The Academy of Medical Sciences' response to the Commons Science and Technology Select Committee inquiry on antimicrobial resistance

November 2013

Summary

- Antimicrobial resistance (AMR) is an issue which currently has an enormous global impact; the severity of which will only increase if this is not addressed appropriately. If current trends continue there is the threat of a return to a pre-antimicrobial era.
- The Academy acknowledges the degree of excellent research that UK and international medical scientists are performing in this area, but many significant gaps in our knowledge of AMR remain and can only be addressed with increased and sustained funding for research.
- Pharmaceutical companies cannot be expected to be solely responsible for the production of new antimicrobial therapies; governments need to develop a strong role in facilitating this, particularly by funding intermediary clinical trials.
- Increased public awareness about AMR and antimicrobial treatment use, and education of clinicians, general practitioners and veterinary surgeons about antimicrobial 'stewardship' (good practice for prescribing and using therapies), are vital. This should reduce the prescription of antimicrobial treatments to those who will not benefit from them, and improve adherence to prescriptions of those who would.
- International co-ordination and efforts to address AMR are paramount.
- The Academy welcomes the UK Department of Health's 'UK Five Year Antimicrobial Resistance Strategy 2013-2018', and believes it addresses many of the issues that are central to the problem of AMR in the UK.[1]
- However, the strategy should place more emphasis on some critical issues including the role and use of antimicrobials in veterinary medicine and agriculture, how to incentivise the development of new therapies by pharmaceutical companies, global coordination to tackle the issue, sufficient funding allocation for AMR-related research, and the role of vaccines and diagnostics.

Introduction

1. The Academy of Medical Sciences promotes advances in medical science and campaigns to ensure that these are translated into healthcare benefits for society. The Academy welcomes the production of the UK Department of Health's (DH) '*UK Five Year Antimicrobial Resistance Strategy for 2013-2018*' and commends the DH for creating a plan to tackle such an important issue.[1] In particular, the role of Professor Dame Sally Davies DBE FMedSci as a necessary champion of this cause should not be understated, given the need to raise awareness of the severity of the issue in the UK and internationally. We also value the Commons Science and Technology Select Committee's inquiry on antimicrobial resistance (AMR), which will help to determine whether the issue is

[1] The Department of Health (2013). *UK Five year Antimicrobial resistance Strategy 2013-2015*. https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/244058/20130902_UK_5_year_AMR_strategy.pdf

being addressed appropriately. We have provided answers to the six questions posed by the committee, with a particular focus on current and future research issues (questions two, three, five and six) which are central to the Academy's expertise. We would be willing to provide additional oral evidence to the committee's inquiry if requested.

How has antimicrobial resistance developed in the past decade?

2. Antimicrobials are one of the great discoveries of the 20th century, preserving the lives of millions of people worldwide. However, following their rapid development between the 1940s and 1980s, antibiotics and other antimicrobial treatments have been used widely and indiscriminately in both humans and other animals and the resultant misuse and over-use has led to the selection of antimicrobial resistant and multi-resistant organisms. In particular, previously curable infectious diseases, such as tuberculosis (TB), are now resurgent public health problems as multi-drug resistant variants emerge, leading to untreatable infections. Organisms resistant to all available drugs have already been identified, and their emergence and spread could result in a return to the pre-antimicrobial era.[2] The impact of these drug-resistant organisms is far-reaching, leading not only to increased mortality from infectious diseases, but also compromising modern medicine as a whole by affecting the efficacy of surgery, treatment of organ transplant patients, cancer patients, pre-term infants and all those reliant on immunosuppressant therapies.

3. Hospital-acquired bacterial infections have increased this decade, with the NHS reporting that 6% of patients entering hospital required treatment for infection following their stay.[3] This figure is an improvement on previous years due to interventions put into place to stem the spread of methicillin resistant *Staphylcoccus aureus* (MRSA). However, these interventions have done little to prevent the spread of drug resistant variants of *E. coli* and *Klebsiella.* Antimicrobial resistance has the potential to create a massive financial burden on the NHS, which will increase as organisms become gradually resistant to all available antimicrobials.

