RESOLVING THE CRISIS OF ANTIBIOTIC RESISTANCE

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At the June meeting of the Parliamentary and Scientific Committee, co-organised with the British Society for Antimicrobial Chemotherapy initiative (BSAC) Antibiotic Action, there was standing room only with some unable to gain access to the room. The magnitude of the response mirrored the concern of Parliamentarians and Stakeholders about antibiotic resistance and implications for the health of UK citizens.

The introduction of antibiotics in the 1940s led to a revolution in health care, saving millions of lives around the world and facilitated modern day care of cancer patients, organ transplants and commonplace orthopaedic surgery such as knee and hip replacements. However, over the last decade there have been increasing numbers of infections in people by multidrug resistant Gram negative bacteria including *Escherichia coli* and *Klebsiella pneumoniae*. In parallel, there has been a reduction in the number of pharmaceutical companies producing new antibiotics, and the new drugs that have reached the patient have been predominantly those active against Gram positive bacteria such as MRSA. Together antibiotic resistance and lack of new antibiotics presents as serious a crisis to human health globally as the AIDs pandemic did in the 1980s and 1990s.

Antibiotic resistance knows no demographic or geographical boundaries and affects everyone, so raising awareness of the crisis of antibiotic resistance and lack of new antibiotics is extremely important. Dame Sally Davies,

the UK Chief Medical Officer, has done much since March 2013 and in her presentation on June 11th she outlined the size of the problem and the societal and financial costs to UK citizens and 'UK plc'. Indeed, antibiotic resistance is of such concern that she has called for the protection and preservation of the few antibiotics effective against bacteria by encouraging appropriate use of these valuable drugs. She also recommended the stimulation of development of new antibacterial treatments and further research to understand and track resistance.

. . . Antibiotic resistance knows no demographic or geographical boundaries . . .

Dr Nicholas Brown, President of BSAC, spoke about the effect that antibiotic resistance has upon the ability of doctors to treat bacterial infections effectively and showed how important antibiotics are to many specialist areas of medicine. He stated that having to use treatments comprising second or third choice antibacterial drugs is much less effective than is the first choice antibiotic for antibiotic-susceptible infections. He also discussed the issues of having to prescribe an antibiotic without knowing the bacterial species causing the infection and the impact of making the wrong choice thereby showing why following the Department of Health's 'Start Smart, then Focus' campaign for antibiotic prescribing is so important.

However, preserving antibiotics is only one part of the

solution to antibiotic resistance and as many multidrug resistant infections are by Gram negative bacteria, for which there are few useful drugs, action is required to stimulate the development of new treatments for such infections. Dr Richard Bax, who has a wealth of experience in antibacterial drug development in the pharmaceutical industry shared with the audience some of the reasons why 'big Pharma' have largely withdrawn from this product area. These include the high costs of development and uncertainties over regulatory success and obtaining a product licence. The regulatory requirements have been considered complicated, onerous and expensive and, moreover, difficult to achieve for antibacterial drugs. Current discussions at the European Medicines Agency and the USA Food and Drugs Administration about changes in the clinical trial paradigm will hopefully lead to new and clear guidelines so that the requisite studies to obtain a licence are feasible and not subject to change during the process.

Disussion was lively and covered several topics. It was clear to all that the problems are complex and the solutions are myriad so to do this at a global level requires partnerships between governments and various departments from health, to business, to overseas aid. While incentives to encourage the pharmaceutical industry to

invest in this area are important, without new entities entering the pipeline there will be nothing for Pharma to develop. In January, the World Economic Forum Global Risks Report 2013 indicated the magnitude of that global burden and placed antibiotic resistance on the global risks register. This information was based upon a handful of studies and is considered by all to represent an underestimate of the true burden. There needs to be action by all governments to increase funding for research into antibiotic resistance so that we can fully understand how it occurs, how it is spread and the magnitude of the true cost to Society. This information is essential if antibacterial discovery,

research and development is to find and produce new treatments. Academia and SMEs have much to offer in increasing understanding of antibiotic resistance and discovering new molecules and ways to combat bacterial infection. A dedicated funding mechanism for research will not only further the scientific base for understanding the biology of antibiotic resistance and facilitate drug development, but will also stimulate economic development.

