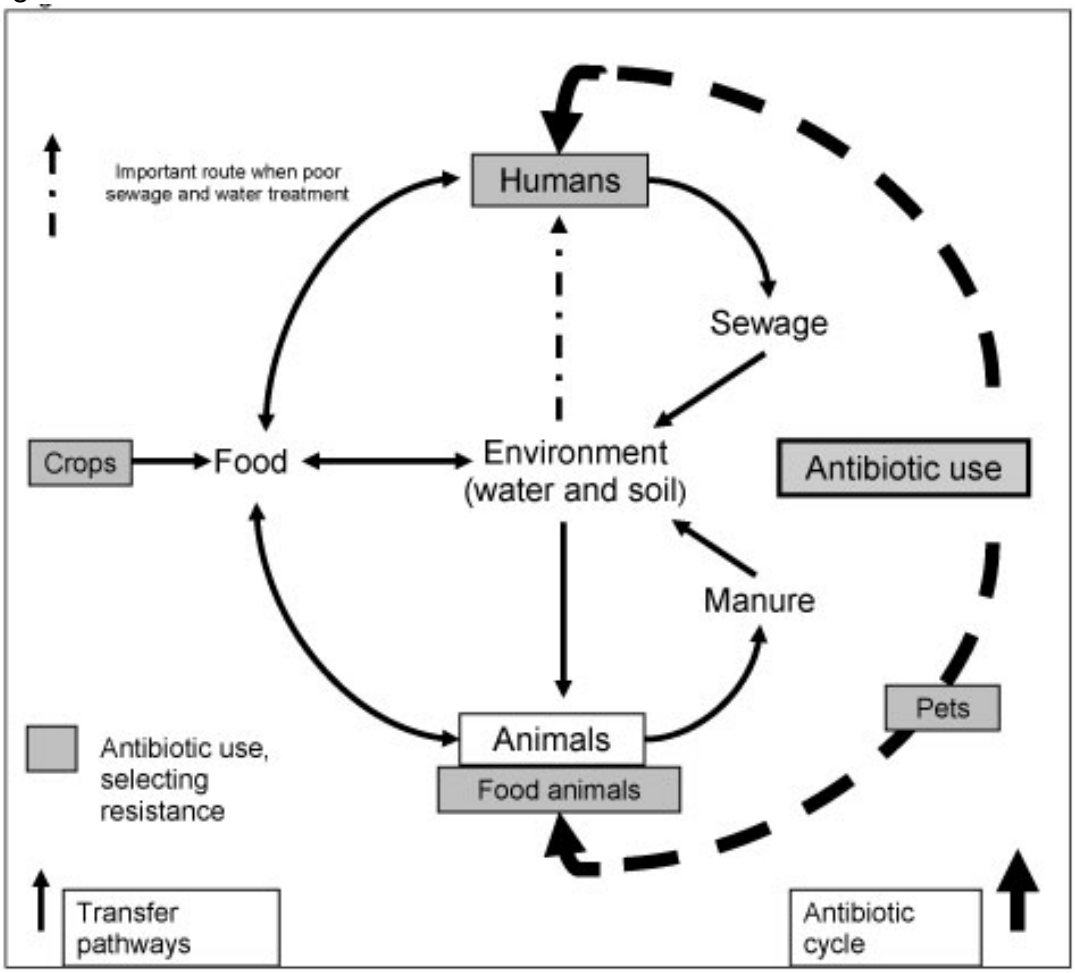
Antimicrobial resistance – A complex issue

The development of antimicrobial resistance is a natural biological outcome which occurs when microbes adapt to their environment by yielding strains that are resistant to antimicrobials in order to survive or thrive. Bacteria which host loops of DNA known as plasmids, may carry resistance genes that can be passed from one bacterium to another, spreading resistance against antibiotics and also make enzymes that inactivate many antibiotics. This has meant that many antibacterials available are becoming ineffective against certain bacteria. The widespread use of antibiotics has contributed to the accumulation of antibiotic resistance**.**

The environment in which we live contains many man made products or waste that may select for antimicrobial resistance activity. This leads to an ever changing disease burden made more challenging by increased travel and changes to the population demographics. The picture is a dynamic one with a number of contributing factors that select for and facilitate the spread of antibiotic resistance as shown in Figure 1 below. [1]

[1] ESBLs – A threat to human and animal health? Report by the Joint Working Group of DARC and ARHAI. (Pg. 8)
http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/@dh/@en/documents/digitalasset/dh_132534.pdf

Figure 1



The diagram (figure 1) shows connections in the ecosystem and how the use of antimicrobials in one part of it has an effect on others. Given the dynamic and interrelated nature of the system, controls are needed in the environmental, agricultural, food production, animal and human health sectors. Failure to act promptly and comprehensively could mean that we will be faced with impending problems with implications for animal health and welfare and the consequential knock on effects for food supply and food safety, as well as human health.

Whilst there is little evidence of transmission of AMR from animals to humans, the concern is that if bacteria in food producing and companion animals develop resistance to drugs used in human medicine these could be transferred to humans via food or through direct contact. In veterinary medicine antibiotics are essential for ensuring the health and welfare of food-producing and companion animals, and in the UK they do not constitute an acceptable alternative to or replace good farm management and animal husbandry systems.

Development of AMR in animal pathogens is a significant concern for the sustainability of production of food of animal origin. Controls in the veterinary sector need to be carefully balanced so as to minimise undesirable animal welfare issues or hamper the efficiency of food production which could

disadvantage the UK industry in relation to other countries where controls might not be implemented as well or easily enforced.

There is a need for stricter infection control and antibiotic use, backed up by efforts to minimise antibiotics entering the environment via sewage systems. More information on environmental reservoirs of resistance is also required to have early warning of potential resistance mechanisms and take proactive measures to address the issue.

The Case for Action

There is scientific consensus that use of antimicrobials in human medicine rather than antimicrobial use in the veterinary sector is the driving force for antimicrobial resistant human infections, although the latter also contributes to overall resistance rates. [2]

Multi-drug resistance is a growing concern in both human and veterinary fields. The speed at which multi-drug resistant (MDR) bacteria are spreading is a particular concern, particularly as the treatment options for patients with these infections are limited. AMR in Gram negative pathogens, particularly members of the Enterobacteriaceae family is a primary concern in the UK. As with the rest of Europe, the rise in absolute numbers, and resistance patterns of Gram negative bacteria within the UK is increasing rapidly, most notably from pathogens exhibiting ESBL and, more recently, carbapenemase production. This was confirmed by the recent Point Prevalence Surveys (PPS) on healthcare associated infections (HCAI) carried out across UK.[3],[45]

The rapid spread of carbapenemase-producing bacteria in humans which are resistant to the broad spectrum carbapenem antibiotics normally used as the last line of treatment for otherwise multi-resistant infections highlights the seriousness of the issue. The recent emergence and rapid global spread of the New Delhi metallo-β-lactamase 1 (NDM-1) resistance in certain bacteria[6] is a reminder that resistance will continue to evolve and has the capacity to significantly limit our ability to treat infections in humans and animals.

Responsible prescribing is required for infections caused both by resistant and susceptible pathogens. As the box below illustrates, threats exists from both

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[2] ECDC fact sheet for professionals http://ecdc.europa.eu/en/healthtopics/antimicrobial_resistance/basic_facts/Pages/factsheet_experts.aspx Factsheet for experts

[3] Health Protection Agency. English National Point Prevalence Survey on Healthcare-associated Infections and Antimicrobial Use, 2011. http://www.hpa.org.uk/webc/HPAwebFile/HPAweb_C/1317134304594 (accessed 14 July 2012).

[4] HealthProtection Scotland. Scottish National Point Prevalene Survey of Healthcare Associated Infection and Antimicrobial Prescribing 2011. Health Protection Scotland. 2012 (http://www.documents.hps.scot.nhs.uk

[5] Point Prevalence Survey of Healthcare Associated Infections, Medical Device Usage and antimicrobial usage report, 2011 (http://www.wales.nhs.uk

[6] Karthikeyan K Kumarasamy, Mark A Toleman, Prof Timothy R Walsh, Jay Bagaria, Fafhana Butt, Ravikumar Balakrishnan, Uma Chaudhary, Michel Doumith, Christian G Giske, Seema Irfan, Padma Krishnan, Anil V Kumar, Sunil Maharjan, Shazad Mushtaq, Tabassum Noorie, David L Paterson, Andrew Pearson, Claire Perry, Rachel Pike, Bhargavi Rao, Ujjwayini Ray, Jayanta B Sarma, Madhu Sharma, Elizabeth Sheridan, Mandayam A Thirunarayan, Jane Turton, Supriya Upadhyay, Marina Warner, William Welfare, David M Livermore, Neil Woodford Emergence of a new antibiotic resistance mechanism in India, Pakistan, and the UK: a molecular, biological, and epidemiological study The Lancet Infectious Diseases, Volume 10, Issue 9, Pages 597 - 602, September 2010 http://www.thelancet.com/journals/laninf/article/PIIS1473-3099%2810%2970143-2/abstract Issue 9, Pages 597 - 602, September 2010 http://www.thelancet.com/journals/laninf/article/PIIS1473-3099%2810%2970143-2/abstract

domestic prescribing fuelling resistance and the import of resistant bacteria from overseas infections. The relative risk from these two sources isn't readily definable and almost certainly varies with the particular pathogen and resistance, but action against both is required. For example, professionals need to be aware of the risk from imported infection so that they seek information on foreign travel (and, especially, foreign healthcare and hospitalisation), or consider isolation to prevent transmission. Guidance is available to help professionals, and this needs to be kept under review to take account of changes in epidemiology and to provide up-to-date treatment advice. Clearly. improved international collaboration on surveillance data is needed and will also help identify emerging problems and risks.

Increasing AMR in *E. coli* and other Gram negative bacteria bloodstream infections

Surveillance data from 2005 – 2010 shows a continued Europe-wide increase of AMR observed in bloodstream infections due to *E. coli* and other Gram-negative bacteria. The percentage of *E. coli* resistant to third-generation cephalosporins (e.g. cefotaxime) has increased significantly in over half of the countries in Europe. In addition EARS-Net data has shown a significant and alarming increase in carbapenem resistance in invasive *K. pneumoniae* isolates reported in Europe between 2005 and 2010. In 2009, carbapenem resistance in *K. pneumoniae* was established in Greece and within a year carbapenem resistance was also reported in Austria, Cyprus, Hungary and Italy. On an international scale rising rates of resistance among Gram-negative bacteria pose a growing threat to high technology healthcare such as major complex surgery and intensive care. European data [7], suggests that mortality of patients with multi-resistant *E. coli* septicaemia would double.

Increase in resistant gonorrhoea infections.

The number of diagnoses of the sexually transmitted infection gonorrhoea has increased by an "unprecedented" 25% in the past year. Gonorrhoea, the second most common bacterial sexually transmitted infection in the UK, is becoming increasingly resistant to antibiotic treatment and we face "the very real danger of untreatable gonorrhoea in the future".

Hard to treat tuberculosis (TB)

TB is a global public health problem and control of tuberculosis in human medicine is an area where international collaboration continues to be required. The WHO has a consolidated action plan to prevent and combat multi-drug resistant (MDR) and extremely drug resistant (XDR) tuberculosis (TB) in the WHO European Region 2011-2013.