What are the gaps in our knowledge about antimicrobial resistance?

4. Despite excellent and productive research in many fields relating to AMR (in which UK researchers are often world leading experts), research into new antimicrobial agents, the mechanisms of resistance and clinical research into antimicrobial practice have been under-resourced and disproportionate to the increasing magnitude of the problem in the past several decades. There are therefore a significant number of areas in which our knowledge is lacking, ranging from basic science to the implementation and evaluation of response strategies, as follows:

- **Basic Research:** there are many gaps in the basic scientific knowledge underpinning AMR, including understanding of the different *mechanisms* by which resistance arises (whether by point mutation or by lateral transfer) and whether being resistant to antimicrobials

[2] Tzouvelekis LS, *et al.* (2012). *Carbapenemases in Klebsiella pneumoniae and Other Enterobacteriaceae: an Evolving Crisis of Global Dimensions.* Clinical Microbiology Reviews **25(4)**, 682-707.

[3] The Health Protection Agency (2012). *English National Point Prevalence Survey on Healthcare-associated Infections and Antimicrobial Use, 2011: preliminary data.* http://www.hpa.org.uk/Publications/InfectiousDiseases/AntimicrobialAndHealthcareAssociatedInfections/1205HCAIEnglishPPSforhcaiandamu2011prelim/

influences the *growth, proliferation* and *pathogenicity* of microbes. As a further example, we currently know little about the huge numbers of microbial species that cannot be cultured within a laboratory environment, including many of the bacteria present in the normal gut flora and commensal microbiota, which might act as a reservoir for AMR genes.

- **Epidemiological data** about AMR organisms and treatments at several levels (locally, nationally, and internationally) can be inconsistent or non-existent and many more detailed studies are warranted. In particular, two areas require more scrutiny:
    - **Transmission:** the routes of transmission of AMR infections, between humans, from animals to humans, and from humans to animals are not well studied. Understanding transmission of resistance genes between microbes is also important.
    - **Surveillance**: to prevent future AMR pandemics it is of the utmost importance that good quality incidence and surveillance data are obtained internationally, particularly from developing countries, whence many AMR organisms are likely to originate and where surveillance capacity is lower than in more developed countries.
- **Clinical research** including *intervention studies*, *behavioural studies*, and *drug therapy duration studies* would be advantageous to assess improvements needed in clinical practice for preventing future infections and deaths arising from AMR.
- **Current antimicrobial use:** it is unclear whether halting the use of antimicrobial treatments that are losing their efficacy as a result of AMR would lead to the re-emergence of susceptible organisms in populations of AMR organisms, and if and when treatments could be re-introduced. Data on the use of antimicrobial treatments in care settings in response to outbreaks of AMR organisms are scarce.
- **Diagnosis:** there has been concern about the lack of consistency between the susceptibility of microbes to antimicrobials in laboratory testing compared to susceptibility to treatments observed in patients, indicating that our current laboratory tests may not be accurately detecting AMR or that the microbes are inaccessible to antimicrobials in the patient. AMR measured by laboratory assays is, by definition, an *in vitro* phenomenon; therefore the precise clinical impact of AMR is potentially poorly defined. This is reflected in the lack of correlation between laboratory testing of microbes' susceptibility to antimicrobials and clinical outcomes. For example, although penicillin resistant *Streptococcus pneumoniae* is frequently reported *in vitro*, cases of treatment are rare when adequate doses of penicillin are used, suggesting that the *in vitro* phenotype does not necessarily translate into a clinical effect.[4]

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

5. Resistance to antimicrobial agents is a widespread threat to the future of human health. Continued and extensive research is required from basic science through to clinical and epidemiological studies, and clinical trials of new treatments are required in order to fill the gaps in our knowledge and comprehensively tackle the current and future burden of antimicrobial resistance on human health. It is paramount that fundamental research that

[4] Pallares R, *et al*. (1995). *Resistance to Penicillin and Cephalosporin and Mortality from Severe Pneumococcal Pneumonia in Barcelona, Spain*. New England Journal of Medicine **333,** 474-480.

will lead to identification of novel drug compounds and anti-infective strategies is funded sufficiently in order to increase the possibility of tackling AMR.