As antibiotics are used widely in many settings, discouraging their use other than to treat infection is essential. This includes use where there is no bacterial infection and purchase of antibiotics by the general

public, which is widespread in some countries. In addition, new ways to prevent and treat bacterial infections would be welcomed. It should be noted, however, that licensing of any new therapeutic, including phages are subject to the same regulatory processes as antibacterial drugs.

In the UK antibiotic resistance and lack of new treatments is recognised such that the UK has taken a global leadership role. Futhermore, support for addressing the issue crosses all political parties; following the P&SC meeting, on June 12th

. . . There needs to be action by all governments . . .

there was the inaugural meeting of the All Party Parliamentary Group on Antibiotics, chaired by the Shadow Health Minister, Jamie Reed, MP. Kevin Barron MP is Deputy Chair, Zac Goldsmith MP is Treasurer and Baroness Masham is secretary. This APPG will provide cross-party parliamentarians a forum in which they can hear evidence, contribute to debate and identify solutions that the UK can offer to the Grand Challenge of antibiotic resistance and will further support delivery of the 2013 UK five year Antimicrobial Resistance Strategy 2013-2018.

ANTIBIOTICS
Meeting of the Parliamentary and Scientific Committee on Tuesday 11th June

THE SCIENTIFIC CHALLENGE POSED BY ANTIMICROBIAL RESISTANCE

Professor Dame Sally C Davies
Chief Medical Officer

Dr Simon J Howard
Public Health Specialty Registrar

For over 150 years, Chief Medical Officers of the United Kingdom have produced annual reports on the state of the public's health. When I came to produce my annual reports, I

chose to break with the precedent set by my recent predecessors and return to the historic format of an annual report in two parts, which I split into separate volumes. The first

volume serves a surveillance function, collating and presenting data on the public's health. The second volume provides a detailed examination of a major issue pertaining to public health. The topic examined in detail in my first annual report is infection, including the rise of antimicrobial resistance.

In a break from the approach of my predecessors, I brought together a collaboration of some of the foremost UK experts to advise on the topics which should be covered, and to write the individual chapters. These chapters informed my summary, and the recommendations I
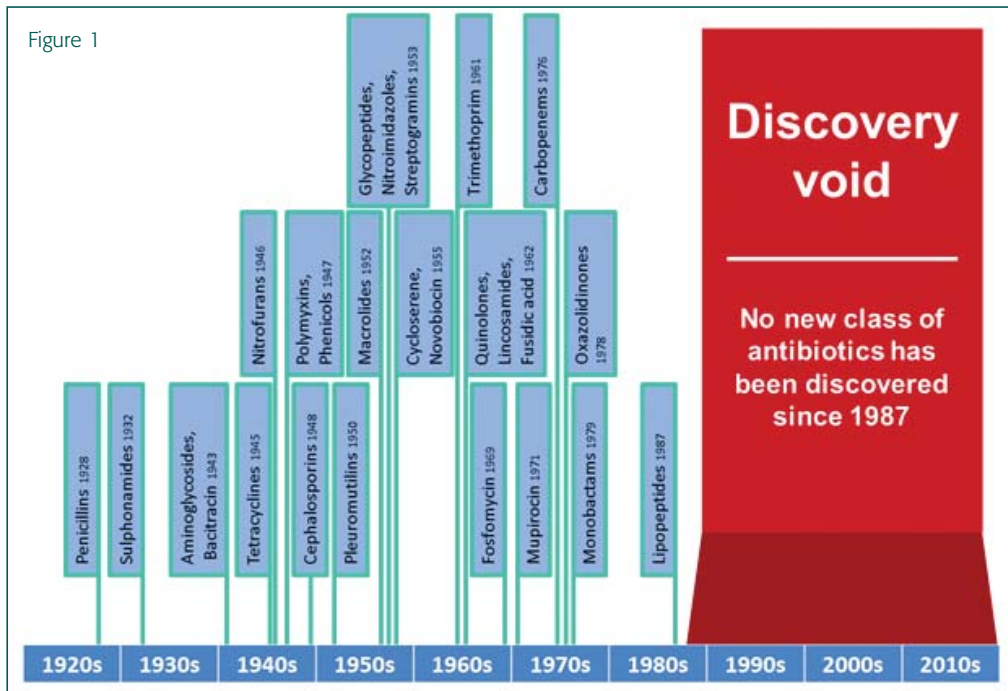
made as Chief Medical Officer for England. The result is an authoritative summary of the current situation, which also reflects on the past and scans the future horizon. It includes explicit, actionable recommendations for named organisations, and outlines the scientific challenge posed by infections and antimicrobial resistance.

