The Urgent Need
Regenerating antibacterial drug discovery development

Report of the British Society for Antimicrobial Chemotherapy Initiative

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The Urgent Need: regenerating antibacterial drug discovery development

"*Antibiotic resistance - one of the three greatest threats to human health*", World Health Organisation, 2009

INTRODUCTION

The British Society for Antimicrobial Chemotherapy is gravely concerned that the relentless rise in antibiotic resistance, occurring at a time when pharmaceutical companies are disinvesting in the discovery and development of antibacterial agents, will have severe and harmful effects on global health and our ability to treat infections in hospitals and the community. The antibiotic pipeline is almost empty, yet the need for new antibiotics to treat the increasing number of drug resistant infections continues to rise.

The models by which antibacterial agents are discovered and subsequently brought to market no longer appear to be as effective as they once were. The magnitude of the problem faced is aptly demonstrated by the IDSA 2004 Report *Bad Bugs, No Drugs*, which reports on sixteen new antibacterial agents being approved and brought to market between 1983-1987, compared with the estimate that between only two and four new antibacterial agents will reach market between 2008-2012. It is by no means clear if even these will address the current clinical issues.

The Urgent Need initiative was established in response to these concerns, to identify barriers discouraging participation in antibacterial drug discovery research, and to consider what opportunities exist to re-stimulate interest in the field, possibly through public / private partnership initiatives.

Our initiative is not unique, but it is an important part of a growing international movement that recognizes the need for, and demands, action before the global medical community is faced with the unthinkable – a post-antibiotic era where the treatment of infections, from the common to complex is no longer possible.

Looking at the three major components required to bring antibacterial agents to market – research, regulation and economics – this report records the discussions held at three expert evidence sessions. It does not seek simply to reiterate problems that have been rehearsed, recorded and reported so many times before, but to identify practical solutions that can be developed, applied and implemented, using existing systems for research, regulation and pricing,

In summary, we aim to offer suggested frameworks for action that if taken forward with imagination and commitment can and will make a real difference.

Professor Richard Wise
Chair, The Urgent Need Initiative

Professor Laura JV Piddock
President, BSAC

EXECUTIVE SUMMARY

The developed world has seen an explosion in the incidence and reporting of multi-resistant drug infections both in hospital and community settings. MRSA, *Clostridium difficile* and most recently Enterobacteriaceae with NDM-1 enzyme feature regularly and prominently in the media. Patient pressure groups demand their eradication, governments set targets for their control and reduction, high-profile deep clean campaigns have been undertaken as part of increasing efforts to control their spread, and a plethora of health interventions have been researched, developed and introduced in a bid to improve surveillance, monitor, record and drive down infection rates.

The concerns are valid and the concerted actions from public, professional and political quarters are to be applauded. Their impact should not be undervalued. However, neither should they mask the critical need to discover, develop and bring to market new agents to combat resistance and treat existing and emerging multi-drug resistant infections. The number of new agents in the pipeline is at its lowest ebb since the early 1940s when penicillin was developed and launched and there is an urgent need for the innovative regeneration of drug discovery and development markets. It is a story that rarely attracts press interest, yet the consequences of failure would be catastrophic.

Without new antibiotics, medicine will change beyond recognition. Nowadays, abdominal, heart and transplant surgeries have become routine, whilst ever-more-targeted and sophisticated chemotherapy regimens have dramatically improved cancer survival rates, but often leave the patient very vulnerable to infection. None of this would be possible without effective antimicrobial treatments. The re-emergence of diseases such as tuberculosis, which were all but eradicated, poses significant threats and treatment challenges in both developed and developing countries, as does the emergence of multi-resistant gonorrhoea.

This call to action is real, and action is needed now.

Looking at the market place for antibacterial discovery and development, there are several areas that require attention, each with differing but interlinked interests.

Public perception

In promoting this cause we begin from an overall position of disadvantage. Patients and their families see it as a right to expect and receive timely and effective treatment. Public education campaigns have raised awareness of the need to use antibiotics appropriately but there is little, if any, evidence to suggest that the general public is aware of the dilemma facing antibiotic research and development. The public are unlikely to be aware that the problem exists, let alone its scale. It is even more unlikely that they have given any thought to what might happen if the market fails. It is incumbent on the infection community to work together to influence public opinion. We need to engage with organisations and bodies such as Cancer Research and the Kidney Alliance, which have successfully forwarded their cause through capturing and maintaining public interest. There is a need to work with such allied professional specialist groups to raise awareness, highlight

the consequences of inaction, mobilise support and bring pressure to bear on governments, regulators and decision makers to engage and support initiatives that will regenerate the market.

Failure of discovery

The science of antibiotic discovery is especially difficult and the failure to bring new antibacterials to the market partly reflects a failure of discovery; during the past 30 years only two new classes of antibiotics have been developed that reached the clinic. In particular, potent commercialisable compounds with anti-Gram negative activity have not been found and, although in the past decade compounds with anti-Gram positive activity have been developed several of these were discovered decades earlier – examples include daptomycin and oritavancin.

The failure of discovery can be attributed to the combined effects of several interacting factors:

- The challenge posed by the fact that an anti-infective, unlike any other pharmaceutical, needs (i) to have multiple targets in terms of bacterial species and (ii) to work in multiple different infection types, arising in different body compartments.

- The genuine rarity of drug classes that can effectively permeate Gram negative bacteria and evade their endogenous efflux. This challenge is particularly great for *Acinetobacter* spp. and *P. aeruginosa*. This challenge is compounded if one further accepts that any single-target drug is likely to be vulnerable to mutational target-mediated resistance and that a desirable drug therefore should have multiple targets – as do the β-lactams, aminoglycosides and fluoroquinolones.

- Over-optimism in the 1990s for genomics, which identified targets but not compounds and, even where compounds were found, underestimated the challenge of getting these molecules into bacteria or preventing their efflux. The corollary of this shift was an abandonment of tried-and-trusted methods of antibacterial discovery, notably natural product screening.

- Mergers among big pharma, which reduced the number and diversity of the teams seeking to discover new antibacterials, simultaneously with a reduction of academic investment in the field.

The research report explores and addresses the above issues in detail.

Failure to bring agents to market

The barriers in bringing new anti-infectives to market hinge primarily on the lack of return on investment. Antibiotics, unlike drugs that treat the symptoms of chronic disease, offer a relatively poor return on investment. Put simply, the patient takes a heart drug for life but only takes an antibiotic for a week or thereabouts; moreover, prescribing a new antibiotic is likely to be restricted for fear it will select resistance. Estimates of the financial return ('Net present value, NPV') for antibacterials have been calculated as being

lower than those for vaccines, or therapeutics used to treat oncology, CNS and musculoskeletal diseases. Only oral contraceptives offer a poorer return. There are many market failures and there is a high cost of antibiotic resistance which is not reflected in the actual cost of the drugs.

Development of narrow-spectrum agents, the push for prudent antibiotic prescribing to reduce resistance rates, and the policy of preserving new agents as last-line treatment options do little to encourage industry to invest. There needs to be a paradigm shift in how antibiotics are perceived and priced to ensure that return on investment is met and interest in the development of agents regenerated.

The lack of attraction of anti-infective development is compounded by the complexity and high cost of Phase III clinical trials. This process is a particular deterrent for smaller biotech companies who might otherwise invest in this area but who are unlikely to be able to raise sufficient funds for Phase III clinical trials.

What is more, whilst there are many patients with antibiotic resistant infections, there are many more with antibiotic-susceptible ones, in whom cheap generic antibiotics can be used. These command a low overall price, and there is no requirement for their producers to evaluate their efficacy against current products; nor were they ever evaluated in clinical trials of the standards, size and statistical quality demanded for new agents. The efficacy of some generics has been questioned, and the ability of the large volume of generic antibiotic use to select for resistance is not routinely documented. Policy directives instructing the use of generics over branded products, further compounds the perception that antibiotics should be low cost.

The research, regulatory and economics reports each encompass commentaries on the economic barriers to bringing new anti-infective agents to market.

The regulatory environment

Licensing and regulation exists to support the public health agenda and ensure the safety of patients. These objectives cannot and should not be compromised. However, new ways of working within existing systems are needed.

By definition, the regulatory process is risk averse, and this can be particularly onerous for the approval of anti-infective agents. The main difficulties lie in the increasing levels of bureaucracy, and lack of clarity, within the regulatory framework and global differentiation in the clinical trials process. Lack of international harmonization, continual changes to processes, and ineffective pathways for dialogue between organizations, industry and regulators are all significant deterrents to the research and development of new anti-infective agents. Whilst there is evidence of progress in clinical trial design, much more work is needed, with a particular need to develop improved diagnostic tests swiftly to identify pathogens and their resistance, and the application of pharmacokinetic/pharmacodynamics data.

The regulatory report highlights what options currently exist to move regulation forward. It highlights options for adapting and utilizing the accelerated approval processes that have been successfully used in other therapeutic areas.

Evaluating societal and human cost

Influencing governments will require more than emotive words and doomsday scenarios. It will also require more than statements of fact on the dwindling antibiotic pipeline and the difficulties faced in the mobilization and funding of research, or on making commercial antibiotic development more financially viable.