[7] Burden of antimicrobial resistance in European hospitals: excess mortality and length of hospital stay associated with bloodstream infections due to Escherichia coli resistant to third-generation cephalosporins. de Kraker ME, et al J Antimicrob Chemother. 2011 Feb;66(2):398-407. Epub 2010 Nov 23.

In the UK human population, multi-drug resistant (MDR) and extensively drug resistant (XDR) TB cases, which are associated with significant mortality and are expensive to treat, are relatively rare – although there has been a sustained increase in case numbers over the last decade. Most cases have been in individuals born in regions of the world with a high burden of drug-resistant TB such as the Indian sub-continent and Eastern Europe. The UK (via the Department for International Development) also supports human TB programmes - including MDR and XDR - in Eastern Europe and Central Asia through its support to the Global Fund to fight AIDS, TB and Malaria.

The spread of multi-drug resistant bacteria highlights the need for increased international collaboration and vigilance. Studies on deaths attributable to a selection of multi-drug resistant (MDR) infections show that, each year, these infections result in an estimated 25,000 deaths in 29 countries in Europe (5.1 per 100,000 inhabitants)[8,9].

While a similar loss of efficacy of antibiotics in veterinary medicine of anywhere near the same scale as human medicine has not yet occurred, statutory surveillance has reported the existence of resistant zoonotic bacteria from farms which may mean that some farm animal diseases may soon become difficult to treat with antibiotics.

Resistant swine dysentery

In Europe only a small proportion of resistance issues arising in human medicine have been linked with food production. MRSA ST398 has appeared in both stockmen and pigs in Europe and *E. coli* with extended spectrum beta lactamase (ESBL) resistance from chicken products has been associated with ill-health in humans although UK farming has not witnessed either of these two issues. It is not fully understood why antimicrobial resistance in farmed animals varies between Member States.

There are only a limited number of antibacterials authorised for use in the EU for the treatment of swine dysentery, a serious and debilitating cause of enteritis in pigs. Resistance to treatment can arise through bacterial mutation, as has been observed in a number of EU Member States. Simultaneous resistance to multipe antibacterials can occur and in those cases treatment options are limited; multiple resistance to all available antibacterials renders the condition effectively untreatable with severe animal welfare and economic repercussions.

The direct costs of dealing with antimicrobial resistance will escalate if the extent of resistance continues to grow at a time when there are very few effective agents left to ensure treatment, and the number of individuals with

[8] Aronsson B, Boscan IS, Cars O, Giamarellou H, Gyssens IC, Lutsar I, et al. The bacterial challenge: time to react. European Centre for Disease Prevention and Control and European Medicines Agency joint report. 2009 www.ema.europa.eu/pdfs/human/antimicrobial_resistance/EMEA-576176-2009.pdf

[9] Zell BL, Goldmann DA. Infect Control Hosp Epidemiol. 2007 Mar;28(3):261-

drug-resistant infections increase and require longer periods in hospital. In addition the associated societal and financial costs of treating antimicrobial-resistant infections in humans need to be factored in.

The costs and benefits associated with preventing illness are more difficult to quantify. Qualitatively, we know that treatment failure caused by AMR contributes to increased costs of care associated with additional investigations such as laboratory tests and X-ray examinations. There are other impacts such as quality of life, lost productivity, greater likelihood of inadequate or delayed treatment and premature mortality that have associated costs for those affected, their dependants, employers, businesses and the wider economy. Yet, quantification is far more complex and problematic; and possibly currently misleading in terms of representing the true scale of the problem.

The Department of Health commissioned the London School of Hygiene and Tropical Medicine and University of Birmingham to estimate the 'burden of AMR'.[10] A number of variables and uncertainties were identified which prevent the full extent of the potential economic burden being calculated at this time.

The researchers report that "*If current trends continue there could be highly significant costs to healthcare and society more generally, as antimicrobials that form the basis of modern healthcare become increasingly ineffective…".* However, assessment of the current burden suggests only a moderate economic impact, as the methods used, and the narrow disease-specific manner with which costs are measured, reflects only a partial picture. Crucially, what current evidence does not do is present a system-wide view of the possible impact of resistance across the range of activities provided by modern healthcare. The authors suggest that "*we need to pursue a path that does not place undue emphasis on the current burden and cost but reflects the importance of stewardship for the future.*" They draw parallels between AMR and climate change in terms of cause, potential impact and measures needed to mobilise action at a societal level to address the issue.

While we are faced with uncertainty concerning the economic impact of AMR because the overall rate of growth for antimicrobial resistance is currently unknown, better data will be needed to assess the extent of the future burden and how quickly it will escalate if we are to be able to estimate the impact of widespread resistance to the health system overall and wider society. However the available evidence suggests that if we incur some cost now in terms of reduced use of antimicrobials we will avert a future greater, cost burden associated with not having antimicrobial therapies.

[10] Publication expected later in 2012.

Impact of growth of AMR on hip replacements.

Antibiotics have always been available since this technology was introduced and without antibiotics the risks associated with such procedures would increase substantially. Initial analyses indicate that infection rates could increase twenty-fold with around 30% of infections ending in death.

If the use of the few remaining agents of last resort become compromised by the further development of resistance then a large number of untreatable infections would result in increased numbers of premature deaths. It would also mean that many of the routine medical treatments we take for granted would, at worst, cease to exist, or at best be significantly more dangerous. Urgent action is therefore required to both understand the scale of such a scenario, and what would be needed to prevent this scenario being realised.

Challenges to Investment in New Pharmaceuticals

It has been suggested that the utility and societal value of the drugs developed has not been appropriately recognised and that there is little commercial incentive to encourage investment in this area, particularly given that phase III trials are expensive and difficult to organise.

The barriers to developing new agents are three-fold:

(i) the scientific difficulty of finding new agents;
(ii) concerns over the cost, complexity and frequent changes of the regulatory approval process (especially from the US-FDA) and
(iii) that antibiotics, taken for a week or two are inherently less lucrative than drugs which are taken for years, especially as resistance may develop in bacteria rapidly after licensing.

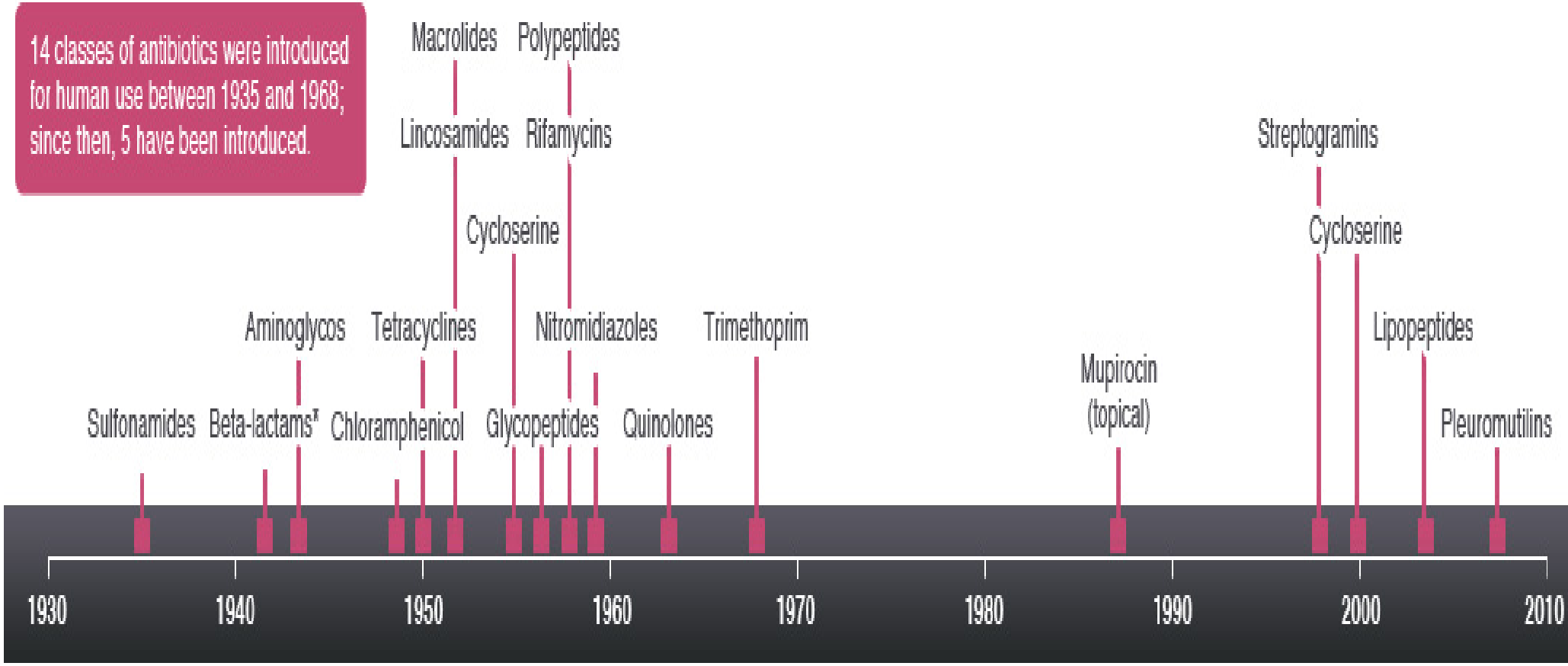
Few new classes of antibiotics have been launched recently as shown in Figure 2. Publicly disclosed information from top pharmaceutical companies shows that only five candidates or 1.6% of the pipeline of new products were antibiotics.[11] Fewer than 15 new agents have reached advanced development and of these only four are active against Gram negative bacteria.[12] The combination of the absence of new classes of antibiotics and increased antibiotic resistance leads to the urgent need to reduce the use of antibiotics, improve infection control, improve initial diagnosis of bacterial infections and reduce the need to prescribe antibiotics.

If we are to continue to be able to prevent and effectively treat infections in future responsible prescribing and antimicrobial stewardship will have an

[11] Spellberg B, Powers J, Brass E, Miller L, Edwards J. trends in antimicrobial drug development: implications for the future. *Clin Infect Dis* 2004; 38: 1279-86.
[12] Aronsson B, Boscan IS, Cars O, Giamarellou H, Gyssens IC, Lutsar I, et al. The bacterial challenge: time to react. European Centre for Disease Prevention and Control and European Medicines Agency joint report. 2009 www.ema.europa.eu/pdfs/human/antimicrobial_resistance/EMEA-576176-2009.pdf.

increasingly important role. We will also need to become better custodians of these valuable resources and encourage better diagnosis, medicine management and use of therapeutics in general.

Figure 2: The introduction of different classes of antibiotics throughout the years



The Journey so Far

The first UK Strategy in 2000[13] was developed in response to the recommendations contained in the Standing Medical Advisory Committee report "*Path of Least Resistance*"[14] produced in 1998. Although a lot of good work has already been undertaken which has delivered positive outcomes, further action is required to strengthen interventions to control resistance.

Improving prescribing in all sectors is important and limiting the veterinary use of antibiotics that are critically important for human medicine or where there is cross resistance has been advocated. Antimicrobial use in both primary and secondary care has an impact on the development of resistance and responsible use is needed in all sectors of health care as they are interconnected. For example, resistance from the community will transfer to secondary care when colonised or infected patients go into hospital and although the risks are greater in hospitals because of the concentration of critically ill patients and greater use of antimicrobials, action is required in both sectors, but the priority has to be secondary care.