SCALE OF SOCIETY'S RELIANCE ON ANTIBIOTICS

The size of the threat posed by antimicrobial resistance is underlined by the scale of

Figure 1

society's reliance on antimicrobials. Prior to Alexander Fleming's discovery of penicillin in 1928, infectious diseases were the leading cause of death in the UK, accounting for 43% of all mortality. In less than a century, this has reduced to just 7%. Antibiotic prophylaxis has allowed development of surgical techniques such as hip replacements, which were unimaginable in the early 20th century, but are routine today. Cancer chemotherapy and radiotherapy are also heavily reliant on antibiotic therapy, as is organ transplantation.

GPs in England prescribe 35 million courses of antibiotics a year, though it is notable that there is substantial variation in antibiotic prescribing practice between surgeries, without concomitant variation in patient outcomes.

Yet as antimicrobials have become less effective, the burden of infectious diseases on society has begun to rise once again. The European Centre for Disease Prevention and Control estimates that antimicrobial resistance results each year in 25,000 deaths across Europe

each year, which is a similar number to those killed in road accidents.

HISTORY OF ANTIMICROBIAL RESISTANCE

Antimicrobial resistance is not a new problem. Alexander Fleming himself acknowledged the threat of resistance during his acceptance speech for the 1945 Nobel Prize in Physiology or Medicine, which he was awarded for discovering

penicillin: "It is not difficult to make microbes resistant to penicillin in the laboratory ... and the same thing has occasionally happened in the body".

Historically, antimicrobial resistance caused little change in patient outcomes, since doctors were able to respond to bacteria becoming resistant to a particular antibiotic by switching to an antibiotic of a different class with a different mechanism of action. For six decades after Fleming's discovery of penicillin,

a steady stream of new classes of antibiotics were discovered (Figure 1). Yet in the late 1980s, the stream ran dry, and no new class of antibiotics has been discovered for over a quarter of a century.

Despite this weakening of the antimicrobial arsenal, society continues to use antibiotics in ways which increase the likelihood of the development of resistant bacteria. Antibiotics are used in agriculture, fish farming, and food production, as well as myriad other areas of life, as shown in Figure 2. Indiscriminate use of antibiotics aid the development of resistant bacteria. Indeed, in Japan and Antarctica, resistant bacteria have now been found in water samples.

CLINICAL IMPACT OF ANTIMICROBIAL RESISTANCE

Antimicrobial resistance is becoming a concern across most branches of clinical practice, but I have chosen to focus on three areas of particular concern in this address: tuberculosis (TB), gonococcal infections, and septicaemia.

Figure 2
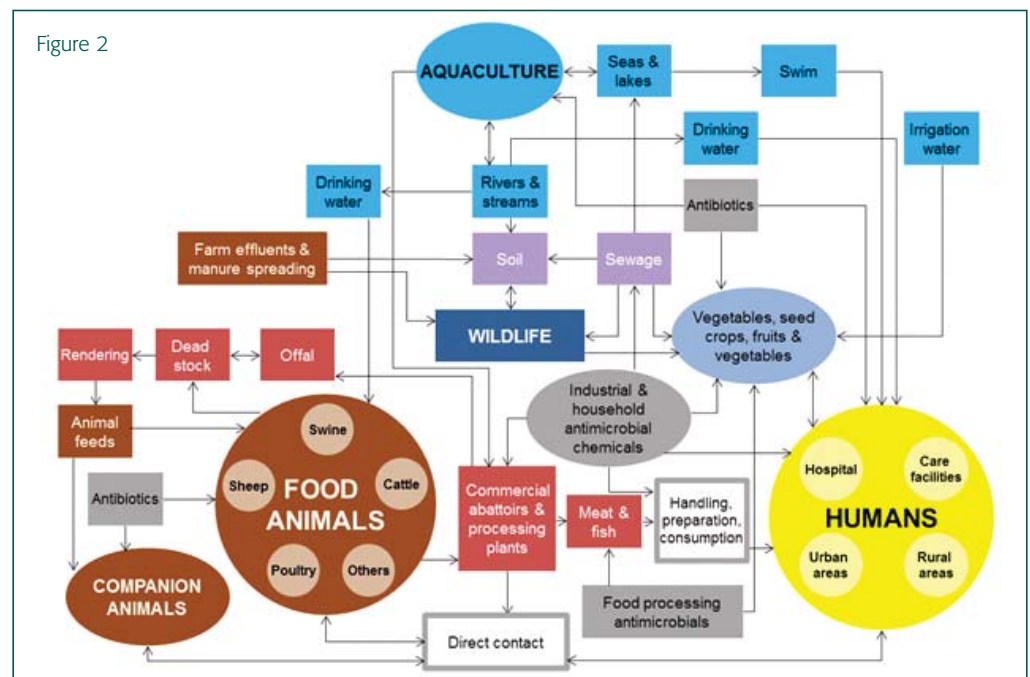
Antimicrobial resistance in TB cases is increasingly common. Multidrug-resistant TB (MDR-TB) refers to infections which are resistant to (at least) isoniazid and rifampicin, two of the first-line antibiotics used in TB treatment. In 2011, there were almost 35,000 cases of