As a profession we need to evidence the economic and human costs of resistance and the potential costs of inaction. The economics report outlines recent initiatives and current models that have been or might be used to determine this. Each initiative has its merits, but it is clear that none are able to comprehensively quantify the economic burden or human cost of resistance or rise in untreatable infections. There is an urgent need for the development of models that help us to do so.

RECOMMENDATIONS

The reports of the three expert evidence days – research, regulatory and economics – each detail options for consideration and action. Our recommendations take the form of a proposed agenda for action, comprising a number of legacy activities that will encompass some or all of these options.

AGENDA FOR ACTION

1 Establishment of an All Party Parliamentary Group Select Committee on Antibacterial Drug Discovery and Development.

2 Identification and implementation of mechanisms by which professional infection organisations within the UK can effectively engage with the international community to maintain and raise the profile of and better promote antibacterial research and science. Possible options/actions include:

- Committing to an annual international symposium for a period of 5 years at a national or international meeting to update delegates on state of play and actions.
- The publication of joint statements with likewise organisations in the international community to add to the collective international pressure for action
- Formation of an intra- governmental task force.
- Establishment of a Global Alliance of Professional Societies that will actively promote antimicrobial science and practice through;
  - development of a joint position statement
  - creation of a road map for action
  - development of an international lobbying platform

3 Commissioning of an international lobbying agency to identify key opportunities for influencing policy/strategy within the EU through, relevant Directorates and international initiatives such as the Transatlantic Taskforce on Antimicrobial Resistance (TATFAR).

4 Establishment of a mechanism by which to engage with research councils, industry and key funders to identify a joint approach to setting the research agenda and open dialogue around options for a relaxing of IP arrangements around grants/funding associated with anti-infective research. This would have the twin benefits of:

A Encouraging/enabling/reducing the barriers to interactions between academics and biotech/Pharma. The tax payer benefits from the increased probability of research leading to translatable outcomes and ultimately new clinical practice rather than in equity or licenses directly.

B Initiation of improved intellectual property (IP) environment for venture capital investment into start-ups and SMEs in the anti-infective sector.

5 Promote the establishment of an endowed *Chair in the Public Understanding & Communication of the Need for Novel Antibacterial Research*? Significant funding would be required. BSAC could be the catalyst for action but does not have resources to pump-prime or fund an initiative of this magnitude.

6 To seek changes in legislation that would streamline the ethics approval process that govern the use of patient samples and information, thus making disease surveillance more cost and time effective.

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APPENDIX ONE

WORKING GROUP ON RESEARCH ISSUES
EXPERT EVIDENCE AND DISCUSSION DAY HELD 4 FEBRUARY 2010
REPORT OF DISCUSSION

1 Introduction

The failure to bring new antibacterials to the market partly reflects a failure of discovery. In particular potent commercialisable compounds with anti-gram-negative activity- simply have not been found and, although compounds with anti-gram-positive activity have been developed in the past decade, several of these were discovered decades earlier – examples include daptomycin and oritavancin.

The failure of discovery can be attributed to the combined effects of several interacting factors:

- The challenge posed by the fact that an anti-infective, unlike any other pharmaceutical, needs (i) to have multiple targets in terms of bacterial species and (ii) to work in multiple different infection types, arising in different body compartments

- The genuine rarity of drug classes that can effectively permeate gram-negative bacteria and evade endogenous efflux. This challenge is particularly great for *Acinetobacter* and *P. aeruginosa*. This challenge is compounded if one further accepts that any single-target drug is likely to be vulnerable to mutational target-mediated resistance and that a desirable drug therefore should have multiple targets –as do the -lactams, aminoglycosides and quinolones

- Over-optimising in the 1990s on genomics, which identified targets but not compounds and, even where compounds were found, underestimated the challenge of getting these into bacteria. The corollary of this shift was an abandonment of tried-and-trusted methods of antibacterial discovery, notably natural product screening.

- Mergers among big pharma, which reduced the number and diversity of the teams seeking to discover new antibacterials, simultaneously with a reduction of academic investment in the field.

2 Aim

To consider the provision and effectiveness of current research into the discovery of new antibacterial agents.

3 Presentations

The following presentations formed the basis for discussion and concluding statements:

- The Seeding Drug Discovery Programme as a model funding scheme for translational research, *Dr Rick Davies, Wellcome Trust*
- The development of translational research skills and encouragement of partnerships with industry, *Dr Steven Projan, Novartis*
- Maintenance and development of natural product expertise in industry and academia
  Dr Mike Dawson, Novacta Ltd

4 'Seeding Drug Discovery': A funding scheme for small molecule drug discovery, Dr Rick Davis, the Wellcome Trust

The Wellcome Trust S*eeding Drug Discovery* scheme was established in 2005 with an 5-year programme budget of £91 million. Its major target was to foster and promote research with the aim of improving human and animal health, a tangible value, but within a charitable portfolio. There was a defined end point and candidate compounds were to be progressed only as far as Phase I studies. The problems of achieving charitable missions at early stage discovery were outlined and included: fostering and promotion of intangible values such as creating jobs, stimulating multidisciplinary research and innovation and generating publications. The science funding encourages curiosity-driven research. The transfer of technology is important to convert scientific discoveries into practical applications. These are based on scientific excellence and unmet medical need rather than commercial objectives. Their scheme has limited exposure to infrastructure costs and where appropriate, activities are outsourced to CROs. They are project managed, with success-driven, milestone-based, programme-related investment. Each funded project must have a demonstrable exit strategy and must meet pre-defined milestones. Funds were not generally available for costly technologies, such as high throughput screening. Multidisciplinary teams were favoured of an optimal size (about 15), supported with experienced advisors.

All therapeutic areas are considered under the scheme, but the major areas (over 50% of all projects) currently funded are oncology and antimicrobial, with 36 antibacterial projects at the preliminary application stage and 8 full applications. The initial portfolio was focussed in the UK but is now global. The majority of applicants funded are from universities and institutions but some are from industry, both small and large. Projects are stopped if they are deemed to be failing. Successful projects are those that act as a springboard for further R & D by the industry. In the antibacterial field there is one compound where Phase I trials are complete, and one trade sale/acquisition. The current antibacterial portfolio has funding available via venture capital (£31M) and public markets (£8.2M).

KEY POINTS ARISING FROM DISCUSSION

The scheme is open to all, including large Pharma companies. All proposals are welcomed, with funding on the basis of excellence, and not on the originator or existing financial health of the proposing organisation / institution. Whilst it is too soon to tell whether successes are more common with companies or academic groups, early indications suggest a bias amongst companies who have the necessary funds, infrastructure and expertise to move forward at a pace; academic teams often need time to develop expertise.

Robust support mechanisms are in place, with advice and support provided to funded groups once funds are awarded. Groups benefit from review meetings every two months, and support from an experienced project manager who monitors progress and checks that milestones are being met. Projects that fail to meet milestones or aims are terminated.

Projects are selected following a rigorous peer review process. It is a deliberate policy not to attempt to have a balanced portfolio but to fund suitable projects as they present themselves.

Projects that reach Phase I are passed over to a suitable company/organisation for forward development. Projects are rarely, if ever, progressed beyond Phase I by the Wellcome Trust.

The scheme is nearing the end of its 5-year term. The scheme is viewed as having been successful and the Wellcome Trust is considering a proposal to continue the scheme. [Since this meeting notification has been received that the scheme has been renewed and will continue for a further five years].

5 **Developing translational research skills & encouraging Academic/ Industrial partnerships, Dr Steven J Projan, Novartis Pharmaceuticals**

There are a number of factors that may be important contributors to the lack of success by the pharmaceutical industry in finding antibacterial agents. These include a need for better target validation and an imperfect understanding of the underlying biology.
Academic research is the bedrock upon which is built successful industrial research but the prime criterion should be scientific excellence and not 'unmet clinical need'.

Funding priorities need to reflect public needs, but unfortunately they are frequently influenced by politics. In contrast, science and medicine should drive the decisions. As an example, aggressive funding of basic research on HIV in the past three decades has been extremely successful, with over 20 drugs now available and more in the pipeline. However, there are nearly ten times more deaths in the US from bacterial nosocomial disease than from HIV. This indicates that there is clearly a relationship between the funding of basic research and the ability of industry to develop new drugs.
There is a great need to change public perceptions of what is important.

Funding can be public funding of academic research and industrial funding of applied research. There are now barriers (e.g. IPR and overhead costs) to collaboration between industrial and academic groups which need to be addressed. These barriers are most pronounced towards the later stages of development and are frequently caused by administration departments in academia. Some new approaches that might bear examining are the possibility of inhibiting host targets required for replication of the pathogen or studying host targets that may ameliorate pathologies; both require good basic research.

There are also surprising gaps in current knowledge of antibacterial resistance – why do some compounds select for resistance more readily than others? The genome size of the pathogen seems to have a positive association with the ability of that pathogen to become resistant – a study of the factors behind this may be

valuable. Antimicrobial compounds can be found, but can they be developed in a cost effective way? The problems are more governmental and regulatory than scientific. The science can be delivered but there are many disincentives, especially the sheer burden (e.g. size, cost) of clinical trials.