6. Excellent microbiological research is currently being conducted, including important consortium studies such as the Human Microbiome Project.[5] Results from this may help to add significantly to our knowledge in several areas, including identifying reservoirs of antibiotic resistant bacteria in the human microflora and the introduction of microbiome data into epidemiological studies.[6,7] Novel research approaches will help to mitigate many aspects of the AMR problem: for example, increased genomics capability will allow point-of-care (POC) diagnostics to be employed to reduce the burden of AMR organisms in care settings. Importantly, the informed application of such new knowledge (for example from microbial genomics) to clinical care will require that those delivering health care (for example clinical microbiologists and infectious disease physicians) have received adequate training in its interpretation and use in clinical practice.

7. A large amount of research is focussed on the development of new antimicrobials. However, the AMR problem is one that can be tackled in a number of ways and investment should not be focussed solely on development of novel antimicrobial drugs. It should also include the development of vaccines to allow for the prevention of infections, and diagnostics to allow for quick and more accurate treatment. Vaccines have historically been used for bacterial infections, such as TB, for preventing disease occurrence and for helping to establish herd immunity. Infections caused by many organisms, including Group B *Streptococcus*, *Chlamydia*, *Helicobacter* and *Neisseria gonorrhoeae,* have all been suggested as important potential targets for new vaccines, and improved vaccines are needed for TB.[8]

8. Despite being vital for the future development of antimicrobials and other treatments, many pharmaceutical companies have had to cease or downscale their antimicrobial development programmes for economic reasons. There is a lack of incentive for companies to produce treatments that may quickly become obsolete due to drug resistance or that will be reserved for use as 'last resort' therapeutics. Collaborations between drug companies and governments, academia and the NHS may allow these programmes to be resurrected or expanded.

9. Furthermore, to encourage and incentivise those in the field to bring new antimicrobials to the market, the production and sales of new antimicrobials should not be under-valued and under-priced, as it has been suggested was the case for previously developed antimicrobial treatments (following low production costs due to the former ease of antimicrobial production, and high demand from widespread, unreserved use). To do this, it will be necessary to highlight the cost to the healthcare system and subsequent loss of life if no solutions for combating AMR are found. However, developing countries should not be prevented from obtaining access to new antimicrobials for economic reasons.

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[5] For more information: http://www.hmpdacc.org/
[6] Morten OA, *et al.* (2009) *Functional characterization of the antibiotic resistance reservoir in the human microflora.* Science **325 (5944)**, 1128-1131.
[7] Foxman B & Rosenthal M. (2013). *Implications of the Human Microbiome Project for epidemiology*. American Journal of Epidemiology. **177(3),** 197-201.
[8] The Institute of Medicine (2000). *Vaccines for the 21st Century: a tool for decision making*. http://www.nap.edu/catalog.php?record_id=5501

10. Incentives for drug development could include 'push' incentives such as early research subsidies to feed into the beginning of the drug discovery pipeline, financial support for clinical trials and harmonisation of drug regulation for new antimicrobials across Europe, Asia and the US, and 'pull' incentives such as patent extensions, minimum pricing agreement and risk-sharing reimbursement.

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

11. It is impossible to eradicate AMR, since it is a natural evolutionary mechanism occurring in microbes. However, the actions of humans influence the frequency and severity of drug resistant infections that are occurring and there are several steps that can be taken to protect existing antimicrobial treatments for current and future generations.

Awareness

12. Public awareness of AMR will play a significant role in its control. A number of measures have been implemented in the UK to increase awareness of prudent antibiotic use. These include the European Antibiotic Awareness Day, which is a cheap and effective way of increasing public awareness of antibiotic resistance and proper use.[9]

13. However, the public expectation of receiving antimicrobials is still very high[10], and this places undue pressure on doctors to prescribe antimicrobials before an accurate diagnosis has been made. This practice of prescribing antimicrobials to meet expectations or to induce a placebo effect in patients should continue to be discouraged. Increased campaigns to improve public awareness of the importance of antimicrobials and the detrimental effect of misuse would help to take pressure to prescribe off doctors.

