TACKLING ANTIMICROBIAL RESISTANCE

Identifying Future Research Themes

Proceedings of the Conference Tackling Antimicrobial Resistance, 6 February 2013

Edited by Jennifer Cole

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Conference Report, August 2013

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Professor Bryan Edwards

Of all the challenges facing the UK today, few are as demanding as those arising in the defence, security and resilience domain. Some are modern variants of those faced for many years. Others are entirely new and are characteristically different to anything that has preceded them. Others again have yet to emerge but no doubt will, given the UK's position in a rapidly evolving world.

One unifying feature of this large and complex array of challenges is that few, if any, lend themselves to a single discipline solution and the interaction between scientific and other considerations is self-evident when considering opportunities for effective, ethically acceptable and cost-effective measures.

With that in mind, the Science and Technology Facilities Council (STFC) is delighted to fund and actively participate in this series of conferences as part of its Defence, Security and Resilience Futures Programme. This aims to identify and facilitate the engagement of the relevant capabilities of the UK National Laboratories, industry and university research groups with some of the most demanding and highest priority challenges in national security in the widest sense (including the disruption of services upon which normal functioning of society is dependent).

Each conference addresses a topical issue within the domain and brings together academics, industrialists and those in government with an interest in or responsibility for aspects of the topic, aiming to explore the interface between academic research and policy, and where the former might contribute to development or refinement of the latter.

I therefore make no apology for this meeting adopting a strategic perspective on the issue, nor the unusually diverse spectrum of experience and expertise present at the meetings. Both are necessary to meet our aims of exploring the potential for step change rather than incremental development, and to understand and identify corresponding areas of uncertainty. Such areas can be addressed by focused academic research and by posing questions which, if answered, will enable policy and decision makers to either do things significantly differently or to do significantly different things.

Thanks must go to RUSI for all their extremely hard work organising and delivering this event. However, the final word of thanks is reserved for all those who participated so enthusiastically on the day, whether as speakers or delegates.

This document will serve as an enduring record of those contributions. More than that, I hope it will encourage academics in all disciplines to consider how their particular expertise might contribute to, in this case, coping with the emergence and spread of infectious diseases that are increasingly resistant to currently available therapeutic agents.

Finally, anyone wishing to know more about the conference programme, STFC's interest in defence, security and resilience or working more with STFC in this domain is invited to contact me using the e-mail address below.

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Introduction: Addressing the Threat from Antimicrobial Resistance

Jennifer Cole

The Resilience and Emergency Management programme at RUSI focuses on the threats and hazards on the UK's National Risk Register, and researches the capabilities we need to prevent, mitigate, respond to and recover from these threats. In addressing antimicrobial resistance, RUSI has also focused on an emerging risk which, while not currently on the National Risk Register, poses an increasingly serious threat to the UK and its interests. Identifying and tackling such risks early is a vital component of resilience. The earlier such threats can be addressed, the more easily they can be planned for, responded to and recovered from; in short, the more resilient to them we will become.

In the past few months, political interest in antimicrobial resistance has reached an important tipping point. AMR has long touched the edges of a number of defence and security issues[1] including immigration policy (where preventing the spread of drug-resistant tuberculosis, gonorrhoea and other diseases into and around the UK is a challenge), the management of refugee camps (in which more than 90 per cent of the cases of dysentery can be resistant to the two most common front-line drugs) and the response to pandemic flu (which would become even more serious if the flu strain involved was drug-resistant).[2] Now, however, AMR is being considered in its own right; the Department of Health has considered how AMR affects existing National Risk Assessment emergency scenarios and has agreed to consider how it affects UK National security interests more widely for the next National Security Risk Assessment (NSRA) in 2014. The NSRA is summarised in the UK's National Security Strategy and this, in turn, informs the National Risk Register.

Moving AMR up the Political Agenda

Such attention is long overdue. At the time of the 9/11 attacks on the USA, in which just under 3,000 people lost their lives, more than 6,000 Americans died every year from MRSA caught in hospitals,[3] yet the issue received

1 J Cole, 'Antimicrobial resistance and healthcare resilience: a game changer for the 21st century?', RUSI.org, 23 August 2013.

2 J Cole, 'Antimicrobial resistance, infection control and planning for pandemics: The importance of knowledge transfer in healthcare resilience and emergency planning', *Journal of Business Continuity and Emergency Planning* (Vol. 6, No. 2, Autumn/Winter 2012–2013) pp 122–23, <http://www.henrystewartpublications.com/jbcep/v6>.

3 E Klein, D L Smith and R Laxminarayan, 'Hospitalisations and Deaths Caused by Methicillin–Resistant *Staphyloccocus aureus*, United States, 1999–2005', *Emerging Infectious Diseases* (Vol. 13, No. 12, December 2007), Centers for Disease Control and

little interest outside of specialist medical circles. It would be more than a decade before the 2011 World Health Day was dedicated to AMR and the topic began to push its way slowly up the political agenda. We need to move faster. As the World Economic Forum Report 2013 recognises: 'We will never stay ahead of the [AMR] mutation curve. A test of our resilience is how far behind it we allow ourselves to fall.'[4]

Policy and academia both tend to move slowly, while at grassroots level, front-line healthcare providers in hospitals and GP surgeries face a threat from AMR that is growing every day. It is essential that early adopters and champions of better antibiotic stewardship are identified; that barriers to the development of novel therapeutics, alternative treatments and the implementation of existing policy are removed; and that the importance of AMR to all sectors of society, not just to health, is communicated widely and effectively.

Internationally, initiatives such as European Antibiotics Awareness Day, held annually on 18 November, and the findings of the Transatlantic Task Force on Antimicrobial Resistance – which suggests that 50 per cent of antibiotic prescribing is 'inappropriate or unnecessary'[5] – are pushing the message out across multiple sectors. In the UK, the NHS and Department of Health are addressing the issue through programmes that encourage better antibiotic prescribing, such as 'Start smart – then focus' (covered in Chapter IV of this report); the National Institute of Clinical Excellence's Guideline 149[6] on reducing antibiotics in neonatal care (where the percentage of antibiotics administered needlessly is estimated to be between 90 and 99 per cent; see Chapter V); and the forthcoming UK Five Year Antimicrobial Resistance Strategy and Action Plan 2013–2018.

Policy only has impact if it is successfully implemented, however, and implementation often relies on robust, evidence-based research that provides support for best practice, encourages changes in behaviour and helps turn good intentions into common use.

Preventions (CDC), Atlanta GA, USA <http://wwwnc.cdc.gov/eid/> last accessed 26 June 2013.

4 See <http://reports.weforum.org/global–risks–2013/view/risk–case–1/the–dangers–of–hubris–on–human–health/> last accessed 17 May 2013.

5 See <http://ecdc.europa.eu/en/activities/diseaseprogrammes/TATFAR/Documents/210911_TATFAR_Report.pdf> last accessed 6 August 2012.

6 'Antibiotics for early–onset neonatal infection: antibiotics for the prevention and treatment of early–onset neonatal infection', see <http://guidance.nice.org.uk/CG/Wave23/7>.

RUSI's Ongoing Research into Tackling AMR

The aim of the conference held at RUSI on 6 February 2013, funded by the Science and Technology Facilities Council (STFC), was to identify research topics that will help to enable and implement existing UK government policy on antimicrobial resistance, which in turn will shape and inform future policy. Morning presentation panels and afternoon discussion forums explained the main challenges, framed the problems and sought to suggest solutions, drawing up a list of research areas and topics the STFC might choose to fund. The results of this conference will be distributed not only through RUSI and the STFC, but also to the other UK funding councils, key UK Government stakeholders, UK universities and research and development organisations including DSTL, the National Institute for Health Research and the Home Office Scientific Development Branch, so that they too may chose to add some of the topics discussed here to their future funding calls.

Addressing AMR needs a cross-governmental, cross-sector and cross-disciplinary approach. Representatives from the World Health Organization, the Department of Health, the National Health Service, the Health Protection Agency, the Ministry of Defence, the Society for General Microbiology and the Chief Medical Officer, Dame Sally Davies, participated in the conference. More than sixty delegates came from a wide range of backgrounds to find solutions together.

RUSI is extremely grateful to the STFC for providing the funding to make this conference possible, to the Department of Health and the Health Protection Agency (now Public Health England) for their support and guidance on the content of the discussions, and to all the speakers, discussion session chairs and rapporteurs. RUSI will continue to highlight the security and resilience implications of AMR over the coming months.

Jennifer Cole is Senior Research Fellow, Resilience and Emergency Management at the Royal United Services Institute. Her research programme includes CBRN prevention, response and recovery; infectious disease outbreaks caused by naturally occurring pandemics and bioterrorism; and strategies for warning and informing the public. Her academic background is in biological anthropology, and she is currently a Reid Scholar in Health, the Human Body and Behaviour at Royal Holloway, University of London.

The Threat from AMR: Global and National Perspectives

I. The UK Five-Year AMR Strategy and Action Plan

Professor Dame Sally Davies

Antibiotics are essential for the treatment of infections in humans and animals, but these uses are seriously jeopardised by the emergence and spread of multi-resistant bacteria and the lack of new antibiotics. As increasing international trade and travel favours the spread of antimicrobial resistance (AMR) between countries, AMR is a global public health concern with action required at both national and international level.

There are few public health threats of greater importance than AMR in terms of impact for society. The harsh reality is that we are at increasing risk of developing infections that cannot be treated. The rapid spread of multi-drug resistant bacteria means that we could be close to reaching a point where everyday infections will become untreatable. European data[1] suggest that the thirty-day mortality of patients with multi-resistant *E coli* blood stream infections is double that of patients with infections caused by susceptible strains. A multi-pronged holistic approach is needed if we are to limit the risk of AMR, conserve existing antibiotics and ensure they are used optimally, as well as facilitate the development of new diagnostics and treatments.

Background

AMR has been recognised at national, European and global level for a long time. The use of antibiotics increases the selective pressure for resistance. Resistance can be managed but not eradicated. Interest in AMR has increased recently due to the rapid spread of multi-resistant bacteria and the lack of new antibiotics. The last two years have seen the agreement of the WHO Regional Office for Europe's European strategic action plan on antibiotic resistance,[2] the EU Strategic Action Plan[3] and EU Council Conclusions[4] on a 'one health' approach.

1 Kraker, M E A, et al, 'Burden of antimicrobial resistance in European hospitals: excess mortality and length of stay associated with bloodstream infections due to *Escherichia coli* resistant to third generation cephalosporins', *Journal of Antimicrobial Chemotherapy* (Vol. 66, No. 3, November 2010) pp. 398–407, see <http://jac.oxfordjournals.org/content/66/2/398.full>, last accessed 18 May 2013.

2 European strategic action plan on antibiotic resistance, 10 June 2011, see <www.euro.who.int/en/who–we–are/governance/regional–committee–for–europe/past–sessions/sixty–first–session/documentation/working–documents/wd14–european–strategic–action–plan–on–antibiotic–resistance>.

3 European strategic action plan on antibiotic resistance 2011–2016, see <https://www.gov.uk/government/publications/european–strategic–action–plan–on–antibiotic–resistance–published>.

4 Council conclusions on the impact of antimicrobial resistance in the human health sector and in the veterinary sector – a 'One Health' perspective, Luxembourg, 22 June 2012, see <http://www.consilium.europa.eu/uedocs/cms_data/docs/pressdata/en/lsa/131126.pdf>.

My own understanding of the threat and risk of antimicrobial resistance increased as I prepared Volume Two of my annual report, which focuses on infection.[5] As a result of this work I called for antimicrobial resistance to be included on the Risk Registers of both the Department of Health and the Department for Environment, Food and Rural Affairs (Defra).

Multi-drug Resistant Bacteria

This increased activity has been prompted by the rapid and dramatic spread of multi-resistant bacteria. The resistance of *Escherichia coli* to third-generation cephalosporins, fluoroquinolones and aminoglycosides has increased significantly in more than half of the countries in Europe. Gonorrhoea is becoming increasingly resistant to antibiotic treatment and may become completely untreatable in the UK in future.

In the UK, the rise in absolute numbers and resistance patterns of Gram-negative bacteria (particularly members of the enterobacteriaceae family) is increasing rapidly, most notably from pathogens exhibiting extended-spectrum beta-lactamase (ESBL) or carbapenemase producing abilities. Public Health England estimates that currently, *E coli* accounts for approximately 10 per cent of all carbapenemase producers in UK isolates.

The rapid spread in humans of carbapenemase-producing bacteria that are resistant to the broad-spectrum carbapenem antibiotics, which are normally used as the last line of treatment in human infections, highlights the seriousness of the issue.

Threats exist from both domestic prescribing practices that fuel resistance, and resistant bacteria imported to the UK from infections acquired overseas. The recent emergence and rapid global spread of the New Delhi metallo-beta-lactamase 1 (NDM-1) resistance in certain bacteria 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. However the risks from imported infections are not totally outside of our control. What we need to do is monitor the threats and take appropriate action to detect and contain infections when they occur.

The Lack of New Drugs

Resistance to an antimicrobial is not a problem if there are others to take its place. However, there are a finite number of antibiotics and very few in the research pipeline. Large pharmaceutical companies are not investing in antibiotic research because there is insufficient return on investment, compared with drugs for other conditions.

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5 Annual Report of the Chief Medical Officer: Volume Two, Department of Health, 11 March 2013 <https://www.gov.uk/government/publications/chief–medical–officer–annual–report–volume–2>.

Given that the conventional pharmaceutical R&D model has not ensured a steady pipeline of new antimicrobials, there is urgent need for action at a global level to facilitate their development. We need to review the business model for development of antimicrobials, and show leadership through the strengthening of international partnerships and coalitions, such as the Innovative Medicines Initiative (IMI)[6] with Europe.

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 supplement this with new and alternative approaches to help mitigate this risk and conserve these valuable medical resources. The need for collective action to ensure antibiotics are used wisely and sparingly has never been more important than now. There is a key role for professionals to promote good practice across human and animal health.

Given our limited understanding of the development of AMR, a greater emphasis will need to be given to research and surveillance activities in addition to the development of effective new antimicrobials and diagnostics. The Medical Research Council (MRC), the National Institute for Health Research (NIHR), UK Clinical Research Collaboration (UKCRC), Defra and others fund research relevant to AMR and the strategy will improve co-ordination between these players.

Given the scale of global travel, it is inevitable that, sporadically, new infections will occur in the UK. What has to happen is a change of practice to ensure that information on travel and hospitalisation abroad is captured on admission to the UK and/or to the NHS. Screening, isolation and enhanced infection control measures need to be introduced as appropriate to reduce transmission. This will require significantly increased awareness and improved practice by both clinicians and managers.

Antimicrobial use in both primary and secondary human healthcare has a large impact on the development of resistance and responsible use is needed in all sectors, as they are interconnected. Infections do transfer from the community to hospital as well as the other way. To date, most activity has focused on secondary care, but this will need to change to involve all healthcare sectors.

A significant amount of work has been carried out in the UK to improve surveillance, infection control and responsible prescribing but more action is needed at a national and global level to accelerate progress on this crucial public health issue. The risk from both domestic selective pressure and imported infections means that we must continue to work with international

6 See <http://www.imi.europa.eu/>, last accessed 18 May 2013.

colleagues and share information on emerging issues. Given the impetus for action, the new UK cross-government AMR Strategy and Action Plan (forthcoming) recognises the global nature of the issue and the need for more action at an international level.

The Strategy

The Department of Health has led work to develop a new UK integrated five-year AMR strategy and action plan in collaboration with Defra, the devolved administrations and other government departments.

The strategy identifies seven key areas of activity:

1. Promoting responsible prescribing and effective administration of antimicrobials to preserve the activity of existing therapies and optimise prescribing practice
2. Improving infection prevention and control in human and animal systems
3. Raising awareness of the problem posed by antimicrobial resistance, improve public and professional knowledge and promoting change in behaviour in order to slow the development of resistance
4. Improving 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. Facilitating and encouraging the development of new drugs, vaccines and other immunotherapeutics
6. Improving the evidence base by strengthening surveillance, epidemiological data, and data linkage arrangements to unlock better-quality healthcare data and improve accessibility of the data
7. Strengthening UK and international collaboration, data and technology sharing across animal and human health fields to tackle this issue at a global level.

The Antimicrobial Resistance Action Plan in the strategy identifies key UK-wide initiatives and will be monitored in the annual report. Delivery of the strategy will be overseen by a UK cross-government steering group led by the Department of Health.

Strategic Outcome Measures

AMR is a complex issue requiring action on a number of fronts and we are keen to ensure that the strategy is challenging and accelerates progress. We have set five strategic national outcome measures. These cover both human and animal aspects and will be used to monitor progress to inform the annual report each November.

One of the outcome measures of particular interest here is: 'To establish robust mechanisms for data collection to monitor trends in key human "drug/bug" combinations identified to successfully control and contain resistance.'

We will focus our efforts on key resistances to help establish trends. The drug/bug combinations that will be monitored in the first instance are shown in Table 1.

Table 1: Bug and Drug Combinations

Bug	Drug	Notes
Klebsiella	carbapenem	non-susceptible to imipenem and/or meropenem
E coli	carbapenem	non-susceptible to ertapenem, meropenem and/or imipenem
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
Pseudomonas	cephalosporin	non-susceptible to ceftazidime
E coli	gentamicin	non-susceptible
S pneumoniae	penicillin	non-susceptible

What we want to do is create a cultural movement at a societal level, similar to what happened for climate change where there is now societal awareness of the issue and acceptance that this a complex challenge requiring action on a large number of fronts by professionals, industry and the wider population to contain the problem. We will be calling on professional bodies and their members to do their bit to show clinical leadership to change behaviour and improve practice.

Summary

The Strategy and Action Plan has been developed with consideration of what is affordable and achievable within the five-year term. It lays a foundation for more aspirational measures, which will involve infrastructure changes to facilitate the delivery of longer-term objectives.

Containing AMR and preventing untreatable illness and premature mortality is a priority given the rapid spread of multi-resistant bacteria and the lack of

new antibiotics. These drivers have given new impetus to our work to tackle AMR and the new strategy will move us forward. Promoting responsible antibiotic prescribing is crucial, but work to encourage the development of new antibiotics is also urgently needed.

Its success depends on active support and commitment and I hope you will become AMR champions. We all have a vested interest in preserving the efficacy of antibiotics so that we, and future generations, have the benefit of antibiotics. I am personally championing the need to tackle antimicrobial resistance through my annual report, my activities and my discussions at every level: at the local level, in the Department of Health; at the national level, across government; and internationally through the World Health Organization.

Professor Dame Sally Davies is the Chief Medical Officer for England and is the Chief Scientific Advisor for the Department of Health. She has been actively involved in NHS research and development: as director-general she established the National Institute for Health Research (NIHR) with a budget of £1 billion. She was awarded a DBE (Dame Commander of the British Empire) in the New Year Honours 2009 for services to medicine, and in 2011 was conferred as Emeritus Professor at Imperial College London.

II. Combating Antimicrobial Drug Resistance: The International Perspective

Dr Charles R Penn

Before penicillin, pneumonia and septicaemia killed nine out of ten of those who became infected. Since antibiotics and the introduction of penicillin, nine out of ten now live. However, the increasing incidence of resistance to the medicines, combined with very few new medicines in the pipeline will lead to rising mortality and rising healthcare costs in future.

This is not over-dramatising the problem. Take, for example, multi-resistant tuberculosis (see map on next page). Between 1994 and 2000, the proportion of multi-drug resistant TB cases was above 25 per cent in many countries and greater than 50 per cent in some.[1] Other maps shows exactly the same pattern but in newly acquired cases – people getting tuberculosis for the first time and for whom treatments, in many cases, are no longer available. There are similar maps for malaria, HIV and other diseases. Some diseases, previously regarded as relatively easy to manage, are becoming untreatable, such as a highly resistant strain of gonorrhoea that is being extensively tracked and monitored worldwide.

The World Economic Forum, in its 2013 Global Risk Report, highlighted antimicrobial resistance. The global impact of antibiotic-resistant bacteria is apparent across the world: in some parts of Africa, antibiotic resistance is having a bigger impact than malaria and some other diseases more readily associated with those regions.

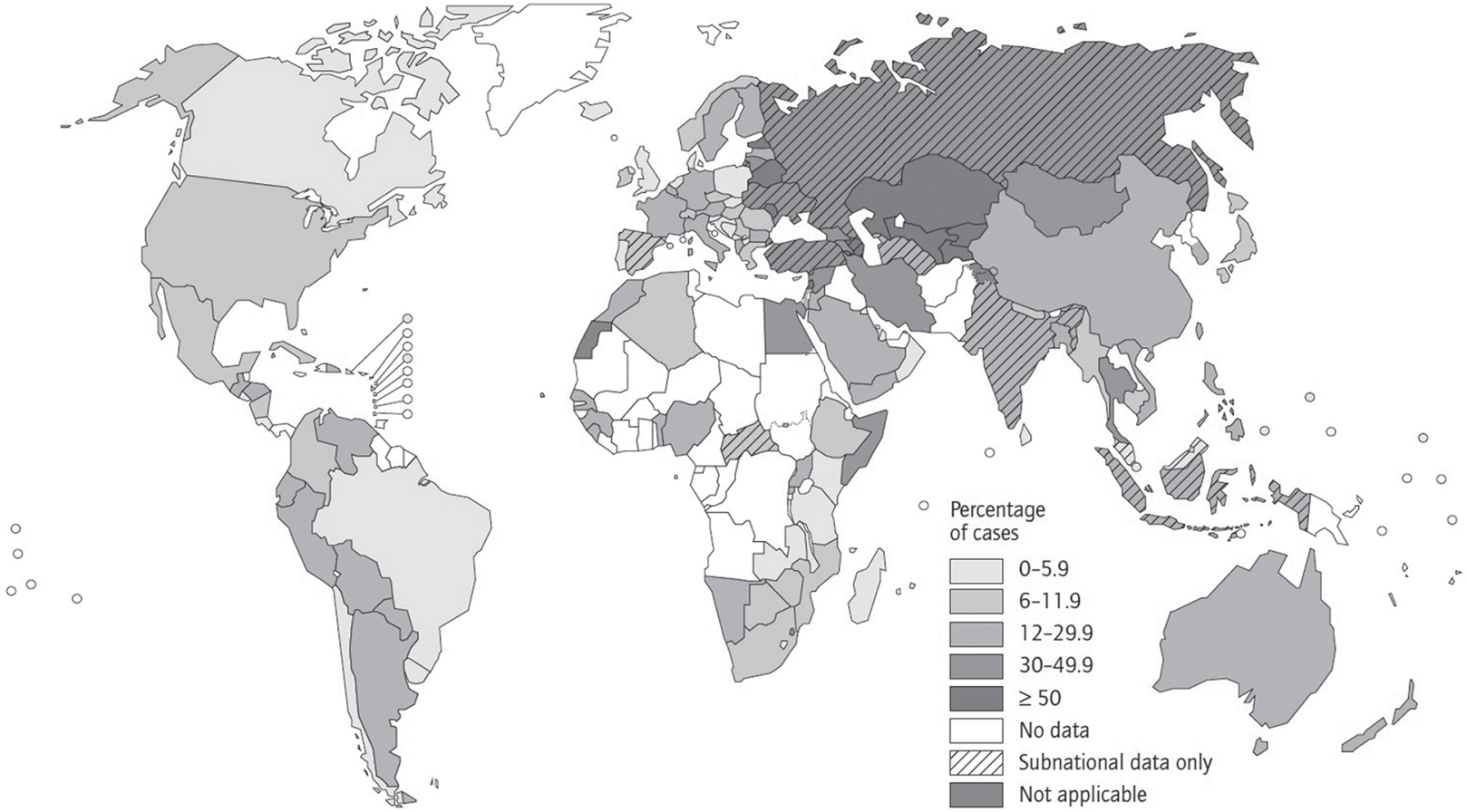
There is a wide range of examples of antibiotic-resistant bacteria occurring in places such as hospitals and the family home. One example is from a rural hospital in India where four neonatal deaths occurred, attributable to the New Delhi metallo-beta-lactamase 1 (NDM-1) gene conferring resistance to a range of antibiotics. While a rural hospital in India might be seen as a relatively low resource setting, it is not an environment entirely lacking in modern health facilities and technology.

