House of Commons Science and Technology Committee: AMR

Response by the Wellcome Trust

November 2013

Key Points

- Antimicrobial resistance (AMR)[1] is an issue which has seen little concerted progress and needs an urgent response. AMR is complex and multifaceted, and poses a real threat to public health in the UK and globally.

- As a funder we support action in this area and believe the key issues to be addressed are as follows:

  - **Focus on fundamental and translational research:** A multifaceted, long term research strategy which draws on expertise across biomedical research disciplines, as well as social, economic, and policy research is required to tackle the complexities of AMR.

  - **Innovative new business models to facilitate drug discovery, diagnostics and new technologies:** Innovation is required in the public and private sector to identify new incentives and business models to facilitate the research and development of new drugs and diagnostics.

  - **Improved evidence based policy:** Improved understanding of what constitutes an optimal drug and dosage regime in any given circumstance is vital if the Government's predominantly stewardship strategy is to have an impact.

  - **Co-ordinated global action:** Coordinated global action and engagement with organisations such as the World Health Organisation is required, otherwise measures taken in the UK face being compromised.

  - **Education and awareness:** Education and awareness must be broader in scope to encourage links between scientists, the clinical community and public health practitioners to ensure that each sector understands the impact of resistance in its different contexts.

[1] A broad definition of AMR is used, which is defined as resistance of a microorganism (bacteria, fungi, virus and parasites) to an antimicrobial medicine (e.g. antibiotics, antifungals, antivirals and antimalarials).

INTRODUCTION

1. Antimicrobial resistance (AMR) is an important issue which has seen little concerted progress and needs an urgent response. The Wellcome Trust is therefore pleased to submit evidence to the Science and Technology Select Committee's inquiry focused on this area. We have consulted Trust funded researchers and external experts in the field as well as internally to develop our response.

2. In the past 10 years, the Wellcome Trust has awarded over £177M on 308 grants covering a broad range of research related to AMR[1], from fundamental research on bacterial transcription to translational research developing new antibiotics. The majority of funding has been allocated to bacteria and parasite resistance. The largest proportion of the Trust's expenditure on antimicrobial related research in this period is through translational funding schemes (16%), which focus on drug discovery and health innovation. The primary research site for approximately half of these awards is in the UK.

Q1. How has AMR developed in the past decade?

3. AMR has risen disproportionately in every part of the world over the last decade. Evolution of microbes to survive exposure to antimicrobials occurs in bacteria, viruses, parasites and fungi. Recent reports from the Centres for Disease Control[2], World Health Organisation (WHO)[3] and the UK Government's Chief Medical Officer[4] highlight the primacy of AMR and its threat to public health. These reports detail important resistant trends, however, there are a number of areas that we feel have been relatively neglected and may pose the greatest future threats. Areas in need of further attention are:

   - **Nosocomial infections:** Incidence of gram-positive infections, such as *MRSA,* has largely fallen over the past decade, perhaps in part due to extensive campaigns. However, incidences of gram-negative infections, which have not captured the same attention, have increased. A recent point prevalence survey reported gram-negative bacteria *Enterobacteraciae* is now the most common healthcare associated infection (32.4% vs. 2.4% for MRSA)[5]. We have funded a number of meetings and researchers specifically focusing on somewhat neglected gram-negative bacteria.[6,7,8] This concern is compounded in the community; both gram-positive and negative infections have continued to rise in the community context[9,10] despite best-practice in the hospital.

   - **HIV:** Over the past decade there have been phenomenal improvements in treatment and access to antiretroviral (ARV) therapy for HIV patients. In low and middle income countries there has been a 1900% increase in the number of patients receiving

[2] http://www.cdc.gov/drugresistance/threat-report-2013/pdf/ar-threats-2013-508.pdf
[3] http://whqlibdoc.who.int/publications/2012/9789241503181_eng.pdf
[4] https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/138331/CMO_Annual_Report_Volume_2_2011.pdf
[5] Health protection Agency. Healthcare associated infections (HCAI). www.hpa.org.uk/Topics/InfectiousDiseases/InfectionsAZ/HCAI/.
[6] Dr Peter O'Hanlon - Novel antibacterials for Gram negative pathogens.
[7] Dr Art Branstrom - Lead optimisation and development of novel bacterial DNA synthesis inhibitors for the treatment of nosocomial infections caused by multi-drug resistant Gram negative-bacteria
[8] Prof Ian Chopra - Fighting resistance to antibiotics with new technologies (a 2-day workshop in London to discuss the creation of new research initiatives for inhibitors of Gram-negative infections)
[9] http://www.cubist.com/downloads/CubistSWG_6811.pdf
[10] http://www.cidrap.umn.edu/news-perspective/2013/04/mrsa-dropping-hospitals-elsewhere-not-so-much