Stewardship

14. Many stewardship initiatives, including 'Treat antibiotics responsibly, guidance and education tool' (TARGET)[11] and 'Stemming the tide of antibiotic resistance' (STAR)[12] have been introduced in the UK to help promote better antibiotic prescribing practice by clinicians. However, the practice of prescription of antimicrobials to those who do not require them still remains a problem. More extensive education of medical students and doctors in training on AMR issues would highlight the negative impact of bad antimicrobial prescribing practice for a future cadre of doctors.

15. Stewardship campaigns should also be extended to veterinary surgeons and animal keepers. Although antimicrobials can no longer be used in the UK or EU for non-therapeutic use, agriculture remains a major user of antimicrobials in the UK and in other countries, where antimicrobials are used without veterinary prescriptions. The UK should act in collaboration with organisations such as the World Health Organization (WHO), the Food and Agriculture Organization of the United Nations (FAO) and the World Organisation for Animal Health (OIE) to actively encourage other nations to cease non-therapeutic use

[9] For more information: http://ecdc.europa.eu/en/EAAD/
[10] Coenen S, *et al.* (2013). *Are patient views about antibiotics related to clinician perceptions, management and outcome? A multi-country study in outpatients with acute cough.* PLoS One **8(10),** e76691.
[11] For more information: http://www.rcgp.org.uk/targetantibiotics/
[12] For more information: http://www.stemmingthetide.org/

of antimicrobials in agriculture. Cost-effective alternatives to the widespread use of antimicrobials, such as procedures trialled in Denmark and elsewhere, should be promoted.[13]

16. An active effort from the UK should be made to encourage stewardship in other countries. Pressure is needed on a global scale to persuade countries which still allow antimicrobials to be sold without prescription, for both human and animal use, to ban these practices as they increase selection of AMR organisms. Infectious AMR organisms that arise overseas may well find their way into the UK via international tourism and travel (and vice versa).

17. Another way to alleviate the problem of patient expectation and to aid prescribing stewardship would be the development of quick, cheap POC diagnostics to allow clinicians to distinguish accurately between various pathogenic infections whilst the patient is still in the clinic/GP office, therefore improving the prescription accuracy of antimicrobial treatments and satisfying the needs of the patient. Crucially, as in (6) above, this would need to be accompanied by training of those using such POC diagnostics in the interpretation and informed use of the resultant diagnostic information.

18. Alongside better POC diagnostics, technology also has a role to play in better stewardship in prescribing. The Imperial Antibiotic Prescribing Policy (IAPP) smartphone app, for example, provides clinical decision support about antibiotics for clinicians at the point of care.[14] This application has been warmly welcomed and adopted by clinicians, 96% of whom said it influenced their prescribing practice.

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

19. AMR is a worldwide problem and the increasing mobility of human populations, in addition to the large-scale transport of livestock and food internationally, has played a pivotal role in the spread of AMR. It is vital that global cooperation is established to stem the spread of AMR as and when it emerges, and it is critical for the UK to build upon its strong domestic strategy and stimulate global coordination and action to address AMR. The UK can play an important role in global action on AMR because of the breadth of expertise in our universities, hospitals, general practices and pharmaceutical industry and also through the experience and expertise gained through the National Health Service, which can be used in global platforms to help countries with less well regulated health care systems, both in developed and developing nations.

20. AMR has yet to be adequately addressed on a global platform. It has been mentioned regularly at events such as the G8 Summit, but its importance has yet to be translated into a proportionate international response. It is critical that the severity of this issue is addressed by trans-national organisations such as WHO and the European Centre for Disease Prevention and Control (ECDC), which have the capacity to stimulate and coordinate global action. The Academy is pleased to see that AMR is being given a platform

[13] The World Health Organization (2002) *Impacts of antimicrobial growth promoter termination in Denmark*. http://www.who.int/qfn/en/Expertsreportgrowthpromoterdenmark.pdf

[14] For more information: http://www1.imperial.ac.uk/medicine/about/institutes/cipm/centre_outputs/antimicrobialstewardship/

at the World Innovation Summit for Health (WISH) 2013[15] and that it is a focus of the Innovative Medicines Initiative (IMI) as part of the European Union's Horizon 2020 funding programme.[16]

21. It is paramount that consortia established to tackle antimicrobial resistance are both international and inclusive, combining representatives from the political, academic and pharmaceutical sectors in order fully to confront the problem.