Guidance for health professionals and veterinarians already exists, but its use is patchy and consideration may need to be given to how to incentivise adherence to best practice and foster greater clinical leadership in this area. Incentives could be national or local and will need to be agreed with commissioners. An example of a local measure could be correct surgical prophylaxis. Increased clinical leadership requires improved collaborative working between senior management, infection prevention and control and antibiotic stewardship teams in healthcare settings, as well as between farmers and veterinary surgeons. This strategy is relevant to those who administer and monitor antibiotics as well as to prescribers.

Interventions in human health in England

Meticillin resistant *Staphylococcus aureus* (MRSA) are a subset of *S. aureus* resistant to most β–lactam antibiotics such as flucloxacillin in that are normally used to treat *S. aureus* infections. Reporting of MRSA bloodstream infections has been mandatory by NHS Trusts in England since April 2001. We have had some notable successes in terms of preventing or reducing the transmission within hospitals and other settings of infections due to meticillin resistant *Staphylococcus aureus* (MRSA)[15]. Over time we have seen large reductions in the number of MRSA bloodstream infection reports in England, with numbers now 86.4% lower than at the peak in 2003/4.

[13] DH action plan UK antimicrobial resistance strategy and action plan : Department of Health - Publications

[14] Standing Medical Advisory Committee (SMAC). *Sub-group on Antimicrobial Resistance*. 1998. The path of least resistance :Department of Health - Publications

[15] Quarterly Epidemiological Commentary: Mandatory MRSA, MSSA and *E. coli* bacteraemia, and *C. difficile* infection data (up to January–March 2012) http://www.hpa.org.uk/webc/HPAwebFile/HPAweb_C/1284473407318

Interventions to support antibiotic prescribing, such as the publication of *Start Smart Then Focus*[16] guidance on antibiotic stewardship in hospitals in 2011 has added to the arsenal to reduce selection pressure for resistance and improves patient outcomes by promoting the right drug, right dose and right duration for every patient. Antibiotics need to be tailored to individual patients to avoid creating a central selective pressure. This lead to approximately a 10% increase in the number of trusts making recording of indication and duration of antimicrobial use in patient notes mandatory

Following focussed messages on antimicrobial stewardship there has been a shift in the prescribing of certain agents in English NHS hospitals. Between 2007 and 2012 fluoroquinolone use has reduced by 24% and cephalosporin use has reduced by 38%.

National antimicrobial guidance for use in primary care produced by the HPA is widely used[17]. A resource to encourage responsible prescribing by GPs has also been developed which will be promoted by the RCGP in Autumn 2012. The RCGP have agreed to make antimicrobial stewardship is a clinical priority until 2015 and are hosting materials for primary care to support this work.

Role of vaccines

Vaccines provide another form of defence against disease causing bacteria, viruses and other microbes, including those that may have developed resistance to antibiotic or other treatments. Vaccination programmes can prevent primary and secondary infections that might need antimicrobial treatment, reduce antimicrobial use, hence reducing opportunities for antimicrobial resistance to develop.

In the UK, the vaccines introduced into the national immunisation programme have dramatically reduced the incidence of a number of infectious diseases, including some treated by antibiotics (e.g. disease caused by types of meningococcal, pneumococcal and *Haemophilus influenzae* type b bacteria). New vaccines are in development against further viral and bacterial pathogens (e.g. Respiratory Syncytial Virus and Meningococcus B, *Clostridium difficile*, *Staphylococcus aureus* and group-B Streptococcus).

The Department of Health and the Joint Committee on Vaccination and Immunisation (JCVI, the independent experts that advise Government on immunisation) conduct an annual horizon scan to identify new vaccines in development and inform evaluations of the potential utility of new vaccine products based on an assessment of their clinical and cost effectiveness.

[16] Start Smart, Then Focus http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_131062

[17] Infection Management guidance for primary care http://www.hpa.org.uk/Topics/InfectiousDiseases/InfectionsAZ/PrimaryCareGuidance

In Scotland there have been a number of improvements in prescribing outcomes as highlighted below:[18] [19]

- decreased primary care prescribing of '4C' antibiotics (reduction of 47% cephalosporins, 37% coamoxiclav and 26% quinolones between 2008 and 2010),
- increased prescribing of recommended antibiotics
- decrease (1.9%) overall antibiotic items prescribed in primary care,
- achievement of the Scottish target of less than 5% seasonal variation in quinolone prescribing
- preliminary data showing 30% reduction in secondary care prescribing of '4C' antibiotics
- 65% decrease C difficile infections in over 65s over same time period 2008 to 2010
- Stable or decreasing trends in antibiotic resistance among Gram negatives between 2008 and 2010 and
- Proportions of ESBL static.

In Wales there has been a focus on reducing use of cephalosporins and fluoroquinolones both to control increasing resistance in Enterobacteriaceae, and to support a reduction in *C. difficile* infections. This has led to significant changes in prescribing habits.

- the number of prescriptions for cephalosporins and fluoroquinolones has decreased by ~30% and ~25% respectively, with a marked reduction seen following the introduction of the Welsh Government's Annual Operating Framework for the Reduction of *C. difficile* in April 2010.

In secondary care, use of both cephalosporins and fluoroquinolones has decreased by ~50%, again with a marked reduction since the introduction of the Annual Operating Framework.

[18] Publication on impact of the Scottish programme
http://www.aricjournal.com/content/1/1/7

[19] The SAPG website also includes the annual reports detailing general progress
http://www.scottishmedicines.org.uk/SAPG/SAPG_Reports_and_Publications

Northern Ireland introduced its first antimicrobial resistance action plan in 2002[20]. It has produced prescribing guidelines for primary care (which have been reviewed and upadted). Within a year of launch of the guidelines antibiotic prescribing per patient was reduced by 6% overall and decreased in 77% of GP practices.[21] It also produced regional secondary care guidelines for antimicrobial prescribing in Northern Ireland which a number of Health and Socail care Trusts have implemented. An account of this work is given in the recently published a strategy for tackling antimicrobial resistance from 2012-2017 which focuses on improvement in the safety and quality of care related to human health[22]. It also commissioned a series of research projects on issues relating to healthcare associated infections[23]. It has delivered CPD programmes for healthcare professions and curculated COMPASS tehraputic notes to GPs, nurses and pharmacists in Northern Ireland to provide topical training for primary care and community staff as well as eduactional materials for schools and public awareness raising activities.
http://www.wales.nhs.uk/sites3/page.cfm?orgid=457&pid=28418

Interventions in animal health in Great Britain

On the veterinary side, the antimicrobial susceptibility of organisms from clinical diagnostic material submitted to Animal Health and Veterinary Laboratories Agency (AHVLA) Regional Laboratories – and through collaboration with Scottish Agricultural Colleges (SAC) - provides a means to monitor antimicrobial susceptibility in bacteria of veterinary origin.

The existing approaches to promote responsible use of antibiotics in animals and reduce the development of antimicrobial resistance have been developed in partnership with industry and the veterinary profession. These include the farming industry's Responsible Use of Medicines in Agriculture (RUMA) Alliance, which publishes sector-based guidance on the responsible use of antibiotics. The British Veterinary Association and the British Small Animal Veterinary Association have both published posters to guide prescribing. The British Poultry Council also introduced a voluntary ban on the use of fluoroquinolones and 3rd and 4th generation cephalosporins in production from January 2012.

This work has helped strengthen surveillance, infection prevention and control and responsible use of antimicrobials in the UK over the years. However the rapid spread of multi-resistant bacteria has provided an impetus for increased activity. As domestic selective pressure and imported infections both pose a risk it is important to work with international colleagues and share information.

[20] www.publichealth.hscni.net/publications/northern-ireland-antimicrobial-guidelines-primary-care-2010

[21] www.dhsspsni.gov.uk/summaryreportofantibioticprescribingaudits.pdf

[22]

[23] www.dhsspsni.gov.uk/researchabstracts2009.pdf

In 2011 the EU announced a 12 point strategic action plan for both the human and veterinary sectors that stress the importance of surveillance, infection control, improved prescribing and research. The Council Conclusions adopted in June 2012 invite Member States to develop and implement national strategies and action plans. It is against this backdrop that we have sought to review and refresh our current strategy and identify measures against which progress can be assessed.

Strategic Approach

Although resistance to all antimicrobials needs to be contained the primary focus of this strategy are antibacterials used in human and veterinary medicine because of the lack of new agents being developed.

This new integrated UK five year AMR strategy builds on the work that has gone before in the various parts of the UK[24] [25] [26] and takes account of developments at EU and international level aimed at limiting the spread of antimicrobial resistance.[27,28,29,30,31]

To effectively control the use of antibiotics, without significant detriment of human or animal health, a wide range of activities are proposed. These include measures to preserve existing therapies, slow down the development and spread of resistance (through improving infection prevention and control and reinforcing the need for improved and optimised prescribing practice) as well as the development of new antibacterial agents and diagnostic tools in all sectors. Previously we have relied on the introduction of new antibacterials to

[24] Changing the Culture 2010 Strategy for tackling Antimicrobial Resistance (STAR) 2012-17. Department of Health, Social services and Public Safety (DHSSPS). http://www.dhsspsni.gov.uk/star-doc.pdf

[25] The Scottish Management of Antimicrobial Resistance Action Plan 2008 (ScotMARAP) Antimicrobial stewardship in Scotland: impact of a national programme. http://www.scotland.gov.uk/Publications/2008/03/12153030/0

[26] Point prevalence survey of healthcare associated infections, medical device usage and antimicrobial usage 2011 report all wales http://www2.nphs.wales.nhs.uk:8080/WHAIPDocs.nsf/3dc04669c9e1eaa880257062003b246b/123aa708972f88c7802579f800389d94/$FILE/Wales%20PPS%20Report%202011%20Final%20Version.pdf
The Welsh Antimicrobial Resistance Programme.
http://www.wales.nhs.uk/sites3/page.cfm?orgid=457&pid=28418

[27] WHO European strategic action plan on antibiotic resistance 2011-2016. http://www.euro.who.int/__data/assets/pdf_file/0011/148988/RC61_Pres_Rodier_antibiotic_resistance.pdf

[28] 10582/12 JR/fm 1 DG B 1 Council of the European Union, Draft conclusions on antimicrobial resistance: http://register.consilium.europa.eu/pdf/en/12/st10/st10582.en12.pdf

[29] WHO's European strategic action plan on antibiotic resistance, 2011. http://www.euro.who.int/__data/assets/pdf_file/0008/147734/wd14E_AntibioticResistance_111380.pdf

[30] EU Action plan against the rising threats from Antimicrobial Resistance, COM (2011) 748. http://ec.europa.eu/health/antimicrobial_resistance/policy/index_en.htm

[31] The World Organisation for Animal Health (OIE) strategy/Terrestrial Animal Health Code 21st Edition 2012. http://www.oie.int/en/international-standard-setting/terrestrial-code/access-online/

overcome developing resistance, but we also need to focus on developing drugs with new targets or novel modes of action.

Action to improve public and professional knowledge and awareness of AMR issues through better training, information and guidelines to facilitate behaviour changes will also be critical. Improved antibiotic stewardship will be required which would be aided by greater use of electronic prescribing for humans. This will require leadership from clinicians, veterinarians and others such as senior managers in health and social care and patient groups.

For the first time five strategic national outcome measures are being set which we will use to monitor progress on an annual basis, assess the impact of the interventions and the success of the strategy in delivering improvements to public health protection across the board.