. . . infectious diseases .. cost the economy £30bn per year . . .

multidrug resistant TB in Europe, representing a six-fold increase over the number of cases reported six years earlier. 81 of these cases were in the UK.

Extensively drug resistant TB (XDR-TB) infections are also resistant to at least two of the second-line antibiotics used in TB treatment (fluoroquinolone, plus either amikacin, capreomycin, and kanamycin). In 2011, there were six reported XDR-TB cases in the UK.

With increasing resistance, the threat of untreatable TB is becoming a reality. While an international definition of totally drug resistant TB (TDR-TB) has yet to be agreed, there are strains of TB collected from South Africa which were, in lab-based testing, resistant to all standard TB antibiotics.

Gonorrhoea is the second commonest bacterial sexually transmitted infection in the UK. 21,000 cases were diagnosed in 2011, representing a 25% increase on 2010. Yet antimicrobial resistance is making it, too, increasingly difficult to treat. Within the last fifty years, gonorrhea has developed resistance to four different antibiotics. Without a

concerted effort on antimicrobial resistance, untreatable cases of gonorrhoea may be seen by 2015.

Similarly, septicaemia is a major cause for concern. More than a third of bloodstream infections in England, Wales and Northern Ireland are now caused by *E. Coli*, and the proportion of *E. Coli* septicaemias which are multidrug resistant has grown to 15%. European data suggest that multidrug-resistant *E. Coli* septicaemias have a mortality rate of 30%, compared with 15% for drug-susceptible cases.

. . . improve antimicrobial prescribing practice . . .

Extrapolating these figures implies that up to 5,000 patients die in the UK each year of a gram-negative sepsis, half with a multidrug-resistant organism. This greatly exceeds the mortality due to MRSA or *C diff*.

ECONOMIC COST OF ANTIMICROBIAL RESISTANCE

In the UK, infectious diseases are estimated to cost the economy £30bn per year. As antimicrobial resistance increases, infectious diseases will have a greater impact on productivity, and this cost will increase substantially. One estimate from the London School of Hygiene and Tropical Medicine estimates that the wider societal costs of

antimicrobial resistance in the UK are already around £10bn per year.

In Europe, the World Economic Forum estimates that antimicrobial resistance already costs €1.5bn, and causes 600 million lost days of productivity. In the USA, the direct healthcare costs alone caused by antimicrobial resistance are estimated at $21-34bn.

ACTION REQUIRED TO TACKLE ANTIMICROBIAL RESISTANCE

There are four facets to the action required to tackle antimicrobial resistance.

The currently available antimicrobials must be conserved. They must not be

squandered through inappropriate overprescription in humans, nor must they be abused through inappropriate overuse in veterinary medicine, farming or wider industry.

The development of new antimicrobials must be made

. . . concerted effort from governments . . .

economically viable. Currently, the rapid development of resistance and short courses of antibiotics used by patients mean that pharmaceutical companies may not see a return on investment in antimicrobial research. The market has failed to deliver.

Surveillance of antimicrobial resistance must be improved at an international level. Infectious diseases do not respect international borders. Improving surveillance is crucial to improving preparedness.