22. The UK is currently working with other Commonwealth countries to set up new laboratories and new surveillance strategies in these to address AMR. These new laboratories will be paired with experienced laboratories including those in the UK, Australia, Canada and Singapore to ensure that they can make the most of their resources. Funding has been contributed by more developed countries in the Commonwealth, including the UK via the Foreign and Commonwealth Office (FCO). If such initiatives appear to be successful on evaluation, the model could be viewed as a pilot for a wider roll-out globally.

23. If the UK is to take a global lead on AMR, the Department for International Development (DfID) could consider investing in developing countries' infrastructures in order to improve surveillance. This investment could reap dividends for the UK in the form of decreased spread of AMR infections internationally in the future.

Use of antimicrobials in animals worldwide

24. Evidence suggests the possibility that antimicrobial resistant infections might be spread zoonotically, and also from humans to other animals, although the extent to which this takes place is currently unclear.[17,18,19] As mentioned in paragraph 4, the pathways by which AMR can be selected for and mechanisms of AMR gene transfer are not fully understood, and the use of antimicrobials in animals might contribute to human AMR infections.

25. As such, AMR and the use of antimicrobial treatments in animals should be considered with equal importance to AMR in humans. We propose that a 'One-Health' approach—in which human and veterinary medicine are considered in parallel and in the context of environmental factors— is the best approach for addressing AMR comprehensively.

26. As described in paragraph 15, poorly regulated use of antimicrobials in agriculture is widespread internationally, and the UK should take a leading role in promoting best practice in this regard.

27. Campaigns should also stress the importance of antimicrobial use in animals to ensure animal keepers and livestock farmers are made fully aware of the implications of misuse of antimicrobials in animals. Farm assurance schemes such as Red Tractor[20] could also be

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[15] For more information: http://www.wish-qatar.org/forums/antimicrobial-resistance
[16] The European Union (2013). *Proposal for a Council Regulation for the Innovative Medicines Initiative 2 Joint Undertaking*. http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=COM:2013:0495:FIN:en:PDF
[17] Sing A, *et al.* (2008). *Methicillin-resistant* Staphylococcus aureus *in a family and its pet cat*. New England Journal of Medicine **358**,1200-1201.
[18] van Duijkeren E, *et al*. (2005). *Transmission of a Panton-Valentine leucocidin-positive, Methicillin-resistant* Staphylococcus aureus *strain between humans and a dog.* Journal of Clinical Microbiology **43(12),** 6209–6211.
[19] Mather AE, *et al.* (2013). *Distinguishable epidemics of multidrug-resistant* Salmonella *t*yphimurium *DT104 in different hosts*. Science, **341(6153)**, 1514-17.
[20] For more information: http://www.redtractor.org.uk/home

promoted in collaboration with these public antimicrobial awareness campaigns to encourage the public to choose meat from UK farms with good antimicrobial practice.

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

28. There are many strengths to the Government's strategy: it lays out a strong domestic plan with immediate, achievable objectives, and it acknowledges the importance of many key issues including research to understand underlying aspects of AMR, the development pathways for new treatments, stewardship, and the 'One-Health' approach to interlinking human and veterinary medicine. However, there are several areas where the strategy could be strengthened, outlined below.