The same thing is happening in much higher resource settings, in any case. Consider another paper published two to three years ago, on the death of two liver transplant patients in the USA.[2] Carbapenemase-producing Klebsiella has already been mentioned, but here is an example of it having

1 See Slide 5, available at <http://www.rusi.org/downloads/assets/Penn.pptx>.

2 R S Arnold et al, 'Emergence of *Klebsiella pneumonia* Carbapenemase (KPC)–Producing Bacteria', *Southern Medical Journal* (Vol. 104, No.1, January 2011), pp. 40–45. See <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3075864/>.

Map 1: Proportion of Multi-drug Resistance among Previously Treated Tuberculosis Cases, 1994–2010



[a] Figures are based on the most recent year for which data have been reported, which varies among countries.

Combining data from all countries and territories: multi-drug resistance in previously treated tuberculosis cases, 19.8%

a different kind of impact: the liver transplant patients both contracted carbapenemase-producing *K. pneumonia* and despite being treated with meropenem, subsequently died. There are many examples of this type.

Global Challenges

AMR is happening all over the world and has an impact on every aspect of health as well as other aspects of our lives. It is having an impact on infectious diseases such as pneumonia, gonorrhoea, tuberculosis, malaria and HIV, as well as on neonatal care, transplant surgery, cancer treatment and other forms of surgery. It is also having an impact on health security, travel, the deployment of people for humanitarian purposes or into conflict situations and on refugees. It potentially falls within the scope of International Health Regulations[3] and better understanding is needed of how this subject will integrate with this international framework for managing health risks around the world in future. The challenge is looking at why the problem has occurred and why it is persisting. There is a lack of awareness and understanding of what is happening across the world, organism by organism, country by country. Some countries have developed or are developing good plans for tackling AMR at a national level, but many countries have not, and there is a need for greater international co-operation.

For WHO, there are conflicting challenges. There is inappropriate use of antimicrobial medicines between human and animal health, and the more these medicines are used, the more they will be lost through resistance. On the other hand, many parts of the world do not have enough access to the antibiotics that do work, so improving equitable access is just as important. It is quite a complex challenge.

Lack of New Medicines

Every antibiotic has a finite fully useful life; resistance to anti-infective medicines will always arise due to natural selection.[4] The challenge is how to best manage those finite lifespans, particularly when there have been relatively few recent introductions. At the moment, there are very few new drugs in the pipeline.

In 2011, AMR was the topic of World Health Day. Six key actions were identified:

1. Develop comprehensive national plans that involve accountability and civil society engagement

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3 World Health Organization, International Health Regulations, 2005, <http://www.who.int/ihr/en>.

4 R Nugent, E Back, A Beith, *The Race Against Drug Resistance*, Center for Global Development, 2010, <http://www.cgdev.org/files/1424207_file_CGD_DRWG_FINAL.pdf>.

2. Strengthen surveillance and laboratory capacity
3. Improve access to essential medicines of assured quality. In some parts of the world, poor quality or counterfeit medicines is part of the problem
4. Rationalise use of medicines
5. Enhance infection prevention and control
6. Foster innovation and research and development for new tools.

Research Needs: Surveillance and Burden of Disease

Better information is needed on what is happening in the world, with better surveillance and tracking of antimicrobial infectious disease resistance. At the moment, there are many networks of surveillance systems. Some are global, looking at specific diseases, while many are at a national or subnational level. The global picture of what is happening is less clear: there needs to be a way of connecting the smaller snapshots to develop a single larger picture, and not just in microbiological terms. The health impact globally needs to be better understood – and also the economic impact. If people are to be persuaded to invest in solutions to the problem, the financial cost needs to be discussed. Evidence is needed to support policy changes and to be able to monitor the impact of those changes so that efforts to combat AMR can be reinforced or adjusted.

A stronger evidence base and better systematic reviews of the available evidence are needed to guide policies and plans to combat AMR. Some of the issues seem clear: agricultural use of antibiotics exceeds the use in human health, for example, and many countries are taking steps to limit their use in areas such as growth promotion and prophylaxis in livestock. The case for such intervention would be stronger with better evidence on the impact of antibiotic use in agriculture on human health on the one hand, and its role in agricultural economy and food security on the other. Even in human health we face similar challenges. An example of the paradox is illustrated by a recent clinical study published in the *New England Journal of Medicine*.[5] The study looked at antibiotic use in malnourished children in Africa. The study showed a benefit to the use of antibiotics but the potential cost in terms of increased risk of antibiotic resistance was not assessed. Again, understanding how to get the balance right is key, and this depends on evidence.

Ways of encouraging investment in new tools, not just the medicines, need to be found. New ways of thinking about return on investment and the business models for investment in research and development are needed. At the moment, the climate to encourage that innovation does not exist;

5 I Trehan, H S Goldbach, L N LaGrone, G J Meuli, R J Wang, K M Maleta, M J Manary, 'Antibiotics as Part of Management of Severe Acute Malnutrition', *The New England Journal of Medicine* (January 31, 2013). See <http://www.ncbi.nlm.nih.gov/pubmed/23363496>, last accessed 18 May 2013.

however, there are research opportunities that go beyond biology – in the fields of economics and social sciences for example.

Avoidable Mortality

AMR is not an issue that can be postponed. Deaths are occurring today – a factsheet published in May 2012 by ReAct,[6] an independent global network for concerned action on antibiotic resistance, shows how in a range of organisms and diseases there is a higher mortality rate if the organism is resistant to antibiotics. There are also examples of where actions are having a positive effect, such as good regulation of animal use and prescribing practices in Australia, which has kept resistance to certain classes of antibiotics very low relative to other countries.

Another example is bedaquiline, the new treatment for tuberculosis, which was approved by the US FDA in December after only Phase II studies[7] – the normal process for licensing a new pharmaceutical involves five phases. There was innovative thinking around approval because there are many people for whom there is no other choice. In another part of the world, Thailand has introduced a programme to educate patients and prescribers on appropriate use of antibiotics.

It is a big challenge and there is much that still needs to be done but there are examples of where actions are having an effect.

Charles R Penn TD PhD FRSPH joined the World Health Organization, Geneva at the start of the 2009 influenza pandemic, and was initially responsible for the use of antivirals in influenza management. He currently oversees programmes on antimicrobial resistance, infection prevention and control, hepatitis and respiratory viruses. He also chairs WHO's Guidelines Review Committee, which monitors the quality of all of WHO's health guidelines.

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6 See http://www.reactgroup.org/uploads/publications/react–publications/ReAct–facts–burden–of–antibiotic–resistance–May–2012.pdf, last accessed 30 May 2013.

7 G Kovacs, 'Future Technologies for Pharmaceutical Resilience', *Pharmaceutical Resilience: Proceedings of the Workshop Pharmaceutical Resilience for Serious Infectious Disease, 5 February 2013,* RUSI, 2013. See http://www.rusi.org/downloads/assets/201304_Pharmaceutical_Resilience_Web.pdf

III. National and International Spread of AMR: Clones and Genes

Professor Alan Johnson

The problem of antimicrobial resistance is immense; it crops up in a range of different pathogens. This paper will focus on three very common pathogens that are experienced in the UK and where resistance is seen: *Streptococcus pneumoniae*, *Staphylococcus aureus* and *Escherichia coli*. Many of the underlying principles of what is known about strain and gene spread are applicable to a whole range of other pathogens, some of which will be discussed later.

Streptococcus pneumoniae

Over recent decades it has become apparent that, in terms of the spread of resistance, there are a number of resistant lineages, or clones of the pathogen *Streptococcus pneumoniae* that are clearly capable of very widespread dissemination. One of the first strains to be characterised, designated Spain^{23F}-1, is resistant to three antibiotics – namely penicillin, tetracycline and chloramphenicol. The story started to unfold in the late 1980s when there was an outbreak of pneumococcal infection and colonisation affecting children in a nursery in Cleveland, Ohio, USA. Local investigators decided to study what was happening and look at the dynamics of strain spread in the nursery but they actually made the unexpected finding that, when characterised at a molecular level, the individual isolates were identical to a multi-resistant strain that had been described in Spain some years previously. This was published in literature as the first documented example of strain spread between continents, and this particular strain has subsequently gone on to spread globally.

Lineages of resistant pneumococci are classified by a body called the Pneumococcal Molecular Epidemiology Network (PMEN) that uses DNA sequencing to characterise clinical isolates of pneumococci, particularly those that are resistant to antibiotics. Isolates characterised at the molecular level are then grouped into series of lineages, or clones, that are capable of widespread dissemination, based on their isolation from geographically diverse locations. It has identified around forty such clones to date. Each strain is assigned a categorisation on the basis of the country from which the first isolate was documented. The serotype is given as a superscript and then the strains are numbered sequentially.

These data are not just of academic interest, but apply to everyday clinical microbiology. Ten years ago, the Health Protection Agency (now Public Health England) collaborated with a district general hospital in Berkshire in a study

where the hospital microbiologists collected all of their invasive pneumococci over a fifteen-month period and sent them to the National Reference Laboratory for characterisation. There were fifty-six cases of pneumococcal bacteraemia over that time period, which shows it is an important pathogen. Around a third of those isolates were antibiotic-resistant. When all the isolates were characterised in the reference laboratory, all of the resistant ones identified were strains that had already been documented by the Pneumococcal Molecular Epidemiology Network. So these sorts of isolates are being seen in everyday clinical practice.

Pneumococci comprise about ninety different serotypes based on their capsular polysaccharide. The capsule coats the bacteria and serves as a virulence factor in that it prevents the organisms being phagocytosed by the polymorphonuclear leucocytes, or white blood cells. In layman's terms, this means it is a mechanism for warding off the body's nonspecific defence mechanisms and is important in virulence. It was shown many decades ago that if antisera was raised to the capsule polysaccharides and in vitro phagocytosis experiments were undertaken, the antisera would opsonise the bacteria – making it more susceptible to the action of phagocytes. Hence it became clear that an antibody response is likely to be a very potent immune mechanism for fighting pneumococcal disease.

Using Vaccination

This led to the idea that it is possible to use vaccination to prevent pneumococcal infections. However, because there are ninety different serotypes of *S pneumoniae*, effective vaccines would need to be made up of multiple capsule antigens. Fortunately, the serotypes do not occur with equal frequency; some are common and others relatively rare. By undertaking surveillance to monitor the distribution of the different serotypes it is possible to choose which serotype antigens to include in the vaccine. Another problem is that because they are polysaccharide antigens, they are not immunogenic in very young children, who comprise one of the two major groups of patients where invasive pneumococcal disease is a particular problem, the other group being the elderly. To make the capsular antigens immunogenic so they can be used to effectively vaccinate children, the polysaccharides are chemically coupled to two protein carriers. In 2006, the 7-valent vaccine (a vaccine made up of the seven commonest pneumococcal serotypes, all immunogenic for children) was introduced; this has recently been superseded by a new 13-valent conjugate vaccine.

A strong correlation between serotype and antimicrobial resistance has been identified and it is also known that a lot of the serotypes that are resistant were included in the vaccine. This led to speculation that if the vaccine was effective, not only would a drop in the incidence of invasive pneumococcal disease be seen, but so too would a drop in resistance.

The UK has been relatively fortunate in terms of penicillin resistance: over the last twenty years or so, the percentage levels of resistance in pneumococci have remained in single figures, which compares favourably with many other parts of the world where penicillin resistance rates can be 30 to 50 per cent or more.

There has been a problem, however, with erythromycin resistance in pneumococci, which has typically been around 15 per cent of all isolates, with even higher rates being seen in isolates from children aged less than two. The higher rate of resistance in very young children is likely to relate to greater use of antibiotics in children. This highlights the issue of antimicrobial stewardship and whether so many antibiotics should be used in children, particularly for minor infections, because the more antibiotics are used, the greater the selective pressure and the higher the resistance rates tend to be.

What is known is that the erythromycin resistance is associated with serotype 14, in particular the England[14]-9 lineage described by the Pneumococcal Molecular Epidemiology Network and referred to above. As the serotype 14 antigen was included in the 7-valent vaccine, it was postulated that when the vaccine was introduced a decline in the proportion of pneumococci resistant to erythromycin would be seen.

In a remarkably short period of time following the introduction of the vaccine in 2006, there was a phenomenal drop in the proportion of pneumococci from young children that were erythromycin-resistant, clearly showing how these sorts of surveillance activities can give rise to interventions that can be quite effective.

Staphylococcus aureus

The proportion of isolates of *Staphylococcus aureus* from blood culture that are methicillin-resistant, referred to as MRSA, has increased dramatically over time. Back in 1990, a patient with staphylococcal sepsis starting treatment with flucloxocillin would have had about a 98 to 99 per cent chance of being on the right drug. Throughout the 1990s however, there was year-on-year increase in methicillin resistance, such that by the turn of the century, the chance that a patient with staphylococcal sepsis would have had MRSA had risen to around 45 per cent.

This had a major impact on treatment: in the early 1990s, flucloxocillin would have been the drug of choice. Throughout the 1990s doctors increasingly had to turn to using glycopeptides, in particular vancomycin, for treatment. Although vancomycin works, it is not as good a drug as flucloxicillin, so patients were arguably receiving less robust treatment.

Epidemic Strains

Two particular strains of MRSA (which are actually now known as EMRSA – the E standing for Epidemic) that emerged in the 1990s had a phenomenal ability to spread both between patients and between hospitals. What is special about these epidemic strains that gives them this tremendous ability to spread? It may be, in part, something quite simple, such as the phenotype. Those two epidemic strains are not only resistant to all the beta-lactam antibiotics – which includes cephalosporins that are widely used in hospitals – but are also characteristically resistant to quinolones, which would include ciprofloxacin and macrolides.

In an important study, the Aberdeen Royal Infirmary tabulated its use of those antibiotics against infections caused by the two epidemic strains and demonstrated the importance of antimicrobial stewardship by highlighting the phenomenally strong correlation between antibiotic use and the spread of resistance.[1] What is going on nationally and internationally is not entirely clear, however, because all the surveillance is based on bacteraemia. It is not clear, for example whether these two epidemic strains are particularly virulent, and hence able to cause bloodstream infections, or if it is their ability to colonise that indirectly leads to invasion of the bloodstream. Bacteraemias (bloodstream infections) are frequently associated with intravenous catheters which are pushed through the skin to access the blood vessels, providing a portal of entry for bacteria on the skin. Hence if EMRSA strains readily colonise the skin, they may be the organisms most likely to be associated with catheter-related bloodstream infections.

Ciprofloxacin, in terms of its pharmacokinetics, is excreted in sweat and this raises the possibility that patients on the drug may actually have a thin film of the antibiotic covering the skin, which may perhaps disrupt normal skin microflora and essentially open up a new ecological niche that the MRSA can then colonise on the skin. When a patient has a line put in, organisms get direct access to the bloodstream; this may be analogous to the disruption of the gut microflora caused by antibiotics seen when *C difficile* infections arise.

The UK is not unique in this situation. The geographical distribution of several different lineages of *S aureus* across Europe have been documented and, mathematically, it can be shown that the distribution strongly correlates with health networks, in terms of referral patterns of patients between hospitals.[2] Nonetheless, some strains of MRSA clearly have much greater epidemic potential than others. Currently research using whole genome sequencing is trying to unravel what is special about those strains, but more understanding is still needed.

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1 See Figure 1, Slide 10, in presentation available at <http://www.rusi.org/downloads/assets/Johnson.ppt>.

2 See Figure 3, Slide 12.

Epidemiology of Cephalosporin: Changing Resistance in the UK

In Chapter 1, Dame Sally Davis refers to the problem of cephalosporin resistance mediated by extended-spectrum beta-lactamases (ESBLs). This problem arose globally in the early/mid 1980s and was a significant problem in the UK throughout the 1980s and 1990s. During that time, the infections had a characteristic epidemiology. They were virtually all seen in hospitals, so it was very much a nosocomial (hospital-acquired) problem and, commonly, in high-dependency units such as intensive care units (ICUs) and neonatal units. The most common pathogen tended to be *K pneumoniae*; other Gram-negative pathogens like *E coli* would crop up occasionally, but *Klebsiellas* dominated the scene. There were two main types of ESBL – TEM and SHV – and these were the dominant enzymes being produced by resistant bacteria.

Around 2003, the situation in the UK changed dramatically. The National Reference Laboratory started getting isolates from hospitals that had isolated *E coli* from urine sent in by GPs that appeared to be producing an ESBL – as this was unusual, the hospitals often asked the Reference Laboratory to check their findings and often they would be right. It subsequently became clear there has been a shift in the epidemiology on three fronts: there has been a shift in the pathogen, with *E coli* increasingly becoming the dominant ESBL-producing organism in the UK. Secondly, the new strains were producing a new type of ESBL, known as a CTX-M type ESBL. This, in turn was leading to a shift in the pattern of infections, with a lot of isolates being found from infections in the community, particularly urinary tract infections.

As many patients with these infections were elderly, with a history of regular healthcare contact, it has been difficult to disentangle how much of it emanates from antibiotic use in hospitals versus the community, and to determine the spread and so on. This is now an active area of research.

Examining the DNA

The isolates that were sent in to the reference lab were characterised using pulsed field gel electrophoresis. This is essentially a DNA fingerprinting tool, which, given that this work was done in about 2005, was a state-of-the-art tool at the time. This was supplemented by another technique of DNA fingerprinting called multi locus sequence typing, or MLST, which involves looking at the genetic similarity of various housekeeping genes. When the isolates were analysed, it became clear that there were a lot of the isolates clustering together, showing that they were very highly genetically related.

One particular strain – designated Strain A – appeared to be spreading quite dramatically, with other strains designated B, C, D and E being found which were related to Strain A. All of the isolates in those five strains belonged to the same serotype – they were all O25:H4. When looked at by MLST, they appeared to be part of the same lineage. In the space of a year or two,

not only had these new strains emerged, but they had spread dramatically around the country. This was similar to what had been seen previously with MRSA and again showed how certain strains of bacteria have a phenomenal ability to spread.

In fact, this particular strain has spread globally – what was seen in the UK had happened in many other countries around the world. Interestingly, a lot of countries had a similar change in the epidemiology, with elderly patients in the community developing urinary tract infections. This particular clone has been subject to whole genome sequencing, and this shows that there are genes encoding virulence determinants associated with an ability to produce urinary tract infections. So the molecular biology inside them goes some way to explaining the clinical correlate that is happening.

In addition to the strains that were spreading, there were many diverse strains with resistance present. This was due to the gene encoding the resistance actually spreading between these diverse strains, adding another layer of complexity. Not only is there spread of pathogens between patients, there is also spread of the genes between different organisms.

The bacterial chromosome[3] is a large circular molecule of DNA but in addition, bacteria have much smaller circles of DNA called plasmids that often encode antibiotic resistance. The problem is that bacteria can transfer their plasmids from one strain to another, or indeed from one species to another.

The donor strain, which is antibiotic-resistant, produces a hollow fibrous coated tube called a sex pilus, which makes physical contact with a recipient strain of bacteria.[4] It makes a copy of the plasmid which is then transferred to the tube through the recipient which then becomes antibiotic-resistant. Because it is transferring a copy of the plasmid, the donor remains antibiotic-resistant but the recipient acquires a new gene and becomes resistant in turn. This happens with strains of *E coli* but there is also inter-species transfer. When gonococci first became penicillin resistant, they actually acquired a gene for penicillin resistance that was originally found in *E coli*. It is the inter-genus transfer of resistance that gives rise to the problems seen today.

Much of what has been mentioned is applicable to a range of other pathogens including vancomycin-resistant enterococci, *K pneumoniae*, *Acinetobacter baumnanii* – a common problem in intensive care units (see Chapter VIII); multi-drug resistant tuberculosis and cephalosporin resistance in gonorrhoea, which is becoming an increasingly serious problem; there are increasing numbers of papers appearing documenting strains spread

3 See Slide 18, in presentation available at <http://www.rusi.org/downloads/assets/Johnson.ppt>.

4 See Slide 19.

between sexual networks. More recently there has been an increasing problem with carbapenamase-producing Gram-negative bacteria (covered in Chapters II and VII).

Summary

Antibiotic resistance is a complex problem because it involves a combination of strain spread and gene spread. There are big questions as to why certain strains of bacteria appear to be remarkably good at spreading while others do not. If these factors were better understood, it might be easier to develop possible interventions, such as vaccination.

One question is: How can strain spread be prevented? If the underlying mechanisms were understood, it may give some possible interventions that could be applied at local, national and international levels. Another is whether plasmid spread can be prevented. This is not possible at the moment but is an important area for research. With the genes encoding resistance and spreading between different types of bacteria, a whole new magnitude of difficulty is being faced.

Thirdly, a lot of gene transfer is believed to take place in the gut, because that is the area where large numbers of bacteria are all in close physical contact, allowing a high propensity for gene spread. Should researchers instead be looking at antibiotic resistance in commensal bacteria in the gut? Much of the work so far has focused on disease-causing organisms and resistance is a concern because it compromises treatment. Can as much be learned from looking at harmless bacteria as well? If a person is colonised in the gut by an antibiotic-resistant strain of the normal part of the gut flora, they would be totally asymptomatic but would have a reservoir of antibiotic resistance that they were unaware of. Should this be a major focus of AMR research?

And lastly, what sort of interventions can are possible? Will rapid diagnostic tests help in terms of screening patients? The whole area of antimicrobial stewardship has been highlighted and it is very important – but there is a lot more work to be done.

Professor Alan Johnson has worked for the Health Protection Agency and Public Health England (PHE) studying various aspects of antimicrobial resistance since the late 1980s. For part of this time he worked in the national Antibiotic Resistance Monitoring and Reference Laboratory, but is currently acting head of the Department of Healthcare-Associated Infection and Antimicrobial Resistance in the Health Protection Directorate of PHE. He is a member of the Advisory Committee on Antimicrobial Resistance and Healthcare-Associated Infections (ARHAI) and is currently Editor-in-Chief of the Journal of Antimicrobial Chemotherapy.

Implementing UK Policy

IV. Smart Use of Antibiotics: Building Confidence in New Approaches

Dr Hayley Wickens

One of the many definitions of antimicrobial stewardship is 'an activity that includes appropriate selection dosage, route and duration of antimicrobial therapy',[1] precluding any avoidable harm in the patients receiving the antimicrobials while avoiding a generation of resistance in the wider population.

In order to attempt to achieve this at the Southampton NHS Trust, evidence-based antimicrobial prescribing guidelines were produced and distributed to prescribers in the form of pocket guides and a smartphone app, to ensure that the best evidence base is being followed. The Trust provides educational programmes in hospitals for all staff who deal with antimicrobials, and audits how guidelines are being implemented. Feedback is also provided, because one of the best ways to get people to change behaviour is to give them information on how they are doing, particularly if there is an element of competition.