ARVs.[11] Whilst not detracting from this remarkable success, it is important to address the scale of resistance that may now be looming. With 9.7 million people worldwide on life-long ARV therapy,[12] even if a minority of patients develop resistance to at least one class of drug, this will be significant. This is compounded by the potential for widespread emergence and transmission of ARV resistance. The impact on health systems in countries with high numbers of HIV cases would be substantial as patients who develop resistance have a decreased likelihood of success with a second-line therapy.[13,14] Furthermore, HIV patients may face a double burden of resistance because their compromised immune system leaves them at high risk of developing bacterial infections for which they rely heavily on antibiotics.

- We have funded 19 grants specifically in HIV antiretroviral resistance over the 2003-2013 period, including surveillance of HIV resistance. One group has developed new models for the interpretation of drug resistance patterns using novel informatics-based approaches, which is more powerful and could have a significant bearing on clinical decisions on choice of therapy for treatment-experienced patients.

- **Malaria:** The current best treatment for Malaria, being artemisinin-based combination therapy, has had a remarkable impact on disease burden.[15] The threat of emergence of *P.falciparum* resistant to artemisinins can be seen in the "emergency response" issues documented by the WHO[16]. This is a key area of funding for the Trust. We have a long-history of supporting malaria research[17], including renewed efforts in the context of resistance; supporting genetic monitoring[18] and an eradication response strategy[19] on the Thai-Burmese border.

4. It is important to note that as well as the prevalence of resistance rising, the potency of antimicrobials generally has been diminishing. In the context of *Staphylococcal bacteria* the minimum inhibitory concentration (MIC), which is a measure of the minimum amount of drug required to inhibit bacterial growth, has risen in the last decade from a MIC of 0.25 to 1-2. Thus current drugs are not as effective as they used to be. Our understanding of this phenomenon is limited; however, it seems to have important clinical outcomes, including increased mortality and prolonged hospital stay.

Practices that have hastened AMR

5. Although evolution of microorganisms to survive antimicrobial drugs is a natural phenomenon, human practices also select for resistance. This includes non-adherence to dosing regimes; inappropriate prescriptions; erroneous self-medication in countries where over-the-counter antibiotics are sold; and use prophylactically and as a growth promoter in animal husbandry[4].

6. Substandard treatment similarly exposes the microbe to a non-lethal dose and promotes resistance. This can include the more sinister practice of propagating substandard,

[11] http://apps.who.int/iris/bitstream/10665/77349/1/9789241504768_eng.pdf
[12] http://www.unaids.org/en/resources/presscentre/pressreleaseandstatementarchive/2013/june/20130630prtreatment/
[13] http://jac.oxfordjournals.org/content/64/suppl_1/i37.long
[14] http://www.who.int/hiv/facts/drug_resistance/en/
[15] http://www.who.int/mediacentre/factsheets/fs094/en/
[16] http://www.who.int/malaria/publications/atoz/9789241505321/en/
[17] http://malaria.wellcome.ac.uk/
[18] http://www.nature.com/ng/journal/v45/n6/full/ng.2624.html
[19] http://www.plosmedicine.org/article/fetchObject.action?uri=info%3Adoi%2F10.1371%2Fjournal.pmed.1000402&representation=PDF

diluted or counterfeit antibiotic medicines. We have hosted a number of high level meetings to explore these issues[20] and funded many projects including a programme to define the extent of counterfeit and substandard drugs in Asia and Africa.[21] Substandard dosing regimes, however unintended, may nonetheless have similarly grave consequences. This is discussed further in paragraph 12.

7. Low standards of public health and a shortage of new drugs do not directly hasten resistance per se; however these factors exacerbate the situation by necessitating the use of increasingly limited drug options. For example, in some countries, such as India, over-the-counter antibiotics were introduced many years before comprehensive immunisation coverage or before measures to improve basic sanitation were introduced.[22] Any long-term strategy to tackle AMR must consider these indirect factors as integral components in the hastening of resistance.