Finally, the scientific challenge of antimicrobial resistance must be met. More basic research can improve understanding of the mechanisms of action of antimicrobials, and also of the mechanisms by which resistance develops. Further research into the human health impact of non-human use of antimicrobials is required. Additional clinical research could improve antimicrobial prescribing practice, and aid in the conservation of the current antimicrobial arsenal. Research into rapid diagnostic testing, including DNA techniques, could result in appropriate antibiotics being prescribed sooner, and avoidance of inappropriate prescription.

PREVIOUS SUCCESSES

The challenge of antimicrobial resistance is not insurmountable. The examples of healthcare associated infections show that action delivers results. Cases of MRSA in hospitals in England have declined by 87.3% from their peak in 2003, and *C diff* infections have fallen by over 60% from their peak in 2007.

However, antimicrobial resistance requires comprehensive action, combining politics, economics and research. It requires a concerted effort from governments around the world, doctors, vets, scientists, and ordinary citizens.

. . . new antimicrobials must be made economically viable . . .

ANTIBIOTICS AND THE CLINICAL IMPACT OF RESISTANCE

Dr Nick Brown
President, British Society for
Antimicrobial Chemotherapy (BSAC)

Resistance to antibiotics is a significant issue and a major threat to the world population. Of course, antibiotics are used to treat bacterial infections, but they also underpin much of modern healthcare. They are used to treat traditional infectious diseases, mainly at the extremes of age, and have transformed the impact of these conditions, many of which would previously have been fatal. However, it is not always appreciated that in specialist fields of healthcare, such as organ transplantation, cancer treatments, or joint replacement surgery, infection is one of the most significant complications arising from the treatment. Without antibiotics, these interventions would not be possible. In addition, in some chronic diseases, such as cystic fibrosis, antibiotics have significantly prolonged the life of sufferers.

The emergence and spread of antibiotic resistance in bacteria has been well documented recently. However, it is not new. Even in 1959, data from Seattle, USA were showing extraordinarily high rates of resistance to the antibiotics that were available[1]. In *Staphylococcus aureus*, 40% of isolates were resistant to four or more antibiotics. This was only a decade after antimicrobial drugs first became widely available for clinical use and the medical literature at the time was expressing a general disillusionment with antibiotics and their utility. The difference between then and now, though, is that this was a very productive time for the development of new antibiotics. An agent with high levels of resistance could be replaced by another as new agents came onto the market. There were 14 different classes of antibiotic developed in the

. . . resistant to four or more antibiotics . . .

period 1935-1968, but only 5 have been developed in the 45 years since.

The bacteria causing concern because of antibiotic resistance are different in the community and in acute healthcare settings, although increasingly there is overlap between these. Gonorrhoea and tuberculosis are mainly community infections, whereas many of the organisms that are causing particular concern in hospitals are the Gram-negative bacteria, such as *Escherichia coli, Klebsiella pneumoniae, Acinetobacter baumannii* and *Pseudomonas aeruginosa*. Gram-positive organisms, including methicillin-

resistant *S. aureus* (MRSA) caused well publicised problems in both hospitals and the community at the turn of the century. Worldwide, MRSA is still a major concern, but currently it is having less of a clinical impact in the UK. This may reflect the success of the initiatives to control MRSA in this country.

In clinical practice in hospital, antibiotic resistance is important, because it has a direct impact on the outcome of treatment. In a large study in several critical care units in the US, the death rate was proportional to the prevalence of infection[2]. The more infections there were, the more patients died. In addition, if infections could not be treated effectively, mortality was significantly higher than if appropriate antibiotic treatment was given. In a study of over 2,000 patients on a critical care unit, the mortality in patients with infections was 52% if an inappropriate antibiotic was given, whereas it was 12% if patients were given an appropriate antibiotic[3]. The most common reason why the therapy was inappropriate in this study was because the organism was resistant to that antibiotic.

Antibiotic resistance also has important consequences for increased morbidity as well as mortality. Often second line antibiotics are not as effective as first line treatment and therefore the response to treatment is not as good. An example would be the poorer response seen with use of the second line antibiotic vancomycin for the treatment of severe *S. aureus* infection when first line treatment with flucloxacillin, or an appropriate alternative beta-lactam antibiotic, is not possible. Poor response has an impact on the length of hospital stay, use of healthcare resources and overall cost. Using more antibiotic treatment also increases the pressure for the selection of even more antibiotic resistance.