Antimicrobial Stewardship in the NHS

According to data generated a few years ago from acute trusts in England,[2] 99 per cent of the trusts surveyed (120 respondents, about 70 per cent of English hospitals) had an empiric antibiotic policy. This is good, as there is something to work from that is evidence-based and can help to inform prescribers about what they should be doing.

Eighty-seven per cent of responding hospitals had an 'intravenous (IV)-oral switch' policy. Switching IV antibiotics to oral antibiotics is a key way of managing risk, and risk of infection. The minute an IV canulla is inserted, the patient is potentially being exposed to a bloodstream infection. It is also unpleasant for patients, takes nursing time and is potentially more expensive than oral therapy. So while IV antibiotics are crucial for treating certain infections, it is important to look at how early patients can be switched to oral where possible, and how that process can be made safer. A third of hospitals also have a potentially controversial 'automatic stop' policy, where all oral antibiotics are stopped after five days unless they are actively reauthorised.

These policies are implemented by multi-disciplinary antimicrobial management teams and this is embedded in Department of Health policy; the Health and Social Care Act of 2008 says that every acute hospital has

1 TH Dellit et al, *Clinical Infectious Diseases* (Vol. 44, No. 2) pp. 159–177.

2 H J Wickens and A Jacklin (2013), *Journal of Antimicrobial Chemotherapy*.

to have one of these teams. These comprise people in the hospital who have an interest in antimicrobial use: consultants in infectious diseases and microbiology, pharmacists concerned with antimicrobial or infectious diseases, clinicians, surgeons, senior nurses, senior pharmacists – all of whom can drive policy through in hospitals.

These teams generate the evidence-based guidelines, produce the audit data, manage antibiotic usage and resistance, and provide education. There may also be also small ward-based teams, such as a consultant microbiologist and pharmacist, who conduct antimicrobial review ward rounds and look to proactively address problems with patients' antibiotics.

There are national steering groups in each of the four devolved administrations, which generate evidence and drive national policy in this area. They are the Antimicrobial Resistance Healthcare Association Infection group for England (ARHAI), Northern Ireland's Antimicrobial Resistance Action Plan (AMRAP) Implementation Group, the Scottish Antimicrobial Prescribing Group (SAPG) and the Welsh Antimicrobial Resistance Programme (WARP).

Start Smart…

A key driver to addressing antimicrobial stewardship is 'Start smart – then focus',[3] a practical document which, along with the NICE guidelines for neonatal sepsis discussed in Chapter VII, provides practical guidance as to what to do to ensure appropriate antimicrobial use.

'Start smart' refers to starting antimicrobials only when there is evidence of bacterial infection. It sounds very straightforward but it is not always so, particularly as it can be very difficult to tell if an infection is bacterial or viral – the latter will not respond to antibiotics. Secondly, it encourages using local guidelines in tandem with national guidelines on prescribing, because epidemiology differs between trusts and areas.

It also encourages documenting decisions on the drug charts and in the notes. It is important to document an antibiotic is being used, what the durational review date for that antibiotic is, what the route is and what the dose is. Again, this sounds very sensible, but there is good evidence that until recently, only 45 to 50 per cent of antibiotics had a documentation in the notes in quite a few hospitals, meaning that pharmacists going round and reviewing the charts could not tell what the antibiotic was for, or how long an intravenous agent should continue for. If care is transferred between medical teams, to a different unit or ward, how are the receiving team meant to know what the treatment is for? This makes a big difference – it could be

3 Department of Health, 'Antimicrobial Stewardship: "Start Smart – Then Focus"', November 2011, see <http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/documents/digitalasset/dh_131181.pdf>.

three days' treatment for an uncomplicated urinary tract infection (UTI) or two or more weeks' treatment for something more complicated.

Another important approach 'Start smart' encourages is to obtain cultures first. This is crucial because if a patient has been receiving IV antibiotics before a blood culture is taken, the organisms grown may not reflect the true picture. Also, it is important to use single-dose surgical antibiotic prophylaxis where appropriate as opposed to using a three- or five-day course. There is a lot of good evidence to suggest that a single dose of an antibiotic is sufficient to prevent the risk of infection during surgery for many procedures. Sometimes twenty-four hours is needed, but routinely extending this is unnecessary in many cases.

…Then Focus

The 'then focus' element of the document is key to ensuring implementation of good antimicrobial stewardship in hospitals. It says that both the diagnosis and the use of antibiotics should be reviewed by forty-eight hours. Patients should not have IV antibiotics for days without good reason. If a very sick patient is brought in, a broad-spectrum antibiotic might be given initially, but this needs to be reviewed after forty-eight hours. This process encourages the use of the term 'antimicrobial prescribing decision'.

At forty-eight hours a decision is taken decision as to what needs to be done. There are five options:

1. Should the antibiotic be stopped? Is there evidence that something other than bacterial infection is causing the problem?
2. Could the patient be switched from IV to oral antibiotics?
3. Could the antibiotic being used be changed or de-escalated? For example, once pathology results show than an infection is not caused by MRSA, can vancomycin be switched to flucloxacillin?
4. Should IV treatment continue – potentially for weeks?
5. Can treatment be switched to outpatient antibiotic therapy (OPAT)? This is a way of delivering IV antibiotics that are not available orally to patients who are otherwise medically well as outpatients or in their home.

The 'Start smart – then focus' document was a product of multi-disciplinary involvement and many people contributed to it. However, slightly controversially, there are gaps in the evidence base. Diagnostics are going to be very important in the coming years. Very often at present, it cannot be proved objectively that a patient has a bacterial infection: it could be viral or some other pro-inflammatory process. Being able to distinguish those from true bacterial infection could prevent antibiotics being started unnecessarily.

More Research Needed

Another issue is that guidelines on antimicrobial use are produced locally and may potentially vary in quality. Also, the definition of what would comply with the guidelines can vary quite markedly between professionals such as pharmacists, internists and infectious diseases doctors.[4] The potential for researching these areas is huge, not just in terms of what antimicrobial stewardship activities and behavioural change methods work, but also on more basic questions. When a doctor asks for evidence that a patient can successfully switch from IV to oral after forty-eight hours with no adverse effects, the evidence is often not there.

Risk of Under-treatment vs Risk of Resistance

Treating a patient with a suspected bacterial infection is always a risk-benefit decision between the very broad-spectrum antibiotic that will kill most of the pathogens likely to be causing the infection and a narrow-spectrum agent that will only kill one type. A doctor may be reasonably sure which pathogen is causing the infection, but not absolutely sure, and will not have a culture for at least twenty-four hours. If a broad-spectrum antibiotic is used, then the patient is being treated, but this runs the risk of generating resistance in the patient's own flora and increasing resistance more widely. This is a basic tenant of choosing antibiotics – the guidelines all advise minimising the use of broad-spectrum antibiotics and using them only where needed; use the narrow-spectrum where possible. But there is a risk.

Doctors are human and want to do the best for their patient, and therefore tend to prescribe broad-spectrum agents over narrow-spectrum agents. On paper, everybody will sign up to using a narrow-spectrum agent wherever they can – but when the sick patient is in front of them doctors tend to prioritise the needs of their individual patient over the public health risk. The wider health problem is even less concerning when someone is very seriously ill with sepsis, for example.

A study conducted in Dutch hospitals[5] looked at several hundred prescriptions and compared these to the doctor's local antibiotic guidelines. The study found that the non-compliant prescribing – where the prescribing did not match the policy – was usually too broad rather than too narrow. A third of all the prescriptions were too broad, even compared to their fairly broad empiric recommendations. When the researchers looked retrospectively at what organisms had caused that infection, by looking at the cultures that were subsequently generated, two-thirds of those prescriptions were too

4 PGM Mol et al, 'Reliability of assessment of adherence to an antimicrobial treatment guideline', *Journal of Hospital Infection* (Vol. 60, 2005), pp. 321–328.

5 P G M Mol et al, 'Limited effect of patient and disease characteristics on compliance with hospital antimicrobial guidelines', *European Journal of Clinical Pharmacology* (Vol. 62, 2006) pp. 297–305.

broad (although obviously, the prescribers did not have the benefit of that knowledge at the time).

The most worrying find was that there was little practice of streamlining or de-escalation. So instead of having broad-spectrum for the first two days then narrowing it down once the pathogen was identified, this was not happening effectively. The patient was getting better but the exposure to the broad-spectrum antibiotic carried on rather than the streamlining occurring.

The study also looked at the availability of culture results and how that influenced prescribing. Culture results had no impact on compliance in sepsis, but was associated with more compliance in UTIs and with respiratory tract infections. The paper states: 'Defensive behaviour may be driven by fear of high mortality rates and the fact that inadequate bacteria coverage has been correlated with increased mortality'. In the 'Surviving Sepsis' recommendations,[6] no-one would dispute that appropriate antimicrobial therapy for very sick patients needs to be started very promptly. This does not mean, however, that the treatment cannot be reviewed afterwards.

Gaps in the Evidence Base

More information is needed on whether the infection needing treatment is bacterial or not. Rapid diagnostics can contribute to this but so too can looking at what combination of signs, symptoms and objective data can be used to ascertain if a patient has a bacterial infection and starting the drug according to the policy. At the moment, prescribing guidelines can ask to provide feedback and appear to be 95 per cent compliant. However, all this shows is that the doctors are writing down the presumed diagnosis and getting the right drug for that diagnosis. It does not record whether the diagnosis was correct. This is the information that is needed to see whether there was a bacterial infection or not.

It is also important to know how likely it is that a resistant organism is being treated. In Chapter III, Professor Johnson mentions the increase in resistance in Gram-negatives causing UTIs. In certain areas of London, an elderly patient from the community with a UTI will have a reasonable chance of carrying an ESBL and will need IV therapy to treat the infection. Other parts of London and rural areas may not have that issue, however.

The key to addressing this is getting good epidemiological data, particularly for community pathogens. What is submitted through hospital laboratories represents the tip of the iceberg, because only patients who have had treatment failures or recurrent infections will have a urinary specimen sent.

6 R P Dellinger et al, 'Surviving Sepsis Campaign: International Guidelines for Management of Severe Sepsis and Septic Shock: 2012', *Critical Care Medicine Journal* (Vol. 41, No. 2, 2013) pp. 580–637.

This misses what is causing the majority of UTIs as specimens are not sent for routine, run-of-the-mill cases. So national data is useful but local data is key – and there is not always good integrated use of such data.

Severity Scoring

Severity scoring is also an issue. There are a few severity scoring methods that could help to decide whether to go for a broad-spectrum or narrow-spectrum antibiotic. Could a narrow-spectrum drug be used if the patient's symptoms are less severe? There are a few scores available such as CURB-65 for community-wide pneumonia,[7] which looks at factors such as blood pressure, respiratory rate and age. The more points a patient scores, the more severely ill they are, so the more likely they are to need a broad-spectrum antibiotic. This is very useful, but there is a lack in the evidence base around which patients could be given narrow-spectrum drugs, and there are a lot of conditions that have no equivalent scoring system. It is also possible that, even when there are scoring systems, clinicians tend to have a low awareness of them.

There is a lack of evidence on de-escalation, too. One weakness in much of the literature in this area is that it is retrospective. For example, if patients who were switched from IV drug *x* to oral drug *y* made a full recovery, it might have been because they were on IVs until they got better, and then had some additional oral treatment at the end. Patients need to be more aggressively switched (while they are still recovering), so that evidence can be built up on what works, and what if any risks are associated with it. At the moment good data on this is not available.

Also, while it is known that treatment of antimicrobials drives resistance and potentially exposes patients to infections such as *C difficile*, the evidence that prolonged courses are associated with negative effect is not well established. It is thought that prolonged use is a bad idea and that *C difficile* is associated with antibiotic use so it makes sense to minimise courses, but there are no studies that show that ten days of augmentin for a community-acquired pneumonia will give worse outcomes than five, for example. This is the type of data needed.

Possible Solutions

One approach used at Southampton is the Antibiotic Therapy Quick-Reference Guide.[8] This has driven a lot of interest in the evidence base and

7 W S Lim et al, 'Defining community acquired pneumonia severity on presentation to hospital: an international derivation and validation study', *Thorax* (Vol. 58, 2003), pp. 377–382.

8 See Figure 1, Slide 8, in presentation available at <http://www.rusi.org/downloads/assets/Wickens.ppt>

similar guides are planned for all common infections, including community-acquired pneumonia and straightforward UTIs.

Each guide has a summary of the evidence at the top with a case definition, so for example for hospital-acquired pneumonia, this will be for patients who have been in hospital for longer than forty-eight hours. Evidence of the infections will include information such as white cell counts, CRP (C-reactive protein) levels, a severity assessment and the epidemiology, in terms of what organisms typically cause this infection. It is known, for example, that in the case of cellulitis it is usually Gram-positive organisms that live on the skin. This information could be derived from studies or local epidemiological information, but suitable data are not always available.

The guide then looks at what can be used in severe and non-severe infections, in penicillin allergy and non-penicillin allergy, and the evidence available to support this. Local epidemiological data is also included, as are all the references. This gives an overview of all the evidence for the treatment of a particular infection, and the information will be centralised so that anybody can access it.

Summary

Implementing antimicrobial stewardship and the 'Start Smart – Then Focus' report highlights the need to make sure that the decision to start an antimicrobial is sound. Important areas for further research are syndromic diagnosis, molecular diagnostics, and also how to determine that a patient has a bacterial infection so that starting an antibiotic is justified.

It is important to know when to choose the narrowest-spectrum antibiotic that will work safely, while not denying the broad-spectrum ones where patients need them. De-escalation is absolutely key. Lastly, more information is needed on clinical outcomes in early discontinuation and also on course lengths, so that they can be reduced safely.

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V. Lessons Identified and Opportunities in Developing and Implementing NICE Clinical Guideline 149: Antibiotics for Early-onset Neonatal Infection

Dr Jim Gray

Neonatal Intensive Care Units (NICUs) represent a microcosm of the general challenges related to antibiotic use in the twenty-first century and to antibiotic resistance in general. Neonates receiving intensive care are at high risk of developing serious bacterial infections. These infections are often difficult to diagnose because the early signs of infection may be subtle and difficult to distinguish from other morbidities. At the same time, prompt institution of antibiotic therapy for true infections in neonates is vital to avoid serious long-term morbidity and mortality. All of this means that there are high levels of antibiotic prescribing on NICUs; however, most neonates who receive antibiotics on NICUs do not have bacterial infections. It is important to limit unnecessary antibiotic use because NICUs are high-risk areas for the selection and spread of antibiotic-resistant bacteria, especially the multi-resistant, extensively drug-resistant and pandrug-resistant Gram-negative bacteria that pose the greatest threat to the ongoing ability to treat infections with current antibiotics.[1]

Faced with the growing threat presented by these bacteria, surveillance programmes have been introduced in many NICUs. Staff at Birmingham Women's Hospital have been undertaking weekly surveillance of all NICU babies for the past two years: during that time 2.6 per cent of babies have been found to be colonised with antibiotic-resistant Gram-negative bacteria. Fortunately, as others have found, very few of these babies have gone on to develop infections with these bacteria. However, it is not known whether or not this background prevalence of antibiotic-resistant Gram-negative bacteria is a stable situation. There must be a risk in any population that as the number of individuals asymptomatically colonised with antibiotic-resistant bacteria increases a threshold will be reached above which these bacteria also become an important, and even predominant, cause of clinical infections.

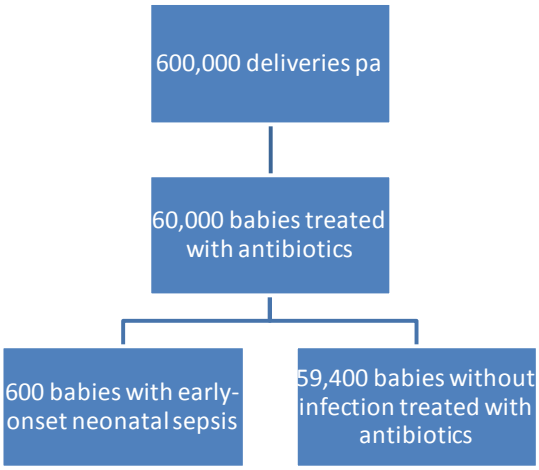
Antibiotic Prescribing for Early-onset Neonatal Sepsis: A Sizeable Problem

The sheer scale of unnecessary antibiotic use in neonates is exemplified by comparing the number of newborn babies who are treated with IV antibiotics with relatively accurate national data on the incidence of early-

1 M Souli, I Galani and H Giamarellou, 'Emergence of extensively drug–resistant and pandrug–resistant Gram–negative bacilli in Europe', *Euro Surveill* (Vol. 13, No. 47, 2008) pp. ii:19045.

onset neonatal sepsis.[2] There are around 600,000 births per year in England. Intravenous antibiotics are administered to around 10 per cent of newborn babies,[3] whereas the incidence of early-onset neonatal sepsis is only around one in a thousand births. It is acknowledged that a proportion of babies with early-onset neonatal sepsis will have negative cultures for one reason or another; nonetheless, it is reasonable to conclude that between 90 and 99 per cent of newborns treated with antibiotics do not have a bacterial infection. Over-prescription of antibiotics in other age groups within and outside hospitals is also common for the same reason, i.e. that prescribers lack certainty that it is safe to withhold empiric antibiotics.

Figure 1: Intravenous Antibiotics Administered to Newborn Babies



Clearer clinical guidance on when it is safe to withhold antibiotics could assist prescribers, but in many healthcare settings (especially in primary care) it may not be seen as safe or logistically feasible to withhold antibiotics because of the need for a further clinical consultation. A more promising approach will be to investigate antibiotic treatment decision-making based on the new generation of miniaturised molecular diagnostic tests that are becoming available. These tests require no skilled hands-on time and offer the potential of detecting (or excluding the presence of) a range of common pathogens in clinical samples at the point of care in under an hour.

Antibiotics are Not without Harm

Antibiotics used correctly are life-saving. However, antibiotic treatment is also associated with adverse clinical effects but this is not well recognised by the public. Perhaps surprisingly, given the publicity around healthcare

2 See Slide 6 in presentation available at <http://www.rusi.org/downloads/assets/Jim_Gray.pptx>.

3 National Institute for Health and Clinical Excellence, 'Antibiotics for early–onset neonatal infection: Antibiotics for the prevention and treatment of early–onset neonatal infection', CG149 (London, August 2012).

associated infections, the general public continue to perceive many adverse effects of medical care as unimportant and unavoidable.[4] There is, of course, some public awareness of the association between antibiotic use in hospitals and *C difficile* infection, especially in the elderly. However, even here there is probably a perception that dirty hospitals, rather than antibiotics, are the chief reason why people get *C difficile* infection.

Also, individuals prescribed antibiotics outside the hospital inpatient setting almost certainly do not perceive any risk of *C difficile* infection. Equally, there appears to be little public concern about the milder but still inconvenient side effects (such as gastrointestinal upset) that trials of new antibiotics suggest are experienced by at least 10 per cent of people treated with these agents. There is also little or no public knowledge of other risks to health associated exposure to broad-spectrum antibiotics, such as the evidence that in early life they may increase the risk of common childhood conditions such as asthma and atopic dermatitis.

Another approach to limiting antibiotic use may therefore be to provide more public education to change the perception that antibiotics offer a no-risk therapeutic option. Of course any such campaign would have to be carefully planned to ensure that individuals with infections that required antibiotic therapy were not discouraged from taking them.

NICE Guideline 149, Antibiotics for Early-onset Neonatal Infection

In August 2012, NICE Guideline 149, 'Antibiotics for early-onset neonatal infection: Antibiotics for the prevention and treatment of early-onset neonatal infection'[5] was published. There are two broad antibiotic-related themes within this guidance. First, it was clearly necessary to recommend antibiotics that are effective and safe for neonates with early-onset systemic infections. The second objective was to limit overall antibiotic use by providing guidance to help restrict the number of patients prescribed antibiotics; guidance on safely stopping antibiotics when infection is excluded; and guidance on limiting the duration of antibiotic therapy for infections.

In developing the guidance, the Guideline Development Group (GDG) was regularly constrained by the limited amount of good-quality published evidence on all aspects of antibiotic treatment of neonatal infections. As a result, the GDG often had to rely on expert opinion rather than evidence from good-quality clinical trials.

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4 J Tanner, W Padley, S Davey, K Murphy and B Brown, 'Patient narratives of surgical site infection: implications for practice', *Journal of Hospital Infection* (Vol. 83, 2013) pp. 41–45.

5 National Institute for Health and Clinical Excellence, 'Antibiotics for early–onset neonatal infection'.

Recommending Safe and Effective Treatment

In order to be able to recommend antibiotics for suspected pathogens, knowledge is needed of the causative organisms of early-onset neonatal sepsis and their antibiotic susceptibilities. The aim of empiric antibiotic therapy is to ensure coverage against the range of expected pathogens, while at the same time minimising the risk of selection of antibiotic resistance. The GDG also heard expert evidence of the risks of long-term morbidity in babies from treatment with broad-spectrum antibiotics, especially the cephalosporins. The GDG was quickly able to reach a consensus that benzyl penicillin plus gentamicin was the most appropriate first-line antibiotic regimen to target the causes of early-onset neonatal sepsis with the least risk of exerting selective pressure on antibiotic resistance. However, when the published literature on causes of early-onset neonatal sepsis was reviewed, it was found that many studies reported – probably inaccurately – that bacteria such as coagulase-negative staphylococci were common causes of early-onset neonatal sepsis. These bacteria are usually resistant to antibiotics such as benzyl penicillin and gentamicin. Thus there is a risk that even when local microbiology data are available to guide selection of antibiotics, clinicians will misinterpret these data. Greater involvement of microbiology services in providing accurate data on the causes of true infection may therefore be helpful in promoting good antibiotic stewardship.

Limiting Antibiotic Exposure

Central to limiting the number of patients treated with antibiotics was stratifying patients according to the risk of infection. The guideline identifies a number of clinical signs ('red flags') that in isolation should be an absolute indication for antibiotic therapy (Table 1). Otherwise, the guideline recommends that antibiotic therapy is indicated only when two or more of a wide range of softer risk factors for infection or signs of infection are present. Importantly, the guideline emphasises that, where indicated, antibiotic therapy must be commenced early, within a target time of thirty to sixty minutes.

A similar risk factor and clinical indicator model for commencing antibiotic therapy could feasibly be applied to other patient groups.

The other element to limiting antibiotic exposure is a set of recommendations about when antibiotics should be discontinued. The GDG considered evidence to support a recommendation that empiric antibiotic therapy could be discontinued at thirty-six hours based on clinical judgement, supported by a normal C-reactive protein (CRP) value at eighteen to twenty-four hours and negative blood cultures at thirty-six hours. Whilst it was recognised that obtaining these laboratory results within strict timescales would force many hospital laboratories to change working practices, the benefits in terms of cost savings and reduction in antibiotic prescribing makes the case for

changing practice compelling. This concept is consistent with the Department of Health's 'Start smart - then focus' campaign, discussed in Chapter IV. There are opportunities for research to investigate if even earlier assessments of the need to continue empiric antibiotic therapy can be made, and also to investigate translating the principles of the NICE Guidance into assessment of other patient groups.