Strengthening The Evidence Base

Improving the evidence base and our understanding of resistance mechanisms is needed to help to strengthen our interventions to contain the spread of resistance and develop safe systems for reducing antibiotics use.

Given our limited understanding of the development of antimicrobial resistance, a greater emphasis will need to be given to research and surveillance activities as well as the development and discovery of effective new antimicrobials and diagnostics. The control of antibiotic resistance will also require research into the mechanisms that generate resistance and optimise antibiotic use.

There are a number of bodies supporting and funding research in the field of AMR.

The Medical Research Council (MRC) supports basic and translational research into AMR through:

- response mode Research and Programme Grants funded through the Infections and Immunity Board;
- Developmental Pathway Funding Scheme/Developmental Clinical Studies funded research;
- the UK-Canada Joint Partnership on Antibiotic Resistance in collaboration with the Canadian Institutes of Health Research;
- relevant research undertaken at the MRC Centre for Molecular Bacteriology and Infection at Imperial College London.

The National Institute for Health Research (NIHR) supports substantial research relevant to AMR. The research includes:

- translational biomedical research within the NIHR Biomedical Research Centres and Units with a number having specific research themes relevant to AMR,
- research undertaken at the NIHR Centre for Health Protection Research,
- NIHR Invention for Innovation-funded research,

- research into physical environment and AMR funded as part of the NIHR Physical Environment Programme and clinical research funded by the NIHR Health Technology Assessment Programme,
- NIHR Programme Grants for Applied Research, NIHR Research for Patient Benefit**.**

The Microbiology and Infection Translational Research Group (MITReG) promotes collaboration between researchers involved in all aspects of infection and microbiology research, from basic science through to clinical delivery to promote high quality translational research in this area. This is to be achieved by:

- establishment of a network of researchers across Wales and south west England
- development of Research Development Groups in the areas of:
    - Host pathogen interactions
    - Clinical and molecular epidemiology
    - Novel diagnostics
    - Novel therapies
    - Evaluation and Implementation

Defra and the Veterinary Medicine Directorate (VMD) also have funded significant research into the factors influencing antimicrobial resistance over many years. This remains a key area of interest for research and development (R&D), but with much fundamental work done we are now devoting attention to using the information gained to promote more responsible use of antimicrobials and strategies to minimise the development of resistance. However, where appropriate research is conducted on emerging issues.

Currently VMD sponsors research into a number of areas including:

- The occurrence of ESBLs on farms; and
- Motivations and drivers of antimicrobials prescribing practises in farmed animals.

VMD will seek to continue this research and along with relevant bodies/organisations consider how the results can be made more widely available to veterinarians, farmers and other interested stakeholders.

The Wales School of Primary Care Research (WSPCR) also supports research and its themes are:

- Infections and antibiotic resistance
- Integrated care for the frail / long term and / or chronic conditions
- Rehabilitation
- Out of hours care
- Effectiveness of interventions/quality of care
- Health communication and behaviour change
- Cancer in primary care
- Research leadership

Details of the extensive portfolio of WSPCR projects on antibiotic resistance is available at http://www.wspcr.ac.uk/research-portfolio.php

Funding for research projects in antimicrobial resistance is also available through the National Institute for Social Care and Health Research (NISCHR)'s responsive funding scheme on a competitive basis.

In Scotland, the Scottish Infection Research Network receives funding from the Scottish Government's HCAI programme to undertake specific remit around translational research for HAi and AMR.

We will seek to maximise the use of biomedical and clinical fundamental science to stimulate the development and implementation of new detection, prevention and treatment strategies (e.g. vaccines, antimicrobials, diagnostics, linking surveillance and epidemiological studies with molecular biology, host response, behaviour and health systems research).

We will also need to ensure data from surveillance is used better to improve our understanding of epidemiology and through better linkage of AMR surveillance data in human, animal, food and environmental settings.

Our expert scientific advisory committees will continue their horizon scanning activities to identify emerging issues in this area and we will keep the strategy and action plan under review.

Strategic Aims

This integrated UK AMR five year strategy and accompanying action plan identify key areas for development and measures against which progress can be assessed. We will focus on the following seven key aspects:

1. Promote responsible prescribing to preserve the activity of existing therapies and optimise prescribing practice;
2. Improve infection prevention controls for both bacterial and viral infections in human and animal systems;
3. Raise awareness of the problem posed by antimicrobial resistance, improve public and professional knowledge and promote change in behaviour in order to slow development of resistance
4. Improve the evidence base through research to inform understanding of microbial pathogenesis resistance, alternatives to new drugs and new or improved diagnostic tests, for humans and animals.
5. Facilitate and encourage the development of new drugs, vaccines and other immunotherapeutics;
6. Improving the evidence base by strengthening surveillance, epidemiological data, and data linkage arrangements
7. Strengthening UK and international collaboration, data and technology sharing across animal and human health fields to tackle this issue at a global level.

A wide range of activities have been identified to address these aspects, and are detailed in Annex 1. The Annex should be read in conjunction with the action plan, which sets out the main activities planned across the UK for 2013-2018. Our aim is to show by the end of this five year period we have made significant progress in controlling antimicrobial resistance and contributed to improving public health.

Strategic Outcome Measures

These measures have been developed to provide a means of assessing trends in resistance and in particular susceptibility of key bacteria to critically important antibiotics (CIA) used in human medicine to ensure we are making progress in controlling resistance in a way which avoids undesirable and unintended consequences. Progress will be tracked against the action plan and an annual report produced for each constituent part of the UK.

I. Monitor success in controlling the development of resistance by establishing the baseline and subsequent trends in a group of key "drug/bug" combinations identified by analysis of surveillance data;

II. Improve public and professional knowledge and understanding of antimicrobials and their appropriate use by embedding antimicrobial stewardship practice in human and animal medicine and improve the responsible prescribing in primary and secondary care settings compared to the position in 2012;

III. Aim to reduce the prevalence of resistance in farmed animals to critically important antibiotics in human medicine and those with cross resistance by promoting more appropriate use of antibiotics and reducing veterinary sales of such antibiotics by 5% through improvements in usage and antibiotic stewardship to be reflected in a reduction in amount of active ingredient sold for each Kg of meat produced;

IV. Maintain the good health of farmed animals by encouraging/promoting more effective usage of preventative approaches as alternatives to the use of antibiotics.

V. Identify options to facilitate (a) investigation of the changing epidemiology of AMR in human and/or animal populations, (b) implementing use of new point of care tests and rapid infectious disease diagnostics, and (c) management of focused clinical trials in antimicrobials for uncommon highly resistant pathogens to reduce delays associated with introducing new diagnostics etc.

Each country within the UK will determine appropriate means of measuring and monitoring progress towards delivery of the outcome measures in their country. Further details of monitoring aspects are outlined in Annex 2. Each part of the UK will produce an annual report in November which will focus on the progress made in that year in terms of implementing the action plan and an assessment of their effectiveness.

Conclusion

AMR is a complex issue which requires a comprehensive and concerted effort to tackle it effectively. To be truly successful in our endeavours we need to collaborate with others, keep abreast of and contribute to developments at a local, national, European and international level.

The UK's new strategy and will help improve the evidence base, tackle antimicrobial resistance, support the development of new antibacterials and other technologies such as diagnostics. The delivery measures that have been identified will help us monitor progress, assess the effectiveness of our actions and their impact for public health.

October 2012

Annex 1: The Seven Key Areas of Action

1. Promote responsible prescribing to preserve existing therapies and optimise prescribing practice for both bacterial and viral infections

Antibiotics and antivirals can save lives by fighting infections, but they must be prescribed carefully to optimise their use, treat patients effectively and reduce the risk of resistance. This involves establishing microbial sensitivity before starting therapy, apart from in severe acute cases, and closely monitoring this to prevent emergence of resistance. An increase in the number of infections that cannot be treated would affect everyone, and lead to a larger number of serious infections and probably more premature deaths as therapies to control these infections become less effective. Widespread development of resistance in animal pathogens could ultimately also lead to higher food prices.

Prescribing in all settings should be based on robust initial diagnosis to identify where antimicrobials are required with subsequent re-evaluations to re-consider the appropriateness of the diagnosis and ensure the right drug, right dose and right duration to optimise antibiotic use and limit unnecessary antibiotic exposure. Interventions to support antibiotic prescribing, such as the publication of *Start Smart Then Focus*[32] guidance on antibiotic stewardship in hospitals last year has added to the arsenal to reduce selection pressure for resistance and improves patient outcomes. The effectiveness of this resource has been evaluated and will be used to encourage wider use of this guidance to embed best practice further in hospital settings[33]. A similar resource (TARGET) is also being developed for use by GPs[34].

The First Point Prevalence survey of antimicrobial use in humans has provided a baseline from which to monitor prescribing and identify areas for intervention at a local and national level.[35] Prescribers will be aided in this

[32] Start Smart, Then Focus http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_131062

[33] to be added when available

[34] to be added when available

[35] English National Point Prevalence Survey on Healthcare-associated Infections and Antimicrobial Use, 2011: preliminary data http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_4007783

Scottish National Point Prevalence Survey of Healthcare Associated Infection and Antimicrobial Prescribing 2011http://www.hps.scot.nhs.uk/haiic/sshaip/publicationsdetail.aspx?id=51028

Point Prevalence Survey 2011 http://www.wales.nhs.uk/sites3/home.cfm?orgid=379

by having access to information on trends in resistance and when accompanied by training to interpret it will be better able to act on the information correctly.

2. Improve infection prevention controls in human and animal systems

Significant progress has been made in terms of improving infection prevention and control practices, largely due to the development of an extensive range of guidance, education and clinical expert support measures including audit tools as well as industry sponsored initiatives to promote the responsible use of antibiotics in animals. We now need to focus on embedding good practice, ensuring the evidence base is up to date and encouraging greater collaborative working to build competence in this area.

Government guidance has also been produced on biosecurity on farms and farm health planning for each of the major farming sectors. [36,37] Work with farmers and veterinarians is underway to develop National Control Plans for a number of the major farming sectors. These resources will give farmers the tools to reduce the risk of disease occurring in their animals.

Arrangements are expected to be strengthened in future when European law which is expected to require livestock farmers to take steps to prevent disease in animals demonstrate use of appropriate farm health plans as well as biosecurity and animal husbandry measures.

3. Raise awareness of the problem posed by antimicrobial resistance, improve public and professional knowledge and promote change in behaviour in order to slow development of resistance

Successful containment of antibiotic resistance ultimately depends on improved knowledge and responsibility by health care providers and veterinarians in prescribing and dispensing antibiotics, as well as on patients', public and farmer adherence.

We will continue to promote the need for responsible use of antibiotics in healthcare and other settings by encouraging greater development and use of local antibiotic prescribing policies. In addition, we will continue to promotion and awareness activities to optimise vaccine uptake which has a pivotal role in reducing infections and antimicrobial use.

Awareness-raising initiatives, such as the annual EU Antibiotics Awareness Day (EAAD), have been used since 2008 to remind both the public and professionals of the need to use antibiotics appropriately, launch best practice guidance on prescribing practices, and make available education materials and other resources to support local activity across the health

[36] http://www.defra.gov.uk/animal-diseases/biosecurity/
[37] http://archive.defra.gov.uk/foodfarm/farmanimal/fhp/index.htm; http://www.defra.gov.uk/food-farm/animals/

service. The 2011 EAAD activities in England have been evaluated to assess their effect and impact on raising awareness, change prescribing patterns and we will share this data nationally and internationally[38].