Geopolitical shifts that have impacted on AMR

8. Geopolitical shifts are accelerating the prevalence of AMR.[23] Newly prosperous countries such as China and India are populous with humans and animals. Both have a growing middle class with access to sophisticated medical services that have now surpassed infection control and antimicrobial drug regulation. In China and India resistance is thought to be rampant; current estimates for *E.Coli* and *K.pneumoniae* are 50-80% in both countries.[24] The impact of such geopolitical shifts will be far reaching in an increasingly globalised marketplace, which affords an unprecedented movement of commodities and people. Pathogens are not confined to borders and can travel between humans, animals and foods. To combat this global health issue a global response is required; however incentives and interventions may need to be country-specific to be effective.

Q2. What are the gaps in our knowledge about AMR?

9. AMR will require expertise from a broad range of scientific disciplines including epidemiology, pharmacology, modelling, health systems as well as classical microbiology and pathogen genetics to address the challenges it raises. Our most pressing concerns regarding crucial knowledge gaps that require imminent attention are discussed below.

10. **Development and spread of resistance:** Integral to tackling AMR is the need to improve our understanding of the development and spread of resistance. Basic questions remain as to why a microbe may develop resistance to one class of drug and remain sensitive to another. For example, syphilis (*Treponema pallidum)* has never developed resistance to penicillin despite decades of use but showed resistance to erythromycin within a year or two of use. Mechanisms that spread resistance are poorly understood. This is particularly concerning in the case of gram-negative bacilli because of its remarkable capacity to share genes on a large scale and in a short time frame through horizontal gene transfer. Wider questions regarding the spread of resistance concern the extent to which antimicrobial use in farm animals has contributed to AMR in

[20] http://www.wellcome.ac.uk/about-us/policy/spotlight-issues/counterfeit-medicines/
[21] http://www.wellcome.ac.uk/Funding/International/Major-Overseas-Programmes/Thailand-and-Laos/WTDV027671.htm
[22] http://www.cddep.org/sites/cddep.org/files/publication_files/India-report-web.pdf
[23] Livermore, D.M. (2012). Fourteen years in resistance. International Journal of Antimicrobial Agents.
[24] Chaudhuri B.N., Rodrigues C., Balaji V., Iyer R., Sekar U., Wattal C., et al. (2011). Incidence of ESBL producers amongst Gram-negative bacilli isolated from intra-abdominal infections across India. Journal of the Association of Physicians Indian.

humans. More research evidence is required to quantify this threat. Epidemiology and modelling approaches may be critical for answering these questions.

11. **Diagnosing resistance:** Consistent, precise and accurate diagnosis of pathogen and resistance is a formidable but important challenge. Rapid diagnostic tools are crucial for delivering personalised treatment, and reducing prescription rates for viral infections. Lack of precise diagnostics is also driving the use of broad-spectrum antimicrobial drugs. Consistent measures and standards are required for effective surveillance strategies. Real-time sequencing of bacterial infections and inferring resistant phenotypes should be possible in the near future but further research is required to refine application and address the practical development challenges.

12. **Strategy for drug use:** The Government's predominant strategy in seeking to tackle AMR has been to emphasise adherence to optimal drug regimes. Current prescribing guidelines increasingly determine the dosage and treatment choice. Unfortunately, our understanding of what constitutes the optimal drug and dosage in any given circumstance is limited and needs to be improved for the Government's strategy to have maximum impact. Further research is needed to determine optimum stewardship based on evidence. This includes pharmacology research examining pharmacokinetic and pharmacodynamic factors for informing dosage and treatment regimes[25], and the impact of narrowing diversity in the range of drugs used. We have funded several projects for predicting the drug sensitivities of pathogens including TB, HIV and MRSA.

13. **Behavioural factors:** In order to stem the flow of AMR, we need to understand how prescribing andhealth behaviours have an impact. This includes the complexity of getting practitioners to abide by the correct set of procedures, and understanding why, in the presence of evidence, examples of positive change are not adopted. We need strategies that recognise the complexity of behaviour when we seek to regulate the use of antimicrobial agents, and this must transcend 'good' behaviour on the part of the diverse users of these agents. It might be important to consider here what incentivises behaviour change, how this is likely to differ across cultures, and how this can be adopted to promote stewardship. To answer these questions an interdisciplinary response is needed, which engages a wide range of funders.

