Antimicrobial Resistance
A contribution from the Society of Biology to the
House of Commons Science and Technology Select Committee

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The Society of Biology is a single unified voice, representing a diverse membership of individuals, learned societies and other organisations. We are committed to ensuring that we provide Government and other policy makers - including funders of biological education and research – with a distinct point of access to authoritative, independent, and evidence-based opinion, representative of the widest range of bioscience disciplines.

The Society welcomes the interest of the Committee and is pleased to offer these comments structured around the six main questions set out by the inquiry gathered in consultation with our members, member organisations and advisors. The majority of our response focuses on the issues surrounding antibacterial resistance, although we briefly highlight issues surrounding fungal research.

Overview

1. The prevalence of pathogenic organisms with acquired antimicrobial resistance (AMR) has been increasing in the UK and globally over the past decade. Antimicrobial resistance cannot be eradicated, but it can be managed to limit the threat to human and animal health. This must be done urgently otherwise we risk returning to an era where routine infections and operations become life-threatening. Combatting AMR will require a multi-faceted approach including improving infection prevention and control measures, optimising prescribing practices and prioritising research and development.

2. Research into bacterial pathogenicity (ability to cause disease), antimicrobials and antibiotic resistance has historically been under-resourced relative to their importance for public health and societal impact. This is extremely concerning, since infectious disease remains one of the leading causes of human death each year.[1]

3. The Society of Biology welcomed the publication of the Department of Health's UK Five Year Antimicrobial Resistance Strategy for 2013 – 2018, which sets out actions to slow the development and spread of antimicrobial resistance. This action plan focuses largely, and appropriately, on the behaviour of prescribers and the need to reduce antibiotic consumption. While this goal is important, the Committee should recognise that antimicrobial resistance has continued to develop despite reduced prescribing in primary care and restrictive antibiotic policies in hospitals.

4. Research into new antibiotics and alternative approaches such as vaccines as well as point of care diagnostics is critical. However we caution that this should not focus solely on existing agents in development. We are facing a post-antibiotic era with a rapidly diminishing armory to combat multi-drug resistant infections. Development of novel therapies must exploit basic research aimed at understanding the pathogen and the process of infection. The forward strategy should aim to

[1] Davies, S.C., Fowler, T., Watson, J. *et al. Lancet*, **2013**, *381*, 1606.

support the UK's world-leading life science and technology sectors to increase the pipeline of new technologies and products in this area. Crucially, a multi-faceted, long-term research strategy is needed.

How has antimicrobial resistance developed in the past decade?

5. Antimicrobial resistance has existed since the first development and introduction of antibiotics and has been well recognised and documented since the 1960s.[2] Indiscriminate or inappropriate use of antibiotics in human and veterinary medicine has been a key driver in the spread of antibiotic resistance in the past decade. GPs prescribe 35 million courses of antibiotics in England alone each year[3] and the vast majority of surgical procedures involve antibiotic use. Antibiotics are also commonplace in farming practices and are routinely given to animals, both as treatments and to prevent infection. Action must be taken to ensure that antibiotics are used only when absolutely necessary and are not relied on as an 'easy option'; this includes curtailment of use where there is no bacterial infection (particularly prevalent in animal health management) and reducing patient expectation to receive an antibiotic treatment. Patient compliance is also a factor; it is imperative that the full course of an antibiotic is completed. To this end, more research on dosage and treatment durations is required.

What are the gaps in our knowledge about antimicrobial resistance?

6. Although this is a complex area, a complete understanding of what forms of antimicrobial resistance are clinically important, and how they develop, will help to identify where the development priorities lie.