For neonates who remain on antibiotic therapy for confirmed or suspected systemic sepsis, the GDG found an absence of clinical trial data on which to base recommendations on duration of treatment. It was concluded that in the absence of evidence of meningitis, seven days' treatment was adequate for uncomplicated infections, but it is likely that many clinicians err towards giving longer courses of treatment than that, and it is possible that courses of less than seven days would be equally effective.

Summary

The NICE Guideline 'Antibiotics for Early-onset Neonatal Infection' aimed to define clear criteria for commencing and discontinuing antibiotic therapy. Many of the principles contained within this guideline could be applicable to other patient groups. There are opportunities for further research around almost all aspects of antibiotic therapy. In particular, the growing trend towards point of care testing and the development of new diagnostic strategies for infections that are not dependent on overnight incubation for results offer real potential to better target antibiotic therapy towards those patients who need it.

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Table 1: Red Flag and Other Risk Factors for, and Clinical Indicators of, Early-onset Neonatal Infection

Red flag risk factors and clinical indicators (presence of one of these should prompt antibiotic therapy)	**Other risk factors and clinical indicators (two or more must be present before starting antibiotic therapy)**
Parenteral antibiotic treatment given to the mother for confirmed or suspected invasive bacterial infection within twenty-four hours of the birth Seizures in the baby Signs of shock in the baby Mechanical ventilation in a term baby Suspected or confirmed infection in a co-twin Respiratory distress starting more than four hours after birth	Invasive group B streptococcal (GBS) infection in a previous baby Maternal GBS colonisation or infection in the current pregnancy Prelabour rupture of membranes Preterm birth following spontaneous labour (before thirty-seven weeks' gestation) Suspected or confirmed rupture of membranes for >18 hours in a preterm birth Intrapartum fever higher than 38°C, or confirmed or suspected chorioamnionitis Altered behaviour or responsiveness Altered muscle tone Feeding difficulties or feed intolerance Abnormal heart rate Signs of respiratory distress or apnoea Hypoxia Jaundice within twenty-four hours of birth Apnoea Signs of neonatal encephalopathy Need for cardio–pulmonary resuscitation Mechanical ventilation in a preterm baby Persistent fetal circulation Temperature abnormality Unexplained excessive bleeding, thrombocytopenia or abnormal coagulation Oliguria persisting >24 hours after birth Altered glucose homeostasis Metabolic acidosis Local infection (eg, of skin or eye)

VI. Optimising Treatments to Tackle Anti-microbial Challenges: Nanomedicines and Molecular Targeted Medicines

Dr Andreas Schätzlein

Finding new treatments for cancer and tackling antimicrobial resistance are closely linked. Many of the cancer treatments used widely at present, including chemotherapy and radiotherapy, compromise the patient's immune system and leave them more susceptible to infection; antibiotics are therefore often given to patients as a prophylactic, or preventative treatment, to prevent infection from taking hold. Surgery, which is also required in many cancer treatments, also leaves patients vulnerable to infection. Nanomedicines offer an alternative that targets cancer cells while leaving the immune system unaffected and thus would enable antibiotics to be used less widely.

Cancer evolves from a local disease into a systemic disease, i.e. it spreads throughout the body. So while the best treatment for local cancer is surgery, or radiotherapy if it is more advanced, there are few options other than systemic treatment when a cancer has spread and develops into what is called metastasis. A large proportion of cancers that reach that stage remain incurable even today.

Some cytotoxic therapies (therapies that kill cells) have been useful in treating some forms of cancer, especially if the cancers are discovered early. They do have some side effects, however, and this is where, in improving systemic cancer therapies through the use of nanonmedicines, there may be scope in reducing some of the side effects. The history and development of cytotoxic therapies is rather unpleasant: alkalyting agents, one of the mainstays of chemotherapy applications, were developed during the first and second world wars for use in trench warfare, as mustard gas. Mustard gas is an agent that gave rise to nitrogen mustards; then, in 1942 it was discovered in the US that these types of agents can be used to treat lymphomas, heralding the age of chemotherapy. Chemotherapy agents used today have similar mechanisms and actions and are tremendously important.

These agents are, however, relatively non-specific: for example, they covalently crosslink DNA molecules, which inhibits cell proliferation and leads to apoptosis – the programmed death of those cancer cells. This type of treatment is most effective against rapidly proliferating cells such as cancer cells, but it also affects all other rapidly growing cells in the body. This causes the familiar side effects of diarrhoea and loss of hair, because cells in those tissues also grow rapidly and are also poisoned by the treatment. Agents such as cyclophosphomid, one of the derivatives of mustard gases, can be

altered to change their reactivity and make them less aggressive though still workable; but treatment is still unpleasant for the patient.

A War of Attrition

Unfortunately, cancer is a war of attrition in which all the cancer cells need to be killed off; even if only a very small fraction remain, this is likely to lead to an eventual regrowth of the cancer. So it is essential to kill all the cancer cells, but at the same time deal with the side effects. The most relevant of these for antimicrobial resistance are to do with immuno-suppression, induced by shutting down the production of new immune cells in the bone marrow.

A balance has to be found between maximising the dose of chemotherapeutic drug in order to kill as many cancer cells as possible and, on the other hand, minimising the damage these agents do to normal cells, including immune cells. If the quantity of immune cells in the patient's blood is reduced too far, the patient is left with insufficient capacity to fight off microbes. They become immune-suppressed and are more likely to have microbial infections.

To avoid this situation, chemotherapeutic cancer therapies are typically interrupted by treatment breaks to allow the number of immune cells to recover before the next cycle of treatment. During each recovery period, however, the cancer cells continue to grow. Whether the patient is eventually cured – or at least has a temporary respite from the cancer – or whether the cancer wins will therefore depend on how well a drug's toxicity to normal cells and cancer cells can be balanced.

In order to maximise the effect against cancer, combinations of drugs with different side-effect profiles are often used. When the drugs' side effects and toxicity affect different tissues or do not occur at the same time, it becomes possible to combine their therapeutic effects to achieve better cancer-cell kill rates while avoiding additive toxicity and extreme damage to the patient.

Drug combinations are also important in terms of avoiding resistance – this problem is as important in cancer as it is in microbiological diseases. By using drugs which have different modes of actions it is much more likely that all cancer cells will be killed because it is much less likely that cells with two or more resistance mechanisms will be present or will be able to develop during treatment.

Cancer-specific Targets

Current cytotoxic therapies and their use resemble the broad-spectrum agents used in antimicrobial therapy. However, a paradigm shift has led to a focusing of drug development efforts on the use of more specific drugs. The research efforts of recent decades have led to the discovery of a range of cancer-specific targets. While there is a huge amount of data available

on molecular variations of various cancers, however, it is often difficult to understand how they all may be connected to drive the development and evolution of cancers.

One way of understanding the organising principles of the molecular changes in cancer cells was proposed by Hanahan and Wineberg in 2000.[1] They identified a number of typical properties, so-called hallmarks, which are central to the progression of every cancer. All cancers that reach a point where they kill their patient will eventually acquire these hallmark properties.

For example, one of the properties cancers have to acquire is the ability for sustained growth independent of normal regulation. Normally, cell growth is tightly regulated to make sure it only occurs when needed, but cancer cells acquire the ability to grow in the absence of these normal growth signals. There are different ways in which cancer cells can acquire this capability; for instance, different cancers will be reliant on different signalling pathways and regulatory molecules, but all cancers need to find a way to acquire this hallmark in order to grow to the point where they kill the patient.

Another example for such a hallmark characteristic would be the ability of cancer cells to resist cell death – they are able to ignore physiological signals that should induce cell death. Again, individual cancers may have different pathways, but ultimately all aggressive cancers have to acquire the ability to resist cell death.

The application of these insights to therapy raises the potential of cancer-specific drug treatments. If it is possible to interfere with targets and pathways that a cancer uses to acquire a hallmark property, such treatments would have little effect on normal cells, but would offer a strategy to treat cancer in a more specific way compared to the non-specific, 'broad-spectrum' chemotherapeutic drugs.

A prototypical example for a drug that targets a cancer specific pathway would be the use of Glivec in chronic myelogenous leukaemia (CML), a cancer of the bone marrow. Here precursors of certain blood cells become cancerous and start to proliferate. Over time, they displace the healthy cells. The cause for this excessive proliferation is a mutation caused by a chromosome displacement: about 95 per cent of CML patients have this so called 'Philadelphia' chromosome, caused by the breaking and incorrect fusion of two different chromosomes. As a consequence, the structural part of one gene responsible for making a growth factor is now linked to a regulatory sequence of an altogether different gene. The resulting molecule

1 See Figure 1, Slide 5 in presentation available at <http://www.rusi.org/downloads/assets/Schatzlein_Part_One.pdf>.

– the Abl-kinase – drives inappropriate blood-cell proliferation and thus leads to the development of the CML cancer.

The BCR-Abl Kinase is a good example of a cancer-specific target as this molecule is the result of a mutation that does not exist in healthy cells. Targeting drug development efforts to try to inhibit this faulty molecule has led to the discovery of Imatinib, which is marketed as the drug Glivec. This drug stops the BCR-Abl kinase from activating proliferation and is essentially a cancer specific drug. It has been very successful and has changed the way CML is treated. The side effect profile is completely different from that of chemotherapeutic drugs; for example, it does not show the same tendency to suppress the immune system and make the patient vulnerable to infections. Clearly, such molecular targeted drugs demonstrate the potential of more cancer specific therapies and have heralded a new area of cancer treatment.

The Options

If cancer-specific molecular targets are known, the best approach may be to try to create drugs that target these. Given the complexity, time and resource implications of developing drugs for all the relevant targets, other strategies to increase drug specificity and avoid side effects are also being explored.

A conceptually simple approach is to try to maximise exposure of the tumour to the drug and minimise exposure of the healthy tissues. This is the strategy followed in the development of nano-medicines. Nano-medicines enable the use of drugs which may be more toxic and less specific, but by creating a situation where the drug is carried to the site of the disease while avoiding healthy tissue, it can effectively treat a tumour and avoid the side effects that would otherwise occur. The general principle used to achieve this effect using nano-medicines is to create a carrier in which the drug can be encapsulated. If it is possible to control where in the body the carrier goes, this can be used to direct the drug to the site of the disease.

The Nano Scale

One of the obvious properties of nanomaterials is that they are very small – in the order of 1/1000th the thickness of a human hair. Apart from being small, nano-scaled materials acquire new and useful properties. For example, as the diameter of a particle becomes smaller, its surface becomes relatively more important compared to its volume: more and more of its molecules are in direct contact with the environment. These surface molecules will therefore determine how these particles behave in a biological environment. By systematically modifying the surface molecules, nanoparticles can then be targeted to tumours to deliver their cargo.

Biocompatible polymers can be engineered through chemical modifications to self-assemble into nanoparticles that have the capacity to carry drug

molecules. When drugs are carried in these nanoparticles, they are protected from the enzymatic degradation that can occur in the blood or the gut. In addition, they are also able to dramatically increase the amount of drug that can be transported across biological barriers such as the gut.

For example, taken orally, peptides are normally degraded in the gut and have no effect but by putting them in polymer carriers they can be given orally and taken up into the bloodstream.[2] This method can be used to treat pancreatic cancer in animals using a nano-enabled oral peptide pill and, as it is a very specific therapy, there are no problems with side effects such as immune-suppression.

A similar strategy to enhance the amount of drug that can be given is a nano-enabled form of the anti-cancer drug lomustine. This drug is poorly water soluble, which can make it difficult to give in sufficient quantity or may require patients to receive it as prolonged infusions. Lomustine is a drug which, in principle, is effective against brain cancer. Most drugs do not easily reach the brain because it is separated from the rest of the body and blood stream by the blood–brain barrier. This normally protects the brain from toxic molecules and metabolites but its presence can make the treatment of brain cancers difficult because drugs do not reach the tumour. Increasing the concentration in the blood can increase the amount of drug that reaches the brain but for cytotoxic drugs, this increase of drug dose is typically associated with an increase in toxicity, i.e. immunosuppression.

Loumistine has been packaged into nanoparticles to treat animals with brain cancer, reducing cancer growth and extending the animals' survival. In fact, packing drugs into nanoparticles can increase the amount of the drug given by a factor of ten. Importantly, by using the nanoparticles it becomes possible not only to increase the dose and increase the amount of drug in the brain but also to avoid the expected increase in side effects. This is illustrated by the lack of effect on body weight, a surrogate marker for toxicity, or numbers of white blood cells. Even with ten times the amount of drug, the toxicity does not increase.[3]

Another way in which specificity of cancer therapies can be increased while minimising side effects involves direct use of our understanding of the genetic differences between healthy cells and tumour cells through genetic therapies. These types of therapies provide ways to be highly specific – more so than is possible with proteins – but the current bottleneck to their wider

2 See Slide 10, in presentation available at <http://www.rusi.org/downloads/assets/Schatzlein_Part_One.pdf>.

3 See Slide 1, in presentation available at <http://www.rusi.org/downloads/assets/Schatzlein_Part_Two.pdf>.

use stems from the problems associated with the delivery of these genetic medicines to the cancer cells.

Currently the key challenge for the wider use of these therapies lies in the safe and efficacious delivery of the gene to the tumour. Again, nanoparticles are one of the strategies used. Nanoparticles have been developed that contain the gene for tumour necrosis factor alpha (TNFα), a very potent cytokine. TNFα given as a protein provides a very effective, but potentially dangerous, way of treating some tumours as the side effects can kill the patient. The only way to use this drug for treatment at the moment is by treating tumours in a part of the body that can be isolated from the general blood circulation, such as sarcomas of a limb.

Genetic therapies could make a difference here, particularly if given intravenously. By comparing animals treated with hTR-mMTNF (human telomerase RNA-murine Tumour Necrosis Factor) Dufrès et all (2005)[4] showed that in the treated animals, the tumours disappear rapidly; in the untreated animals they do not.

The molecule is effective and body weight does not change between the different treatment groups, which also suggests that it is very safe. About 80 per cent of the animals can be cured completely using this method. By using nanoparticles to deliver the gene for TNFα, this therapy can be given safely intravenously to treat tumours without the toxicity that is associated with the adminsitrarion of the TNFα protein.

Nano-enabled Anti-infectives: Amphotericin B

Nanomedicines enable more effective use of antibiotic drugs; one example of this is a nano-enabled form amphotericin B, a drug effective against leishmaniasis and systemic fungal infections. The main limitations to its use are related to its kidney toxicity and the need for administration by intravenous infusion. A nano-enabled form of this drug that can be given orally as a capsule targets the drug away from the kidney towards the liver and lung, where the disease resides.

More specific cancer therapies can therefore help to avoid side effects such as immunosuppression frequently associated with high dose chemotherapy, which makes patients susceptible to microbial infections and requires the use of antibiotics. Such improved specificity can come from drugs directed against cancer-specific molecular targets or, alternatively, nano-sized carriers can be used to direct the drug to the tumour and spare the healthy cells. Thus, cancer pharmacology and nanotechnology can be used to reduce the pressure on antimicrobial therapy.

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4 See Slide 4, in presentation available at <http://www.rusi.org/downloads/assets/Schatzlein_Part_Two.pdf>.

Learning from AMR

Cancer research may also be able to learn from the experience of microbiologists in particular with respect to AMR, as there are some common biological mechanisms at play. Cancer cells work as populations: they evolve based on their ability to rapidly acquire genetic changes. By acquiring new mutations, cancer cells in a tumour can evolve into a heterogeneous population. When such populations are exposed to anti-cancer drugs, a selective pressure is exerted which will give the fittest cells – those with mutations conferring drug resistance – a survival advantage. These resistant mutants may thrive once the majority of tumour cells have been killed and may give rise to a resistant tumour that could eventually kill the patient.

The idea that tumours evolve along Darwinian principles has been developing and, at the end of 2012, an artilce in *The New England Journal of Medicine* showed a kidney cancer[5] for which the expression of specific genes in different parts of the tumour had been determined. It becomes clear that the tumour is not a homogenous mass where all the cancer cells are the same, but rather they exist as a population of cells that can compete and adapt. The research team not only looked at the original tumour but also the metastases where the cancer had spread to the patient's lungs and chest wall. The gene expression profiles in those metastases, together with those in the original tumour, allowed the research team to create a phylogenetic tree tracing the tumour development and the sequence mutations in subpopulations that were involved in the process.

The Importance of Population

The tumour therefore represents a heterogeneous population of cancer cells that evolve following Darwinian principles. When cancer is treated with any type of drug, the population is exposed to a selective pressure. The more heterogeneous the cell population, the higher the risk that cells may exist which may have some resistance against the therapy. Such cells would be likely to survive therapy and would be able to pass this resistance on or to the daughter cells on division. While non-resistant cells would be killed, resistant cells would have a growth advantage and would be likely to thrive.

Furthermore, in some cases cancer cells go further in adapting to their 'biotope'; for example, they may take advantage of anti-apoptotic signals (signals that indicate a delay in, or prevention of, cell death) secreted by non-cancer cells such as some immune cells within the tumour, which may come to play an involuntary role in supporting the cancer cells. Again, there is potential overlap here with the development of AMR. Populations are very important in the area of AMR: biofilms work together, they evolve to create properties which make them much more difficult to treat. Thus for cancer

5 See Slide 7, in presentation available at <http://www.rusi.org/downloads/assets/Schatzlein_Part_Two.pdf>.

and microbiology, understanding how heterogeneous populations fit into their 'biotope' and co-develop may become increasingly important as a way to develop new ways for treating diseases which can constantly evolve in response to a changing environment.

The infections that are relevant to AMR may depend on an abnormal biotope or 'pathobiotope' and treatment strategies that tackle changes in the biotope may become more important as a way to control evolving and adaptable pathogens. It may be important not only to think about the patients, but also about their wider environment as a biotope, as an ecosystem that needs to be considered in terms of how it works together, in order to understand how pathological infections can be limited.

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Containing and Mapping the Spread of Drug Resistance

VII. The Rise of Carbapenem-resistant Organisms

Professor Mike Sharland

Carbapenem resistant organisms (CROs) are Gram-negative members of the Enterobacteriaceae group (bacteria present within the human gut). These organisms are difficult to treat because they have high levels of resistance to carbapenems, a powerful group of broad-spectrum beta-lactam (penicillin-related) antibiotics. Carbapenems (imipenem, meropenem, and ertapenem) are considered a last-resort antibiotic regimen for the treatment of infections caused by multi-resistant bacteria. CROs are resistant to carbapenems as they are able to produce carbapenem-hydrolysing beta-lactamases. Over the last decade, carbapenem resistance has steadily increased among Enterobacteriaceae isolates including *Klebsiella* species and *E coli*.

Infections caused by CROs are rare in healthy individuals and are most commonly seen in patients with weaker immune systems, such as and those with chronic underlying medical problems, the very young or old and those in intensive care units. Once introduced into a healthcare facility, CROs can quite rapidly become endemic if not identified and efficient infection control measures need to be implemented swiftly to limit the spread of these pathogens. CRO infections are extremely difficult to treat and are commonly associated with significantly increased mortality and morbidity. Only one or two older antibiotics, including colistin, remain to treat such infections. The increased use of these antibiotics of last resort will increase the potential for the development of pan-resistant organisms – where there are no effective antibiotics at all.

The names given to resistant organisms are complicated but generally include the name of the bacteria (e.g. *Klebsiella pneumoniae*), the enzyme they carry (e.g. carbapenemase), and the antibiotic-resistant gene(s) within the bacteria.

Klebsiella pneumoniae Carbapenemase

K pneumoniae carbapenemase (KPC) producing bacteria are a type of CRO whose emergence, increased incidence and rapid clonal spread in recent years is of considerable concern nationally and internationally. Since their emergence in the last decade KPC and its clones have rapidly become endemic in regions of the United States, Italy and Greece, as well as in countries of South America and the Far East.

The ability of resistant clones to spread and to quickly become endemic is best exemplified by the alarming and rapid spread of KPCs within healthcare facilities in Italy, where KPC clones were first isolated in two hospitals in late 2008. At the time, this was not regarded as a major problem but by

2009, isolates were identified in a few of the larger Italian hospitals and by late 2012 it had become endemic in many more hospitals within the Italian healthcare system.[1]

Managing the Spread

Israel provides an example of how prompt and concerted action might be managed. KPC was first identified as an issue in Israel in 2006, at which time surveillance indicated a significant and rapid escalation in the number of KPC isolates reported. The Israeli government responded swiftly to the threat, implementing mandatory measures to screen, isolate and decolonise individuals. A large team was mobilised to effect all aspects of the country's infection prevention and control process. The speed and thoroughness of the response successfully reversed the increasing incidence of KPCs.[2]

Global travel remains a key issue in the global spread of these multi-resistant Gram-negative organisms as they are common in many of the countries that UK residents travel to. CROs could potentially be introduced into the UK through the arrival of colonised individuals, particularly those individuals who have previously been hospitalised in endemic countries, including visitors from abroad or residents returning to the UK following medical treatment abroad (including medical tourists) and armed forces personnel. Historically, many visitors come to the UK to visit friends and relations and may stay for extended periods. Many are elderly and may require healthcare both in their own country and the areas to which they are travelling.

UK Incidence of CROs

Whilst the spread of infection within the UK has been linked to inter-hospital transfers, the role of community carriage in promulgating infection remains uncertain: the precise number of overseas patients admitted to NHS hospitals is unknown as these data are not collected centrally, though it is conservatively estimated that there are many tens of thousands per year, many of whom may potentially carry multi-resistant organisms. Unpublished data provided by Public Health England indicates that from 2003 to 2012, more than 1,500 isolates of carbapenemase-producing organisms were identified in England. Analysis of the isolates shows that, while early cases were few and generally imported, since 2008 the number of isolates has increased and isolates now include those thought to be related both to importation and spread within England.[3]

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1 See Figure 1, Slide 8, in presentation available at <http://www.rusi.org/downloads/assets/Sharland_Part_1.ppt>.

2 L F Chen et al, 'Overview of the epidemiology and the threat of *Klebsiella pnuemoniae carbapenmenases* (KPC) resistance, *Infection and Drug Resistance* (Vol. 5, 2012) pp. 133–141.

3 See Figure 1, Slide 18, in presentation available at <http://www.rusi.org/downloads/assets/Sharland_Part_1.ppt>.

The Research Agenda

Our current knowledge of even the basic epidemiology of multi-resistant bacteria is limited. Gaps include the duration of carriage of CROs within the human intestine; the relation between carriage and invasive disease; whether specific high-risk groups or individuals exist; and whether and how these might be targeted for screening to minimise the potential for transmission. If screening is to be undertaken as part of an infection prevention and control process, how should it be undertaken optimally? How effective is isolation and is decolonisation a feasible option? What is the cost effectiveness of the numerous potential interventions?

Currently, all elective or emergency admissions to the NHS are screened for MRSA via a nose swab, which has been relatively acceptable to patients. To determine carriage of organisms that are carried within the intestine requires the use of rectal swab. It is likely that these will be found to be significantly less acceptable to patients than nasal swabs and methods of improving the acceptability need to be developed.

Summary

Concerted, strategic and harmonised action to tackle CROs is required across all areas – including prescribing and stewardship, surveillance and diagnostics – and across all professions from clinicians to policy-makers. Whilst universally acknowledged as good, the UK's levels of infection prevention and control, and methods for screening and isolation, will need to be optimised and guidance adhered to if we are to minimise the potential for spread of CROs within the UK.