14. **International monitoring and surveillance:** Coordinated data on antimicrobial distribution in humans, animals and the environment, and the trends of resistance are crucial for understanding the magnitude of resistance and how selection pressures drive its spread. There is however a lack of surveillance data on antimicrobial drug use and resistance. Most initiatives are micro-organism specific and do not allow comparison across pathogens. Comprehensive surveillance is particularly challenging in low and middle income countries where there is a paucity of effective reporting structures. However lessons can be learnt from projects such as *WAARN*[26] *and SATuRN*[27]*,* where collaborative networks across institutions, countries and funders, have comprehensively tracked the emergence and spread of disease and resistance. We support these vital networks through our five Major Overseas Programmes, in Kenya, Thailand and Laos, Malawi, South Africa and Vietnam. These programmes carry out vital studies and build research capacity in low-income countries. We also support several other individual surveillance projects in specific locations including HIV, TB and malaria surveillance.

[25] Rynak M. J. (2006). Pharmacodynamics: Relation to antimicrobial resistance. American Journal of Infection Control.
[26] http://www.wwarn.org/
[27] http://www.bioafrica.net/workshops/7thsaturnresitanceworkshop.html

Q3. 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?

15. **Incentivising for new drug development:** There is a shortage of new antimicrobial drugs being developed to replace the older ones to which organisms have developed resistance. Since 2000, 22 new antibiotics have been launched, only 5 of which are new classes and very few of which are effective against gram-negative bacteria.[28] In 1990 there were 18 big pharmaceutical companies working in this area, now there are only four: AstraZeneca, Novartis, GSK and Sanofi-Aventis. Efforts are likely to be further compromised by cuts in the research budget affecting these programmes.[29] Research discoveries are now largely made by a growing sector of small and medium-size enterprises (SMEs) and biotechnology companies, with big pharmaceuticals supporting late stage development (i.e. Phase III). The development costs involved in bringing a new drug to market represents a key development bottleneck. The priority of drug development must be safety and efficacy however, innovative ways to streamline, assess and evaluate this process, particularly the prohibitive cost of Phase III trials may be crucial for overcoming this bottleneck.

16. Lessons for invigorating the drug pipeline can be learnt from the 'orphan drug' scheme, where manufactures were incentivised to develop drugs for rare diseases by delinking revenues from sales. De-linked incentives such as fee waivers, extended patent protections or priority review vouchers could be crucial in enticing pharmaceutical companies to resume research and development of antimicrobial drugs. One such initiative is the Generation Antibiotics Incentives Act (GAIN) in the USA which provides automatic priority review and a patent extension of 5-7 years for infectious disease products.[30,31]

17. Alternative de-linkage models may be Payor Licenses, whereby an upfront global payment would be agreed by relevant private and public payors for an antibiotic thereby incentivising companies to commit funds to research and development. Another model is an Antibiotic Health Fund, where governments would create a fund that will pay for the actual health impact of an antibiotic, including stewardship and impact on future generations. This approach has been broadly endorsed by industry stakeholders[32,33] and international bodies[34]. Promising new innovations may also be realised through the Innovative Medicines Initiative funding call for "new business models for antibiotic development", which opened for proposals this year.[35]

18. Tiered pricing, as used in the context of HIV, could be important in ensuring proportionate remuneration and considered as an alternative business model.

19. To address the problem of discovering new antibiotics, the pharmaceutical industry has focused its attention and expenditure on genomics and proteomics methods to identify targets, however, these have been unsuccessful to date.[29]

[28] Butler M. S., Blaskovich M. A. & Cooper M. A. (2013). Antibiotics in the clinical pipeline in 2013. Nature.
[29] http://www.economist.com/node/18483671
[30] http://www.biocentury.com/biotech-pharma-news/coverstory/2012-11-19/gain-act-fda-stance-only-first-steps-to-refilling-antibiotic-pipeline-in-us-a1
[31] The 'orphan drugs' scheme however has not been wholly successful and the two vouchers awarded were both controversial.
[32] Richard Bergstom: EFPIA: http://www.reactgroup.org/uploads/news/Richard-Bergstrom-EP-Brussels-March-2011.pdf
[33] Kalin S. (2013). Antibiotic Commercial Models Under Revision To Tackle Stewardship Tension. The Pink Sheet
[34] http://apps.who.int/gb/ebwha/pdf_files/A61/A61_9-en.pdf
[35] http://www.imi.europa.eu/content/press-release-imi-9th-call-proposals