Funding

29. The strategy has many goals to attain if it is to be considered a success. Despite this, the financial resources to support it are unclear. The UK's funding streams described within the strategy (approximately £42m of existing funding, and "up to" £4 million for a new NIHR Health Protection Research Unit on AMR and Health Care Associated Infections) do not accurately reflect the scale of the problem at hand. AMR is likely to be a significant drain on the NHS in the future and it is vital that appropriate funds are allocated to tackle this emerging problem. Lack of current investment may lead to larger remedial funds being required in the future if AMR increases in severity and scale. Antimicrobial resistant infections are already exceptionally costly to treat, with US data indicating that these may generate as much as $20 billion in excess healthcare costs [21]

Pharmaceutical incentives

30. Pharmaceutical companies will clearly be instrumental in achieving many of the goals set out in the strategy. However, the list of objectives outlined for these companies is not supplemented with incentives for them to achieve them. As described in paragraphs 8 to 10, the production of new antimicrobials may no longer be profitable for pharmaceutical companies. These companies have a responsibility to their shareholders to make a profit on their products, and therefore may not produce future antimicrobial products based simply on the public health imperative to do so. In situations of gravity, such as this, governments and drug companies have often collaborated, and more emphasis on this is required for the strategy's goals to be achieved.

Global perspective

31. In order for this strategy to achieve its objectives, it must be more globally focussed. Even with best practice in containing AMR being used in the UK, AMR infections will enter our population from overseas. As described in paragraph 16, international migration is a potentially huge contributor to the spread of AMR organisms, but this is largely overlooked in the strategy.

32. As already highlighted, it is vital that the strategy brings its objectives to the world stage and ensures that bad practices that encourage AMR, such as over-the-counter

[21] The US Centers for Disease Control and Prevention (2013). *Antibiotic resistance threats in the United States.* http://www.cdc.gov/drugresistance/threat-report-2013/pdf/ar-threats-2013-508.pdf

antimicrobial sales and extensive and poorly regulated use of antimicrobials in agriculture in some parts of the world, are ceased. The UK's participation in global forums on AMR should be seen as an opportunity to inform those who do not regulate antimicrobials appropriately, and ensure that there is awareness of the problems that these stand to create if these practices are maintained. However, the complexity of this issue must be acknowledged; for example, in some countries without universal health coverage, cheap over-the-counter antimicrobials can have very beneficial health effects for individuals that may not be able to afford doctors' consultation fees.

Inclusion of other microbes

33. The exclusive focus of the strategy on bacterial antibiotic resistance is understandable given its wider public recognition compared to AMR in other microbes, but AMR in fungi, viruses and parasites should not be overlooked at this stage. This will only serve to create a crisis point in the future for life-threatening infections from these organisms. Antifungal resistance, for example, is already an emerging problem because excessive use of triazoles for the prevention of fungal infection in the agricultural sector has led to triazole resistant fungal infections in humans.[22] This bad practice, if continued, will result in an antifungal situation that mirrors the antibiotic resistance landscape. The antifungal drug pool is significantly smaller than the antibiotic pool and therefore resistance will develop more quickly and will have a profound effect on treatment of many conditions.
    The growing number of effective antiviral drugs in use also illustrates this point. In many cases their development has been catalysed by the HIV pandemic, but these are finding application in the treatment of important persistent viral pathogens in addition to HIV, such as hepatitis C. New antivirals against influenza virus are also being used at the population level. This increasing and widespread use of antiviral drugs will inevitably be accompanied by the growing emergence of AMR in viruses (as already seen for HIV).[23]
    Thus many of the proposals outlined in the strategy may be equally applied to responses to resistance in organisms besides bacteria, and these should be given appropriate weighting in the strategy's objectives. For brevity, we have not addressed each aspect of AMR (such as occurrences in virology, mycology and parasitology) in detail individually in this response, but would be willing to provide further information to the committee if requested.

This response was prepared by Dr Jennifer Dow (Policy Intern) and informed by the Academy's Fellows. For further information, please contact Dr Dylan Williams (dylan.williams@acmedsci.ac.uk; +44(0)20 3176 2167).

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[22] The European Centre for Disease Prevention and Control (2013). *Risk assessment on environmental use of triazoles*. http://www.ecdc.europa.eu/en/publications/publications/risk-assessment-impact-environmental-usage-of-triazoles-on-aspergillus-spp-resistance-to-medical-triazoles.pdf

[23] The World Health Organization (2008) *HIV Drug resistance fact sheet.* http://www.who.int/hiv/facts/drug_resistance/en/