There is a need for focused research to enhance our understanding and provide cost-effective approaches to dealing with this serious threat. The UK has been effective in implementing changes that have driven down infections caused by MRSA and *C difficile*. As a priority, attention and research activity should now be refocused to address the rising threat of multi-resistant Gram-negative infections, including CROs. This will be complicated and challenging: new initiatives by the Chief Medical Officer and the Department of Health are very welcome and are key to ensuring success in this area.

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VIII. The Sentinel Soldier

Group Captain A D Green

The public perception of the people who make up the military is that they are all young, fit and healthy and are representative of the civilian population in the UK. This is not necessarily true – the British Armed Forces have recruited extensively from overseas for many years, with the Gurkhas from Nepal and the Irish Regiments perhaps being the best-known examples. In fact, any individual from a Commonwealth country may join the services, and up to 5 per cent of recruits may be from overseas. On occasions, the proportion has been even greater than this; in 2011, 7.9 per cent of the British Army were foreign nationals.[1] Recruits may be fit on entry but go on to develop illness or injury during their service, so that many serving personnel have impaired immunity that makes them susceptible to infectious diseases. In addition, an increasing proportion of deployed personnel are drawn from Reserve Forces, some of whom will have increased risk factors for disease and will return to their civilian place of work after duty overseas.

Military Travel

The armed forces go overseas for a variety of reasons, each of which carries particular risks for the acquisition of infectious diseases. Military activities include operational deployments up to and including warfare, which may be in conjunction with a variety of coalition or allied forces and in association with host-nation personnel. These may be as part of a formal international intervention by the United Nations or NATO, or as bilateral agreements with individual countries. Missions to support civilian populations range from evacuation of non-combatants from war zones to humanitarian work and disaster-relief operations. The Royal Navy maintains a maritime presence worldwide, with port visits forming an integral part of its role.

A key element of any force preparation is training, and there are well-established overseas training locations in a number of hot and cold climates, as well as regular exercises held overseas.

In addition to formed units in operational and training missions, there are also large numbers of military personnel who travel as a part of small groups or alone. These include diplomatic staff, individuals seconded to foreign armed forces, specialist military groups such as special forces and weapons inspectors, and expeditions including adventurous training.

In every situation, safe food and water supplies may be compromised, personnel may be exposed to arthropod and animal vectors of disease,

1 Defence Analytical and Statistics Agency, *UK Defence Statistics 2011* (Chapter 2, Table 2.14). See <www.dasa.mod.uk/modintranet/UKDS/UKDS2011/c2/table214.php>.

have limited access to medical care and be in close contact with local populations during times of heightened disease transmission. Each of these activities involves exposure to a different level of risk from that experienced by a civilian holiday-maker or businessman, and leads to the term 'sentinel soldier' reflecting the possibility of a novel disease appearing for the first time in this group.

Medical Issues

Bullets and bombs are often considered to be the greatest health threat to deployed military forces, but personnel are in fact far more likely to be incapacitated by infectious disease. Recent advances in medical care mean that death from these causes is far less likely today than it has been in the past, but the numbers of casualties overall still outnumber trauma cases by a factor of five to ten.[2]

Military personnel who become ill or are injured overseas will receive immediate medical care, but how and where this is delivered will depend on their circumstances. Large operational deployments will have full medical support, including immediate first aid if required, primary care, hospital care and aeromedical evacuation if required. Individuals on isolated detachments, on the other hand, may be entirely dependent on local healthcare facilities and/or will be repatriated to the UK by aeromedical evacuation if necessary.

In 2010, there were just under 5,000 patients repatriated to the UK, of which more than 100 were intensive-care patients requiring Critical Care Air Support Team (CCAST) deployment and dedicated aircraft. Most, but not all, of these were trauma patients from the current conflict in Afghanistan.[3]

Severely injured battle-trauma patients are likely to be colonised or infected with organisms. This results from the heavy inoculation of environmental material at time of injury, either as a result of gunshot wounds or improvised explosive devices, auto-inoculation by their own microflora from gut or other organs, or healthcare associated infection (HAI). Without aggressive surgical management to remove dead and dying tissues and foreign material, the organisms present may become invasive and cause severe disease. Historically, the leading cause of death from trauma after the initial resuscitation was sepsis, and even with modern management techniques it remains a significant cause of late morbidity and mortality.[4]

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2 M R Smallman–Raynor, A D Cliff, *War Epidemics: an Historical Geography of Infectious Diseases in Military Conflict and Civil Strife, 1850–2000* (Oxford University Press, 2004).

3 Ministry of Defence's Op Herrick casualty and fatality tables. See <https://www.gov.uk/government/publications/op–herrick–casualty–and–fatality–tables>

4 E J Hutley, A D Green, 'Infection in wounds of conflict – old lessons and new challenges', *J R Army Med Corps* (Vol. 155, No. 4, December 2009) pp. 315–319.

Trauma patents injured in Afghanistan are repatriated to the UK as soon as they have had immediately life-saving surgery and have been stabilised, which is usually within twenty-four to forty-eight hours. Patients repatriated from other locations, such as civilian hospitals elsewhere in the world, may have been in-patients for many days or sometime weeks. Both scenarios raise the possibility of transfer of individuals with multi-resistant organisms – acquired from primary environmental exposure or HAI related to their hospital stay – into UK healthcare settings.

MDR Bacteria Imported by the Military

Within days of the start of the Iraq War in 2003, US military medical facilities that were treating local civilian casualties were reporting incidences of multi-resistant bacteria. These were predominantly related to *Acinetobacter baumannii*, which is an organism commonly isolated from hospitals worldwide and often noted to be resistant to a wide range of antimicrobial agents. Over the following months and years this organism in particular became widely reported as being problematic in military personnel, primarily in the US.[5] It has also been observed in injured personnel from other nations, though not to the same degree. The organism is regarded as being a low-grade pathogen, as it is commonly found colonising patients (present, but not causing disease) and only rarely progresses to infection in individuals with other pre-disposing factors for invasive disease (such as IV lines or ventilatory support).[6] In common with other related bacteria, it has become important because on those occasions when therapy is indicated there are few available antimicrobial agents available. As such, it means that individuals who are identified as being colonised or infected are managed using infection control measures to prevent spread in the hospital environment to other, more susceptible patients.

In the UK, there have been regular admissions of military trauma patients colonised with *A baumannii* which has generally been identified at an early stage – the spread to other patients has been prevented by good infection control practices. However, there have been occasional outbreaks related to the breakdown of these practices, with spread from military personnel to civilian patients.[7]

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5 CK Murray, 'Epidemiology of infections associated with combat–related injuries in Iraq and Afghanistan', *The Journal of Trauma* (Vol. 64, No. 3 Suppl, March 2008) pp. 232–238. See <http://www.ncbi.nlm.nih.gov/pubmed/18316967>.

6 T L Stuart, M Mulvey, A E Simor, H C Tien, A Battad, G Taylor, J V Vayalumkal, C Weir, M Ofner, D Gravel, S Paton, 'Acinetobacter baumannii in casualties returning from Afghanistan', *Canadian Journal of Infection Control* (Vol. 22, No. 3, fall 2007) pp. 152–4.

7 A Jones, D Morgan, A Walsh, J Turton, D Livermore, T Pitt, A Green, M Gill, D Mortiboy, 'Importation of multi drug–resistant Acinetobacter spp infections with casualties from Iraq', *The Lancet Infectious Diseases* (Vol. 6, No. 6, June 2006), pp. 317–8.

MDR Bacteria and Current Operations: A Multinational Melting Pot

The current NATO mission in Afghanistan comprises fifty nations contributing personnel, which provides an opportunity for sharing of micro-organisms from many different parts of the world, particularly when operating in a harsh environment and sharing healthcare facilities. South Asia is also well recognised as being a reservoir for many multi-resistant infectious diseases in local populations for reasons that are not entirely clear, but may reflect both the unregulated use of antimicrobial agents for therapy and environmental selective pressure from saprophytic organisms.[8]

Examples of endemic micro-organisms with inherent multi-resistance include common gastrointestinal pathogens such as *Salmonella* species and *Shigella flexneri*,[9] *Mycobacterium tuberculosis*,[10] extended spectrum beta-lactamase-producing *E coli* (ESBL) and methicillin-resistant *S aureus* (MRSA). Whilst NATO personnel have regularly acquired gastrointestinal infections, infections with the other organisms have been rare to date, which may reflect limited close contact with local populations that would facilitate transmission.

NATO partner nations often adopt different disease prevention strategies, and this may inadvertently lead to selection of multi-resistant strains of bacteria. For example, the US armed forces in Afghanistan are issued with field treatment packs that include broad-spectrum antimicrobial agents to be taken if they are injured.[11] Such regimens are generally ineffective at reducing the incidence of infection and deliver low concentrations of antimicrobial agents to devitalised and heavily contaminated tissues, which in turn provides ideal conditions for the generation of resistance. A particular concern is the use at forward locations of injectable carbapenem agents, in a region where the appearance of novel multi-resistance in some bacteria poses a global threat.[12]

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8 E M Wellington, A B Boxall, P Cross, E J Feil, W H Gaze, P M Hawkey, A A Johnson–Rollings, D L Jones, N M Lee, W Otten, C M Thomas, A P Williams, 'The role of the natural environment in the emergence of antibiotic resistance in Gram–negative bacteria', *The Lancet Infectious Diseases* (Vol. 13, No. 2, February 2013), pp. 155–65.

9 E J Threlfall, 'Antimicrobial drug resistance in Salmonella: problems and perspectives in food– and water–borne infections', *FEMS Microbiology Reviews* (Vol. 26, No. 2, June 2002) pp. 141–148.

10 World Health Organization, 'Global Tuberculosis Report 2012'. See <www.who.int/tb/publications/global_report/gtbr12_main.pdf >

11 D R Hospenthal, C K Murray, R C Andersen, et al, 'Guidelines for the prevention of infections associated with combat–related injuries', *Journal of Trauma* (Vol. 71, No 2 Suppl 2, August 2011), pp. 210–34.

12 P McGann, M Millo, R Clifford, et al, 'Detection of New Delhi Metallo–β–Lactamase (blaNDM–1) in Acinetobacter schindleri during routine surveillance', *Journal of Clinical Microbiology* (Vol. 51, No. 6, June 2013), pp. 1942–1944 (published ahead of print, 3 April 2013). See <http://jcm.asm.org/content/early/2013/03/29/JCM.00281–13.abstract#aff–1>

Military forces may also pose a threat to the host environment, rather than being at risk themselves. The increasing use of multinational forces across the world for disaster relief and peace-keeping operations means that fragile ecosystems may be exposed to novel infective agents. In 2010 in Haiti, an outbreak of cholera affected large numbers of internally displaced civilians following a major earthquake, with more than 7,600 dying. The subsequent investigation indicated that the likely source was a Nepalese military unit deployed to assist the Haitian population as part of a United Nations mission.[13] The organism involved was not highly drug resistant, but the case serves as an example of how easily infections that may have profound consequences can spread around the globe.

Infection Control

The threat posed by multi-resistant organisms during medical care of casualties on operational deployments means that infection control is critically important in all military medical facilities, including care at point of injury, medical evacuation from the battlefield, Role 3 care (Field Hospital), and strategic aeromedical evacuation to the UK.

All British field hospitals such as that at Camp Bastion include a trained Infection Control Practitioner as part of their permanent manning, and clinical practices follow UK civilian best-practice whenever possible within operational constraints. The hospital is inspected at intervals by the UK Care Quality Commission, which has found the standards of infection control practice to be 'exceptionally high'.[14] A recent review of infection control at all NATO medical facilities in Afghanistan found the practices at Camp Bastion to be significantly better than at any other location.[15]

Most patients arrive at the receiving centre in the UK, at Queen Elizabeth University Hospital Birmingham, within forty-eight hours of injury. This is before any microbiological results from initial assessment at Camp Bastion are available and therefore all patients are managed as potentially colonised with multi-resistant bacteria. By careful isolation of these patients, the risk of transmission is minimised. Such policies have been refined over a decade of experience with such cases.

In 2011, the UK government accepted more than fifty trauma casualties from the Libya conflict, who had been treated in a variety of hospitals in

13 A Cravioto, C F Lanata, D S Lantagne, G B Nair, 'Final report of the independent panel of experts on the cholera outbreak in Haiti', United Nations, 4 May 2011. See <http://www.un.org/News/dh/infocus/haiti/UN–cholera–report–final.pdf>

14 Care Quality Commission, 'Defence Medical Services: A review of compliance with the essential standards of quality and safety', June 2012. See <http://www.cqc.org.uk/public/reports–surveys–and–reviews/reviews–and–studies/defence–medical–services>

15 Personal communication between the author and C K Murray.

the Mediterranean region. These cases were widely distributed across NHS hospitals to share the workload, but in common with casualties managed elsewhere in Europe, most were colonised with multi-resistant bacteria, which in turn could potentially have led to widespread distribution of the organisms within UK hospitals.[16]

Geopolitical Issues and Multi-resistant Bacteria

Infectious diseases have played a role in fashioning the development of societies throughout history, with effects ranging from a direct impact on civilian populations, such as the Black Death,[17] to the limitation of human settlement by the geographical distribution of diseases such as malaria.[18] In addition, they have influenced the course of many military campaigns, and in some cases changed the outcome of a conflict.[19]

Antimicrobial resistance may influence these effects. During the Rwandan Civil War in the 1990s, large numbers of refuges and internally displaced personnel were accommodated in temporary camps with limited water and sanitation. Outbreaks of bacillary dysentery were complicated by the appearance of a MDR strain of *Shigella dysenteriae* Type 1, which was resistant to all available therapies and associated with increased mortality in casualties.[20]

Resistance is also becoming more common in other pathogens associated with significant morbidity and mortality in developing countries. Examples include lower respiratory tract infections due to *Streptococcus pneumoniae*[21] and severe sepsis due to *Neisseria meningitidis*.[22]

The consequences of widespread drug resistance amongst bacteria that cause common and severe infections are significant. Many of the diseases

16 K Koole, P M Ellerbroek, R Lagendijk et al, 'Colonization of Libyan civil war casualties with multidrug–resistant bacteria', *Clinical Microbiology and Infection* (Vol. 19, No. 7, July 2013), pp. 285–7 (e–published ahead of print).

17 P Slack, 'The black death past and present. 2. Some historical problems', *Transactions of the Royal Society of Tropical Medicine and Hygiene,* Vol. 83, No. 4, July–August 1989), pp. 461–463.

18 R Carter, N Kamini, K Mendis, 'Evolutionary and Historical Aspects of the Burden of Malaria', *Clinical Microbiology Review*s (Vol. 15, No. 4, October 2002), pp. 564–594.

19 M J Zapor, K A Moran, 'Infectious diseases during wartime', *Current Opinion in Infectious Diseases* (Vol 18, No. 5, October 2005), pp. 395–9.

20 S Kernéis, P J Guerin, L von Seidlein et al, 'A Look Back at an Ongoing Problem: Shigella dysenteriae Type 1 Epidemics in Refugee Settings in Central Africa (1993–1995)', *PLOS ONE* (Vol. 4, No. 2).

21 S J Schrag, B Beall, S Dowell, 'Resistant pneumococcal infections: the burden of disease and challenges in monitoring and controlling antimicrobial resistance', World Health Organization, 2002.

22 B Oppenheim, 'Antibiotic Resistance in Neisseria meningitidis', *Clinical Infectious Diseases* (Vol 24, No 1, 1997), pp. 98–101.

predominantly affect children and young adults, which may in turn lead to changes in population demographics if infections with high mortality become refractory to therapy. Similar effects have been seen in societies where HIV is common, with the loss of large numbers of economically active adults consequently having a destabilising effect on society.[23]

Summary

The military has the same interest as civilian health authorities in controlling the spread of antimicrobial drug resistance. Treatment of infections on the battlefield will become more complex, both for trauma and infectious diseases as AMR increases; in addition, military patients may return multi-resistant organisms from overseas to their homeland. However, the increased use of multinational forces to provide humanitarian aid and disaster relief means that they in turn might export novel bacteria to receptive environments. There also remains the potential destabilising effect of MDR on fragile societies, which may have unpredictable consequences.

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23 T Barnett, A Whiteside, C Desmond, 'The social and economic impact of HIV/AIDS in poor countries: a review of studies and lessons', *Progress in Development Studies* (Vol. 1, No. 2, April 2001) pp. 151–170.

IX. Social Technologies for Community Response to Epidemics

Chris Watkins and Jennifer Cole

The best defence against any disease is to not catch it. Technologies such as smartphones and online social networks offer new possibilities of collective response that can both help people to avoid catching a disease and, if they do catch it, to avoid passing it on. This principle is true for any epidemic but becomes increasingly important as the severity of the disease and number of cases increases or the efficacy of available treatments decreases.

While the issues discussed in this paper relate to outbreaks of serious infectious disease in general, and are not specific to those caused by or involving drug-resistant organisms, the issues covered are equally applicable to tackling AMR. Any outbreak of serious infectious disease that involved drug-resistance would be exacerbated by that resistance and, equally, the methods discussed to monitor emerging cases and contain the spread are just as applicable to non-pandemic resistant strains.

Studies of the 1918 H1N1 influenza pandemic[1] show that US cities which implemented vigorous measures for public health and social distancing were measurably less affected than those that did not. Could today's social media technologies enable an even more efficient public response than was possible in 1918? Could epidemic spread in the UK even be stopped with suitably co-ordinated community behavioural responses?

Stopping an epidemic on a national scale is not an extreme point of view. People are generally healthy because conventional community behaviour – which can be something as simple as covering one's mouth when coughing, using tissues and taking a day off work when feeling ill – stops many infectious diseases from spreading. What could be done to co-ordinate the temporary and reactive changes in community behaviour needed to halt a severe epidemic?

If a severe pandemic broke out tomorrow, it is likely that ordinary people in the UK would want to make the fullest use of their digital devices to inform themselves about the disease and to get the latest information on the epidemic. They would use online social networking to spread news and

1 Martin Bootsma, Neil Ferguson, 'The effect of public health measures on the 1918 influenza pandemic in US cities', PNAS (Vol. 104, No. 8, April 2007) pp. 7588–7593; Richard Hatchett, Carter Mecher and Marc Lipsitch, 'Public health interventions and epidemic intensity during the 1918 influenza pandemic', PNAS (Vol. 104, No. 18, April 2007) pp. 7582–7587

engage in discussion. They would use social networks to discover if any of their family, friends, colleagues and acquaintances were sick. It is likely that they would want the latest and most accurate information; that they would use every means available to them to get it; and that they would try to use this information to avoid catching the disease themselves.

This paper will briefly discuss four technologies that could help empower a community to control an epidemic:

1. Online social networking
2. Localisation and tracking using smartphones
3. Voted discussion systems
4. Online co-ordination of local community support.

Before considering possible technological tools, however, let us consider more carefully what the aim of preparedness planning should be.

Pandemics: Mild and Severe

During a mild pandemic such as the 2009 H1N1 'Swine flu' pandemic, life carries on as usual for the majority of people, but the health service may be critically overloaded. It is difficult to motivate effective mass community response because for most people, the disease is mild and regarded as a normal risk of life, particularly when the additional work going on within the NHS is largely invisible to anyone not directly affected – a situation commonly described as the 'emergency planner's dilemma': handle the emergency well, and it can sometimes be perceived by outsiders as a fuss about nothing.

A fast-spreading pandemic of a severe disease, such as the 1918 outbreak, has not occurred within the living memory of UK citizens, and is entirely outside the experience of ordinary people. The societal consequences may be severe however, and many of them may be unforeseeable because of poor understanding of supply-chain disruption and the tipping points at which some teams and organisations become unable to function with reduced numbers. During the 2009–10 pandemic, much research was carried out on, for example, the effects on a company of a significant proportion of the accounts department being off sick simultaneously, particularly if temping agencies were similarly stretched and unable to make up any shortfalls; or at what levels of staff sickness a Police Air Support Unit would no longer be able to fly its helicopter. During a more serious epidemic, observation and prediction of such tipping points would become a great motivator for people to temporarily change their behaviour.

In making such considerations, there is a need to compare two distinct pandemic scenarios:

Case A: Mild pandemic disease, with effects only slightly more severe than typical influenza and which most people in the UK would accept as one of the normal risks of life. There would be little motivation for the majority of people to make a great effort to avoid it.

Case B: Severe pandemic disease with rapid spread and substantial mortality. No such epidemic has occurred in the UK within living memory. Under such circumstances, large sections of the community might be more prepared to co-operate in extraordinary measures and make substantial behavioural changes to avoid and prevent epidemic spread.

The pandemic preparedness plans recently refined by the Department of Health[2] have been prepared with enormous care and, along with additional planning carried out through the Cabinet Office's Civil Contingencies Secretariat, they held up well during the 2009 H1N1 pandemic, which was broadly appropriate for the mild Case A. Should the UK be faced with a pandemic more similar to Case B, these plans would be used in conjunction with other Civil Contingencies Secretariat planning, in particular for mass casualties and mass fatalities,[3] and would dovetail with more generic chemical, biological, radiological and nuclear (CBRN) planning for large-scale bioterrorism attacks. These plans generally focus on how to deal with large numbers of the sick and deceased. Less attention has been given to how, faced with a rapid and severe pandemic, a sufficiently aggressive plan to stop its spread could be developed.

Current UK planning assumptions for R_0 (the basic reproductive ratio) of a pandemic influenza are that it is likely to lie between 1.4 and 2.5.[4] If community behaviour could temporarily change so that each person who caught the disease passed it on to one fewer person on average than would normally happen, this would help to suppress the epidemic and restrict it to a succession of local outbreaks. This might seem an absurdly optimistic goal – but digital technologies are vigorous. For example, when Wikipedia was launched in 2001, few people predicted that within a few years it would become the world's largest encyclopaedia, that it would often be more accurate than traditional encyclopaedias, and that it would penetrate so widely into society that it would become normal to consult it during conversations in pubs.

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2 UK Department of Health, 'UK Influenza Preparedness Strategy 2011', 10 November 2011. See https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/134747/dh_131040.pdf.pdf.

3 See as example London Resilience 'London Mass Fatality Plan' (Vol. 4, April 2014), <http://www.london.gov.uk/sites/default/files/archives/london–prepared–London–Mass–Fatality–Plan–v4.pdf >.

4 UK Scientific Pandemic Influenza Advisory Committee, 2009.

Changing Community Behaviour

The above demonstrates how rapidly (and unexpectedly) society can change its behaviour when sufficient drivers are in place to encourage it to do so. It is reasonable, therefore, to conclude that an epidemic could be stopped if enough people changed their behaviour in reaction to it. The report from Discussion Group 1, later in this report, outlines factors that need to be considered when encouraging behavioural change, and it would also seem to be common sense that to induce a large number of people to change their behaviour, the following steps are needed:

- Set a goal that is really worth achieving. In a severe pandemic, the goal should be to stop a national epidemic so that the spread is restricted to small local outbreaks
- Communicate a clear and credible plan through well understood and tested communication channels
- Provide necessary information and tools for people to co-operate in suppressing the epidemic. Information should include both health advice and real-time local and personalised news
- Encourage and facilitate open mass discussion, so that there is a rapid learning and dissemination of refinements of plan and of good practice as it is developed.

This paper will now consider technologies for providing real-time information about an epidemic and personalised information about people's risk. It will also mention a new technology that could be very useful for open discussion and debate.

Online Social Networking

At present, the dominant online social network is Facebook; other widely used networks with slightly different characteristics are Google+ and FourSquare. Facebook is less than ten years old – it was only founded in 2004 – but it now has hundreds of millions of active users worldwide, including a majority of thirteen-to-thirty year-olds in the UK, which is an epidemiologically significant cohort.