On the veterinary side, our focus includes educating veterinarians and farmers of the risks arising from antimicrobial resistance in animal husbandry, working with major retailers to encourage better husbandry and responsible use. We will also be encouraging farming sector events to disseminate responsible use messages. An EU survey of veterinary surgeons and their prescribing habits has recently been undertaken and this information will be used to inform the most effective steps/methods to improve prescribing

Greater awareness and practice of good hygiene by food businesses and consumers is important in protecting consumers from pathogens and other bacteria some of which may be resistant to antimicrobials. The Food Standards Agency continues to promote the 4Cs (cleaning, avoiding cross contamination, cooking and chilling) in its food hygiene messaging to both industry and consumers. The HPA also hosts the e-Bug educational resource for teachers and schoolchildren[39].

Work to ensure that prescribing and resistance issues are embedded in medicine, veterinary, nursing, pharmacy undergraduate and post graduate curricula will also be taken forward. Currently on the veterinary side VMD/Defra provide a contribution to veterinary undergraduate teaching on veterinary medicines, including antimicrobial resistance, at all seven of the UK veterinary colleges.

4. Improve the evidence base through research to inform understanding of microbial pathogenesis resistance, alternatives to new drugs, and new or improved diagnostic tests for humans and animals.

While there is a recognised need to encourage the development of new antibiotics, it is now widely accepted that this should be accompanied by development of vaccines and novel therapeutic approaches for humans and animals.

With increasing resistance caused by extended-spectrum beta-lactamases (ESBL) and carbapenemase producers, treatment of Gram negative infections in human medicine has become difficult as “pan-resistance” to all known classes of antibiotics has emerged among some pathogens. DH and Defra have commissioned research on ESBLs.

The NIHR’s research interests include translational work such as the Invention for Innovation programme and more basic research. The joint

[38] Ref to be added when available
[39] http://www.e-bug.eu/

MRC/NIHR Public Heath Infections Research Strategy (2010)[40] has identified the need for AMR research capability in the following areas:

- Novel approaches to surveillance and better integration of information infrastructure to determine spread of infectious disease (including across species) and disease burden, including antibiotic prescribing activity and patient and health professional behaviour
- Development and use of rapid diagnostics, including point of care diagnostics to avoid inappropriate treatment and reduce antibiotic misuse
- Innovation in antimicrobial development and the provision of evidence for novel molecules to be developed into drugs.

It also recognised the need for public sector investment to stimulate early stage work and promoting public-private product development partnerships; support of international initiatives to combat antimicrobial resistance, stimulate antimicrobial development and encourage prioritisation of anti-infectives in drug screening programmes.

Human and veterinary rapid diagnostic tests are also needed to differentiate between bacterial and viral infections, and enable fast identification of pathogens, high-risk strains and their resistance in hours rather than days. These tests, especially if available at the point of care, will better guide empiric therapies. Development of such diagnostics would provide the tools needed to develop targeted therapies, and reduce reliance on broad-spectrum drugs often used in treatment today.

The Technology Strategy Board which is government sponsored, also has a programme of work to fund developments in new and improved health-economics tools or products that will assist and improve the design and evaluation of diagnostic clinical trials for infectious agents[41]. This programme also includes the Small Business Research Initiative.

5. Facilitate and encourage the development of new drugs, vaccines and other immunotherapeutics

We can no longer rely on new antibacterials to control antibiotic resistance being developed at the same rate as in the past. Processes to facilitate the development of new drugs and international collaboration will be especially important.

The Office of health economics (OHE) report[42]makes a useful contribution to the debate and identifies a number of potential actions to improve the drug pipeline. Of particular interest are the ideas relating to introducing a fast track

[40] http://www.mrc.ac.uk/Utilities/Documentrecord/index.htm?d=MRC008110

[41] http://www.innovateuk.org/content/competition-announcements/new-development-projects-will-improve-the-assessme.ashx

[42] http://www.innovateuk.org/content/competition-announcements/new-development-projects-will-improve-the-assessme.ashx

priority review arrangement for new antimicrobials and encouraging the development of a European product development partnership scheme for antimicrobial drugs. Both these aspects are being explored at EU level. Further consideration also needs to be given at an EU level to the possibility of setting up a task force to come up with proposals for implementing incentives for antimicrobial research and development.

MRC will continue to fund basic and translational research in the areas of microbial pathogenesis, antimicrobial resistance and the development of new antimicrobials. Training in bacteriology and clinical microbiology will be supported through Fellowship schemes and the newly established MRC Centre for Molecular Bacteriology and Infection at Imperial College London will address the current lack of UK-trained expertise in the field. MRC will also lead UK participation in the EU Joint Programming Initiative on AMR.

Technologies such as whole genome sequencing may also have the potential to increase our ability to investigate the epidemiology of bacterial outbreaks and clusters in the medium term as their cost decreases. If these or other diagnostics can identify high-risk / prevalent strains of bacteria, and to infer their likely resistance directly in clinical specimens (i.e. blood urine or sputum), rather than after the 24 hours needed for culture, then there is a major opportunity to tailor patients' treatment at an earlier stage. This would be beneficial for both individual treatment and antibiotic stewardship. The use of genome base analyses in treatment of viral infections shows the potential of such developments on a wider scale

Alternatives to antibiotics for veterinary medicine include the investigation of best practice principles to reduce the reliance on antibiotics as well as alternatives to antibiotics including vaccines. Research on combination therapy and optimal dosing is needed. The One Health Agenda[43] will aid the development of both veterinary and human vaccines and therapeutics.

6. Improving the evidence base by strengthening surveillance, epidemiological data, and data linkage arrangements

Surveillance is essential to measure progress and to detect emerging problems. While national data are important, it is crucial to have local information available to inform local action. Resistance Alerts and enhanced surveillance (operated by HPA and in the future PHE[44]) will continue to be used to alert consultant microbiologists to the new and emerging antibiotic resistance issues, provide guidance and instigate enhanced surveillance. Ways of alerting a wider range of professionals and making better use of routine susceptibility data from human infections will be investigated.

[43] http://www.consilium.europa.eu/uedocs/cms_data/docs/pressdata/en/lsa/131126.pdf

[44] HPA's core functions will pass to Public Health England (PHE) from April 2013

Work is underway in England to develop and facilitate update of surveillance systems such as *Vitek 2 antibiotic susceptibility testing (AST) and AmSURV web based reporting tool* to improve the identification and control of resistant human infections and dissemination of the data to ensure that resistance data are fed back to prescribers .

Further opportunities for data linkage will also be explored. The HIV resistance database has shown the value of linking clinical and laboratory data. With the recent emergence of directly acting antiviral agents to treat chronic hepatitis C infection, robust surveillance of hepatitis C drug resistance, building on the successful precedent of HIV drug resistance surveillance will be required. There will also be scope to develop surveillance of hepatitis B drug resistance.

In addition, opportunities for linking human and veterinary data need to be investigated and consideration of sharing laboratory/testing methods between the sectors is required. There may also be scope for testing samples collected for other projects for resistant organisms, thus maximising outcomes from existing work.

In farming, the AHVLA in England and Wales, and the SAC in Scotland and DARDNI in Northern Ireland carry out surveillance of antimicrobial resistant zoonotic bacteria, animal pathogens and some commensal organisms, which are reported and published, principally on the VMDs website. Where significant resistance is detected in a zoonotic organism, which is a comparatively rare event, this is reported directly to the HPA or HPS, which assesses the risk to consumers.

In addition there is an initiative co-ordinated at EU level, which builds on work from the veterinary industry to improve target animal pathogen surveillance- the 'Target Pathogen Monitoring Programme'.In addition the HPA and Food Standards Agency (FSA) undertake screening of bacteria for antimicrobial resistance as part of food surveillance activities. Again new technologies such as whole genome sequencing could enhance our ability to investigate and attribute foodborne outbreaks and clusters including those involving antimicrobial resistance strains.

The UK will continue to participate in EU surveillance activities and the following four key EU networks:

- European Antimicrobial Resistance Surveillance network (EARS - net), which collects resistance information on invasive isolates of *S*. *aureus, S*. *pneumoniae, Enterococcus faecium*, *Enterococcus faecalis, E*. *coli*, *Klebsiella* spp. and *Pseudomonas aeruginosa.* The HPA will encourage more UK laboratories to participate in this work;
- European Surveillance of Antibiotic Consumption network (ESAC - net), which monitors antibiotic consumption in ambulatory and hospital care.

- European Surveillance of Veterinary Antimicrobial Consumption project, which collects information on how antimicrobial medicines are used in animals across the European Union (EU).
- The European Food Safety Authority EU Summary Report for Antimicrobial Resistance

7. Strengthening UK and international collaboration, data and technology sharing across animal and human health fields to tackle this issue at a global level

Access to clinical data for research is a key focus of the UK Strategy for Life Sciences launched in December 2011.The Department of Health has lead responsibility for the provision of and access to clinical data for research through the Clinical Practice Research datalink (CPRD)[45] launched in March 2012 by MHRA working with NIHR.

Increased collaborative working is needed to foster innovation in the development of new antimicrobial agents, diagnostics and multi-disciplinary collaborations between researchers working on AMR in humans and animals to address the 'One-Medicine' agenda. MRC will be involved in European-wide work to map what research is ongoing across Europe to help identify gaps and opportunities.

We will also seek to respond constructively to the WHO Action to establish a co-ordinated platform to facilitate effective interaction of stakeholders to strengthen efforts to reduce the public health risk of anti-microbial drug resistance. This is expected to involve contributing to WHO led work to:

- Promote inter and intra sectoral co-ordination and collaboration to foster exchange of ideas, identification of priority issues and alignment of strategies;
- Raise awareness of AMR as a global problem and promote best practices worldwide, including prudent use of antimicrobials, effective infection control measures and on strengthening health and regulatory systems;
- Identify gaps in knowledge and evidence and advocate research to fill these gaps;
- Develop policies and strategies to eliminate inappropriate sue of antimicrobials and reduce spread of AMR;
- Support the collection and collation of surveillance and epidemiological data by member States through development of standards and protocols for data collection and reporting. In this way information can be shared at a country, regional and global levels with confidence.

[45] http://www.cprd.com/intro.asp

Annex 2 _ Monitoring of national outcome measures

Measure 1: Monitor success in controlling the development of resistance by establishing the baseline and subsequent trends in key "drug/bug" combinations as determined by surveillance data.

The following drug/bug combinations will be monitored in the first instance:

- Klebsiella - carbapenem (% non-susceptible to imipenem &/or meropenem)
- *E. coli* - cephalosporin (% non-susceptible to cefotaxime &/or ceftazidime)
- *E. coli* - fluoroquinolone (% non-susceptible to ciprofloxacin)*
- Pseudomonas - carbapenem (% non-susceptible to imipenem &/or meropenem)
- *N. gonorrhoeae* - ceftriaxone (% non-susceptible
- Klebsiella – cephalosporin- (% non-susceptible to cefotaxime &/or ceftazidime)
- Pseudomonas - cephalosporin (% non-susceptible to ceftazidime)
- *E. coli* - gentamicin (% non-susceptible)
- *S. pneumoniae* - penicillin (% non-susceptible)

With the exception of *N. gonorrhoeae* the surveillance will focus on blood isolates and for this measure non-susceptible includes both intermediate and resistant results. In England this will probably be achieved through improved reporting to the PHE's LabBase system but the options for using AmSurv will be investigated. In Scotland standardised susceptibility data derived from VITEK 2 systems on relevant combinations of antimicrobial agents and organisms causing bacteraemia (in line with EARS-net) have been collected via electronic reporting (via ECOSS) and reported routinely in joint annual antimicrobial use and resistance reports since 2008. Susceptibility data on Neisseria gonorrhoeae will be obtained from the existing Gonococcal antibiotic surveillance in Scotland (GASS) (data are available since 2007).