20. Alternative approaches to drug discovery include using small molecule approaches coupled with novel strategies for drug delivery and mode of action. We fund this type of research through our *Seeding Drug Discovery* scheme. For example:

    - Developing a methodology to smuggle genes or gene fragments into bacteria which will compromise their metabolism;

    - Developing therapies based on defective-interfering viruses - the focus of Wellcome Trust funded researcher Prof Nigel Dimmock at the University of Warwick.[36]

21. **Public-private partnerships:** Public-private partnerships will provide much needed acceleration of research and development of new antibiotic drugs. Significant public-private collaborations have been launched by the EU's Innovative Medicines Initiative[37] and the Joint Programming Initiative[38]; the NIH's National Institute of Allergy and Infectious Diseases[39] and the Bill & Melinda Gates Foundation; Biomedical Advanced Research and Development Authority and GSK.[40] A recent successful collaboration - the TB Alliance led by the Bill & Melinda Gates Foundation - has produced the first new FDA-approved drug for TB infection in 40 years.

22. **Open access and data sharing:** Open access and harmonised data sharing between researchers, pharmaceutical companies, ministries of health and public health agencies will stimulate innovation and new opportunities. Pharmaceutical companies are currently limited by their restricted class of chemicals. Sharing chemical classes and pre-competitive information would provide much needed diversity to the sector and shared insight. This could be better facilitated by public-private-partnerships. Data sharing with key national, European and international agencies is also important and will be facilitated by harmonised data standards.

Other treatments and methods

23. Promising alternative therapies include methods to target the pathogen, such as anti-virulence initiatives and bacteriophage viruses, and methods to enhance the immune response, such as probiotics and vaccinations. These methods however are at a relatively early stage and substantial research is required to support these innovations. Research we have funded in this field includes the following:

    - Research focused on Lytic enzymes encoded by DNA bacteriophages of Pseudomonas aeruginosa: properties, structure and engineering.

    - Studies focused on combination therapy of quorum sensing inhibitors and biofilm blockers for the treatment of Pseudomonas aeruginosa infection in those with cystic fibrosis

24. The most promising current alternative approaches include rapid diagnostic tools for personalised treatment by real-time sequencing of bacterial infections and inferring resistant phenotypes. Reverse vaccinology is an exciting genomic approach to vaccine

[36] http://www2.warwick.ac.uk/fac/sci/lifesci/people/1/ndimmock/
[37] http://www.imi.europa.eu/content/combacte
[38] http://www.jpiamr.eu/download/JPIAMR%20flyer%202013.pdf
[39] http://www.niaid.nih.gov/topics/antimicrobialresistance/research/pages/partners.aspx
[40] http://www.gsk.com/media/press-releases/2013/glaxosmithkline-awarded-up-to--200-million-by-u-s--government-to.html

discovery, which allows for all antigens to be predicted and exploits novel aspects of the immune system. This technique has been applied to 'superbugs' with some success[41] and may overcome the inevitable resistance cycle associated with drug treatments.

Q4. 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?

25. **Education and Awareness:** Education and awareness has been the cornerstone of a very successful targeted UK campaign to reduce *MRSA*. This has included public health initiatives to increase awareness and improve sanitation. Although the precise impact of these initiatives is not clear, four years after the "Clean your hands campaign" was launched in 2004, incidence of hospital acquired infections such as *MRSA* and *Clostridium difficile* fell by as much as half in some hospitals.[42] Mandatory surveillance of *MRSA*, hospital 'league tables' of incidence, and fines also encourage accountability. The Trust has funded three projects with the aim of supporting education and awareness raising in this field.[43] Although these measures have been effective for the targeted pathogen, by concentrating campaigns on one specific problem the overall picture may be obscured. We would encourage a broader approach to education and awareness of antimicrobial resistance, rather than simply redefining targets to account for emerging threats.

26. **Legislation:** Legislation has had a significant impact on the amount of antimicrobial drugs prescribed, however these measures have not been universally implemented. Impactful legislation adopted in the UK and countries across the world has included the banning of financial incentives for selling antimicrobial drugs for both animals and humans, and banning the use of antibiotic as growth promoters in animal husbandry. Denmark has comprehensively documented the impact of these measures, reporting a 30% decrease in antibiotic prescriptions when profiting was banned without compromising production efficiency.[44] The UK has also established similar practices and should be commended; however there is a need to influence globally to encourage a legislative approach alongside public engagement.