There is a need to examine how public perceptions can be changed to provide a voice and will to improve antibacterial drug discovery and development, as was/is the case for HIV and cancer treatments. There is a need to identify who is best placed to lobby the antibacterial 'cause' and to whom.

Many research groups expend much time and effort in attempting to develop antibacterial agents with little success. There is a need to identify new novel therapeutic strategies such as those to identify and validate new targets, especially those that do not need to be inhibited all of the time to have an effect. This is a route supported and adopted by both Novartis and GSK in recent years,

Stimulating industry interest in research of antibacterials will require significant effort and a shift in attitude on all sides. Regulatory authorities cannot be blamed for the inability of industry to undertake clinical trials in a cost effective way, and should consider only undertaking studies which will show if a compound is better than an existing therapy. The FDA should be encouraged to assist this process by providing a trial design that allows for a reasonable number of patients and provide incentives similar to those provided by EMEA (e.g. funding from bodies like the Bill Gates Foundation).

There also needs to be better funding in academia to draw and retain new talent into the system. This would ultimately result in increasing the scientific expertise/talent within industry also.

There is a need to address and resolve or avoid current tensions between academia and industry. There need to be improved pathways for negotiating better deals between academia and industry, with greater emphasis placed on involving those involved in technology transfer in negotiations. A model is needed to adequately reflect and reimburse the full economic costs of research undertaken by academia, and current examples of successful collaborative research models should be identified and promoted.

It is important to consider how to look at new uses for existing compounds, including how industry might be incentivised to take an interest in this area.

6 Maintenance and development of natural product expertise in industry and academia, Dr Mike Dawson

Natural products and development of 'legacy' leads can result in the discovery of compounds with true novelty. Natural product work requires intensive efforts, and re-evaluating legacy leads may need complex chemistry. Some companies are still working in the field, notably Sanofi-Aventis and Novartis. In addition there are several small companies mostly working on 'inherited' compounds, with limited success.

Work in academia is very limited but there is scope for small teams in academia or biotechnology companies to progress, especially in the re-evaluation of legacy compounds. The main problems are the availability of the producing organisms many of which have not been deposited in culture collections, a general lack of

expertise, as much of this has now disappeared, especially in natural product chemistry and knowledge of the micro-organisms. Approaches that could help include the use of IT to scan older publications and patents and persuading pharmaceutical companies who have worked in the field in the past to make their old data bases of organisms and/or compounds available.

There is the potential for the centralised production of interesting compounds, possibly with publicly funded fermentation facilities. A major strength of academia is in biosynthetic engineering, a key factor in natural product work. In addition, both academic groups and biotechnology companies have the ability to carry out mode of action studies and to test for biological activity. It has been estimated that there is still a huge scope for finding novel compounds from existing known microbes, for example <3% of antibiotics from streptomycetes have been discovered to date. Although genomics has not proved of much value in finding novel compounds, it could be used in conjunction with a novel antibiotics approach. Using unusual organisms is another possible way forward. Traditional medicines from plants are also a possible source. It is possible that the area fell out of favour just as the technologies needed to make it feasible appeared; in particular molecular biology has transformed many areas of research and could do here. Although there are undoubtedly some skills gaps, there may be ways round this.

KEY POINTS ARISING FROM DISCUSSION

A large number of companies exited the natural compounds market which began to decline from the 1960's onwards. This decline was due in part to lack of returns (natural product lead times are much longer that in synthetic chemistry) and due in part to technological advances such as robotics and automation. Despite a significant amount of natural product work being linked with antibacterial activity, successes were very limited. Small biotech companies were established to work on natural product development, however many found it difficult to raise adequate venture capital and turned to other areas of activity to ensure their survival.

There has been a recent modest revival, with some companies re-entering the field and collaborating with smaller companies (e.g. GSK has re-entered the market and formed a collaborative partnership with Biofocus). The employment of new and emerging technologies should make natural product research much more productive than before.

Despite a loss of some expertise in the area, expertise has shifted / exists in other areas such as chemistry. There is evidence that the natural product chemists currently training in the UK are phytochemists, most of whom are post doctoral researchers from countries with a strong tradition of plant based medicine. Some companies also still retain expertise, for example in microbiology of unusual organisms.

There is a need to restimulate interest, particularly in the area of exploring legacy compounds. Consideration should be given to requesting companies to make their archives available for this purpose, and also to encouraging funding agencies such as Wellcome to support work in this area, possibly by approaching/targeting senior personnel in industry.

Another route might be the endowment of Professorships in the area of natural product development. It might prove to be more cost effective than trying to get companies to regenerate activity in the area,

especially as the infrastructures to support this work no longer exist, and would encourage the development of new skills and expertise.

CLOSING DISCUSSION: KEY POINTS

There are a number of alternative types of therapy for bacterial infections documented in the literature, such a phages, enzyme immunomodulators and cationic peptides Whilst clinical trials of phage therapy have rarely demonstrated any significant effect, and the likely success of peptidoglycan hydrolase enzyme therapy was questionable, promising progress has been shown in the area of cationic peptides. Despite progress being very slow in this area, it may be an area of value and worth pursuing.

New chemistry might have a role to play in identifying new compounds. GSK is pursuing compound development using Boron chemistry, and it is anticipated that a number of compounds of interest might emerge.

Compound discovery, and subsequent developments, might benefit from public/private partnerships and consideration could be given to identifying how such initiatives can be pump-primed.

All parties should acknowledge that the current initiatives under which antibacterial drug discovery and development fall are not working. There needs to be a move to collaborative working across agencies. The IDSA has worked for over a decade to energise the process and encourage new and innovative ways of working, the most recent initiative being the '10x20' effort – that aims to bring 10 new antibacterials to market by 2020. The IDSA has engaged with the National Institute of Allergy and Infectious Disease (NIAID) and is proposing a new approach which will depend on biotech collaboration with industry/academia/philanthropy. There are major hurdles such as technology transfer, but IDSA needs to get their attention and agreement, and a formal acknowledgement that current initiatives are not working.

CONCLUSIONS

The key findings and messages are:

- When funding is available, it should be for scientific excellence whether within industry or academia.
- Academic translational research may benefit from external advisors with industrial experience as demonstrated by the Wellcome Trust SDDI management structure
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- Models for academic/industrial collaboration should be further explored – the Wellcome Trust initiative is an excellent one but more are needed – perhaps even more imaginative ones.
- The need to promote interest and awareness if antimicrobial research at senior levels in the Grant awarding bodies.
- Training is required in various specialist skills – the key specialist skills that are required for the future and how that training could be given should be identified. Placement in industry as part of undergraduate courses or PhD training is proposed.

- More funding overall is needed; imagination is required as in the current economic climate Governments cannot be relied upon.
- Basic research needs to identify targets for antimicrobials and whether combinations with other molecules that prevent symptoms are advantageous.
- There is a need to understand at a fundamental level, both the mechanisms and the transmission of antibacterial resistance.
- The anti-bacterial 'community' needs to influence public opinion.
- Flexibility in regulatory affairs is crucial to progress – this will be addressed at meeting 2 of this working party.

APPENDIX TWO

WORKING GROUP ON REGULATORY ISSUES
EXPERT EVIDENCE AND DISCUSSION DAY HELD 2 MARCH 2010
REPORT OF DISCUSSION

1 Aim

To discuss how the regulatory and legislative processes that govern the registration, licensing and regulation of antibacterial agents can be improved to encourage and advance new uses of existing antibacterial agents and the bringing of new agents to the market place. Through presentations and discussion the group examined:

- How far is the regulatory process fit for purpose?
- What are the important new proposals / approaches that have been used or might be considered?
- What is the likely time frame for delivery of new proposals and approaches?
- What can we do to accelerate change within the regulatory process?

2 Presentations

The following presentations formed the basis for discussion and concluding statements:

Registering, licensing and regulating antibiotics: Removing barriers to innovation
- A pharmaceutical company perspective, *Glenn Tillotson, Head of Medical Affairs, ViroPharma*
- A regulatory perspective , *John Powers, Assistant Clinical Professor of Medicine George Washington University School of Medicine University of Maryland School of Medicine*

What New Initiatives for Regulators Are the Best Ones: Criticisms and issues with the current position and priorities for action?
- *S Ragnar Norrby, Emeritus Professor, Swedish Institute for Infectious Disease Control*
- *Roger Finch, Chair, Professor of Infectious Diseases, University of Nottingham, UK*

3 A pharmaceutical company perspective, *Glenn Tillotson, Head of Medical Affairs, ViroPharma*

Regulatory difficulties faced by the pharmaceutical industry
The current regulatory framework differs within US, Europe and the rest of the world, and as such poses significant difficulties for the pharmaceutical industry. Increasing levels of bureaucracy, changing processes within the regulatory framework and global differentiation in the clinical trials process provides too many hurdles for the researching of a new anti-infective agent. Coupled with the perception that antibiotics should be inexpensive, companies are unable to easily identify or predict what the net present value (NPV) of a new antibacterial agent would be. Pharmaceutical companies have a responsibility to shareholders, and

identifying NPV is a primary driver in deciding whether to invest in the development of a new product. The regulatory framework and perceived market value of antibiotics are both significant deterrents to the research and development of new antibacterial agents.