Facebook and other social networks accumulate a vast database of personal data about their users and most particularly on their users' interactions: this database is known as the 'social graph'. Data in the social graph can be mined to infer much about a person's social contacts. For example, although individuals often may not physically meet their Facebook friends, the social graph contains physical addresses, workplaces, clubs, meetings, parties and other information that can allow physical meetings and potential infectious contacts to be inferred. One rich source of information on

infectious contacts is co-tagging is photographs: Professor Jon Crowcroft[5] of Cambridge University's Computer Science Laboratory has observed that if people are co-tagged in a photograph, then they physically met. Facebook has implemented face-recognition technology to give the option of tagging people in photographs automatically and many people use Facebook to record their lives in real time – a photograph may be taken and uploaded immediately.

Facebook – and similar networks – are potentially important in epidemic control. For about a century, epidemiologists have posited a graph of infectious contacts through which a contagious disease spreads: now parts of this graph may be explicitly represented in the social graph of Facebook. This suggests that new methods of enabling people to assess their personal risk of infection are possible. Information can spread through an online social network faster than a disease can spread between people. If a person comes to know that some contacts of contacts of their regular friends have fallen sick, then they would have a personal incentive to react by reducing their social contacts for a while. If people ringing a flu helpline could be persuaded to inform their friends of their infected status by Facebook, this would be a rapid and effective way of spreading local news of increased infection risk.

Suggestions such as these raise many technical, factual and ethical questions however, including:

- Does contagious disease tend to spread along links that can be accurately inferred from the social graph?
- What would be the best technical mechanisms for helping the community inform itself about collective infection risk using the social graph?
- What ethical and privacy issues would arise in assisting information spread on the social network?
- What could be done to improve the accuracy of information spread through a social network?
- Social networks are run by competitive commercial companies and funded by advertising. What roles would these commercial companies be willing to play during a pandemic emergency?

These questions are hard – but there are potentially extraordinary benefits to be had from enabling human social networks to actively respond to an emerging disease as it attempts to spread.

5 'D Querica, M Bodaghi, J Crowcroft, 'Loosing "Friends" on Facebook', <http://www.cl.cam.ac.uk/~dq209/publications/websci_loosing.pdf >

Smartphone Localisation and Tracking

There are more mobile phones in the UK today than there are people. An increasing percentage of these phones are smartphones, which are capable of running apps in the background throughout the day. There is intense research to make smartphones both location-aware and context-aware – that is, the phone should know where it is and what its user is currently doing. This mass ownership of smartphones gives the technical possibility of real-time monitoring of an epidemic as well as mass personalised public health interventions.

Suppose that, when faced with an emergency, millions of people would be willing to co-operate in doing whatever was necessary to control the epidemic. To do this, they might be willing to allow uses of their personal data that in normal times would be considered unacceptable breaches of privacy. What might be done? How might their smartphones be used in a collectively productive way to control the epidemic?

A natural technological possibility would be for people, en masse, to record their movements on their smartphones. This could be done in a way that respects privacy: people could download an application that would run on their phone in the background, and which would record their movements in detail, but in an encrypted file. This encrypted file could be uploaded to a central server where it could then be read – but it would not be readable on the smartphone itself. The upload of the file should be at the phone user's discretion. The movements of all mobile phones are tracked anyway by the phone base stations, to a precision of roughly 100 metres, and the records are kept: users apparently do not object to this even in normal times. But a smartphone running an application could track its position more precisely and more frequently.

One natural localisation technology to use would be for the phone to record the identities of the Wi-Fi networks it can currently detect, together with their signal strengths. The phone could passively record this information at frequent intervals, and then store it in encrypted form; at the user's discretion, the encrypted trail could be uploaded to a trusted site that would decrypt the trail, and collate the trails of many people, to provide an analysis of potentially infectious contacts. Again, no information would be readable from the phone itself: the encrypted information would be given to a central site at each user's discretion. The pattern of signal strengths of the currently detectable Wi-Fi networks is not directly interpretable as a precise geographical location – but it is a spatially rapidly variable signal that can be used to tell if two phones are close to each other. Most importantly, it works particularly well indoors: under favourable conditions, if two phones can detect similar Wi-Fi strengths, they are likely to be in the same room.

In this way, those who volunteered to record their trails of movement could do so. If a sufficient number of people chose to do this – and in a crisis, many people might – then the movements and close contacts of large numbers of people could be tracked in unprecedented detail. If any person fell sick, potential contacts could be traced in real time. A database of a large number of contact trails could enable the modes of transmission of the disease to be established rapidly and comprehensively. Another method of mapping the contact network is the 'FluPhone' project.[6]

Voted Discussion Forums

During a severe pandemic, infection control policies and public health advice should be discussed as widely, as fully and as productively as possible. Advice should, of course, be broadcast from experts to the public, but this is not the only direction in which information should flow. Many people will have valid questions about the expert advice and others may come up with useful suggestions of their own, which deserve to be broadcast and discussed in turn. Some people may misunderstand the expert advice, and others will doubt it and will need to be persuaded to follow it. There will be many situations and circumstances that the expert advice as given will not cover. In short, during a pandemic emergency, there would be a need for rapid, decentralised, high-quality discussions on many issues.

Ordinary people, of course, would discuss the pandemic emergency in every possible way, but certain types of online forum would be particularly valuable. Issues of personal health and infection are highly emotive, and some people will wish to express strongly held opinions that may be eccentric, irrational, unhelpful or plain wrong. A simple public forum, such as a typical newspaper comments column, tends to be swamped by low-value comments whenever emotive issues are discussed. In contrast, voted discussion forums such as Reddit and Slashdot are a subtly powerful technology that allows users to moderate discussions in a distributed way, by voting comments up or down, or by providing more structured moderation (as in Slashdot).

The key feature of a voted discussion forums is that user moderation determines how comments are displayed. In Reddit, for example, down-voted comments go to the end of the list. This user-moderation – the 'voting' – has a powerful effect in improving the general quality of discussion, and in rapidly identifying those comments that are well thought out and well expressed. Comments that are poorly expressed, incoherent, or which present tiresome or inane points of view are typically voted down. The almost magical effect of moderation from the mass of users is that people

6 Eiko Yoneki, 'Fluphone study: virtual disease spread using haggle', pp 65–66, paper presented to the 6th ACM conference on challenged networks, 2011. See http://www.cl.cam.ac.uk/~ey204/pubs/2011_CHANTS.pdf.

posting comments have an incentive to think and write better: nobody wants their comment to be voted down.

Voted forum technology is a key element in the new 'massively open online courses' (MOOCs) provided by companies such as Coursera and Udacity: in some of these, tens of thousands of learners are actively involved online and they communicate effectively in online discussion forums. Students answer each other's questions – and questions that need the instructor's comments are voted up for their attention. In this way, a large community of learners can share a common, interactive instructional experience. Voted discussion forums are one possible model for mass communication of infection control advice. In a pandemic emergency, existing forums would be intensively used in this way – but planning could ensure that expert advice is fed into the discussion from an early stage.

Non-pharmaceutical interventions can be more than simple interventions by the health authorities – community-wide responses also have an important role to play. Well-designed forums for active community-wide discussion could help the community itself to adopt and refine its non-pharmaceutical responses to the epidemic.

Distributed Community Support

Distributed community support has so far received little academic attention, but it could be important. During an epidemic, a local community (the residents of a single tower block, for example) might wish to organise mutual assistance. They might wish to assist in household quarantine by arranging to do the shopping for people who might be infectious. They might wish to discuss and co-operate in many ways, such as organising volunteers. They might wish to do all this without having a physical mass meeting – for very good reason, as such a mass meeting is likely to ensure the infection would spread. Online tools could help to ensure that all meetings were virtual. Protocols and guidance for communities in organising mutual assistance and recruiting volunteers under such circumstances would be useful public health information.

Summary

This paper has suggested that preparedness planning for a severe pandemic should have the aggressive and ambitious goal of stopping the epidemic on a national scale. Less ambitious plans are defeatist. The best defence against a new, severe disease is not to catch it and planning should emphasise changing community behaviour to stop transmission during and epidemic. Further research into how communities behave with regard to infectious diseases would be extremely beneficial. It would be reasonable to assume that people will be willing to change their behaviour most effectively in response

to a well-presented plan for stopping an epidemic, rather than a plan that implicitly assumes that an epidemic can only be somewhat mitigated.

In preparing such a plan, digital communications technology should be used to the fullest extent possible. Research should be done on preparedness planning using digital communications technologies for real-time epidemiology, automatic contact tracing and providing personalised estimates of infection risk, as well as for promoting efficient public discussion and for enabling local co-ordination of volunteers. Research is also needed to smooth the technical, ethical, practical and legal problems that will inevitably arise.

Dr Chris Watkins is a Reader in Computer Science at Royal Holloway, University of London. His research interests include machine learning, evolutionary theory and theoretical epidemiology. He is interested in radical uses of modern communications technology for co-ordinating mass response to epidemics. A theoretical model of the effect of population response on epidemic spread was presented in 'The Spread of Awareness and its Impact on Epidemic Outbreaks',[7] and he believes that technology now exists that might enable some of these theoretically possible effects to be achieved.

His Google Scholar page is <http://scholar.google.co.uk/citations?user=v8QhiOwAAAAJ&hl=en>.

Jennifer Cole is Senior Research Fellow, Resilience and Emergency Management at the Royal United Services Institute. Her research programme includes CBRN prevention, response and recovery; infectious disease outbreaks caused by naturally occurring pandemics and bioterrorism; and strategies for warning and informing the public. Her academic background is in biological anthropology, and she is currently a Reid Scholar in Health, the Human Body and Behaviour at Royal Holloway, University of London. Dr Chris Watkins is her PhD supervisor.

7 Sebastian Funk, Erez Gilad, Chris Watkins and Vincent Jansen, 'The spread of awareness and its impact on epidemic outbreaks', *PNAS* (Vol. 106, No. 16, 2009) p. 6872–6877.

Discussion Groups

During the afternoon, the conference broke down into focused discussion groups, each comprising between ten and twenty delegates. The outcomes of these discussion forums are presented over the following pages.

Discussions were without attribution. The information presented here seeks to represent the discussions that took place; there is not always robust academic referencing to support the views offered, but it has been assumed that if comments made by individual delegates were not credible they would have been rejected by the other members of that group during the discussions. Views presented are therefore assumed to be broadly supported by the majority of those present. Where possible, transcripts of the discussion forums were distributed to the participants during the editing process for further comment and clarification.

There was, inevitably, some crossover of subject matter and topic discussion between one group and the next, and where this has occurred, comments have been amalgamated under one heading to avoid repetition. For example, comments on the importance of accurate, point-of-care diagnostics raised in the discussion forum 'Changing Behaviour in Antibiotic Prescribing' have been amalgamated with the discussion forum 'Improving Diagnostic Techniques', and comments on the role of the media raised in discussions regarding barriers to implementing AMR strategy have been amalgamated under the heading 'Communicating the AMR Message'.

Discussion Group 1: Changing Behaviour in Antibiotic Prescribing

Chair and Rapporteur: Jennifer Cole

Key Issues and Challenges

Behavioural

- Systematic ways to eliminate overprescribing need to be built in to the NHS
- Consultants need to take the lead in encouraging young doctors to keep abreast of the latest thinking, policy and guidelines on antibiotic prescribing and stewardship
- Patients need to be better educated on when antibiotics should be prescribed and why, in certain cases, there are good reasons for withholding them
- The ways in which 'champions' and 'early adopters' of behavioural change emerge and influence others needs to be better understood
- There needs to be a systematic review of which health education campaigns have been most successful in the past, and why.

Technical

- There needs to be greater consistency in the way infection data is collected
- There needs to be better data collection on the reason(s) why antibiotics have been prescribed, particularly where it is subsequently identified that infection is not present
- Rapid diagnostic techniques, that can rule out infection more quickly and which can give results at point of care (including at the GPs surgery or the hospital bedside), need to be developed.

Significantly reducing the quantity of antibiotics prescribed in the UK depends on changing the behavioural patterns of two distinct groups: those who are prescribing the antibiotics (i.e. doctors and other healthcare professionals) and those to whom the antibiotics are being prescribed (i.e. patients). Adult care and neonatal care were discussed separately at the conference, as there are significant differences inherent to the use of antibiotics for each group. The discussions from both age-specific groups have been combined in the report, however, as there is sufficient overlap of the challenges and suggested solutions to warrant this.

Reasons Why Antibiotics are Overprescribed

Doctors overprescribe antibiotics for a number of reasons, which include, but are not limited to:

- 'Just in case' – when the doctor is not immediately sure whether the infection is viral or bacterial, or whether infection is present at all. Prescribing antibiotics in such cases ensures the patient's condition does not deteriorate if bacterial infection is present
- 'Keeping the patient happy' – patients often expect to be given 'something' if they have gone to the trouble of seeking medical advice and help. Antibiotics may be prescribed even if the doctor is aware they will have no effect
- 'As protection (prophylaxis)' – when patients are undergoing procedures such as chemotherapy or surgery, that leave them more prone to infection. In such cases, the antibiotics offer protection against the risk of infection rather than treating existing infections.

All of the above are widespread reasons why antibiotics are overprescribed. Such practices have built up over the past sixty years because historically, antibiotics have been readily available and relatively cheap, and they have relatively few side effects. In other words, there have been relatively few disadvantages to prescribing antibiotics to a patient, even if that patient does not need them. By contrast, the risk factors associated with not prescribing antibiotics to a patient who does need them can be high and, in extreme circumstances, may even prove fatal. Behaviour has, therefore, understandably been heavily weighted in favour of erring on the side of prescription. The increasing prevalence of AMR unbalances the current equilibrium, however, with the added complication that the increased (and increasing) risks now associated with prescribing are to the community as a whole and to the future efficacy of antibiotic therapies; on a case-by-case basis, the risks associated with prescribing or not prescribing antibiotics to an individual patient at a particular point in time has not significantly changed.

Determining Risk Thresholds

Antibiotics are often administered on very low risk thresholds (for example, as discussed in Chapter V, between an estimated 90 and 99 per cent of neonates treated with antibiotics do not have an infection). Nonetheless, a level of risk does exist even where it is very low, and one of the key challenges to re-evaluating the thresholds is the lack of available evidence on the effects and outcomes of withholding antibiotics, temporarily or permanently, to the low(er) risk patients. Without such evidence, it is difficult for healthcare professionals to feel confident in judging when it is safe not to prescribe antibiotics at all, to delay prescribing antibiotics until the presence of infection has been (more strongly) confirmed, or to give a very narrow-spectrum drug. An additional challenge is that any such studies that might be proposed are likely to have difficulty gaining ethics committee approval.

Another difficult issue is how long the course of antibiotics, once prescribed, needs to be taken for before it is safe to stop: either because the infection has been treated successfully; because the time has passed when the suspected infection, if present, would have become apparent and it is therefore safe to assume it is not present; or because the infection has cleared up independently of the antibiotics. An example was given of patients with a urinary tract infection (UTI) who were given antibiotics but told to wait a day before starting to take the drugs. When the patients returned for further treatment and consultation, half of those who had been prescribed the antibiotics had never taken them, but there was no difference in outcomes between those who did and those who did not. There was a strong feeling within the discussion groups that there is a need for better collection of data relating to cases such as this, and better interrogation and analysis of such data to help build better understanding of, and prescribing guidelines on, the appropriate duration of treatment. In some cases, five, six or seven day regimens are prescribed, when, in the words of one delegate, '[the infection] might have cleared up earlier – sometimes with a single dose'.

The above issues lead to particular challenges in neonatal care. Neonates are very vulnerable to infections, which can take hold very quickly and this drives even greater caution and 'just in case' behaviour than in adult care. Close observation as an alternative to administering antibiotics, while further symptoms do or do not appear, puts a huge burden of responsibility on the healthcare professional tasked with making the observations. Symptoms can be missed, particularly as the baby is not able to describe how it feels, and in such cases the consequences could be fatal. This is particularly problematic in the current economic environment when staff time and resources are extremely stretched.

Healthcare professionals are concerned about being blamed for 'getting it wrong' if they miss infections, particularly in the modern 'blame-and-compensation' culture where there is little tolerance for error. This inhibits potential early adopters of suggested new behaviour from coming forward to act as influencers and champions to their peer group. Personal fears based on actual experience also lead to a lack of willingness to take risks; seeing one patient die because an infection has been missed is likely to increase over-caution to ensure the same mistake is not made again. The above barriers result in staff tending to focus on their individual patients to the detriment of the bigger picture. Neonatal vulnerability means that hospital staff and management, particularly in Special Care Baby Units and Neonatal Intensive Care Units, are particularly reluctant to change what they are comfortable with and what they know works.

Building Confidence in Changing Behaviour

The key to overcoming the concerns expressed above is better understanding of the outcomes and consequences of reducing antibiotic use and of withholding antibiotics in certain situations. The more confident the healthcare professional is that withholding antibiotics will have no serious adverse effect on their patient, the more willing they are likely to be to change their behaviour. Quantitative and qualitative data on case studies in which antibiotics have been withheld, with no detrimental effect on patient outcome, will help to build this confidence.

There is, however, a marked lack of studies of this type and a corresponding lack of data. While it is scientifically and technically possible to collect data on the outcomes of withholding or delaying antibiotic therapies, there are serious ethical issues attached to doing so, and this makes studies to determine safety or otherwise of changes in procedure very difficult to undertake. What data there are tend to be either decades old, from before antibiotics were widely available (are therefore also before medical technology was as advanced as it is today) or from developing countries where access to antibiotics may not be available at all (and therefore the data does not show what happened if antibiotics are withheld for a day or a week, but what happens if antibiotics are never administered). One delegate remarked that the result of this is that: 'You have the situation where nobody gets antibiotics or everyone gets a broad-spectrum drug. It's difficult to find studies that look only at cases where you are sure that the patient is given the right treatment for the right infection, and then you look at the outcomes'. She further remarked that it was difficult to find data on studies conducted in countries which have 'good' (i.e. modern Western-standard) medical care. Her remarks were made in relation to care of elderly patients with UTI infections, but the group agreed that the principle applies universally.

The Lack of Useful Data

Another challenge is that there is very little data collected on cases where antibiotics are administered but no infection is then identified, even though such data may help to understand why the decision to prescribe was inappropriate. There is very little questioning of why antibiotics are administered in such situations, or of what might have caused the sign/symptom that was attributed to possible infection once infection is ruled out. Too few healthcare professionals see the original misdiagnosis in such cases as an issue.

Currently, there is no standardised way of collecting data on infection. There are no defined metrics that are universally accepted for measuring the outcomes of antimicrobial stewardship programmes, nor any consensus on how prescribing or clinical information and resistance data is defined. Should it be the number of patients on antibiotics or daily doses per 100

patient admissions, for example? At present, reviewing such data requires a significant amount of time spent looking back over patient records; staff carrying out such checks would need to get feedback quickly that would prove that what they are doing is making a difference (or at least not making things worse).

Better antibiotic stewardship might also be encouraged by increasing awareness of the disadvantages of overprescribing and by encouraging overprescription to be actively challenged. Managers and colleagues need to be encouraged to ask questions such as: 'Why were antibiotics administered [in this case]? What had actually caused the sign/symptom that you thought was due to infection?', and the reasons recorded so that they can be easily analysed. Professionals need to understand why overuse is an increasingly important issue.

The discussion groups felt that small amounts of funding for short pilot studies, to be undertaken by staff willing to instigate new behaviour, would be very useful; as little as £10,000–£20,000 for studies lasting three to six months was suggested. These pilot studies could be used quickly to develop and test new practices in one healthcare facility and then push this out to others. This was seen as being potentially more valuable than long, academic studies which may take four to five years to yield results, as the short studies could be used to 'test' if a theory is worth exploring further. This type of funding is currently difficult to obtain, but many felt it can have the most practical results, particularly if it could be awarded directly after new policy and guidelines are issued to help support early adopters of suggested new behaviours.

The Need for an AMR Public Health Campaign

'Getting the AMR message out' is a key challenge. Healthcare professionals and patients need to accept that AMR is a significant-enough issue that it requires a fundamental change in traditional prescription practices. However, it can be very difficult to get busy professionals to read literature on antibiotic prescribing and to keep up-to-date with current policy and guidance. An e-learning module may have more effect than written material, as may taught seminars (although consultants and senior doctors would have to make attendance a priority, not leave attendance to choice).

The campaign around the most recent (2012) European Antibiotics Awareness Day (EAAD) was considered to have been 'rather insular', due to a general lack of investment/interest in AMR. There had been a more significant push in 2011, when AMR was tied to World Health Day; but interest in EAAD, which happens annually in November, has been negligible in other years.

The over-use of antibiotics requires a high-profile campaign along the lines of the 'Clean Your Hands' campaign, which successfully changed behaviour and had a significant impact on both MRSA and swine flu transmission rates. This shows that where there is sufficient will, an appropriate change in behaviour can follow.

Peer pressure, as well as the message itself, played an important part in the 'Clean Your Hands' campaign, and caused a tipping point at which new behaviour became so acceptable, and the old behaviour so unacceptable, that junior doctors and nurses felt confident in challenging senior colleagues on non-compliance. Such a tipping point could be particularly relevant to antibiotics prescribing: many of the delegates in the discussion forums had examples of where they, or colleagues, felt that a prescribing decision had been questionable but that they had lacked confidence in tackling more senior colleagues on their behaviour. Within neonatal care, there is a noticeable split between midwives, who are strongly in favour of reducing antibiotic use, and doctors and pharmacists, who appear more reluctant. One delegate recounted a discussion she had had with two of her hospital's pharmacists about how they were actively looking at ways to avoid implement NICE Guideline 149[1], including not reducing the drug dosage because 'our way is fine'. This observation is consistent with experience of the 'Clean Your Hands' campaign: doctors were less compliant than nurses with the campaign's messages.

The behaviour of middle-ranking doctors in particular is seen as being challengingly 'ingrained'. At medical schools, deaneries are starting to recognise over-prescribing and to address the issue. Over the last decade, younger doctors have become much better informed about antibiotic prescribing and use, and senior doctors who have significant teaching roles are also being reached through this process. Medical training in microbiology and infection control is still seen as 'patchy and piecemeal' around UK medical schools, however, and there is a need for greater standardisation. Targeting medical students now so that good practices are embedded for the future should be a priority.

Different demographics may need to be targeted differently; older doctors need to be encouraged to change bad habits, medical students need to be encouraged not to adopt them, and different groups may react better to different delivery routes and messaging platforms; a mixed approach may prove to be the most effective. Identifying staff who are willing to act as advocates to encourage uptake of new behaviour is key to developing a more practical approach.

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1 'Antibiotics for early–onset neonatal infection: antibiotics for the prevention and treatment of early–onset neonatal infection', see <http://guidance.nice.org.uk/CG/Wave23/7>.

Evaluating Previous Public Health Campaigns

Changing behaviour to address AMR challenges would benefit from a strong public health campaign aimed at medical professionals and patients. In planning such a campaign, it would be useful to have a good understanding of which public health campaigns have worked well in the past, which have been less successful, and the reasons why. There are important lessons to be learned from a number of past public health campaigns, aimed at both healthcare professionals (e.g. hand-washing in hospitals to reduce MRSA transmission) and at the general public (e.g. smoking, AIDS). A better understanding of public attitudes towards vaccination programmes, including reasons for the low uptake of seasonal flu vaccines amongst some groups and the negative perception of vaccines such as MMR, would also help to inform future planning. This suggests that a systematic review of public health campaigns is needed.