7. The precise clinical impact of antimicrobial resistance is poorly defined. This is reflected in the lack of correlation between laboratory susceptibility testing and clinical outcome. For example, although penicillin resistant *Streptococcus pneumoniae* is frequently reported, cases of treatment failure due to penicillin resistant *S. pneumoniae* are rare when treated with adequate doses of penicillin, suggesting that the laboratory phenomenon does not necessarily translate into a clinical effect.[4]

8. Some bacteria are inherently resistant to certain classes of antibiotics while resistance in others is acquired by genetic mutation or gene transfer. Therefore acquisition and transmission rates between bacteria are important areas for consideration.

9. Once resistance is acquired it is essential to understand how pathogens are then spread within human populations. Recent research using genome sequencing approaches suggests that the vast majority of *C. difficile* infections in one study arose due to inappropriate antimicrobial use rather than person to person transmission. This disproved, to some extent, the longstanding belief that poor hygiene and transmission are responsible for the majority of infections.[5] These findings raise a centrally important question in AMR research because many of the existing hospital interventions are based around hand hygiene, cohorting, barrier nursing, etc. While these approaches have led to some success in the reduction of MRSA infections for example, further research in this area is needed.

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[2] Hansman D., Bullen M.M. *Lancet*, **1967**, ii, 264.
[3] Department of Health, *Chief Medical Officer Annual Report: Volume 2*. London, 2013
[4] Pallares R., Linares J., Vadillo, M. et al. *N. Engl. J. Med.* **1995**, *333*, 474.
[5] Eyre D.W., Cule M.L., Wilson D.J. et al. *N. Engl. J. Med.* **2013**, *123*, 1495.

10. The existing “reservoirs” of resistant bacteria need to be identified and researched urgently.

11. There is also a growing appreciation of the polymicrobial nature of antibiotic resistant microbial infections. Polymicrobial infections involve several infectious agents and may also be referred to as complex, complicated, mixed, dual, secondary, synergistic, concurrent or co-infections. It is now felt that such microbial communities contribute to the development of resistance. These mixed microbial communities are able to share resistance determinants between the same or different species. At present there are no specific strategies to prevent transmission of antimicrobial resistance determinants in polymicrobial infections and only limited knowledge of the mechanisms for resistance transmission and microbial interaction in this context. Obtaining an improved understanding of the interactions between organisms and the transmission of resistance determinants within such complex communities is essential for reducing population level antibiotic resistance.
12. For fungal diseases there is still a question regarding the extent to which antifungals used in crop protection may inadvertently select for antifungal resistance in human fungal pathogens. Again, this is an area that requires more research. Although not generally highlighted, there is a particular shortage of antifungal antibiotics which can be used safely in humans.

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?

13. We are entering a period where standard frontline antibiotics used in clinical practice will become obsolete in treating life-threatening infections. Coupling this to the lack of investment from both the pharmaceutical industry and academic research funders in the development of novel antimicrobial strategies, it is clear that we are about to reach crisis point.[6] The reasons for this situation have been well documented, and include a lack of perceived return on investment for pharmaceutical companies and difficulties in identifying suitable broad-spectrum antimicrobials.[7]

14. Additional research into prevention and targeted treatment of infections would be one of the most effective measures to reduce resistance. However research into these areas has been neglected historically. Such areas include: prevention methods such as vaccination; point of care pathogen identification and methods that reduce the unnecessary use of antimicrobials, such as rapid diagnostics.

15. A recent study undertook detailed analysis of the proportion of total infection research spend dedicated to research into antimicrobial resistance.[8] It found that despite the rapid emergence and far-reaching consequences of AMR, the proportion of UK infection-research spend targeting this critical area remained small, comprising 3.9% of the total spend (£102 million of the £2.6 billion total) during the period 1997-2010. Despite the global impact and clinical importance of antimicrobial resistance, this research area ranked 14th out of the 38 primary disease categories according to funding allocation. The study concluded that the UK government must continue to fund antimicrobial resistance research in a sustained, targeted manner.