Measure II: Improve public and professional knowledge and understanding of antimicrobials and their appropriate use by embedding antimicrobial stewardship practice in human and animal medicine and improve the responsible prescribing in primary and secondary care settings compared to the position in 2012.

In England this will be taken forward through ARHAI. In Scotland the quality of prescribing (and trends in those) will be monitored through a range of qualitative and quantitative prescribing indicators including sets of HEAT target indicators for hospitals, primary care indicators and national therapeutic indicators (related to practice around use of antimicrobials). Quantitative data on antimicrobial usage will be collected through the national databases PRISMS (primary care) and HMUD (hospitals), and local surveillance, and through annual audits of hospital prescribing (in the form of a point prevalence

study aligned with ESAC methodology) and primary care prescribing (using a national audit tool).

Measure III: Aim to reduce the prevalence of resistance in farmed animals to critically important antibiotics in human medicine and those with cross resistance by promoting more appropriate use of antibiotics and reducing veterinary sales of such antibiotics by 5% through improvements in usage and antibiotic stewardship to be reflected in a reduction in amount of active ingredient used for each Kg of meat produced.

In England this will use data collected on antimicrobial susceptibility of bacteria of veterinary origin (from clinical diagnostic material submitted) to provide information on resistance, and the sales of antimicrobial products data that VMD collate. In Scotland the approach will be in line with that used in England, antimicrobial susceptibility of bacteria of veterinary origin submitted from clinical diagnostic material will be provided by SAC. Sales of antimicrobials will be obtained from VMD.

Measure IV: Maintain the good health of farmed animals by encouraging/promoting more effective usage of preventative approaches as alternatives to the use of antibiotics.

Quantitative measurement of this would be difficult but it is anticipated we should be able to provide some qualitative information.

Measure V: Identify options to facilitate (a) investigation of the changing epidemiology of AMR in human and/or animal populations, (b) implementing use of new point of care tests and rapid infectious disease diagnostics, and (c) management of focused clinical trials in antimicrobials for uncommon highly resistant pathogens to reduce delays associated with introducing new diagnostics etc.

Identifying options to facilitate advances in research, improved surveillance, diagnostics and clinical trials will require a collaboration with a number of partners at both UK and sub-national levels. In England the HPA will lead on surveillance and discussions held with NIHR, MRC and NICE on potential gaps in the translational research programmes. In Scotland research and development will be progressed through SIRN. HPS will lead on projects involving national AMR datasets. Rapid diagnostics/point of care testing is evaluated via NICE and clinical trials will be developed through collaboration with ECDC, CDC and other international lobbying groups.

Annex 3: Impact of Antimicrobial Resistance Strategy

Please see page 14 for a summary of the questions asked in relation to the impact of the strategy

Introduction

1. The rapid spread of multi-resistant bacteria and the lack of new antibiotics poses a rapidly increasing threat to public and animal health and needs to be tackled if we are to contain the problem and prevent untreatable illness becoming a reality. Antimicrobials (i.e. antibiotics, vaccines) are the cornerstone in modern medical practice for treatment and prophylaxis and the lack of new antibiotics has provided a driver for action in this area. Containing the problem and preventing untreatable illness and premature mortality is a clear priority. The need for collective action to ensure antibiotics are used wisely and sparingly has never been more important than now.

2. The 2013-2018 UK AMR strategy builds on the 2000 UK Strategy and Action Plan and takes account of developments at EU and international level, including the 2011 EU Strategic Action Plan, and 2012 EU Council Conclusions. It also provides a framework for collaborative work to champion the responsible use of antibiotics, strengthen research and surveillance capability, facilitate behaviour change through more responsible prescribing and use of better use of antibiotics.

Strategic Aims

3. This integrated UK AMR five year strategy and accompanying action plan identify key areas for development and measures against which progress can be assessed. We will focus on the following seven key aspects:
    (a) Promote responsible prescribing to preserve the activity of existing therapies and optimise prescribing practice;
    (b) Improve infection prevention controls in health care and husbandry for animal systems;
    (c) Raise awareness of the problem posed by antimicrobial resistance, improve public and professional knowledge and promote change in behaviour in order to slow development of resistance
    (d) Improve the evidence base through research to inform understanding of microbial pathogenesis resistance, alternatives to new drugs and new or improved diagnostic tests, for humans and animals.
    (e) Facilitate and encourage the development of new drugs, vaccines and other immunotherapeutics;
    (f) Improving the evidence base by strengthening surveillance, epidemiological data, and data linkage arrangements
    (g) Strengthening UK and international collaboration, data and technology sharing across animal and human health fields to tackle this issue at a global level.

Strategic Outcome Measures

4. These measures have been developed to provide a means of assessing trends in resistance and in particular susceptibility of key bacteria to critically important antibiotics (CIA) used in human medicine to ensure we are making

progress in controlling resistance in a way which avoids undesirable and unintended consequences. Progress will be tracked against the action plan and an annual report produced for each constituent part of the UK.

Strategic Outcome Measures

I. Monitor success in controlling the development of resistance by establishing the baseline and subsequent trends in a group of key "drug/bug" combinations identified by analysis of surveillance data;

II. Improve public and professional knowledge and understanding of antimicrobials and their appropriate use by embedding antimicrobial stewardship practice in human and animal medicine and improve the responsible prescribing in primary and secondary care settings compared to the position in 2012;

III. Aim to reduce the prevalence of resistance in farmed animals to critically important antibiotics in human medicine and those with cross resistance by promoting more appropriate use of antibiotics and reducing veterinary sales of such antibiotics by 5%; through improvements in usage and antibiotic stewardship to be reflected in a reduction in amount of active ingredient sold for each Kg of meat produced

IV. Maintain the good health of farmed animals by encouraging/promoting more effective usage of preventative approaches as alternatives to the use of antibiotics.

V. Identify options to facilitate (a) investigation of the changing epidemiology of AMR in human and/or animal populations, (b) implementing use of new point of care tests and rapid infectious disease diagnostics, and (c) management of focused clinical trials in antimicrobials for uncommon highly resistant pathogens to reduce delays associated with introducing new diagnostics etc.

Scope of the calculations

5. The strategy brings together a number of existing, new and planned actions, described in more detail in the Action Plan. This annex estimates the major new effects as a result of the publication of the strategy. These include new activities and increasing the effectiveness of existing measures, and embedding interventions which appear to be effective. Existing initiatives that will not be substantially affected, along with future planned initiatives are not included here.

6. The following actions have been identified as the focus of these calculations (although there will be further effects):
    (a) Monitor current levels of resistance in specific microbe-drug combinations
    (b) Improved uptake of Start Smart Then Focus in secondary care
    (c) Improved usage of Target web-based tool by GPs
    (d) Summit on Antimicrobial Resistance
    (e) Improved antimicrobial stewardship programmes in the farmed animals sector.

Number of antibiotics

7. The main estimates of the impact of the strategy assume that there will be no substantial change in the *number* of antibiotics used (and antimicrobials more widely), with the exception of the farmed animal sector, where there is an ambition to reduce usage of critically important antibiotics (CIAs). The main impact in the other sectors comes through a change in the type and appropriateness of antibiotics used, as well as changes to antimicrobial stewardship programmes. The effects of varying this assumption are described in the 'risks and alternative scenarios' section.

Question 1: is the strategy likely to lead to a substantial impact on the number of antibiotics prescribed (in any of the sectors)?

Geographical scope

8. The following calculations focus on England only. It is assumed that the effects in England will provide a suitable proxy for the United Kingdom as a whole.

Question 2: are there any substantial differences between England and the rest of the UK that would change the results of the analysis?

Publication of strategy

Benefits

9. The publication of the strategy itself is expected to have a positive impact on antimicrobial stewardship and therefore a reduction in antimicrobial resistance. This is through generally raising awareness of existing programmes and reminding individuals involved of general best practice. This is the main benefit of introducing the strategy, but it is difficult to quantify or monetise.

10. The up-front effects of resistance are small, as many infections that are resistant to one antimicrobial agent may be sensitive to another. While the other agent might be more expensive, this cost is relatively small. However, more substantial problems arise when infections become resistant to multiple drugs. In such a scenario, some infections would become untreatable, carrying high risks of mortality. This would make routine surgery (with its reliance on antibiotics) very risky. Appropriate antimicrobial stewardship reduces the likelihood of this scenario and postpones its arrival, generating further time in which new antimicrobials can be created.

11. By its very nature, it is uncertain what effects would be and when they may occur, in the absence of any further intervention. However, the benefit of postponing and reducing the likelihood of this scenario is substantial, and likely to outweigh the costs presented in the analysis below. It should be noted that each of the actions (i) to (v), while they have benefits specific to their area, all combine to contribute to this primary benefit.

Costs

12. In order for the publication of the strategy to have this impact, there will be time costs for relevant individuals to read and reflect on the strategy, and to introduce any subsequent changes in practice. It is assumed that each relevant person will take around three hours to do this. This will cover five main sectors: primary care, secondary care (consultants, registrars and pharmacists), farmers, veterinarians, and academic researchers. These costs may be in the region of £3.1m in year one (with no additional costs in future years). This is detailed in the table below. There may be other interested parties who read the strategy, but the following outlines the main groups.

Table 1. Time cost of reading reflecting on strategy

Sector	Persons involved	Annual salary (£)	Salary per hour (£)	Number reading strategy	Total cost (£)
Primary care	One GP per practice *(1)*	109,400	65.51	8,316	1,634,000
Secondary care	One consultant per hospital *(2)*	117,000	70.06	200	42,000
	One registrar per hospital *(3)*	55,600	33.29	200	20,000
	Senior hospital pharmacists *(4)*	63,000	37.74	1354	153,000
Farming	One senior farmer per farm *(5)*	-	9.00	31,892	861,000
Vets	One vet per practice *(6)*	49,000	29.34	4,162	366,000
Research	Approx 50 across the country *(7)*	47,348	28.35	50	4,000
Total					**3,081,000**

Notes to table 1:
(1) Mean basic salary for GPMS general practitioner (2009/10) from Information Centre (www.ic.nhs.uk); number of GP practices (2011) from Information Centre
(2) Mean basic salary of consultant on new contract (Q2 2011/12) from Information Centre; number of NHS trusts (September 2012) from NACS (www.connectingforhealth.nhs.uk/systemsandservices/data/ods/datafiles/data-files)
(3) Mean basic salary of registrar (Q2 2011/12) from Information centre; number of NHS trusts (September 2012) from NACS
(4) Mid-point of salary range for Band 8b to 8d staff (www.nhscareers.nhs.uk/working-in-the-nhs/pay-and-benefits/agenda-for-change-pay-rates/); Number of Band 8b to 8d pharmacists in Hospitals from Table 23 "Pharmacy Workforce Census 2008" (www.rpharms.com/about-pharmacy-pdfs/census08.pdf)
(5) Hourly wage for Band 5 farmer from DEFRA report "Farm Labour and Wage Statistics 2012"; number of relevant farms from Farm Business Survey 2010/11 (www.www.farmbusinesssurvey.co.uk)
(6) Average basic salary of veterinarians working in the sector from "The 2010 RCVS Survey of the UK Veterinary and Veterinary Nursing Professions"; number of practices from Royal College of Veterinary Surgeons report "RCVS Facts 2012"
(7) Average salary of full-time academic staff (2011) from Times Higher Education report on "Average Salary of Full Time Academic Staff 2010/11"; number of researchers based on internal expert opinion
* Figures may not sum due to rounding

Question 3: in terms of reading the published strategy, are there any other major groups to include; are those included reasonable?