Regulatory uncertainty exists for a number of reasons. Non approval of drugs (e.g. ceftibiprole is a better example of non-approval, as telavancin was given a limited approval in USA) and increasing amounts of bureaucracy including changes to processes are both significant deterrents to the industry. Another deterrent is the lack of harmonization of processes in different countries. One recent study was conducted across 27 countries, each with their own clinical trials process. The absence of a single pathway for experimental agents poses significant difficulties for smaller companies.

Regulatory agencies have issued a number of guidelines in recent years, which have been constructively reviewed and commented on by industry. Whilst industry and regulators have engaged in this way, regulators have been slow to respond – in one instance there has been no active dialogue in 18 months following the submission of a formal response to the FDA. The EMEA has issued numerous guidelines for consultation in many areas, but only one in the area of infective bacterial infections. Industry responded but has yet to receive any feedback.

Whilst some progress has been made in the area of clinical trial design, much more work is needed. Expert guidance from regulatory agencies can be called upon, but is sometimes not as deep as it needs to be and can lead to a lengthening of timelines. Industry has in recent times lent its expertise to the regulatory process and is keen to progress this.

Financial hurdles – the perceived value of antibacterials

Consideration was given to the financial issues that might underpin industry reluctance to develop antibacterials. There is evidence that antibiotics are being given away in the US, creating a perception that antibiotics have no intrinsic value. Similarly the requirement by some PCTs in the UK to prescribe generics before branded anti-infectives adds to this perception. The need to evaluate the efficacy of generics against originating products needs to be addressed. Recent studies comparing generics against branded products showed significant variances in activity, with generics having 16% lower activity, with some generics showing the ability to select for resistance in proven models.

It is estimated that it costs in excess of 800 million pounds to bring a new anti-infective to market. Factors such as single dose treatment regimens and unknown life-span of the product due to resistance dramatically reduce the financial attraction to companies to develop anti-infectives. The purchase cost for antibiotics needs to increase between 4-8 fold to realize the same return on investment as a decade ago. The treatment of infections does not carry the same perceived value as treatments in other areas, e.g. cancer. Trusts are able to spend tens of thousands of pounds extending the life of cancer patients by, for example, six months, yet expect life-saving antibiotics to cost tens of pounds. There must be a paradigm shift in attitude and an acknowledgement / acceptance of the true value of life-saving antibiotics before it is too late.

The orphan drug approach

Industry could consider whether the Orphan Drug approach could be used for particularly challenging indications or specific infections (e.g. ventilator associated pneumonia (VAP) caused by *Pseudomonas aeruginosa*). The orphan drug methodology would enable the implementation of more rapid timelines, with provisional approval given on the basis of good Phase II data. This approach would provide for an accelerated provisional approval and is a well-known and accepted approach in the cancer world. The accelerated approach is applied to the evaluation of new therapies for life threatening diseases; latitude would be needed in this definition if the approach was to be applied to infectious diseases.

FDA Accelerated and Restricted Approvals under Subpart H (drugs) and Subpart E (biologics) for serious or life-threatening illnesses

The FDA may grant marketing approval for a new drug product or biological product on the basis of adequate and well-controlled clinical trials, establishing that the drug / biological product has an effect on a surrogate endpoint that is reasonably likely, based on epidemiological, therapeutic, pathophysiological or other evidence, to predict clinical benefit or on the basis of an effect on a clinical endpoint other than survival or mortality. The accelerated approval process is subject to confirmatory studies being conducted post-approval. Both approaches can, and have been used, to greatly reduce the development time to market. There is a requirement that post-marketing studies are adequate, well controlled and carried out with due diligence in a timely fashion. Approval can be withdrawn for a number of reasons including the failure of the post marketing clinical study to prove or verify the clinical benefit, or if other evidence demonstrates that the drug is not shown to be safe or effective under its conditions of use.

Both accelerated processes have been regularly used in recent years, particularly in the area of anti-HIV agents even though this is no longer considered a life-threatening condition. Consideration could be given to exploring if there is room for a modification of the processes to include anti-infective drugs, in particular nosocomial infections, the majority of which are serious and/or life threatening. Part of this could be to restrict the use of approved products for hospital prescribing only, where careful monitoring of use and rapid reporting of adverse events could be undertaken by hospital pharmacists. Example: Of the 1 million patients with pneumonia in the US each year, only 12-30,000 will have *Pseudomonas aeruginosa* VAP. These numbers bring this life threatening infection into orphan drug territory. Can we look at the subpart H approach to accelerate bringing drugs to market for this indication?

KEY POINTS ARISING FROM DISCUSSION

Accelerated approval: Industry is reluctant to talk to regulators about pursuing Subpart E & Subpart H approaches as there is a fear of wasting time and resources; they do not see the 'door' to this route open. Companies might be happier to consider employing these approaches if the regulatory agencies offered them as an avenue for companies to pursue. This would require a mind shift amongst regulators who remain strictly risk averse.

Orphan Drug (OD) route: This approach was successfully employed for the development of an agent for anthrax, where surrogate data was used as there was no human model available. Due to the political

pressures regulatory agencies offered the OD approach to industry, rather than industry making the approach. Political will existed in this instance and proved to be a powerful driver.

Would encouraging companies to pursue the OD route result in a tradeoff in terms of healthcare? Products approved via the OD use would receive significant market advantage, with receipt of 7 years market protection. This advantage might act as a deterrent for further innovation and might prevent the identification and development of better interventions. The reverse view is that this is valid in a market where there are numerous developments in progress – this is not the case for anti-infectives. Indeed, a 7 year approval for example treatment for *Acinetobacter* infections, where there are no products under development, would be extremely beneficial.

The IDSA has tried to explore the OD route, but no progress achieved. For infections the OD model does not apply as to qualify for OD status there is a need to have a precise diagnosis.

Rapid diagnostics & PK/PD: In addition to movement in terms of regulatory attitude, there is also a need for healthcare to shift in the way it defines infection or responses. Exploring the use of surrogates and link that with diagnostics might be a very useful way forward, as would providing PK/PD data. It might be very attractive to companies if the profession could facilitate trials in terms of patient definition by rapid diagnostics and PK/PD data, which would facilitate the enrollment of patients with an actual infection, thus reducing the need to have large clinical trials.

4 A regulatory perspective, *John Powers, Assistant Clinical Professor of Medicine George Washington University School of Medicine*

Purpose of regulation

The purpose of regulation is to advance/promote health. To fulfill this purpose companies must provide evidence for the claims they make about their products, with overall approval being based on a balance of harm and benefits of a product. As such it is incumbent on regulatory agencies to quantify risks and benefits against defined criteria for what a drug must do. Regulatory considerations are linked to appropriate scientific considerations, and are not rules for rules sake.

Does the regulatory process really inhibit antibacterial development?

Contrary to perception, anti-infectives already have the highest approval rate and lowest development costs of all agents. In seeking to identify more rapid routes to market it is important to ensure we do not shift uncertainty from sponsors to patients; this would be an entirely inappropriate public health strategy.
The legal standards for the approval of drugs remain the same for life threatening or non-life threatening conditions. Whilst there is a perception that regulatory criteria are too strict, the outcome of a test case between industry and the FDA established that the FDA sets minimum standards for evidence. It is important to be aware of what regulators are asked to do when a deviation from regulation and good science is requested, particularly in the absence of any scientific or regulatory basis for reducing evidence. Furthermore, the FDA has no interest in the economics of a product, and does not / cannot base decisions on monetary returns.

The FDA approves interventions for recognized diseases and conditions – not organisms. Drugs are approved for diseases for which they are studied; the idea that a drug can be approved for a proposed resistant organism does not fit the regulatory model. Companies cannot claim efficacy in an area they have not studied as it is considered misleading; superiority cannot be claimed where it has not been clearly demonstrated in evidence.
One area that does cause difficulties is the misfit between older and newer guidance, which leads to inconsistency in guidance for the design of clinical trials. The FDA is aware of the difficulties caused and has undertaken to update the guidance. Another issue is variance in regulations across difference countries; there is an urgent need to harmonize guidance to facilitate research and clinical trials.

What can be considered?
Having considered what regulators can and cannot do, what can the profession and industry do to improve the situation? The following needs / options were identified:

- To develop interventions that are better for patients – not striving for perfection, but rather the need to get greatest probability of improvement. Are we getting the data we need to inform patients and clinicians?
- Shift in industry attitude and a move away from the "blockbuster" money making mentality.
- To refocus on quality of drugs rather than quantity of drugs.
- To consider the role of bedside diagnostics in improving patient measurement and reducing trial size.
- To acknowledge that appropriate bedside diagnostics will reduce drug use; companies want broad spectrum approvals that will see products used for as many indications as possible to ensure the greatest financial gain.
- To accept that trials must be designed to detect any differences that do exist, and therefore must include patients with and without the disease. We cannot expect to dispense with comparative studies.
- Consider what tools can be developed and provided to regulatory agencies to assist them – this might be development of better research definitions, diagnostics and outcome measures. Oncology has clear metrics on 1, 3 & 5 year survival rates). Would such staging indices be helpful for anti-infectives?