[6] *Nature* **2013**, *495*, 141 | doi:10.1038/495141a
[7] Boucher, H.W., Talbot, G.H., Bradley, J.S. et al. *Clin. Infect. Dis.* **2009**, *48*,1.
[8] Head, M.G., Fitchett, J.R. Cooke, M.K. et al. *J. Antimicrob. Chemother.* 2013, doi: 10.1093/jac/dkt349

16. To maximise progress in AMR research, it will be important for industry and academia to work together to accelerate discovery and development, as recently highlighted in the Witty Review.[9] As part of the Drug Discovery Pathways Group, the Society of Biology, in partnership with the Academy of Medical Sciences, the Biochemical Society, the British Pharmacological Society and the Royal Society of Chemistry, advocates that collaboration between industry and academia is vital to enable the translation of biomedical opportunities into new effective therapies. There are few areas of research where this approach is more important than in AMR. Public-private partnerships, precompetitive data sharing, SMEs and the development of targeted therapeutic centres of excellence will all have a role to play. It is vital that the Government acts to promote and ensure funding incentives for such initiatives.

17. Though still not enough, there have been a number of recent developments to improve the funding atmosphere for antibiotic research. Our members highlighted several programmes including the NIHR Health Technology Assessment (HTA) antimicrobial resistance themed call, the Wellcome Trust's Seeding Drug Discovery initiative which funds partnerships between academia and GSK and the pan-European Innovative Medicines Initiative (IMI) New Drugs 4 Bad Bugs[10] fund. The Government should consider these as good models and seek to develop similar programmes.

18. Sustained progress towards addressing AMR will only be achieved through a combination of both basic and translational science, so it would be highly beneficial if public funding bodies considered themed calls for antimicrobial, vaccine and point of care diagnostics research. The Government is well-placed to encourage such programmes via the Research Councils, with an expectation of cross-council funding, between the MRC and BBSRC for example.

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?

19. Measures that have shown some success in controlling the spread of resistant pathogens are broadly described in the Department of Health's Five-Year Strategy document. These include: infection control measures including hand hygiene, barrier nursing and, to some extent, screening and surveillance; restriction of high-risk antibiotics and targeted interventions to reduce inappropriate antimicrobial use and mandatory reporting of MRSA and *C. difficile*. However, despite success in reducing MRSA, it is vital that the community does not become complacent, as these and other organisms may re-emerge as serious clinical problems.

20. The withdrawal of antibiotics as growth promoters in the EU has been a highly effective measure in controlling the appearance and spread of some, mainly Gram-positive, organisms in food animals and hence their spread to humans through the food chain.[11] Similar controls for the prophylactic use of certain antibiotics in food production may have some effect, but such measures need to be balanced against possible effects on animal health and on food production. A typical example is the antibiotic treatment of weaner pigs, which is seen as a crucial preventative measure. Parallel controls on the use of prophylactic use of antibiotics in humans should also be considered.

21. EU-wide legislative controls to reduce the occurrence of pathogenic bacteria such as *Salmonella Enteritidis* and *Salmonella Typhimurium* in poultry have been highly effective in reducing the

[9] *Encouraging a British invention revolution: Sir Andrew Witty's review of universities and growth*, 2013
[10] http://www.imi.europa.eu/content/8th-call-2012
[11] Cogliani, C., Goossens, H., Greko, C. *Microbe*, **2011**, *6*, 274.

occurrence of such bacteria, including antibiotic-resistant strains.[12] These bacteria are frequently resistant to commonly used antibiotics as a consequence of antibiotic use in certain food production animals.

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

22. The UK Government can contribute to tackling the problem of antimicrobial resistance globally by acting to harness the UK's world-class life sciences and technology sector to identify new drug and vaccine targets and develop technologies for pathogen detection and inhibition. It is the view of our members that the Government's main focus should not only be on managing prescriber behaviour and antibiotic use in UK healthcare. While this is very important, these interventions will have limited applicability globally, where healthcare is resourced and provided very differently. Instead, the Government should also focus on enabling research and development in the diverse areas previously highlighted. A multi-faceted long-term research strategy is needed.