Within this, it would also be valuable to assess how attitudes to health information have changed over time. During the 1950s, the public tended to be more deferential to government and believed 'doctor knows best', whereas today there can be more skepticism over the truth of messages coming from central government and more of a desire to research information on the internet. The way this affects public health campaigns needs to be better understood. In particular, what drives public perceptions of health risk is not necessarily well known, nor are the reasons why the public react in a way that can seem illogical to healthcare professionals – for example, one of the demographic groups most opposed to the MMR vaccine is university educated women, so the issue is not due to lack of education or language barriers. It would be useful to understand if some health opinions, such as taking an anti-MMR stance, are used as a 'badge of belief/identity' by certain groups so that targeting these groups, as well as individuals, might be advantageous.

Negative Messages

Negative imagery in public education campaigns is hard-hitting and can be the most effective, particularly when combined with peer pressure. Anti-smoking campaigns showing cancer tumours, for example, and anti drink-drive adverts that show crash victims, have a strong impact on the public. Incorporating negative messages and imagery into an AMR campaign, such as by highlighting the links between antibiotics and childhood asthma, or antibiotics and childhood obesity, could help to encourage parents to accept antibiotics being withheld; empirical evidence comparing the health risk of withholding the antibiotics with the health risk from administering them would help both the professional and public understanding of this, and would help to determine where risk thresholds should and do lie.

Changing the attitude of the population is as important as changing the behaviour of individuals. There is a need to identify and work towards tipping points where behavioural change starts to take hold and become the norm, and to better understand the drivers of these macro-level changes. This could lead to certain groups feeling a sense of ownership and responsibility in seeing certain changes implemented and becoming champions of the message to the wider population. There is a potential role here for charitable or philanthropic organisations in tackling AMR, and perhaps even an 'AMR-UK' style charity on the model of Cancer Research UK, which has been highly effective in channelling money into cancer research. Such a charity may help to drive funding towards research that there is little incentive for profit-driven pharmaceutical companies to invest in.

Only a small investment would be required to gauge public opinion. Commissioning a poll to evaluate the effectiveness of awareness campaigns would be a good use of money, as would a short study to explore the best media outlets and the best means of engaging the public interest. A two-year study, first looking retrospectively at previous campaigns, and then at a new targeted information campaign, would be a sensible approach.

Systematic Support for Behavioural Change

Changing behaviour is not just about the message, however: it requires processes to be built into systems that encourage and enable people to choose to accept the message and to take appropriate action. For example, if the message is that antibiotics should not be prescribed for every cough and cold, then they should not be readily available in every hospital drug cupboard. Similarly, drug charts and documentation should be designed to encourage uptake of new behaviours: if a doctor is prescribing antibiotics in the absence of a red flag from the NICE Guidelines list, and in the presence of only one clinical indictor or risk factor (and therefore is acting against the recommendations of the guideline), they should be expected to list and explain the reason for this in the documentation. If a significant percentage of their prescribing decisions go against the recommendations of the guideline, they need to be questioned by senior management and perhaps even a central watchdog body.

What might appear to be relatively minor or irrelevant issues can affect antibiotic stewardship quite profoundly. For example, on which day of the week a patient starts their course of antibiotics can be important. A patient starting a course on a Thursday will almost inevitably continue to take the drug over the weekend, whereas it might have been possible to stop the treatment after only a day or so had the course started earlier.

There is a huge amount of information available on prescribing practices but no standard way of measuring how behaviour is affected by it; some

hospitals and health trusts measure changes in prescribing following new literature and guidance, but others do not. There is a need to define clear strategies on implementation of new guidance, and to standardise the data to be collected as well as the way in which they should be collected. This will enable better assessment of stewardship programmes, not just in terms of prescribing but also in terms of clinical and microbial outcomes. Results should be fed back to a central point to help build evidence relating to the behavioural change itself, and the patient outcomes resulting from it.

Changing the Behaviour of Patients

Patients, as well as doctors, need to be encouraged to change behaviour and to understand when they should and should not expect to be prescribed antibiotics so that they do not feel annoyed with their doctor when antibiotics are withheld (and may also be better able to challenge a prescription they feel is unnecessary). Changing patient expectations about their treatment is vital. Doctors should not be afraid to admit to patients that they are unsure whether or not the patient has an infection; whether the infection is bacterial or viral; and to discuss options and risks of delaying treatment until the diagnosis is more certain.

Managing people's expectations of the time for recovery from illness and the effectiveness of medical intervention is a crucial factor in encouraging them not to demand additional medicines from their doctor. Explaining that choosing not to take additional medicines will have long-term benefits to the wider population may also help them to make the best decisions.

Information, given at the point-of-care, about the side effects both directly and indirectly affecting the patient is also important. Being honest about the links between neonatal antibiotic exposure and childhood conditions such as asthma and atopic dermatitis might help to explain stewardship programmes to parents.

Public education campaigns that include the public as well as medical professionals are essential to bringing down antibiotic use.

Rapid Diagnostic Techniques

Rapid diagnostic techniques that are able to quickly identify whether infection is present and what particular infection is present would help to reduce the 'just in case' nature of prescribing by increasing the certainty that an infection is of is not present; this would be particularly valuable in neonatal care. The discussion groups felt that more research into biomarkers that indicate quickly whether an infection is present is needed in particular.

Research Topic Suggestions

1. In light of the new NICE Guideline 149 on Neonatal Infection, which is intended to reduce the unnecessary administration of antibiotics to neonates, short monitoring pilot projects in one or more hospitals over the next twelve months to record information on the cases where previously antibiotics might have been administered but withholding them is now recommended, to record whether there was any adverse outcome associated with withholding them, what (if any) this was, and what was the actual cause of the Clinical Indicator or Risk Factor listed in the NICE Guideline.

2. Short studies that gather and analyse statistics relating to the likelihood of outcomes, and severity of outcomes, could help to build confidence in new behaviours [e.g. in 2,000 instances of this clinical indicator, only 5 per cent will be caused by infection. Of babies first treated with antibiotics at four hours after onset of clinical indicator, survival rate is 100 per cent, after eight hours it is 100 per cent, at twenty-four hours it is 100 per cent, at seventy-two hours it is 98 per cent, and so on].

3. Conduct a systematic review of past public health campaigns to suggest what messages, and which delivery methods, may best inform an AMR awareness campaign and campaigns to reduce the use of antibiotics.

4. A study to determine the link between neonates born following maternal hyperthermia in labour (where the hyperthermia might be consequence of vasodilation secondary to epidural analgesics rather than infection) and the administration of antibiotics on suspicion of infection.

Discussion Group 2: Communicating the AMR Message

Chair and Rapporteur: Ian Cameron

Key Issues and Challenges:

- The most effective communication strategy for AMR messages is likely to be one that uses a mixture of traditional and new media
- Celebrity campaigners will help to engage the public and promote the message
- Social media can be used to counter incorrect or misleading newspaper stories
- Large companies that understand social marketing well, such as supermarket chains and large pharmaceutical companies, could be useful partners in any campaign
- Social media can be harnessed to provide real-time information on emerging diseases and disease spread.

Successful communication strategies depend on both the content of the message and its delivery mechanism. Once a message is sent, it has to be received, read and believed. The recipient has to decide to act on it and be supported in their decision to act. This is the same regardless of whether the message is communicated via traditional broadcast or print media, online or social media or by word of mouth. As different demographic groups access and take notice of different media platforms in different ways, the most effective communication strategy is likely to be a mixed approach using old and new media, local and national media, trade and general media and personal messaging from, for example, GPs, the NHS and celebrity campaign supporters. There are advantages and disadvantages to all.

Understanding the sources from which patients derive information is particularly important in enabling them to make informed decisions. Information must come from an informed and trusted source. Experience from other areas of resilience, in particular flood messaging, shows that local newspapers and local radio (and their associated websites) are trusted more than the national media. A personal contact, such as a patient's own GP, is likely to be more influential than the NHS; a GP handing over a leaflet as if they are personally recommending it will make a difference to how the patient assimilates the information. The public is also more likely to take messages from local media than to go directly to the Department of Health or NHS websites; the latter are more likely to be consulted for further information, however, so ways to drive the public to them will be beneficial.

In the US, community resilience campaigns are run in association with major sports clubs and the supermarket giant Walmart. Large sports stadia and supermarkets are seen as key centres of the local community, places which everyone uses and which can help to convey messages to large numbers of people and to most demographic groups. Such an approach might work equally well in the UK, particularly as supermarkets are very adept at sophisticated marketing campaigns and may be able to lend expertise to the development and communication strategy of a campaign under corporate and social responsibility programmes. Drug companies use social marketing to great effect and may be willing to help an AMR campaign as part of corporate responsibility even if they are less interested in investing in research into new antibiotics.

With respect to engaging traditional newspaper media in AMR campaigns, the main challenge will be that good news does not (always) sell papers: media coverage may tend towards alarmist or negative stories. For example, there is a danger that the media might try to link the spread of drug-resistant diseases such as tuberculosis to immigrants or immigrant populations, suggesting a racist undercurrent that could make the broader population less willing to engage.

If engaged properly, the media can be used to good effect as a conduit for distributing public information, while negative mainstream media impressions can be reversed by spreading alternate messages through social media. More novel outlets, such as the online game 'Pandemic', can also be used to educate the public by teaching the importance of conservatism in drug prescribing and promoting the importance of research to find effective drugs. Computer games that help to get the message to younger people may help to instill a culture of more appropriate use of drugs at an early age.

Television, radio and newspaper audiences are no longer passive. While in the past public health messages tended to be preached at the audience from press releases written by the Department of Health and filtered through newspapers, today's engagement is more of a two-way conversation, in which information can flow both ways. The public are active commentators and can even drive the traditional media news agenda through social media. Just like drug-resistant microbes, media and communication strategies constantly adapt and evolve; a story that leads a TV news bulletin one day might not even make the running order the next, but conversations on Twitter and Facebook, not to mention influential discussion sites such as Mumsnet, may still be going strong and may enable the message's influence to increase steadily through viral spread, the digital equivalent of word of mouth.

Any communications campaign, whether it involves traditional or new media, depends on trust and empathy; the message must come from a trusted source,

be believable, reliable and verifiable. While social media enables healthcare professionals to bypass journalistic filters and biases and talk directly to their audience, they need to be sure the audience will take notice. The public may be more likely to listen to celebrities than medical or academic experts: engaging a celebrity face in any public communication campaign may be the difference between its success or failure, as discussed in Discussion Group 5. Research by Opinion Leader, part of Chime Research and Engagement Division published in *Marketing Week* in May 2009[1] refers to the modern day as the 'Age of Emotional Proximity' where peer recommendations surpass all other forms of marketing. A Department of Health survey in October 2002 showed that when the public were asked which source they trusted to give facts on MMR, only 7 per cent said a medical spokesperson, while 34 per cent said the TV presenters Richard Madeley and Judy Finnigan.

Reliability of Social Media Information

As well as helping to spread the message, social media can also help to provide information and data into the healthcare sector by crowd-sourcing information. An excellent example of how this has been used to good effect is Google flu trends, which uses aggregated Google search data to estimate current flu activity around the world in near-real time[2] by working on the assumption that an increase in the number of people searching for flu-related information suggests an increase in cases of flu. While the absolute accuracy of information obtained through Google flu maps is questionable, the tool does have value in showing which areas are, in general, more likely to be affected than others.

Concerns that crowd-sourced information may be inaccurate due to the public maliciously or mistakenly feeding in false information appear to be largely unfounded; where false information is posted it tends to be taken down just as quickly. For example, false information posted during bushfires in Australia and during the 2012 summer riots in the UK was countered very quickly by other posters.[3] The public self-censor social media sites and this can be used to good effect to spread valid information and also to counter rumours and negative information put out through other mainstream or social media channels.

There are a number of free tools available to analyse social media. Twitter shows what subjects are 'trending' by counting the number of times certain words are used in messages and some sites will also translate text data into visual forms so that popular subjects can be spotted easily. Others sites sift and monitor social media to turn information into intelligence. Aggregators

1 J Roberts, 'How deference became reference', *Marketing Week*, 13 May 2009.
2 See < http://www.google.org/flutrends/>, last accessed 20 May 2013.
3 See <http://www.dontpaniccorrectingmythsaboutthecrowd.blogspot.co.uk/2011/09/riots–not–incited–by–twitter–shock.html>, last accessed 20 May 2013.

like Addict-o-matic can search for a subject such as AMR and display what people are saying about it on various platforms such as Twitter, Facebook, YouTube and Flickr, as well as in traditional newspapers, radio and TV. Tools such as these can be used to find conversations on Twitter and Facebook and will enable professionals to join in, and can potentially provide near real-time feedback and qualitative information from the public.

Language Issues

With any planned public information campaign, there will be a need to be aware of language and literacy barriers within some demographic groups. This can be a particular issue with AMR as in some of the immigrant populations in the UK that are known to have high rates of tuberculosis and gonorrhoea, for example, illiteracy is as high as 80 per cent. This can be due to a strong culture of oral tradition rather than a lack of access to education, so providing translated written information may not help. There is, however, no indication that is significantly more of a challenge in AMR than in other areas of healthcare, though the difficulty of communicating information on gonorrhoea to a woman who may be using her young child as a translator was noted.

Research Topic Suggestions

There were no specific research topics suggested by this group.

Discussion Group 3: Improving Diagnostic Techniques

Chair: Professor Jodi Lindsay

Rapporteur: Mark Gould

Key Issues and Challenges

- More research is needed into biomarkers that can indicate quickly whether a bacterial infection that will respond to therapy is present
- Rapid (point of care) diagnostic tests that can quickly distinguish between bacterial and viral infection would be valuable.

A significant challenge to tackling antibiotic resistance is reducing the overuse of antibiotics. This includes reducing the quantity of antibiotics prescribed and improving the quality of antibiotic prescribing so that narrow-spectrum drugs are used to target specific infections. Both of these approaches depend on rapid, accurate point-of-care diagnosis that, ideally, can give instant results at the hospital bedside or the GP's surgery, or at the border for immigration screening. In particular, rapid diagnostic tools are needed that can help to bring down the number of times antibiotics are prescribed to patients who have no infection at all, or who have a viral infection on which antibiotics will have no effect.

At present, accurate diagnosis for infection can take days, weeks, or even months to confirm whether infection is present at all and whether the infection is bacterial or viral. During this time, patients may be prescribed antibiotics as a precaution, until the presence of infection is ruled out. This course of action has relatively few side effects for the individual patient but such extensive use of antibiotics increases the likelihood and prevalence of resistant strains developing and therefore has a detrimental effect on community and future population health. It is also important to remember 'relatively few' side effects does not mean none; approximately one in every hundred people has an adverse reaction of some kind to antibiotics, and approximately one in every 10,000 has a true allergic reaction; the latter can prove fatal. Antibiotics have been linked to inner-ear damage and increased risks of childhood obesity and asthma. There is increasing evidence that harmless bacteria in the human body that play a key role in controlling infection susceptibility, autoimmunity, obesity and brain function are heavily altered by antibiotic prescribing.

Rapid diagnostic techniques that are able to quickly identify whether infection is present and what particular infection is present would help to reduce this

precautionary prescribing by increasing the certainty that an infection is or is not present at an earlier stage in the treatment cycle.

Current Challenges to (Rapid) Diagnosis

At present, bacterial infection is largely determined or ruled out through a combination of direct observation of signs and symptoms indicative of infection by a medical professional (which includes, but is not limited to, high body temperature, fever, rash, fatigue, general aches and pains and nausea); the recently published NICE Guideline 149[1] lists a number of biomarkers that are considered to be risk factors or clinical indicators of neonatal infection, for example. The presence of directly observed biomarkers is often then followed by a blood, urine or sputum sample (plus spinal fluid in the case of brain infection) that is taken from the patient and cultured (grown) in a microbiology laboratory to both confirm the presence of bacterial infection and to identify the specific pathogen responsible.

It can take two to three days for the bacteria to actually culture to the stage where the specific bacterium can be determined; add to this the time to deliver the fluid sample to the laboratory and for results to be returned, if the laboratory is not on-site at the healthcare facility where the patient is being treated (the loss of on-site hospital microbiology laboratories to more centralised facilities is seen as a particular challenge). In addition, over a further two-to-three days, small amounts of antibiotics may be applied to the culture to determine which might be the most effective in treating the infection (a process known as determining antibiotic sensitivity).[2] In some cases, the time between the fluid sample being taken and a positive culture growth obtained can be much longer than a few days – for instance, a positive result for tuberculosis can take up to three months to yield a result,[3] which poses particular challenges for infection control at immigration and border control points.

The main disadvantages of results taking at least two-to-three days to obtain is that during this time, the patient will often be given antibiotics as a precautionary measure until bacterial infection is ruled out. This may require the patient to remain in hospital, particularly if the antibiotics need to be administered intravenously, when they do not in fact have an infection and could be managed elsewhere, for instance in the community. An added complication is the collateral damage associated with misuse of antibiotics; particularly with regard to colonisation and/or infection with super bugs like MRSA, *C difficile* and other healthcare acquired infections.

1 See: <guidance.nice.org.uk/CG149>, last accessed 22 August 2012.

2 Basic introductions to bacterial culture tests can be found at: <http://healthengine.com.au/info/Bacterial_Culture_Test>.

3 See <www.who.int/tb/features_archive/new_rapid_test/en/>, last accessed 8 August 2012.

Intravenous administration of antibiotics in particular, brings with it a risk of healthcare acquired infections due to cannulas becoming infected. A further consideration is the financial burden on the NHS.

Not administering antibiotics immediately on suspicion of infection, however, may result in the patient's condition worsening, and, in extreme cases, may be fatal.

The risks to the patient of withholding antibiotics until an accurate diagnosis has been made have to be weighed against the risks to the patient associated with administering antibiotics that are not needed and the risks to the community and population of increasing AMR. The solution to these challenges is to provide accurate diagnosis more quickly, so that decisions to begin or stop antibiotics can be made as quickly as possible – preferably at the hospital bedside or at the GPs surgery and, in the case of immigration control, at the point of departure from or arrival at international borders. In particular, doctors would like to have a way to determine quickly whether an infection is bacterial rather than viral. Such tests have to be simple but also sensitive and accurate, and need to give answers in minutes, similar to the way in which pregnancy tests give very quick results.

A key question for the discussion forum was the scientific, technological and economic feasibility of developing a test that could enable such a rapid but accurate diagnosis. Ideally, it would be able to be administered by non-specialists with limited training and would not need to be sent away to a lab (though samples may be sent to a lab for further analysis). To what extent specialists – such as specialist sepsis diagnosticians – would need to be included in any such process was also discussed, as was where the test should be taken (for example, identifying sepsis in accident and emergency patients).

To add an additional challenge, an increasing use of, and push towards increasing use of, narrow-spectrum drugs increases the requirement for rapid, accurate diagnosis. In the words of one doctor: 'if narrow-spectrum drugs are being developed that only treat, for example, *C. difficile*, you've really got to know what you are treating or it won't work'.

There are a number of options that increase the speed and accuracy of diagnosis and much research and development work is already being funded and carried out in this area. For example, the Home Office's Office of Security and Counter Terrorism ran a conference on this specific topic in June 2013 at the Royal Society in London.

Droplets of fluid samples taken at the bedside might be transferred to a glass slide or other device for immediate microscopy analysis; ideally, this

would be conducted on a simple-to-operate, handheld device that would automatically identify likely pathogens in the sample and would require minimal microbiology to determine and understand results. This could help to make immediate decisions on whether antibiotics should be prescribed or not.

In this case, diagnostic techniques that are able to identify positive culture growths incrementally would also be advantageous; for example, such a test might initially identifying broad groupings, such as Gram-negative *bacilli*, or Gram-positive *cocci*, with further analysis then narrowing down to identification of the specific pathogen, such as *E coli* or *S aureus.* This may help to target specific antibiotics, and enable a switch from broad-spectrum to narrow(er)-spectrum drugs to happen more quickly.

The use of molecular assays in particular was mentioned as a new area of research that is improving the current situation[4] and can overcome some of the limitations of microscopy and delays due to growing cultures of infectious organisms. Molecular tests for specific pathogens and resistant variants are already on the market for specific applications. The current limitation is that they are generally only able to detect one or two markers, and therefore provide only a Yes or No answer to the presence of specific pathogens.

It is important to remember, however, that detecting 'something' is present so that a further test can determine what that 'something' is, may not necessarily be helpful, as the 'something' may not be of clinical importance.

Future Options

Sequencing

All living organisms have a genome that dictates the function of that organism. Humans are covered in bacteria, fungi and viruses that may or may not cause disease, and patient specimens may contain a wide variety of genomes that can be universally identified using sequencing technologies. The first human genome was sequenced in 1997, but already thousands of human genomes and millions of pathogen genomes have been sequenced using faster, cheaper and more flexible next-generation sequencing platforms. Diagnostics based on sequencing will centre on identification of sequence markers associated with clinical infection and response to interventions such as specific antibiotics. Sequencing studies are also likely to identify cheaper and faster specific molecular tests for certain clinical scenarios.

4 E M Burd, 'Validation of Laboratory–Developed Molecular Assays for Infectious Disease', *Clinical Microbiology Reviews* (Vol. 23, No. 3, July 2010) pp. 550–576. See <http://cmr.asm.org/content/23/3/550.full>, last accessed 24 April 2013.

Sequencing is one way by which diagnosis may be speeded up as well as being able to test for a wide range of pathogens and resistance markers at the same time. Developing this technology will include identifying known and novel sequence biomarkers that are associated with clinical importance and response to interventions.

The technology currently available is not yet sufficiently advanced to be available to the clinician at the bedside; the sequencing would have to be carried in a laboratory. In addition, sequencing is not yet sufficiently speedy and responsive to provide more rapid diagnosis than the currently used tests. While costs are falling, they are still too high for universal NHS use. It is likely to be another ten to twenty years before sequencing will be at a stage where a mainstream application is feasible.

Nonetheless, sequencing has the potential to speed up current diagnosis as culturing may not be necessary, or the bacteria may be able to be sequenced much earlier on during the culturing process.

Biomarkers

A biomarker, or biological marker, is a biological indicator or characteristic that can be measured or evaluated to provide information on a biological state. For example, the presence of an antibody in a blood sample may indicate infection; raised temperature may also indicate infection. During both this conference and the conference held the previous day, on Pharmaceutical Resilience,[5] there was considerable discussion about whether a challenge in modern research and technology is that we focus too heavily on refining the measurement of biomarkers we have always used to determine infection (for example, developing digital thermometers rather than mercury thermometers, or developing ways to increase the speed of culture growth) rather than researching completely different biomarkers that might be more accurate indicators of infection. Suggestions given might be changes in skin colour or sweat production that are imperceptible to human senses but which could be monitored electronically, rather than body temperature. Could research into potential alternative biomarkers provide more accurate and timely diagnosis and, if so, what might these alternative biomarkers be?

Next-generation sequencing and molecular techniques are currently in development and/or may be developed in the future to identify host factors associated with infection. These may be extremely useful in identifying the biomarkers that might turn into useful point-of-care diagnostics. It is important to acknowledge that there will be a number of different situations in which biomarkers may need to be measured, each requiring different diagnostic requirements, different samples and different outcomes, so there are likely to be a number of solutions rather than just one. Choosing

5 'Pharmaceutical Resilience', RUSI workshop report, 5 February 2013.

appropriate biomarkers might also involve developing ways to better identify which people do not need to be treated as well as those who do, or those on whom treatment might not work.