KEY POINTS ARISING FROM DISCUSSION

Quality and perceived value: If quality of anti-infective agents is more important than the number of available agents why aren't there more antibiotics in the pipeline? The overall anti-infective market is quite large and companies are not interested in developing narrow spectrum agents as the financial benefits are limited. To address this it is important to document and promote information on the appropriate pricing of agents and what they are worth to Society. It has been suggested under the current regulatory process the outcome of a study is more determined by how that study is undertaken rather than the effect of the drug. The value of a prescription to the patient is not defined within the current trial design. We need to identify a 'middle path' for earlier registration but major benefits are undertaken post marketing.

A joint approach to aiding the clinical trials process: There is a need to develop tools for trials for investigators to use – could government play a role in funding this type of research, or could industry be persuaded to co-support the development of a tool that would be available for use by all? This might enable

direct targeted treatments for infection, similar to that for treatment in oncology. Need to shift the emphasis towards the development of rapid diagnostics to focus better on who needs drugs and who doesn't, in addition to carefully examining the duration of therapy.

5 What New Initiatives for Regulators Are the Best Ones: Criticisms and issues with the current position and priorities for action? *S Ragnar Norrby, Emeritus Professor, Swedish Institute for Infectious Disease Control*

Guidance – the current position: The publication of new guidelines in 1992 (US) and 1993 (Europe) for clinical trials resulted in a vast improvement in the quality of trials undertaken. One consequence of the guidance that was jointly developed by FDA, IDSA and ESCMID was a huge increase in the number of patients included in Phase II trials. A resultant improvement was the routine use of intention-to-treat analyses. However, a number of weaknesses remain – including the need for training of investigators, and the lack of requirement for industry representatives to involve ID specialists in decision-making processes. The guidance drastically increased costs of bringing products to market. Whilst a number of guidance and notes have been issued by FDA and EMEA since, no thorough revision has been undertaken and problems specific for various types of infections have not be revisited.

Issues & solutions

Many indications: The number of phase III trials required can pose problems, with at least one (more often two) required for each indication. US regulations require documentation of efficacy against specific pathogens for each indication – meaning it is often impossible to get statistically meaningful results. The number of possible indications has proliferated, e.g. community acquired, hospital acquired. Consideration could be given to allowing extrapolation between indications with similar aetiology and similar pharmacokinetic properties, e.g. intraabdominal and gynaecological infections and otitis and sinusitis. Suggested solutions include:

- Allowing extrapolation between indications with similar aetiology and similar pharmacokinetic properties, e.g. intraabdominal and gynaecological infections and otitis and sinusitis
- Pooling of data for different types of infection to document efficacy against specific pathogens

Binomial End-Points: Efficacy is registered as cured/improved versus failed. This leads to requirements for very large sample sizes in clinical trials (up to 300 evaluable patients per treatment group). One solution might be to intensify the search for, and validation, of continuous end-points (e.g. # of loose stools; time with fever; scoring systems).

Dilution of patient samples: A large proportion of patients included in antibiotic trials do not have bacterial infections. The consequence is that in non-inferiority trials the chance of detecting differences is markedy reduced. A proposed solution would be to search for new, rapid and more precise diagnostic tools, with preference given to those available at the point of care, rather than those requiring access to microbiological laboratories.

Increased Use of PK/PD Data: Solid PK/PD data should reduce the need for phase III trials to one per indication, a development that regulatory agencies appear to favour.

Early licensure Both FDA and EMEA have procedures that allow early registration based on limited data if an antibiotic has properties that overcome resistance problems.

KEY POINTS ARISING FROM DISCUSSION

Guidelines: The need for new antibiotics is recognised by all parties. Whilst there are no major controversies between industry and regulators, guidelines need to be revised in a way that allows more rapid licensure at a lower cost for the clinical documentation. Acknowledged as a timely process, it was agreed that the group might influence the revision and development of new guidance, whilst working on ways of working smarter within the current framework (possibly through the CHMP 2004 guidance).

Extrapolation and pooling of data: There was concern that regulators would be nervous of this potentially controversial approach. However, the aim would be to allow earlier general marketing of anti-infective products by increasing post marketing commitment to assess both safety and efficacy.

Indications: There is a need to revisit indications, e.g. pneumonia, rather than HAP / VAP it could be split as ventilator or non-ventilator. This would not be attractive to industry as it would decrease the number of indications for which a product is shown to be effective. There is a need to stratify by patient rather than organism type.

6 What New Initiatives for Regulators Are the Best Ones: Criticisms and issues with the current position and priorities for action? *Roger Finch, Professor of Infectious Diseases, University of Nottingham, UK*

Regulation: The principle that regulation and licensing supports and protects public health was reinforced. Whilst not a regulatory responsibility, a process by which the flow of medicines can be facilitated is urgently needed, but only provided public safety can be addressed.

Regulators must recognise that therapeutics remains an experimental science, and as such licensing will not provide the last word in terms of efficacy, safety and use of medicines. It is therefore frustrating that they can only be prescribed, certainly in the US, in accordance with licensing indications. This can lead to prolonged duration of therapy (e.g. CAP 10-12 days), which, in reality, does not happen in the UK. Whilst contentious, we do need to ensure flexibility to enable the practice of medicine in areas that are not just regulatory controlled.

Barriers: There are 3 main issues (a) increasing demands in design of phase III studies – equivalence > non-inferiority > superiority > placebo-controlled; (b) requirement for all licensed indications to be microbiologically documented; and (c) increasing stringency of safety requirements pre- and post-licensing YET defining risk/benefit remains problematic. The risk/benefit is an imprecise science, often subjectively interpreted within regulatory process rather than by a set of robust criteria.

From a clinical viewpoint there are a number of concerns:

- Narrow spectrum agents largely licensed for microbiologically defined infections
- Indications have been selected for regulatory expediency rather than clinical utility e.g. cSSTI, UTI, CAP
- Organism specific indications often difficult to recruit e.g. MRSA/MSSA HAP, endocarditis
- Trial populations have increasingly shifted from hospital to community where disease severity differs e.g. CAP

Off-patent generics dominate over 80% of the anti-infective market. Despite this majority share of the market there is no regulatory requirement to monitor resistance rate for generics, or even guidance on what might be considered acceptable resistance rates. The profession must question whether current rates for some agents are acceptable; for generics there are clearly rates would be unacceptable for a new agent. A further issue is that there are no additional safety requirements for generics, leaving public health inadequately addressed, with the cost advantage of generics remaining largely based on superficial and imprecise economic assessments.

What new initiatives can be identified?

The recruitment of more-challenging, drug-resistant pathogens could be encouraged by looking at a broad range of studies that includes organisms recruited from large randomised controlled studies and smaller studies (e.g. pooling of data). However studies must be prospective to satisfy a regulatory process.

The use of PK/PD is now an accepted modality for supporting the definition of a dose regimen. Consideration can be given to extending PK/PD data to support or replace efficacy requirements where large trials are difficult to conduct. This is a bold proposal that will need to be considered carefully.

Can evidence on efficacy across selected indications that share common pathogens and drug profile be extrapolated? There are a number of issues to consider, but it is an area that could be explored.

Another frustration is that comparative agents are often generic drugs and database information is often poor. Is there an opportunity within prospective CTs to obtain PK/PD from the control agent as well as test population? This would add to the scientific database of the performance of generic agents. The remaining question is whether generic agents perform as well as the test branded agent(s) and thus have their dominant position in therapeutics sustained.

Can permission be given for extrapolations between pathogens with similar susceptibility profiles or pathogenic profiles? It might also be possible to extrapolate data by looking at pathogens that share common susceptibility profiles there being enough data on population distribution of susceptibility profiles to support this.

Serious consideration should be given to encouraging the development of rapid diagnostics, which could have a major impact on regulatory requirements. Licensed, approved point of care diagnostics that are adopted in clinical practice for use should facilitate recruitment of patients, help reduce the number of non-documented infections, improve efficiency of trial data and reduce the costs of Phase III trials. If regulatory

statements support, and incentivise, the process of microbiological definition of infections it might encourage industry to become actively involved in the development of diagnostics.

One potential development within Europe is the creation of a special status for infections caused by Gram-negative bacteria where there are inadequate options for therapeutic management. This status would provide early access to named regulatory advice to facilitate the design of studies and help identify the best patient cohorts. Such a service could/might be charged for.

The approval and implementation of a rolling approval arrangement might encourage further investment in the anti-infectives market. Such a process could see the granting of early conditional approval for a single indication and subsequent submission and approval of new indications, leading to accelerated final approval. There will be clear a requirement that ensures robust safety data prior to early conditional approval.

Finally, there is a need to develop new models for developing performance of comparator agents versus generics. These models should be outcome, rather than cost, driven.

KEY POINTS ARISING FROM DISCUSSION

The need to reinforce the importance of licensing and regulation to support the public health agenda was acknowledged.

International harmonization of the regulatory process needs to become a reality to support global industry development of new anti-infectives.