Q5. What global coordination and action is required to fight AMR and is the UK contributing enough towards cross-border initiatives?

27. We would encourage increased global action and coordination on AMR. The UK Government contributes to the EU Joint Programme Initiative on AMR. The UK has also taken a leading role in highlighting the global threat of AMR by calling G8 countries' science ministers together for the first time in five years to discuss this issue.[45]

28. Cross-border initiatives require coordinated sharing of data. To facilitate this, harmonised data sets are needed. The Global Microbial Identifier[46] is an exciting possibility, which would allow simple identification of all microorganisms in a clinical setting and would facilitate surveillance by providing a total database of sequences of all relevant

[41] http://news.bbc.co.uk/1/hi/health/6098210.stm
[42] http://www.nhs.uk/news/2012/05may/Pages/mrsa-hospital-acquired-infection-rates.aspx
[43] One creating a film piece about malaria parasite resistance and counterfeit drugs in Cambodia, one creating a documentary about the personal/global impact of MDR-TB, one education project to raise awareness amongst schoolchildren about drug-resistant 'superbugs' and hygiene/hand washing.
[44] http://wwwnc.cdc.gov/eid/article/13/11/07-0421_article.htm
[45] http://www.nature.com/news/seven-days-14-20-june-2013-1.13223
[46] http://www.globalmicrobialidentifier.org/

microbiological strains globally. The Trust urges the development of such important initiatives, but encourages pragmatic consideration of what actions would be engendered as a result.

29. Further engagement is required from organisations such as the WHO to ensure a global approach to the challenges presented by AMR.

Q6. What are the strengths and weaknesses of the Government's 2013-2018 strategy for tackling AMR? What changes might be made to further strengthen the Government's action plan?

30. The UK Government's five-year strategy to address AMR is welcome and areas of action to address this threat to healthcare are laudable. At the outset, this serves to raise the profile of this issue and reaffirm the UKs commitment to these issues. The 'One Health' approach is to be praised for its recognition of this being a complex issue linking humans, animals and the environment. We welcome calls to put AMR on the national risk register ensuring that this issue is given full attention. We would also urge AMR to be considered in the same framework as Emerging Infectious Diseases.

31. The important issues of cataloguing and surveillance are highlighted in the strategy, however the Trust is concerned that the primacy of these issues is disproportionate and the importance of fundamental research and development for tackling antimicrobial research is not given sufficient focus. Further details are needed regarding new research and develop practices to support innovative solutions and drug development. Novel strategies to tackle infection require a culture of innovation; however the current health-care culture levies fines for bacteria detection in secondary and tertiary healthcare rather than encouraging ingenuity to approach these issues.

32. AMR is a global problem requiring international, coordinated action. The DH's strategy however is primarily UK focused. Specific reference to AMR in the developing world context, where it is most severe and likely to be where resistance spreads from, is noticeable in its absence. Whilst we appreciate that the focus of this strategy must be on the UK, if these issues are not addressed contemporaneously, at the global level, measures in the UK will be compromised and will serve only to stem the tide against imported resistance. International collaboration is highlighted as a key area, but this focuses on successful western collaborations. Whilst these should be commended, the strategy does not address engagement with the developing world, which may require a very different approach.

33. A key priority is to ensure prudent use of antimicrobial drugs and equitable access, which will require different approaches in different contexts. In the UK the focus of the DH strategy is to reduce the use and misuse of drugs in people and animals. In the developing world context an alternative approach may be needed since over-the-counter access to antimicrobial medicines, which hastens resistance, may also be vital in countries lacking appropriate health systems and infrastructure to support effective prescription-only access.

34. AMR is a complex and long-standing problem. Many of the key strategies outlined are well-documented approaches that have not been shown to have a clear impact. In order for this strategy to deliver change where others have not, clear tractable solutions are required with formal ownership and multi-stakeholder engagement. Crucial here will be

to address some of the perverse incentives that undermine key areas of the strategy. The UK five-year strategy outlines commendable objectives but further clarity is required on proposed actions and the budget that will be made available to meet this ambitious plan.