(a) Monitor current levels of resistance in specific microbe-drug combinations

13. Under this action, laboratories will report susceptibility data on a specified set of bacteria and drug combinations (for example, the percentage of people with *E. coli* bacteraemia and treated with gentamicin who are not susceptible to gentamicin – see the appendix for the full list). These particular combinations have been chosen as they represent areas that are difficult to treat. A number of laboratories already provide this information, but it is not comprehensive. While this option will not make such surveillance mandatory, such a request from the HPA will encourage all laboratories to report this data.

Costs

14. There are approximately 160 acute trust laboratories. Current estimates from the HPA suggest that 80-90% of laboratories routinely report clinically significant bacteraemia, and 70-80% of these provide susceptibility data to the HPA. Therefore, around 60 laboratories would need to introduce this type of reporting. This would require altering their data extracting process from the lab system. Estimates from the HPA suggest that such an alteration would involve a one-off cost of half a day of qualified scientist staff time in year one, at an annual salary of £38,800.[46] This suggests a total cost of around £5,000 in year one only across all relevant laboratories.

15. Further costs will be incurred for testing gonorrhoea samples. To obtain better information on trends in susceptibility the testing method will need to be changed for about 15,000 samples a year. Estimates from the HPA suggest this will cost approximately £10 per sample to the laboratory, in terms of materials and technician time. Therefore, there will be ongoing costs of

[46] Based on the mean total earnings of a Qualified Scientific, Therapeutic and Technical Staff member (Q2 2012), assuming around 223 working days a year (www.ic.nhs.uk)

around £150,000 per year. In addition to NHS laboratory costs there will be resource implications for the HPA in collation and analysis of the data and gonorrhoea samples. This is expected to require a total of five days of consultant time (valued at an average annual salary of £117,000)[47] and five days of qualified scientist time (valued at an average annual salary of £38,800) each year. This totals £3,500 p.a. Therefore, the total costs of gonorrhoea testing are therefore expected to be approximately £154,000 per year.

16. The total cost for this action would be around £160,000 per year (taking into account the costs to laboratories and the HPA in reporting susceptibility and reporting and testing gonorrhoea samples). Over ten years, the total cost would be £1.4m, when discounted at 3.5% per year.

Question 4: Will there be any additional costs in monitoring bacteraemias and susceptibility; are the costs included reasonable?

Benefits

17. Increased monitoring is likely to lead to an improved understanding of the geographical spread and trends over time in specific areas of resistance. It may also enable more rapid identification of any outbreak of resistant bacteria, leading to a swifter response. However, such benefits are not possible to quantify and will be dependent on how resistance changes and develops over time.

(b) Improved uptake of Start Smart Then Focus in secondary care

18. The Start Smart Then Focus (SSTF) guidance in secondary care was launched in November 2011. It provides an outline of evidence-based antimicrobial stewardship in secondary healthcare settings.

[47] Based on the mean total earnings of a consultant on a new contract (Q2 2012) (www.ic.nhs.uk)

Start Smart is:

- Do not start antibiotics in the absence of clinical evidence of bacterial infection
- If there is evidence/suspicion of bacterial infection, use local guidelines to initiate prompt effective antibiotic treatment
- Document on drug chart and in medical notes: clinical indication, duration or review date, route and dose
- Obtain cultures first
- Prescribe single dose antibiotics for surgical prophylaxis; where antibiotics have been shown to be effective

Then Focus is:

- Review the clinical diagnosis and the continuing need for antibiotics by 48 hours and make a clear plan of action - the "Antimicrobial Prescribing Decision"
- The five Antimicrobial Prescribing Decision options are: Stop, Switch IV to Oral, Change, Continue and Outpatient Parenteral Antibiotic Therapy (OPAT).
- It is essential that the review and subsequent decision is clearly documented in the medical notes.

19. Initial intelligence suggests some initial returns from the policy. Introduction of the strategy may raise its profile and increase implementation across NHS acute hospitals, with associated costs and benefits.

Costs

20. Data from a UK Clinical Pharmacy Association survey (in conjunction with the University of Leeds and Leeds Teaching Hospital) suggests that over 90% of hospitals have performed at least an short information review based on the SSTF guidance. However, only around 45% had conducted a formal written review. In these latter set of hospitals, only a short half-day review may be required, while a full day review may be needed in the remaining hospitals. Further evidence from the UKCPA suggests there remain variations in practice, for example around the existence of antimicrobial stewardship ward rounds.

21. These reviews may require one consultant and one administrative staff member for this period of time each. With average total earnings of £117,000 for a consultant and £28,000 for a member of administrative staff,[48] the cost of a short review would be around £600 and a longer review £1,300. With approximately 100 trusts falling into each category, the total cost of such a review would be around £200,000. This would fall in year one only.

22. There will be increased time costs for consultants due to this rise in documentation. While the amount of time may be small for each course of antibiotics, there are a substantial number dispensed in hospitals. The Point Prevalence Survey[49] found that approximately 26,000 antibiotics were prescribed among the 52,000 patients investigated, suggesting that around

[48] Based on the mean total earnings of a consultant on a new contract and the mean total earnings of a member of administrative staff (Q2 2012) (www.ic.nhs.uk)
[49] www.hpa.org.uk/Topics/InfectiousDiseases/InfectionsAZ/HCAI/HCAIPointPrevalenceSurvey/ (main publication, p.44)

0.5 antibiotics are prescribed per patient investigated. With 14.9m admissions to NHS hospitals in 2010/11,[50] this implies around 7.4m antibiotics may be used each year. Evidence from the UK CPA suggest that less than 80% of those surveyed in hospitals fully documented the indication and duration of prescribed drugs. Therefore, it is plausible that this policy may increase documentation in around 10% of those cases, i.e. amongst 0.7m antibiotics. This increased documentation is relatively small, so an indicative figure of a minute of extra time is used. This would translate into 12,000 consultant-hours, or around 7.4 consultant-years p.a. Assuming The mean total annual earnings of a consultant are around £116,900, which translates into an ongoing cost of £860,000 per year.

23. The total cost of this option is therefore likely to be in the region of £0.9m per year, with an additional £0.2m in year one. This takes into account the one-off cost of reviewing procedures and the ongoing cost of increased time in documenting prescribing. Over ten years, the total cost would be £7.6m, when discounted at 3.5% per year.

Question 5: will there be any further costs to the increase in SSTF across secondary care; is the strategy likely to lead to this level of change?

Benefits

24. Improved implementation of SSTF is likely to lead to improved quality of prescribing in NHS acute trusts. For example, a UK CPS survey found that, among those hospitals that had conducted a formal review of their antimicrobial stewardship programme, over 75% of hospitals had seen a reduction in inappropriate prescribing following SSTF.There may be a slight reduction in the quantity prescribed (as patients are taken off unnecessary antibiotics sooner than before), leading to a cost saving for hospitals. However, this is likely to be small, as the main benefit comes from more appropriate prescribing.

25. The effect of improved quality of prescribing will be twofold – affecting both the short run and the long run. In the long run, improved quality of antibiotic prescribing will lead better tailored antibiotics, following the Start Smart Then Focus description: “Right Drug, Right Dose, Right Time, Right Duration, Every Patient”. This is likely to lead to reduced antimicrobial resistance over time, as inappropriate antimicrobials are reduced.

26. There is also likely to be a more immediate effect of this policy, but one which would be ongoing. Improved quality of prescribing would reduce the amount of time patients’ suffer infection and prevent the onset of other infections, thereby improving their quality of life and reducing their length of stay in hospital (freeing up resources to be used for other patients). It is difficult to quantify this benefit, as it will have an impact on a wide range of patients, who will have varying conditions. This is consistent with the evidence from the UK CPA survey, which found that over 10% of hospitals experienced a demonstrable reduction in length of stay and mortality metrics following the introduction of SSTF.

27. One area where improved quality may have a measurable impact is in the treatment of sepsis. Patients with sepsis will spend extended periods of time

[50] Total admissions from Hospital Episode Statistics (2010/11)

in critical care beds, with organ support required. The average cost to the NHS of a critical care bed is £1,200 per day.[51] There are around 25,000 cases of septicaemia each year that may be affected.[52] While it is not known how many of these would be affected, or for how much time, it is plausible that 5% of these patients may benefit from around two fewer days in critical care. This would suggest ongoing cost savings of around £3.0m per year. There would be further health benefits that are not monetised here.

28. The total quantifiable benefit of this action over ten years may be around £26.2m, when discounted at 3.5% per year. Again, there would be further health benefits from improving treatment of septicaemia, as well as the longer term benefits of reducing antimicrobial resistance. Tentative evidence from the UK CPA survey suggests that nearly a quarter of hospitals have already demonstrated a reduction in antimicrobial resistance in their settings. The effects of this are likely to be felt much more widely, are resistant strains of infections are therefore less likely to be carried in the general population. However, these benefits cannot be quantified.

Question 6: is the reduction in sepsis reasonable; are there any further measurable benefits from this action?

Independent Sector

29. The independent sector providing acute services generally have similar AMR polices to NHS hospitals but a higher proportion of their patients are prescribed antibiotics in England compared to the NHS. This may reflect their casemix. By reviewing their policies and practices, it is likely that they would be able to improve patient care, and possibly reduce costs. Data on antibiotic use in the independent sector is limited, so these costs (and associated benefits) have not been included.

(c) Improved usage of Target web-based tool by GPs

30. Work is underway by the Royal College of General Practitioners (RCGP) and the Health Protection Agency (HPA) to launch a new web based toolkit (Target) to support GP prescribing this November. The toolkit will be trialled at a conference in the early autumn. We would expect at least 50% of GPs to consult the website and use some of the materials in their practice.

31. The strategy plus European Antibiotic Awareness Day (EAAD) on 18 November will publicise this tool. This is likely to help embed its use into practice but the work will proceed irrespective of the strategy. Mention of it is the strategy is expected to increase professional awareness and perhaps encourage another 10% of GPs to access it.

Costs

32. Acquainting themselves with the tool will take a small portion of GPs time. With around 40,000 GPs in England,[53] 10% of these would represent 4,000

[51] Based on an average cost of the different levels of support (from zero to six organs), weighted by activity, from NHS reference costs (2010/11).
[52] Based on long stay non-elective inpatient activity levels for septicaemia with intermediate and major complications (WA03V and WA03X) from NHS reference costs (2010/11)
[53] Based on the headcount number of all General Practitioners, as at 2011 (www.ic.nhs.uk)

individuals. Assuming an average salary of approximately £109,400 per year,[54] the cost per hour of their time is around £66. Assuming that it takes each GP an hour to acquaint themselves with the tool, this will result in a one-off cost in year one of £260,000. GPs are not expected to incur any significant ongoing costs once they are acquainted with the tool.