The evidence to correlate these outcome measures and antibiotic resistance has been reviewed recently in a meta-analysis of the published data. This confirmed that the clinical outcome of the treatment of infection due to antibiotic-resistant organisms is worse in critically ill patients, for blood stream infections and, in particular, infections due to Gram-negative organisms with multiple resistance[4].

Why is this such a problem? One of the main reasons is that most antibiotic prescribing is empirical. That is, at the time the prescription is written, the exact cause of the infection is not known. Usually the diagnosis of infection is made on the basis of a clinical assessment and antibiotics are given on a best guess basis. This may be because the currently available diagnostic tests do not give a quick answer, or sometimes, especially in the very young or very elderly, because the clinical

signs of infection might not be obvious.

The consequences are that the wrong antibiotic may be given, or the wrong organism targeted. The Centers for Disease Control and Prevention (CDC) in the US have summarised this (Figure). Antibiotic resistance increases the likelihood of inappropriate initial empirical antibiotic therapy, which results in treatment failure, which leads to more antibiotic usage, which promotes the further emergence of

. . . MRSA is still a major concern . . .

resistance, which leads to more inappropriate therapy.

In practice, this has had some very obvious implications. Over a short period of time, the choice of empirical antibiotic therapy has evolved from one antibiotic to the next to try to keep one step ahead of increasing resistance. Using urinary tract infection as an example, empirical use of amoxicillin, then trimethoprim and then ciprofloxacin has been seen. In some infections, for example gonorrhoea, there are very few or no antibiotic options remaining.

Another very important consideration is the control of

the spread of antibiotic resistance. This might be considered as damage limitation, rather than preventing resistance emerging, but does aim to prolong the useful life of the antibiotics we now have. Infection control measures in healthcare settings can prevent the transmission of bacteria from one person to another. Basic precautions, such as hand hygiene, hospital cleanliness, and, in some circumstances, segregation of patients may be used (ie isolation). These measures are effective and were shown to prevent resistant bacteria such as MRSA spreading within a hospital in the 1990s, despite repeated introductions from outside[5]. However, when isolation facilities were swamped, control became much more difficult and the number of infections increased exponentially.

Currently, many hospitals in the UK are being challenged repeatedly by the introduction of multiply-resistant Gram-negative organisms transferred with patients from areas of the world where the prevalence of these organisms is higher than it is in the UK. Two examples are

K. pneumoniae or *E. coli* carrying *K. pneumoniae* carbapenemase (KPC) enzyme or the New Delhi metalo-beta-lactamase (NDM) enzyme that cause resistance to carbapenem antibiotics, the drug class often thought of as the antibiotics of last resort. The NDM resistance mechanism was described in patients who had come back to the UK from the Indian subcontinent. Many UK hospitals have reported repeated introductions, rather then spread within institutions, although outbreaks have also been described in some settings.

In some parts of Europe, carbapenem resistance is spreading rapidly. Data published by the European surveillance network EARS-NET has shown that Italy and Greece have carbapenem resistance levels of over 50% in some organisms[6]. Transfer of patients from these countries to the UK is not uncommon and it is vital that we learn from our previous experience of MRSA and do not allow repeated introduction to lead to further transmission here.
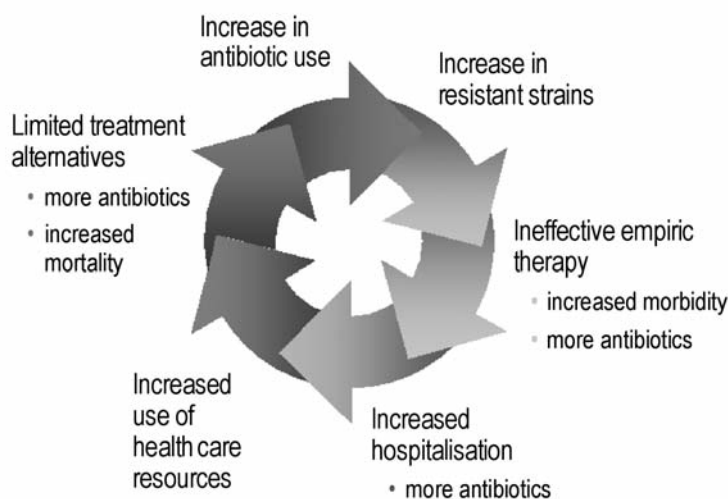
To summarise, the link between antibiotic use and the emergence of resistance is clear.