Research Topic Suggestions

1. Develop a set of biomarkers for elective surgery patients to tell which patient might have a bacterium and who might also be resistant. This may be too broad a remit for a small project, but an initial step could be to consider what methodology might be used and which biomarkers should be considered.

2. Determine whether point of care tests such as for procalcitonin (from a blood drop or urine) can determine the presence or absence of bacterial infection. A secondary question would be: could this test help in reducing unnecessary antibiotics? Ideally the test should be like a pregnancy test, which can be used in any clinic or GP practice in the UK or abroad (and even potentially at home by the patient) and should not be more expensive than the cost of the antibiotics.

3. Develop a rapid point-of-care diagnostic tool for neonatal infections. This would need to detect up to six pathogens in a very small volume of blood.

4. Develop a rapid point-of-care system to detect for suspected severe sepsis in order to narrow the specific diagnosis. The object of this would be to decrease the overall prescribing of antibiotics. Any rapid point-of-care system would need to detect sepsis across all main infectious bacterium. A useful test may only need to focus on the main infectious bacteria that respond to therapy. There are a range of platforms that could be considered.

Further Reading

S Banoo et al, 'Evaluation of diagnostic tests for infectious diseases: general principles', *Nature Reviews Microbiology* (S16-S28). See <http://www.nature.com/nrmicro/journal/v8/n12_supp/full/nrmicro1523.html>.

Group 4: Data Collection and Sharing

Chair: Ashley Truluck CBE

Rapporteur: Philippa Morrell

Key Issues and Challenges

- There are currently no defined standards for the collection of data that may be of use to AMR research and therefore no consistency to the way data is collected
- There is a poor understanding of what data is already available, who owns it and how it might be used; consequently, there is also no clear understanding of what additional data is needed
- Addressing the two points above will help to determine future data-collection requirements.

Good data and good data sets provide an evidence base that can be used to understand and analyse the current situation; predict and model future scenarios; determine the efficiency of current and suggested new practices; inform policy decisions; and help in the development of new clinical practices and guidelines. At present, however, while there is undoubtedly a wealth of data available which may be of use in tackling AMR, this is neither well-catalogued nor available in formats that can be easily interrogated, amalgamated or analysed.

There is no systematic collection of data on the criteria against which patients are given which antibiotics, and whether some patients, or demographics, respond differently to different antibiotics. The information that is collected is neither readily available nor systematically shared, even though this may help to change how prescribing decisions are made and how antibiotics are prescribed in future.

There is no clear picture of who is collecting and reporting data that might be of use to AMR researchers, nor of what further data collection may be needed. The WHO collects significant amounts of data on related topics, and holds significant data sets including feedback on former outbreaks, information from Centres of Excellence on diseases, and information from disaster relief operations, but this is neither easily usable by other researches nor easy to incorporate into other studies; some of the information is also classified. The majority of the relevant information is probably already available; the issue is where to find it and how to use it, as well as who owns it and what can legally be done with it under (real or imagined) data protection constraints.

The Importance of Standards

A further complicating issue is that there is little standardisation to the way in which data that may be relevant to AMR is collected, stored and shared. For example, while a lot of data is collected against the International Classification of Diseases (ICD)[1] diagnostic tool, which is used in WHO member states and followed by the NHS and the American Medical Association, there are no data standards related to the information.

Standards need to be in place to ensure that data is collected and recorded in a consistent way so that sharing and analysis is possible. This includes procedural and implementation standards as well as standards for quality, format and definitions. If set correctly, such standards will enable data sharing across as well as within sectors, for example between the medical and veterinary sectors.

Standards are also very important to how data is stored: one single databank holding a vast amount of data might be the 'perfect world' solution, but a federated network of data banks with consistent standards that enable sharing is probably a more realistic aim, particularly as significant amounts of data already exist.

The Strategic Aims of Data Collection

Before embarking on any large-scale data project, it will be important to set clear strategic aims, including: what is the data being collected for and does it need to be shared; in particular, any potential barriers need to be understood before data collection commences. Data protection may differ depending on whether the data is being collected by the NHS as part of a patient's personal health record; to inform academic research or government policy formation; or by a private-sector pharmaceutical company for commercial purposes.

In the context of AMR, data collection and sharing should aim to enable better understanding of the spread of drug-resistant diseases and how resistance emerges and increases. In the event of new outbreaks, quick collection, sharing and analysis of such data could provide a single operating picture that would help to quickly identify outbreak hotspots, aid accurate diagnoses and could help understanding of the cause or emergence of resistance. In a more academic context, interrogating and analysing existing data can help us to understand what has happened in the past so that we can learn from experience and plan differently for the future. Data can help to ensure that mistakes are not repeated and that best practice is identified and proved.

Existing Data

An audit of what data is already available, what is in the process of being collected, and where it is held would benefit researchers hugely; this will help

1 See <www.who.int/classifications/icd/en/>, last accessed 17 May 2013.

researchers to decide what can be done with it, and also what information is currently missing.

A better understanding of the research that has already been carried out and the data already available will help to devise the optimum strategy for the use of antibiotics. Optimum strategy should be based on a combination of factors including clinical outcome and financial considerations; the latter is important as a business case that helps to show how money can be saved may help to fund future research.

Such an approach could, for example, help to measure the impact of current strategies, behaviours and programmes. Better diagnostics is very important, as narrowed use of antibiotics will help to reduce resistance, but few statistics are collected on how accurate a diagnosis was; whether a patient really needed the antibiotics that were prescribed to them; and what was the cause of the symptoms if a bacterial infection was not present. In addition, the doctor doing the prescribing may not always know the full diagnosis; more detailed recording of the patient's case history to that point may help to rule out bacterial infection, or to suggest other, more likely causes of the symptoms the patient is displaying.

Summary

There needs to be a strategic audit of all the data available and where it is held, including what was the purpose of collecting the data, followed by the introduction of standards for collecting and sharing data within a national (if not international) framework. This is likely to require a champion at both the national and NHS Trust level. It will enable decisions to be made on what information still needs to be collected and how currently existing data can be shared. Sharing of data should be possible from both the 'bottom up' and the 'top down'; clinicians need to be able to share data quickly on local outbreaks and resistance, and the WHO needs to facilitate better holding and sharing of strategic data. Such data sharing, however, will require the development of a comprehensive standard for data collection and data reporting. This could be a role for NHS Trusts, but it needs to be carefully planned, and data-protection issues need to be taken into account.

Research Topic Suggestions and Further Actions Needed

1. Fund an audit of existing data sets and databases that might be of value to research into antimicrobial resistance, including what data exists, who owns it, how it has been recorded and how, or if, it can be shared.

2. Develop standards for the collection of future data so that it can be more easily shared, aggregated and analysed.

Group 5: Barriers to Implementing AMR Strategy

Chair: Dr Jo Wallace

Rapporteur: Benjamin Toomer

Key issues and Challenges

- AMR needs cross-departmental government support
- Some AMR strategies conflict with other health sector policies such as the Quality and Outcomes Framework. These need to be de-conflicted
- Government support is needed to extend GP and hospital appointments to allow time for more accurate diagnosis and increased patient counselling. Short-term cost implications will be offset by long-term benefits
- Tacking AMR needs to be seen as a public good, for which international and UK government intervention (and if necessary, funding), is essential
- Better information and widespread education would dispel the impression that antibiotics are cheap, readily available and harmless, and thus help to encourage support for better stewardship.

Political engagement and support for tacking AMR will become increasingly necessary as the risk from resilient strains of disease-causing pathogens grows larger; AMR being placed upon the National Risk Register, which is likely to happen following its current consideration in the National Security Risk Assessment, is welcomed and will help to stress the seriousness of the situation.

Tackling AMR still requires substantial cross-government support; in particular, the Department of Health, the Department for Environment, Food and Rural Affairs (Defra), Business, Industry and Skills (BIS) and the Treasury all need to work together. While the Department of Health arguably owns the risk and should take the lead in tackling it, addressing the issue from a number of perspectives will help to highlight the importance of AMR to all sectors of business and society. Cross-governmental collaboration is essential for developing situational awareness and sharing information, as well as for enabling the real-time monitoring of patient health and movements to mitigate risk and to support public awareness campaigns to get the message out widely.

NHS Engagement

Across the NHS, the current level of engagement with AMR issues is considered to be low, while certain health policies create barriers to tacking AMR. For

example, NHS league tables and the Quality and Outcomes Framework (QOF) indicators put pressure on GPs to cure patients as quickly as possible, but this may be without consideration for the longer-term implications. If policy-makers better understood the long-term risk AMR poses, they may remove current time pressures and give GPs more discretion in the prescription of antibiotics.

Government reforms are essential if the number of broad-spectrum antibiotics given to patients is to be reduced: giving GPs and hospital staff extra time to diagnose illness and therefore giving them more chance of prescribing the correct antibiotics, or of diagnosing a viral rather than bacterial infection, would be better for the patient and for the wider population even though it might cost more in the short-term. Government funding is needed to improve patient counselling and to extend appointments so that fewer antibiotics are distributed. At present there are insufficient incentives for tackling AMR and little questioning of, or penalties for, poor prescribing practice.

European Engagement

At the international level, political support for AMR programmes is relatively strong. The EU's European Antibiotic Awareness Day, held annually on 18 November[1] since 2008, provides a good platform on which to engage the issue in the wider political context. The Transatlantic Task Force on Antimicrobial Resistance (TATFAR),[2] a joint venture between the European Centre for Disease Prevention and Control (ECDC) and the US Centers for Disease Control (CDC), has helped to drive understanding and policy forward. European Antibiotic Awareness Day is the perfect platform on which to push messages on AMR but it needs to be better utilised in the UK with a number of government departments, GPs, hospitals and pharmacies all reinforcing the same message. Other international approaches, such as the Innovative Medicines Initiative,[3] are also helping to drive action forward, although AMR is too important an issue to be left dependent on the private sector. International and UK governments must be encouraged to see investment in tackling AMR as a 'public good'.

Should the UK choose to leave the EU in future (or the EU disintegrate entirely), separation may lead to reduced cohesion in the approaches to tackling AMR, and could mean fewer collaboratively funded research programmes. Any loss of free trade between member states might also potentially harm interest from multi-national pharmaceutical businesses: given the dependence upon the private sector for expertise and manufacturing capability, leaving the EU

1 See < http://ecdc.europa.eu/en/EAAD/Pages/Home.aspx/>, last accessed 17 May 2013.

2 See < http://www.ecdc.europa.eu/en/activities/diseaseprogrammes/tatfar/Pages/index.aspx?MasterPage=1>, last accessed 17 May 2013.

3 See < http://www.imi.europa.eu/>, last accessed 17 May 2013.

could have a destabilising effect on the development pipeline. On the other hand, restricted immigration may help to isolate the UK population from resistant strains that emerge overseas and slow the mutation of bacterial infection.

The Cost of Antibiotics

Financial considerations may prove key to tacking AMR. Members of the general public take it for granted that antibiotics are cheap and readily accessible even though they have no specific knowledge of the price, or of the price comparison with other treatments, such as those for cancer, which are perceived as being highly expensive. While antibiotics are relatively inexpensive compared to other treatments, they are a cornerstone of modern medical practice and inappropriate use threatens to undermine this. Better information and widespread education is needed to dispel the impression that antibiotics are 'cheap and easy'; this should be addressed in a public awareness campaign and would help to counter any impression that reducing the use of antibiotics is a government cost-cutting measure driven by austerity.

Such messages may have more impact on the public if they come from medical practitioners rather than from politicians or senior government officials. In particular, if the reasons for not prescribing drugs were explained by GPs at the point of care, patients would understand the benefits to the medical industry and public health. By focusing entirely on the scientific evidence for growing resistance to conventional drugs, it should be possible to avoid any accusations of financial cost saving.

The Influence of the Media

The coverage of any stories relating to AMR in the media will have a huge influence on public attitudes to new government policies and, in turn, to those government policies and approaches. Media coverage tends to focus on negative stories – such as increased prevalence of 'superbugs' and wasteful NHS expenditure – whereas more positive stories of medical breakthroughs and successes in the curtailment of AMR receive less coverage. In particular, there is a danger that the media might latch onto the spread of resistant strains through migration and turn AMR into an anti-immigration issue with a political dimension, or accuse efforts to reduce the number of antibiotics prescribed of being cost-cutting measures that put patient health at risk.

Journalists are often pressed for time and have to cover a wide range of subject matter; they are not AMR specialists and so may not be able to fully grasp the subtleties of the subject quickly. Explaining the key points as succinctly as possible is key to ensuring information is not misinterpreted, as is finding an interesting perspective on AMR that is likely to engage the media, and therefore will help the media to engage the audience. There are

strong advantages to focusing on the development and supply of information in a media-friendly and easily understood format: newspapers do tend to respond well to statistics and data. Providing evidence of the long-term cost savings of AMR efforts while showing that this has no detrimental effect on patient outcome, or encouraging newspapers to run stories showing how one demographic (or region) is reducing local use of antibiotics more successfully than another, to encourage others to try harder, could be useful approaches. Regional league tables of some kind might help with such an approach.

The role of the media is further explored in Discussion Group 2.

Public Motivation

Public pressure has a huge role to play: a key challenge is how to educate the public and engage them in the debate so that they will lobby their MPs to take action. Educating the public about AMR will also encourage them to question why GPs and other medical professionals *are* prescribing antibiotics as opposed to why they are not.

Encouraging patients to take more responsibility for their own care and long-term health is an important part of any AMR message. Handing out leaflets at the point of care would be a good way to educate people on the reasons why their doctor might have chosen not to give them medicines they expected to receive.

Inviting experts in the field of AMR to appear on current affairs programmes such as *Today* and *Newsnight* would also serve to increase awareness of the issue. The format of these shows allows important issues to be explored in more depth, helping to both press and reinforce the message. As such shows have a regular audience, it would also help the message to reach people who are not actively seeking information on AMR but who might, nonetheless, take action.

Existing recognisable and reputable celebrities are ideal candidates to champion AMR strategies and to encourage the public to take on the cause for themselves. Celebrities such as Stephen Fry can be hugely influential and the recent association of Bill Bailey with Prostate Cancer UK shows how celebrities can help to highlight medical and health causes. Similarly, exploiting the already large audience of ongoing TV soaps such as *Eastenders* and *Coronation Street* by inserting a storyline around the theme of AMR would also be good exposure.

Emulating the success of the ‘Catch it, Bin it, Kill it’ campaign used during the swine flu pandemic was described as being a good target for AMR awareness. Strategies for engaging the public in getting the message out are further discussed in Group 2.

Suggested Research Topics

1. Develop strategies that focus on the scientific evidence for growing resistance to conventional drugs and which highlight the long-term harm this will cause. This will make it clear that any drive to reduce the use of antibiotics is not just a cost-saving measure.

2. Develop and supply data and statistics on AMR in a media-friendly and easily understood format, so that this can be used to raise awareness and highlight success and cannot be misinterpreted.

3. Fund short studies into comparing the long-term benefits with the short-term cost increase of extending GP and hospital appointments to improve diagnosis and increase patient counselling so that fewer antibiotics are distributed.

Conclusions and Summary

Research Themes Identified

Chapter I: Professor Dame Sally Davies
A multi-pronged holistic approach is needed: there is urgent need for action at a global level to facilitate antibiotic development.

Surveillance activities and practices need to change to ensure that information on travel and hospitalisation abroad is captured on admission to the UK or to the NHS. Screening, isolation and enhanced infection control measures need to be introduced, as appropriate, to reduce transmission.

Chapter II: Dr Charles R Penn
Research is needed that takes an overview of the numerous infection-tracking systems in place across the world to provide a better global picture, in terms of the microbiological impact, the health impact and the economic impact of AMR, and the interaction between them.

Chapter III: Professor Alan Johnson
Research is needed into why certain strains of bacteria are better at spreading than others. If the underlying mechanisms were better understood, it might be easier to develop possible interventions at local, national and international levels, and to determine which interventions are likely to be most effective.

A second important area for research is whether plasmid spread can be prevented. With the genes encoding resistance spreading between different types of bacteria, a whole new magnitude of difficulty is being faced.

Thirdly, since a lot of gene transfer is believed to take place in the gut, researchers could look at antibiotic resistance in gut bacteria and how this affects resistance in general.

Chapter IV: Dr Hayley Wickens
Gaps are present in the evidence base. An example of this is that when a doctor asks for evidence that a patient can successfully switch from IV to oral antibiotics after forty-eight hours with no adverse effects, the evidence is often not there. Research is needed to plug such gaps.

More information is needed on whether infections are bacterial or not. Rapid diagnostics can contribute to this, but so too can looking at what combination of signs, symptoms and objective data can be used to determine the likelihood or certainty of (clinically relevant) bacterial infection.

Good epidemiological data is needed on community pathogens; what is submitted through hospital laboratories misses what is causing the majority

of UTIs, for example, as specimens are not sent for routine, run-of-the-mill cases.

There is a lack of evidence on de-escalation of antibiotics, especially de-escalation from IV to oral drugs. Patients need to be more aggressively switched while they are still recovering, so that evidence can be built up on what works, and what if any risks are associated with it. At the moment, good data on this is not available.

The evidence that prolonged courses are associated with more positive effects is not well established. There are no studies that show that ten days of augmentin for a community-acquired pneumonia will give worse outcomes than five, for example. This type of data is needed, along with more information on clinical outcomes on optimal course lengths and early discontinuation.

Chapter V: Dr Jim Gray
Improved testing at point of care and the development of new diagnostic strategies that are not dependent on overnight incubation for results offer real potential to better target antibiotic therapy towards only those patients who need it. Investigation into antibiotic treatment decision-making based on emerging miniaturised molecular diagnostic tests would also be advantageous.

Clearer clinical guidance is needed, backed up with evidence, on when it is safe to withhold antibiotics.

In August 2012, NICE Guideline 149 was published. In developing the guidance, the Guideline Development Group was regularly constrained by the limited amount of good-quality published evidence on all aspects of antibiotic treatment of neonatal infections. Greater involvement of microbiology services in providing accurate data on the causes of true infection may therefore be helpful in promoting good antibiotic stewardship in neonates.

For neonates who remain on antibiotic therapy for confirmed or suspected systemic sepsis, the Guideline Development Group found an absence of clinical trial data on which to base recommendations on duration of treatment; more research is needed.

Chapter VI: Dr Andreas Schätzlein
Understanding how heterogeneous populations fit into their ‘biotope’ and co-develop may become increasingly important as a way to develop new ways for treating diseases which can constantly evolve in response to a changing environment.

It may be important not only to think about the patients, but also about their wider environment as a biotope – as an ecosystem that needs to be considered in terms of how it works together, in order to understand how pathological infections can be limited.

Chapter VII: Professor Mike Sharland
Current knowledge of even the basic epidemiology of multi-resistant bacteria is limited.

Gaps include the duration of carriage of resistant organisms within the human intestine; the relation between carriage and invasive disease; whether specific high-risk groups or individuals exist; and whether and how these might be targeted for screening to minimise the potential for transmission.

Research is also needed to determine how, if screening is to be undertaken as part of an infection prevention and control process, it can be undertaken optimally. How effective is isolation and is decolonisation a feasible option? What is the cost effectiveness of the numerous potential interventions?

Chapter VIII: Group Captain A D Green
As AMR increases, the treatment of casualties on the battlefield will become more complex, both for trauma and infectious diseases as AMR increases; how this can be managed needs to be researched.

More research is needed into how military patients return multi-resistant organisms from overseas to their homeland.

The increased use of multinational forces to provide humanitarian aid and disaster relief means that they in turn might export novel bacteria to receptive environments and ways to ensure this does not happen need to be better understood.

Chapter IX: Chris Watkins and Jennifer Cole
Research needs to be done on preparedness planning using digital communications technologies for real-time epidemiology, automatic contact tracing and providing personalised estimates of infection risk, as well as for promoting efficient public discussion and for enabling local co-ordination of volunteers.

Research is also needed to smooth the technical, ethical, practical and legal problems that will inevitably arise from collecting, storing and sharing large amounts of patient or population data.

Discussion Group 1: Changing Behaviour in Antibiotic Prescribing
In light of the new NICE Guideline 149 on Neonatal Infection, which is intended to reduce the unnecessary administration of antibiotics to neonates, short monitoring pilot projects in one or more hospital are required over the next 12 months to record information on the cases where previously antibiotics might have been administered but withholding them is now recommended, to record whether there was any adverse outcome associated with withholding them, what (if any) this was, and what was the actual cause of the Clinical Indicator or Risk Factor listed in the NICE Guideline.

Short studies that gather and analyse statistics relating to the likelihood of outcomes, and severity of outcomes, would help to build confidence in new behaviours; in particular, it would help to know the percentage of patients displaying particular clinical indicators in whom infection was confirmed, and if there is likely to be any adverse outcome to the patient associated with delaying antibiotic treatment until infection is more certain or confirmed.

A study is needed to determine the link between neonates born following maternal hyperthermia in labour (where the hyperthermia might be consequence of vasodilation secondary to epidural analgesics rather than infection) and the administration of antibiotics on suspicion of infection.

A systematic review of past public health campaigns needs to be conducted to suggest what messages, and which delivery methods, may best inform an AMR awareness campaign and campaigns to reduce the use of antibiotics.

Discussion Group 2: Communicating the AMR Message
No specific research themes were suggested by this discussion group

Discussion Group 3: Improving Diagnostic Techniques
A set of biomarkers for elective surgery patients needs to be developed, to tell which patient might have a bacterium and who might also be resistant. This may be too broad a remit for a small project, but an initial step could be to consider what methodology might be used and which biomarkers should be considered.

Determine whether point of care tests such as for procalcitonin (from a blood drop or urine) can determine the presence or absence of bacterial infection. A secondary question would be whether this test could help in reducing unnecessary antibiotics. Ideally, the test should be like a pregnancy test, which can be used in any clinic or GP practice in the UK or abroad (and even potentially at home by the patient) and should not be more expensive than the cost of the antibiotics.

Develop a rapid point-of-care diagnostic tool for neonatal infections. This would need to detect up to six pathogens in a very small volume of blood.

Develop a rapid point of care system to detect for suspected severe sepsis in order to narrow the specific diagnosis. The object of this would be to decrease the overall prescribing of antibiotics. Any rapid point of care system would need to detect sepsis across all main infectious bacterium.

Discussion Group 4: Data Collection and Sharing

An audit is needed of existing data sets and databases that might be of value to research into antimicrobial resistance, including what data sets exist, who owns them, how they have been recorded and how, or if, they can be shared.

Standards need to be developed for the collection of future data to enable the data available to be more easily shared.

Discussion Group 5: Barriers to Implementing AMR Strategy

Strategies need to be researched that focus on the scientific evidence for growing resistance to conventional drugs and which highlight the long-term harm this will cause, so it is clear that any drive to reduce the use of antibiotics is not just a cost-saving measure.

Data and statistics on AMR need to be developed and disseminated in a media-friendly and easily understood format, so that they can be used to raise awareness and highlight success and cannot be misinterpreted.

Funding is needed for short studies that can compare the long-term benefits of extending GP and hospital appointments to improve diagnosis and increase patient counselling so that fewer antibiotics are distributed, with the short-term cost implications.