There is a clear need for rapid diagnostics to come on stream to facilitate notnly medical practice but also drug development. The initial emphasis should be on the development of simple bedside diagnostics (e.g. a test to distinguish between a viral and bacterial infection). The expansion of PK/PD applications would also be useful and timely.

There needs to be greater flexibility in developing a full information database on efficacy and safety, particularly with regard to drug resistant infections

There is a need to address the concerns raised in relation to the use, assessment and continued licensing of generic agents.

WORKING PARTY DISCUSSION

The following priorities were identified by the working party. These will be ranked following consideration of the report of the meeting:

A Better diagnostics to enable:

- Enrolment of patients with genuine bacterial infections in trials
- Facilitate trial design to decrease patient numbers and increase the power
- Better outcome measures, particularly morbidity and allow delineated endpoints in the trials

B Use of PK/PD data, in particular its impact on Phase III trials.

C Stratification of patient groups that might resolve issues of dosing and duration of therapy and also help study design.

D Generics – the need to address the serious concerns raised in relation to the use, assessment and licensing review of generic agents. Should there be a level of resistance to the generic agent (and possibly concomitant cross resistance to agents of the same drug class) that will trigger withdrawal from use? What is the responsibility of the originating company in measuring prevalence of resistance?

E To consider what alternative regulatory routes might improve the process by which antibacterials are approved for use – OD route, Sub-Parts E and H.

F Removal of requirement for minimum numbers of certain organisms in clinical trials.

APPENDIX THREE

WORKING GROUP ON ECONOMICS, VALUE AND COST OF ANTIBIOTIC RESISTANCE AND ITS CONTROL
EXPERT EVIDENCE DAY HELD ON MONDAY MAY 24TH 2010
REPORT OF DISCUSSION

1 AIM

To discuss the value of antibiotics and the societal and healthcare costs of resistance and what should be assessed and utilized to influence and change the economic model in relation to uptake, pricing, reimbursement and return on investment for new agents. The following topics were examined:

- What are the needs for data on the cost of resistance/value of antibiotics (societal and financial) and how should they be used?
- What are the cost and benefit considerations from the payers/users perspectives?
- What can be done to change the economic model and remove barriers to investment in the development of New Chemical Entities?

2 PRESENTATIONS

The following presentations formed the basis for discussion and concluding statements.

The cost of antibiotic resistance to healthcare delivery
- Current key data on impact of resistance – a SWOT analysis, *Dominque Monnet, ECDC*
- How might healthcare better assess the impact of resistance? An economic model for determining the societal costs. *Marcus Keogh-Brown. London School Hygiene and Tropical Medicine*

Current and Future cost-benefit models in relation to uptake of new anti-infectives
- National and local assessments. *Kieran Hand, UKCPA*
- NICE assessments. *Sarah Garner, NICE*.

What are the economic obstacles to resolving the antibacterial gap?
- A view from Big Pharma. *David Findlay, GSK*
- The push: pull strategy. *Chantel Morel, London School of Economics*.

3 Current key data on impact of resistance in Europe – a SWOT analysis, *Dominque Monnet, European Centre for Disease Prevention and Control (ECDC)*

The term 'Antimicrobial Resistance' represents several, inter-related compartments of healthcare, i.e. patients in primary care, hospitals, nursing homes and long-term care facilities, food animals, food and the environment. It includes many types of infection, (such as respiratory tract, urinary tract, skin and

soft tissue, bloodstream, surgical site, related to medical devices, etc.) and a range of bacteria/microorganisms. In addition there are many antimicrobials and mechanisms of resistance. Most importantly, it includes patients with infections caused by bacteria resistant to various antimicrobials.

The EARSS report of 2009 showed that the numbers of MRSA isolates from blood and CSF between 2005 and 2008 decreased significantly in most European countries with the exception of Portugal, where numbers increased significantly. In sharp contrast to this the situation was reversed with isolates from blood and CSF of 3rd generation cephalosporin-resistant *Escherichia coli*, most countries showing a significant increase in resistant isolates. A joint technical report entitled 'The Bacterial Challenge: time to react' has been published recently (September 2009) by ECDC and EMEA. The underlying assumptions used in preparing this report are:

- That the distribution of bacterial species isolated from blood cultures should not vary between countries and a list of the six most frequent bacteria isolated from blood cultures was used.
- A marker for multi-drug resistance for each selected species was used.
- Each resistant isolate in EARSS corresponds to one infected patient (i.e. repeat isolates are excluded)
- Distribution among various body sites (types of samples) is different for each multidrug-resistant bacteria, but should not vary between country/hospital/ward if sampling practices are similar

A limitation to the study is that only six resistant bacterial species were used; MRSA, VRE, penicillin-resistant *Streptococcus pneumoniae*, *Klebsiella pneumoniae* and *E. coli* resistant to 3rd generation cephalosporins, and *Pseudomonas aeruginosa* resistant to carbapenems. The burden of human infections with these six species was extrapolated from the percentage coverage in each country in the EARSS study. Extrapolation was also made for four types of infection – bloodstream, urinary tract, respiratory tract and skin and soft tissue infections. Published literature was used for estimating attributable mortality and extra length of stay in hospital. Full details of the parameters are available on the web
http://ecdc.europa.eu/en/publications/Publications/0909_TER_The_Bacterial_Challenge_Time_to_React.pdf
The study covered the EU, Iceland and Norway.

Important conclusions
Important points emerging from the report are that MRSA isolates are still the most dominant (between 20 and 30%) although their incidence has dropped consistently in recent years. The number of *P. aeruginosa* isolates, although showing a decrease, remain high as do the number of *K. pneumoniae* isolates. The proportion of VRE isolates have decreased gradually to below 10% while *S. pneumoniae* isolates, although still below 10%, have increased. Most notable is the increase year on year of resistant *E. coli* isolates. The human burden of these six organisms in the four types of infections was estimated to be approximately 400,000 infections of which there were 25,000 attributable deaths and 2.5 million extra hospital days. The economic costs were calculated as an approximate € 900 million/year and approximately € 600 million/year in lost productivity.

Study limitations and possible improvements

The study had strict limitations and data that the authors would have liked to have included but were not available were - all infections with all resistant bacteria, all patients, in hospitals and outside hospitals (long-term care facilities, community); details of initial empiric therapy; estimates for attributable mortality, extra length of stay, in-hospital costs and societal costs from a representative sample of patients in each country; better estimates of in-hospital costs; costs for infection control measures (for example screening and isolation) and better estimates of societal costs. It is probable that the study underestimated the burden of Gram-negative infections as some do not produce bacteraemia. When comparing these results with data from the US, the incidence of carbapenem-resistant *P. aeruginosa* was calculated to be similar; 28.6 infections/100,000 people in this study versus 24 infections/100,000 in the US (Spellberg B, *et al*. Infection 2007). The incidence of attributable deaths from five of the selected organisms was 5.1/100,000 and in a study from the US for MRSA, VRE and *C. difficile* the figure was 4.0/100,000. (Zell & Goldmann. Infect Control Hosp Epidemiol 2007). In-hospital costs for multidrug resistant infections was however, substantially lower that in the US

KEY POINTS ARISING FROM DISCUSSION

It is not possible to predict the demographics of an ageing population in the developed world since the study did not include nursing homes; this would be valuable information to have since costs for such patients can be high. In the US, resistance is high in nursing homes and institutions and thus the costs are significant. A study (HART) is in progress in nursing homes and this may provide some data on this important area. It is not possible to identify trends in mortality and length of stay from this study. These data could be obtained from the EARSS 2007, but to identify trends it would be necessary to have similar data from 2006 and 2005 and this is too complex. The way the studies have been set up makes it difficult to get retrospective data; each year the population covered and the bacteria sampled have differed.

It is also difficult to get costs for community infections since the study was designed specifically for MDR bacteria which limit comparisons or extrapolation to point to a common burden. The figures for mortality may seem low but perhaps comparisons are needed with non-infection situations, for example how many deaths are there from road accidents or plane crashes. Such information might help in lobbying for increased funding. Possibly insurance companies could be a good source of data for such comparisons. [recommendation]

4 How might healthcare better assess the impact of resistance? An economic model for determining the societal costs. *Marcus Keogh-Brown. London School Hygiene and Tropical Medicine*

This novel approach uses a model based on the macroeconomic perspective in contrast to traditional health economic approaches which tend to focus on the microeconomics of healthcare sector costs. These centre on the costs of illness and then scale up costs to individual patients. This model attempts to calculate the effects on the UK economy as a whole and considers how absenteeism might impact

on productivity and whether the economy as a whole benefits from government expenditure on health. The model uses a system of equations to specify behaviours of various agents within the economy. These include how Consumers decide what to consume and how much to save, for example given £10 extra income, would this be spent on luxuries or saved? Producers need to maximise profits and/or reduce costs and the Government collects taxes and pays benefits. The equation needs an economic data set of income/expenditure for a given year and this must be balanced. This is then solved using a computer algebraic system.