A new pipeline of antibiotics is needed, not just now, but in the future as antibiotic resistance will always be selected by continuing antibiotic use. We need new antibiotics to improve clinical outcomes in all aspects of healthcare. In order to slow the emergence and spread of resistance, one important challenge is to treat infection appropriately from the outset. This is why current national antibiotic stewardship initiatives, such as the 'start smart then focus', are so important. Development of better diagnostic tests that can influence antibiotic use is important too, and finally we need to think about the repeated introductions of resistant organisms into our hospitals and ensure they are not allowed to spread further.

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Figure. Relationship between antibiotic use, resistance, treatment failure and healthcare burden

Source: US Centers for Disease Control and Prevention (CDC)

Increase in antibiotic use

Increase in resistant strains

Limited treatment alternatives
· more antibiotics
· increased mortality

Ineffective empiric therapy
▪ increased morbidity
▪ more antibiotics

Increased use of health care resources

Increased hospitalisation
· more antibiotics

ANTIBIOTICS R&D – the current situation and prospects for the future

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He has spent 35 years in all aspects of development and use of antibacterials. Richard Bax is a member of the Antibiotic Action Advisory Board of the British Society of Antimicrobial Chemotherapy.

TranScrip Partners is a global and rapidly growing contract organisation that supports biopharmaceutical product development and life cycle management.

CURRENT SITUATION

Since the mid-1980s few novel compounds with unique modes of action have been registered, while those which have are generally used for Gram-positive infections. The lack of new antibiotics has occurred in parallel with a geometric increase in multidrug resistance (MDR) bacteria especially for Gram negative infections; a phenomenon occurring worldwide and spreading globally. This phenomenon not only significantly affects patients in hospitals but also people in the community. For example *E. coli* urinary tract infections, caused by extended beta-lactamase producing strains also, are resistant to all oral and many injectable antibiotics, resulting in a need for treatment with reserve antibiotics, such as the carbapenems intravenously in hospital [1].

The last truly novel antibiotic with a broad spectrum of activity against Gram negative bacteria was nalidixic Acid, the forerunner of potent fluoroquinolones, launched in 1963. There are several new antibiotics, developed from pre-existing classes, with activity against a narrow spectrum of Gram negative MDR bacteria. Currently, there are few novel broad spectrum anti-Gram negative antibiotics in development. Broad spectrum anti-Gram negative antibiotics in development are in the early stages of development, where risks are high. Therefore there is an urgent need to develop new and relevant antibiotics.

BIG PHARMA RESPONSE

Big Pharmaceutical Companies have largely left the field of antibiotic research, considering both the high cost of development and the low likelihood of clinical and regulatory success [2,3]. Currently the potential market is small and, as the antibiotic would only be indicated for a small number of patients, this results in the company launching into a low

. . . the low likelihood of clinical and regulatory success . . .

generic priced market. However, I predict that some large pharmas will re-enter this area, because, in the future, infections caused by resistant pathogens will increase. In addition, courses of antibiotics are rarely used for more than 14-21 days, which results in a low value proposition for the big pharmaceutical companies. This low potential value, with a high cost of development and low likelihood of regulatory success led to the demise of big pharma

involvement. Some research is being carried out in Universities. A small number of small UK companies are in the antibiotic research and development area.

PROSPECTS FOR FUNDING

Currently, limited funding is available for interesting science in this area and progression towards a Phase II study. This funding is likely to increase in the future, sourced from organisations such as the Wellcome Trust, and others. In the EU, the FP7 call for proposals ends this year and will be replaced with FP8 calls next year. The European Commission considers antibacterial resistance a priority area and will fund this

. . . The last truly novel antibiotic . . .

year's antibiotic related activities, such as R&D, as well as activities which would lead a compound towards Phase II.