Question 7: will there be any further costs to the increase in usage of Target across primary care (in particular ongoing costs); is the strategy likely to lead to this level of change?

Benefits

33. Improved uptake of the Target tool is likely to lead to improved quality of prescribing in primary care settings. There may be a slight reduction in the quantity prescribed (as patients are taken off unnecessary antibiotics sooner than before, or are not prescribed them originally), leading to a cost saving for GP surgeries. However, this is likely to be small, as the main benefit comes from more appropriate prescribing.

34. The effect of improved quality of prescribing will be primarily in the long run, in the form of improved quality of antibiotic prescribing. This follows the Start Smart Then Focus description: "Right Drug, Right Dose, Right Time, Right Duration, Every Patient". This is likely to lead to reduced antimicrobial resistance over time, as inappropriate antimicrobials are reduced.

Question 8: are there any measurable benefits from the increase in usage of Target in primary care (in addition to the longer term benefit around resistance)?

(d) Summit on Antimicrobial Resistance

35. Under the strategy, a national summit would take place approximately in year two. This summit would involve some 150 key players and specialists, with international reach. This would involve one-off travel costs for participants paid by the Department of Health, which would be in the region of £10,000. The summit would seek to get support from society in general, generating a benefit by reinforcing the above initiatives.

(e) Improved antimicrobial stewardship in farmed animals sector

36. Following the publication of the strategy, it is expected that farmers will review their antimicrobial stewardship programmes. This is in addition to the time spent reading and reviewing the strategy itself (as presented above). These reviews may cover their Farm Health Plans (or result in their introduction in some farms), and biosecurity measures. The effect of improved antimicrobial stewardship will be felt in the long run, in the form of improved quality of antibiotic usage. This is likely to lead to reduced antimicrobial resistance over

[54] Based on the average salary of GPMS General Practitioners for the most recent year (2009/10) (www.ic.nhs.uk)

time, as inappropriate antimicrobials are reduced. The more immediate and quantifiable costs and benefits are presented below.

Costs to farmers

37. While it is not known how farmers would undertake such reviews, this note makes a number of assumptions to produce some indicative costs. Approximately half of all farms may undertake a more substantial review, lasting around 10 hours, with the remainder undertaking a shorter review of around 5 hours. There are approximately 32,000 grazing and dairy livestock farms in England.[55] The wage of a senior farmer is approximately £9.00 per hour.[56] Therefore, the total cost of this review will be around £2.2m. This will occur in year one only, and there are not expected to be any further substantial ongoing costs.

Question 9: will there be any ongoing costs as a result of the change in antimicrobial stewardship in the farming sector; are these costs reasonable?

Benefits to farmers

38. It is expected that the annual usage of critically important antimicrobials (CIAs) will fall by approximately 5% as a result of this. Existing data suggests that the CIA market in the farmed animals sector is a small proportion of the overall market in that sector, as shown below. While this shows the scale by tonnage, there are currently no robust and comprehensive data on the financial scale of this market.

Table 2. Sales of Critically Important Antibiotics authorised for use as veterinary products (2010)

	Quantity sold (tonnes, 2010)	Percentage of total antimicrobials sold (447 tonnes)
3rd and 4th generation cephalosporins	1.4	0.3%
Fluoroquinolones	2.2	0.5%
Macrolides	35	7.8%

39. In making this reduction, farmers may either switch to other antibiotics, or may not.
    - In the former case, costs for farmers may decrease (if the switch is to cheaper antibiotics, for example from branded to generic ones). There will be an associated loss to pharmaceutical companies in terms of the profits if the switch is from high-profit antibiotics to low-profit ones. The loss in profits may equal the gain to farmers, leading to a neutral outcome.

[55] Farm Business Survey (2010/11) www.farmbusinesssurvey.co.uk
[56] Hourly wage for Band 5 farmer from DEFRA report "Farm Labour and Wage Statistics 2012"; number of farms with dairy and livestock from Farm Business Survey 2010/11 (www.www.farmbusinesssurvey.co.uk)

- In the latter case, farmers will make a saving. Pharmaceutical companies will see a fall in profits. However, this will be smaller than the benefit to farmers (as profits must be less than the price of the antibiotic). This would result in a net gain to the economy.

Question 10: are there are robust sources for the financial size of the antibiotic industry for farmed animals, particularly CIAs; are there any other sources that may provide an indication of this size?

Question 11: are there any measurable benefits from the change in antimicrobial stewardship in the farming sector (in addition to the longer term benefit around resistance)?

Overall impact of strategy

Costs

40. The following table summarises the incremental costs involved in implementing the elements of the strategy described above. As mentioned before, the strategy brings together a number of existing, new and planned initiatives. Those presented here are the major new effects as a result of the publication of the strategy. Existing initiative that will not be substantially affected, along with future planned initiatives are not included here. The final column shows the present value of these costs, as measured over ten years, using the Government's standard discount rate of 3.5% per year.

Table 3. Summary of Costs (£m)

	One-off in year one	**Ongoing per year**	**Total over ten years (discounted)**
Publication of strategy	3.1	-	3.1
(a) Improved monitoring of resistance	-	0.2	1.4
(b) Improved uptake of SSTF in secondary care	0.2	0.9	7.6
(c) Improved usage of Target in primary care	0.3	-	0.3
(d) Summit on Antimicrobial Resistance	0.01	-	0.01
(e) Improved antimicrobial stewardship in farming sector	2.2	-	2.2
Total	**5.7**	**1.0**	**14.5**

* Note: figures may not sum due to rounding

Benefits

41. The following table summarises the incremental benefits involved in implementing the above elements of the strategy. As the table demonstrates, the majority of these cannot be quantified (with the exception of improved treatment of sepsis, through improved uptake of Start Smart Then Focus).

Table 4. Summary of Benefits (£m)

	One-off in year one	Ongoing per year	Total over ten years (discounted)
Publication of strategy	-	Unquantified	Unquantified
(a) Improved monitoring of resistance	-	Unquantified	Unquantified
(b) Improved uptake of SSTF in secondary care	-	3.1 + unquantified	26.3 + unquantified
(c) Improved usage of Target in primary care	-	Unquantified	Unquantified
(d) Summit on Antimicrobial Resistance	-	Unquantified	Unquantified
(e) Improved antimicrobial stewardship in farming sector	-	Unquantified	Unquantified
Total	**-**	**3.1 + unquantified**	**26.3 + unquantified**

Net Benefit

42. Based on the above calculations, the strategy is likely to lead to an increase in costs of around £1.3m per year, with a further cost of £5.6m in year one. The present value of these costs, when measured over ten years and discounted at 3.5% per year, is **£14.4m**.

43. The quantifiable benefits (from reduced sepsis) are likely to be around £3.1m per year. The present value of this over ten years is **£26.3m**. However, there are further benefits as a result of this strategy, primarily around reduced antimicrobial resistance. These are likely to occur in the longer run and have not been possible to quantify.

44. As a result, the net present value of the strategy is likely to be around **£11.8m** over ten years. However, as stated above, this includes only the quantifiable costs and benefits. There are likely to be substantial further benefits that have not been possible to quantify.

45. The beneficial effects of this strategy are likely to be far-reaching, including a deeper understanding of trends in resistance, improved care of patients across care settings (with improved outcomes) and more appropriate prescribing in the animal sector.

46. The main unquantifiable benefit is around reducing antimicrobial resistance. The up-front effects of this are small, as many infections that are resistant to one antimicrobial agent may be sensitive to another. While the other agent might be more expensive, this incremental cost is relatively small. However,

more substantial problems arise when infections become resistant to multiple drugs. In such a scenario, some infections would become untreatable, carrying high risks of mortality. This would make routine surgery (with its reliance on antibiotics) very risky. Appropriate antimicrobial stewardship reduces the likelihood of this scenario and postpones its arrival, generating further time in which new antimicrobials can be created.

47. By its very nature, it is uncertain what effects would be and when they may occur, in the absence of any further intervention. However, the benefit of postponing and reducing the likelihood of this scenario is substantial, and further supports the case in favour of the strategy.

Question 12: are there any further costs and benefits that may occur as a result of this strategy; is it possible to quantify any of these?

Risks and alternative scenarios

48. The above analysis has assumed that the quantity of antibiotics prescribed and used (and antimicrobials more widely) will not change substantially (with the exception of the farmed animals sector). However, there may be a small decrease in the number of antibiotics used. If clinicians use fewer antibiotics, then their costs will decrease. Matching this, there would also be a reduction in revenue for pharmaceutical companies, alongside a reduction in production costs. The net effect for pharmaceutical companies is the reduction in profits from these antibiotic sales.

49. If the number of antibiotics used decreases, this should not lead to an increase in bacterial infections, as long as each reduction is appropriate to the specific case. However, if there is an excessive reduction in use, bacterial infections may rise. This can generally be countered by introducing antibiotics at a later stage. However, the impact in the farming sector may be greater, as disease may spread more rapidly when animals are living in close quarters.

50. However, the likelihood of this is still low, as the strategy does not place any requirements on farmers, clinicians and veterinarians to reduce antibiotic use. As a result, they will be able to continue using antibiotics where appropriate.

Question 13: are there any other risks from the strategy; is the impact of any reduction in antibiotic use likely to be small?

Summary of questions

Question 1: is the strategy likely to lead to a substantial impact on the number of antibiotics prescribed (in any of the sectors)?

Question 2: are there any substantial differences between England and the rest of the UK that would change the analysis?

Question 3: in terms of reading the published strategy, are there any other major groups to include; are those included reasonable?

Question 4: will there be any additional costs in monitoring bacteraemias and susceptibility; are the costs included reasonable?

Question 5: will there be any further costs to the increase in SSTF across secondary care; is the strategy likely to lead to this level of change?

Question 6: is the reduction in sepsis reasonable; are there any further measurable benefits from this action?

Question 7: will there be any further costs to the increase in usage of Target across primary care (in particular ongoing costs); is the strategy likely to lead to this level of change?

Question 8: are there any measurable benefits from the increase in usage of Target in primary care (in addition to the longer term benefit around resistance)?

Question 9: will there be any ongoing costs as a result of the change in antimicrobial stewardship in the farming sector; are these costs reasonable?

Question 10: are there are robust sources for the financial size of the antibiotic industry for farmed animals, particularly CIAs; are there any other other sources that may provide an indication of this size?

Question 11: are there any measurable benefits from the change in antimicrobial stewardship in the farming sector (in addition to the longer term benefit around resistance)?

Question 12: are there any further costs and benefits that may occur as a result of this strategy; is it possible to quantify any of these?

Question 13: are there any other risks from the strategy; is the impact of any reduction in antibiotic use likely to be small?

We would also be interested in any further information or evidence related to the impact of the strategy.

Appendix: Microbe-Drug combinations

Microbe	Drug	Relevant population
Klebsiella	Carbapenem	% non-susceptible to imipenem and/or meropenem
E. coli	Cephalosporin	% non-susceptible to cefotaxime and/or ceftazidime
E. coli	Fluoroquinolone	% non-susceptible to ciprofloxacin
Pseudomonas	Carbapenem	% non-susceptible to imipenem and/or meropenem
N. gonorrhoeae	Ceftriaxone	% non-susceptible
Klebsiella	Cephalosporin	% non-susceptible to cefotaxime and/or ceftazidime
E. coli	Gentamicin	% non-susceptible
S. pneumoniae	Penicillin	% non-susceptible
Pseudomonas	Cephalosporin	% non-susceptible to ceftazidime