Main assumptions on which the model is based

The main assumption made is that antibiotic resistance increases morbidity, reducing labour supply and output. Producing goods requires a combination of labour, capital/land/natural resources and intermediate goods (raw materials). Combinations of these are defined by the equations and parameters of the model. Estimating the reduction in labour supply is done by first estimating the frequency of resistance in future years (such as has been done by Austin *et al* in 1999) and then estimating the frequency of reduced resistance, for example decreasing DDDs to reflect reduced prescribing, or a reduction in resistance after the introduction of a new antibiotic. These calculations are then multiplied by the absence from work as a consequence of infections caused by antibiotic resistant organisms. Unfortunately calculating this value is difficult as more data are needed. GRACE/CHAMP data suggests that LRTI can cause an absence of approximately 2 days/year – 1%. This seems a surprisingly low figure and the model has thus used 1%, 5%, 10% and 15% to calculate the possible economic savings of a reduction in prescribing or of the impact of a new antibiotic. The impact has been calculated as a percentage change in GDP over 5 year periods up to 55 years and as cumulative savings to the GDP. Intervention can be shown to reduce DDDs by 5% and this includes an intervention campaign cost of £6.2m per year. An additional parameter that could be built in is whether an individual can work but at a lower efficiency. The effects on different sectors of the economy vary considerably, with labour intensive sectors losing most and capital intensive sectors (such as agriculture) losing least.

What can be learnt from this model?

The model indicates that a small change in prescribing (5%) could save £billions over time and that the savings are economy-wide not just for the health sector. Intervening early to reduce antibiotic resistance is important but these results are dependent on assumptions and the scenarios reflect campaigns not new antibiotics. Further work is required in several aspects of the model – assumptions need to be refined particularly on the relationship between prescribing, antibiotic resistance and absenteeism and the impact of interventions (or new antibiotics) on the number of antibiotic resistant bacteria. The use of a sigmoid curve as in the Austin data, needs reassessing. Detailed dynamic health sector modelling is needed and the ultimate impact of resistance on health and healthcare calculated.

KEY POINTS ARISING FROM DISCUSSION

The results of the model are highly dependent on the use of the sigmoid curve and whether it is 1%, 5% etc. Some historical data are available on a 30% reduction in community prescribing of antibiotics between 1997 and 2000 – this could prove valuable information to feed into the model, but this has

not been done. A major problem perceived is in trying to get an overall figure from situations where there are many different organisms with different rates of antibiotic resistance. Is the sigmoid curve (as used by Austin *et al*,) sufficiently robust to do this? It was felt that it may not be particularly robust, but it appears to be the best estimate available currently. The point was made that these data are now quite old and perhaps need revisiting since they have been based predominantly on pneumococci. An interesting point which is not included, but could be, is the impact of vaccines; for example, a reduction in erythromycin resistance to pneumococci following the use of pneumococcal vaccine. There is a lot of information on the impact following the introduction of linezolid – nearly a decade of information, data which could also be of value.

5 National UK and local assessments, *Kieran Hand, UKCPA*

if there are unlimited resources then there would be no problem in prescribing an antibiotic with a high rate of cure but with a high cost, however, when resources are finite, this becomes more problematic, although it can often be possible to identify the patients who would benefit from the more expensive agent, giving a greater cost-effectiveness. Within the NHS, however, the situation is not straightforward and is affected by many factors. Improvements in recognising the patients, who would benefit from the expensive drug and thus improve cost-effectiveness, are needed and would help but unfortunately cost-effectiveness is often over-ruled by the political climate. Doctors generally will not accept that there is a finite budget when faced with the possibility of a dying patient. A predominant factor that comes into play within the NHS is a cost comparison where the cheaper drug is usually favoured unless the more expensive option can be shown to free up resources for other patients. The consequences of cost are seen as an incremental cost-effectiveness ratio, i.e. the cost per additional outcome gained or prevented. The cost benefit is the benefits assigned monetary value such as early discharge – this parameter is nevertheless a controversial one.

Local UK assessments

Local considerations differ from national ones. There is usually a positive financial incentive to the hospital to reduce the length of stay. The Trust will still retain the full tariff for the patient as if they had stayed until the trim point. A bed occupied by the patient attracts a new tariff and if a bed is released in the ICU this may allow elective surgery and reduce waiting lists, provided that theatre capacity is available. Problems can arise if the PCT is not able to afford further activity and the Trust can only gain by closing beds. Tariffs can be recalculated to reduce payments to the Trust if it becomes more efficient. Pressure on spending on drugs is viewed independently from outcomes – this is something that is gradually changing. The PCT or family or carers may incur more costs in managing patients who are discharged early; this may lead to patient dissatisfaction. Others factors in this complex equation include the use of unlicensed imported antibiotics used for 'unmet clinical needs' and the use of new and old antibiotics used off-label for difficult infections. There are currently no mechanisms or resources for collecting and sharing outcome data.

Suggested improvements

Possible improvements suggested are increased NHS clinical research fellowships which could provide the resource to collaborate with academia and/or industry and such partnerships with GP

commissioners, PCTs and hospital managers could be invaluable. They could provide support to local D&T committees in more holistic cost-benefit analyses to reveal the true health system value for money. They might also explore novel funding arrangements and collect outcome data.

National UK assessments – the Darzi report

The National perspective has been outlined in the recent report from Lord Darzi summed up as 'high quality care for all: quality at the heart of everything we do.' Major features include two aspects of patient safety; healthcare associated infections and serious adverse drug reactions. Possible innovations suggested by the speaker are avoidance of disturbing normal gut flora and thus the risk of HCAI by use of an antibiotic targeting *S. pneumoniae* alone combined with a highly specific point of care diagnostic. To avoid adverse drug reactions a designer aminoglycoside with low affinity for megalin is suggested and a rapid test kit for serious penicillin allergy. In terms of the patient experience and effectiveness of care, possible approaches are an oral antibiotic which can penetrate tissues well enough to treat bone and joint infections, thus allowing early discharge. To cope with MDR Gram-negative bacteria a bactericidal non-toxic agent active against carbapenem-resistant strains is needed. Faster acting antibiotics are needed to treat severe sepsis or septic shock and possibly reduce the need for admission to the ICU.

The Darzi report has a section on 'Fostering innovation' which states that clinically and cost effective innovation in medicines and medical technologies will be adopted and that new partnerships between the NHS, universities and industry will be created. A Commissioning for Quality and Innovation scheme is planned which is intended to encourage all NHS organisations to pay a higher regards to quality. It states that the scheme will be flexible to suit local circumstances.

Summary of the situation

Antibiotics are under appreciated and taken for granted. More knowledge is required on the burden of infectious disease on society and these needs to be communicated both to the public and to Government. Comparative statistics on the cost-effectiveness of antibiotics relative to drugs in other therapeutic areas are lacking and a stronger case should be made on the value for money that antibiotics provide. Lobbying for reimbursement at a level that reflects their true worth is needed. NICE and the SMC should consider antibiotics as a special case. Investment on antibiotic R&D from public funds, such as the situation in other fields, is needed.

KEY POINTS ARISING FROM DISCUSSION

The dilemma of why cancer drugs demand and get a high price while antibacterials are costed so low was aired. This seems to come down to public perception and cancer being such an emotive area; the debate is rarely logical but emotive. Whether a very expensive antibacterial agent would get used would depend on getting all stakeholders to agree and backing this up with very convincing arguments on its efficacy.

Comparative figures of efficacy for drugs used in other areas such as strokes or heart attacks might prove useful, although they seem hard to get. All of these areas have prominent charities which publicise and fund raise; there is no equivalent for bacterial infections. There is a need to raise public

awareness. Many PCTs do surveys of patients' requirements and antibacterials are hardly ever mentioned, with the exception of MRSA .

Mortality rates are needed to emphasize that antibacterials are saving life in contrast to some other areas (e.g. clot buster drugs) where the underlying disease is still present. Using individual cases is a possibility but carries risks as many patients who died of MDR infections had other underlying problems.

There is a lack of information on outcomes – for example real time information on length of stay; in contrast such data are available for newer cancer drugs. Apparently the PCTs are meant to be monitored but there are often insufficient resources to ensure that this happens. Mortality is difficult to assess as it is often divided into separate sections – UTI, cardiac and finding out precisely what is attributable to infection is difficult.

It was pointed out that liposomal amphotericin B is very expensive compared with conventional amphotericin B and has quite wide use, but this drug is perceived as being more effective/less toxic and is generally being used in bone transplant wards where higher costs are accepted.

6. NICE assessments, *Sarah Garner, National Institute for Clinical Excellence*.

The current NICE recommendations relating to the use of antibiotics in the management of infectious diseases were outlined. These are few and the website lists completed guidelines only on the following areas – feverish illness in children, infection control, surgical site infection, and tuberculosis and urinary tract infection in children. In addition the following guidelines are in development; antibiotics for neonatal infection, bacterial meningitis and meningococcal septicaemia in children, an update on infection control, neutropenic sepsis and an update on interferon gamma tests for tuberculosis. The list of completed appraisals presented did not include any on antibacterials, they were all antivirals. Similarly the public health guidelines under development were all antiviral plus one on tuberculosis in hard to reach groups. There is one guideline completed on the prevention of sexually transmitted infections. To address the question of what consideration is taken by NICE on antibiotic resistance as it impacts on recommendations and what mechanisms there are for reviewing guidance in response to concerns about resistance, a proposed template was presented. This is under discussion and would comprise a list of the available antimicrobials classified as those available for unrestricted use, those limited to specific use for specific conditions, such as co-trimoxazole for *Pneumocystis* and those requiring the approval of a consultant microbiologist. Regimens for the treatment of common infections included first and second line drugs, dose, route of administration, duration of treatment and intravenous to oral switch. The SACAR top 20 would also be considered. The path from evidence to recommendations was described for anti-tubercular therapy, but no such data were presented on other antibacterial.