The Innovative Medicines Initiative (imi) (http://www.imi. europa.eu/) is a unique European public private partnership between the European Commission and the European Federation of Pharmaceutical Industries and associations (EFPIA). It drives collaboration between all relevant stakeholders including large and small biopharmaceutical companies, regulators academia and patients. It is now on its 9th call with more than €200m in

research initiative to speed up the development of much needed new antimicrobials drugs. The hope is that the IMI initiative will assist in the successful R&D coming to the market within the next 5 years.

GLOBAL REGULATORY ISSUES

Part of the antibiotic paradox is that some companies consider that the unreasonable regulations posed by regulators have led to a decrease in new antibiotic development and hence reduced general availability of much needed new antibiotics. The regulatory requirements for new antibiotics demanded by both the European Medicine Agency (EMA) and the United States Food and Drug Agency (FDA), are so complicated, onerous and expensive that there has been a significant reduction in R&D in this area. This at a time when significant infections, caused by MDR pathogens, are increasing and are difficult to treat with a combination of antibiotics. Of note is that doctors who treat seriously ill patients increasingly find that the pathogen is resistant to all known antibiotics.

There are many suggestions being discussed by academics, clinicians, specialists in infectious diseases, clinical trial experts, statisticians, regulators and others to find an acceptable compromise between evidence development, assessment and access. Members of the Infectious Diseases Society of America[4] made an excellent recommendation for different approaches to the clinical programme, according to the estimated benefit-risk ratio, to the regulators in both the EU and US. This change in the clinical trial paradigm suggests a significant reduction in patient numbers and statistical certainty, as the risk of morbidity and mortality increases in patients with MDR infections. Early market access would be restricted and evidence development would continue, allowing increased but also appropriate use. This approach balances the quantity of data needed for registration with the unmet medical need. These proposals are currently being discussed within the EMA and the FDA administration, and may be the subject of several new guidelines on the registration of antibacterial drugs. It is hoped that this proposal will be considered, allowing the rapid and more certain registration and therefore availability of much needed important antibiotics. The FDA has just issued a draft guidance to the Industry [5] endorsing the approach suggested by amongst others John Rex et al[4] but with important caveats. The next guidance document from the EMA is awaited with interest.

CHANGE AND ACTION NEEDED

Several radical changes need to occur soon, in order to increase activities, and allow for the rapid availability of the appropriate agents. Streamlining of clinical trials has been proposed, with adequate financing and support at all times during the R&D of new and important antibiotics. Too often small companies fail, due to the lack of financial and pharmaceutical expertise in the manufacture of the drug substance under Good Manufacturing Practice (GMP) standards. This is the step before Phase I studies in volunteers.

There needs to be a clear and feasible regulatory strategy agreed with the EMA and FDA in advance of the trial programme, with no unexpected changes. This will lead to a robust Phase II study with the appropriate Pharmacokinetics/Pharmaco-dynamics, and with a high likelihood of regulatory success. Combine this with a compelling value of sales which, due to the limited populations defined in the prescribing information, will result in courses of antibiotics typically given for around 10 days becoming relatively expensive. Together these factors are likely to require significant increases in investment, and consequently lead to early availability for patients.

CONCLUDING REMARKS

With the United Kingdom research groups there are many medical Research Institutes such as the National Cancer Research Institute which in partnership with government, industry, and charities promotes cooperation in cancer research. What is needed to combat the urgent bacterial threat is such an institute or even better a number of these.

Other significant changes must occur within R&D, with Big and Small Pharma, academics and investors all having a crucial part to play and quickly. New funding will help to draw the many stakeholders together, boosting the prospects for meaningful R&D, registration and effective use for patients.

Ultimately, the question is "Can the stakeholders research and develop new and effective antibacterial drugs, and make them available, in time to address the looming bacterial resistance threat?"

ACTION NEEDED

Action	Situation
Clear and feasible regulatory strategy (EU/US)	On-going discussions at many levels with many stakeholders. Gain act LPAD and breakthrough category in place at FDA. EMA in discussion on adaptive designs awaiting publication of guidelines.
Streamlining of clinical trials	In progress at the FDA/EMA.
Secure adequate financing	Pricing issues complex. Interest from some venture capital in the US but not the EU. $1 billion available for bioterrorism from the US government and funding of several large and small US pharmas.
Pricing issues settled to allow investment in R&D	Discussion on-going in the US with companies, purchasers and regulators.

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