23. Some of the most successful antimicrobials, among other pharmaceuticals, are derived from fungi; including cephalosporins, cylosporins, griseofulvins, penicillins, pneumocandins, statins, and taxol. Given that only 2-12% of all estimated fungal species have been described, and less than half of those in the GenBank database have been named, it is reasonable to assume that amongst the unknown fungi are those that could yield new antimicrobials.[13] However, natural product discovery work on fungi in major pharmaceutical companies, as well as in smaller biotechnological and drug discovery companies, research institutes, and university laboratories is now significantly hampered by Biodiversity Convention structures and Plant Health[14] regulations. In order to facilitate access to currently unnamed species for scientific studies and screening for exploitable properties, the Government should consider revising the UK Plant Health regulations.

24. The European Medicines Agency (EMA), the European Centre for Disease Prevention and Control (ECDC), and the European Food Safety Authority (EFSA) have all realised the importance afforded to the control of infections caused by antibiotic-resistant bacteria, and many collaborative actions are underway. More pro-active collaborations between appropriate UK agencies, such as Public Health England, and these bodies would be both welcome and desirable.

25. Furthermore, better harmonisation of approval processes between Europe and the USA would be beneficial. Currently, the regulatory procedures of the US Food and Drug Administration and the EMA are unaligned; this means that many clinical trials must effectively be performed twice, increasing expenditure and wasting resources.

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?

26. The Society of Biology welcomed the publication of the Department of Health's UK Five Year Antimicrobial Resistance Strategy for 2013 – 2018 that sets out actions to slow the development and spread of antimicrobial resistance. This action plan focuses largely on the behaviour of prescribers and the need to reduce antibiotic consumption. While this goal is important, the

[12] www.efsa.europa.**eu**/en/efsajournal/doc/115.pdf
[13] *Nature* **2013**, *496*, 169.
[14] www.legislation.gov.uk/uksi/**2005**/2530/pdfs/uksi_**2005**2530_en.pdf

Committee should recognise that antimicrobial resistance in many organisms has continued to develop, despite declines in prescribing in primary care and restrictive antibiotic policies in hospital over the past decade. While notable successes have been achieved in reversing the epidemic of MRSA and *C. difficile* infections, other resistant organisms such as ESBL-producing *Enterobacteriaceae,* have risen over the same period. It is our view that only substantial and sustained investment in basic science to develop diagnostics, vaccines and new antimicrobials can truly tackle antimicrobial resistance.

27. Our members suggested that the seven key areas for future action detailed in the Strategy should be expanded to include emphasis on research into the basic mechanisms of bacterial pathogenicity and the host response to infection. The failure to identify new antimicrobials and new vaccines will only be tackled by increased investment in this area, which has traditionally been under-resourced relative to its importance.

28. Where the strategy discusses new diagnostics and vaccines, the focus is primarily on those already in development or pre-clinical testing and not on the importance of maintaining and expanding that pipeline. This is short-sighted, as evidence suggests many of the current agents and/or vaccines will fail to reach the clinic. There is a danger that many of the recommendations in this document will also appear in the 2018-2023 strategy and beyond if the foundations for solving these difficult problems are not laid now. Developing a strong pipeline necessitates support for basic and translational levels of microbial and antibiotic research and in our view this should be emphasised in the strategy.

29. It is imperative that antimicrobial resistance is consistently monitored by the Government, even after potential solutions have begun to be initiated. To this end, the Society strongly recommends that the Government builds AMR into existing horizon scanning capabilities.

30. It is vital to the health of all nations that effective antibiotics remain the mainstay of modern medicine and are available to all who need them.

The Society of Biology is pleased for this report to be publicly available. For any queries, please contact The Society of Biology Policy Team at Society of Biology, Charles Darwin House, 12 Roger Street, London, WC1N 2JU. Email: policy@societyofbiology.org

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