KEY POINTS ARISING FROM DISCUSSION

It is disheartening that when important surveys have been published such as the House of Lords

report on resistance being a major threat to human health, that NICE still does not seem to have tackled this topic. It is clear that antibacterials are "low on the horizon" for NICE and that there is insufficient engagement with the area of infectious diseases. It was stated that there is confusion as to where the responsibility lies and there is a perception that explicit decision making and the preparation of guidelines are the domain of the HPA. It was also suggested that an advisory group could help even just for a one off piece of work.

It was stated that the reimbursement decision process needs redefining. The starting point from NICE is the licensing indication and these are very specific. The HPA has released very few guidelines, nor have NICE; most guidelines on infectious disease come from the various professional organisations.

Antibiotics are relatively cheap and thus are not submitted to NICE. It is interesting to speculate about a mythical new agent that was very expensive but also exceptionally highly effective. Would NICE approve it for use - this situation has never arisen but apparently NICE examines the ratio of cost to benefit rather than the overall budget. This comes back to the need for better data on mortality and outcomes.

7 A view from Big Pharma, *David Findlay, GSK*

Two key drivers impact on how Big Pharma allocates resources to R&D. One is value in terms of patient need and commercial return. The other is the probability of success of developing the candidate drug. This includes scientific, medical and technical issues as well as regulatory issues. Similarly, investment decisions are affected by the same issues.

ROI and eNPV

The potential return on investment of a development candidate is often measured by risk-adjusted net present value or eNPV. The various sources of pressure on the return on investment (ROI) were described. These include increasing risk, increasing costs and decreasing revenues. Long timelines and high attrition rates in novel classes contribute to the increasing costs in antibacterial drug discovery. Development is becoming longer and more complex, with a success rate now of < 50%. Other factors affecting the increased costs are various pre-launch factors such as the increasingly complex regulatory packages and the changes in clinical end points (for example, superiority studies versus non-inferiority). Post launch factors include the cost of goods, sales and marketing and life-cycle management. The time a compound remains on the market is affected by increasingly complex regulatory requirements and the transition to generic status, leading to decreasing revenues. The volume of sales of anti-infectives can be impacted adversely by restrictions of use for infections caused by antibiotic resistant pathogens. Although anti-infectives save lives, they are not priced in a fashion that is commensurate with this life-saving role since there is a perception that they should be cheap. Will Society be willing to pay for new agents that are active against multi-resistant organisms?

R&D budgets are limited and thus Big Pharma cannot afford to look at the ROI for an individual project in isolation but in comparison with other therapeutic areas, balancing the possible value (low to high) with the probability of success (low to high). Anti-infectives have an approximate third lower

estimated NPV relative to oncology drugs and about tenfold lower than musculoskeletal drugs. Anti-infectives tend to have low volume use in a low price market. These commercial factors present hurdles which limit the potential for a new anti-infective.

Possible solutions

Increased dialogue is needed between all stakeholders – governments, patients, payers, scientific/clinical community and 'Big Pharma', but with a focus on implementation. A variety of hurdles need to be addressed to attract different organisations into antibacterial R&D.

The approach needs to be global, not local. Measure what is important, not what is easy to measure, thus price is easy to measure but efficacy is more important. Antibiotics *are* different, and need to be priced according to value, not in comparison to old, increasingly ineffective products – low price is not necessarily a benefit to society.

R&D is expensive and will suffer if it is not funded through appropriate (non-generic) price (or other financial lever). In contrast generic companies do not need to fund large R&D programmes. The focus should be on value, not cost.

Public/private partnerships have provided external funding in the US.

KEY POINTS ARISING FROM DISCUSSON

Calculations of NPV are frequently not accurate – this is not an exact science, so one cannot predict a precise figure required to make an area worthwhile. In addition, the climate may change affecting the potential of a product, for the good or otherwise – the market for linezolid for example was predicated on a rise in MRSA in the community and ertapenem's success is because of the unexpected rise in ESBL-producing E. coli.

There are no hard and fast rules regarding pricing; it is possible for some countries, including the UK and Germany, to increase prices unilaterally, but this is not possible in all countries.

An agent could be progressed for a narrower market, such as Europe, which is now a substantial size, if the compound had no clear role in the US.

8 Intervention in the market for priority MDR bacterial treatments: Justification and considerations for incentive design. The 'push: pull' strategy, *Chantal Morel, London School of Economics*.

The major factors affecting the lack of new antibacterials are predominantly regulatory, and include problems over clinical trials, with shifting requirements, a lack of good diagnostics, inadequate guidelines for use and a low tolerance for side effects. In addition there is a perception of low profitability caused by the presence of generic products, conservation policies and a limited duration

of treatment. Estimates of the NPV for antibacterials for Gram-positive infections have been calculated as being lower than those for vaccines, oncology, CNS and musculoskeletal diseases. Nevertheless, there is justification for intervention in the market as there is a high probability of an impending health crisis. There are many market failures and there is a high cost of antibiotic resistance which is not reflected in the actual cost of the drugs.

Push or Pull strategies

The use of "Push/Pull" strategies is an approach that suggests that interventions can take the form of 'push' or 'pull' strategies and combinations of these. 'Push' interventions can include incentives such as grants and fellowships, funding for translational research, support for open access research, early R&D tax incentives or product development partnerships. 'Pull' interventions include lump sum monetary prizes, milestone monetary prizes, optional rewards (patent or patent buyout), patent pool, research tournaments and advanced market commitments. Other possibilities are lego-regulatory 'pull' incentives such as accelerated assessment and/or approvals, vouchers for accelerated assessment, pricing and reimbursement adjustments, extensions of IP, wildcard patent extensions, antitrust waivers and use of an antibiotic and conservation effectiveness model. A combination of 'push and pull' could be orphan drug legislation or call options of antibiotics model.

Advantages and disadvantages

The advantages of the 'push' approach are that this requires a smaller financial outlay, removes barriers to entry, attracts SMEs and is useful for encouraging discrete steps in R&D. The disadvantages are that the risks are borne almost entirely by the funder, unsuccessful research may be funded, and there are risks in dampening entrepreneurial momentum. The advantages of the 'pull' strategy are that only successful research is funded, developer inefficiencies are minimized, and it is more likely to encourage final product development. The disadvantages of this approach are that the risk is borne entirely by the developer, it only attracts larger companies with significant funding, the promise of large reward may lack credibility because of political and budgeting changes over the duration of product development and there may be difficulties in predicting an appropriate size of award. The lego-regulatory approach has the advantage of maintaining a link between product use and the size of reward but may impede competition.

Most Promising incentives

This study concludes that the most promising 'push' incentive mechanisms are tax incentives but that these must not be tied to sales or profits; funding for translational research, this would be initially in academia and then passed to companies; and grants and fellowships. The most promising pull/lego-regulatory mechanisms are pricing and reimbursements incentives as marketing exclusivity is very important, and limited IP extensions. Among combination approaches the most attractive are the call options model whereby a given amount is paid, usually less at the beginning, for a future possible drug, and special designations such as for orphan drug status. (Anti-infectives can qualify for orphan dug status but currently as the guidelines are written, they do not cover drugs for short use).

KEY POINTS ARISING FROM DISCUSSION

Many of these ideas are still theoretical and better designs are needed before decisions can be made as to their value.

Call options were discussed - in particular how a company decides on the value and what happens if the company gets into difficulties. This is a very early idea and the final report has less on this. This approach is highly dependant on the initial description of the product.

CLOSING DISCUSSION: KEY POINTS & RECOMMENDATIONS

9 Working Party Discussion.

There were some useful and novel approaches but several were either in an early stage of development or lacked good data to be of much value.

- European SWOT analysis was a good approach but although showing some impact of the increase in resistance was felt to be too difficult to quantify. It also suffered from the lack of important data.
- The economic model might have the potential for estimating societal costs but currently was inadequate and seemed to be trying to do too much with very few facts. Of particular concern is the variability of many organisms with differing types of resistance and seeing how an overall value could be calculated.
- It is clear that NICE have not grasped that resistance to antimicrobials is a subject that they should be tackling.
- The push/pull approach still needs refining.

General points that emerged throughout were:

- Reluctance for the market to pay the true value for an antibacterial although being prepared to pay for niche products and anticancer drugs.
- problems in measuring efficacy of antibacterials
- a need for comparisons in efficacy between infection and other disease areas
- a need for mortality data between infection and other disease area and non-disease areas (e.g. accidents)
- Need for guidelines.

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