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Science Advisory Council

Tackling antibacterial resistance in Europe

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Foreword

Since the discovery of penicillin some 80 years ago, the use of antibiotics has made major contributions to public health. Antibiotics remain of the utmost importance in clinical practice worldwide. However, the earlier forecasts that infectious disease had been conquered were found to be excessively optimistic.

The burden of infectious disease has been compounded by the emergence of resistance to antimicrobial drugs, and this growing resistance undermines many clinical and public health programmes. The remarkable ability of bacteria to develop resistance to the different classes of antibiotic agent also places an increasing economic burden on healthcare systems in Europe, despite the multiple efforts by professional, national and European agencies to contain the threat.

This report is the third in a series published by the European Academies Science Advisory Council (EASAC) on strategic scientific issues in combating infectious disease. Our previous reports:

(i)   'Infectious diseases – importance of co-ordinated activity in Europe' (May 2005); and

(ii)   'Vaccines: innovation and human health' (May 2006);

identified European priorities for public health and innovation associated with disease surveillance and control, infrastructure and skills, and the support for research and development of novel products and services. These themes are further explored in the present report with specific reference to the crucial need to augment efforts to tackle antibacterial resistance.

We recognise that there are a significant number of previous reports dealing with this general area but, in our view, there is a continuing need to provide objective, impartial analysis and dispel complacency. In emphasising the importance of these issues across the European Union, we take this opportunity to describe the valuable contribution that can be made by scientific endeavour, both in providing new tools to tackle the problem and to inform evidence-based policy-making. There is considerable potential for Europe to provide a leadership role in the efforts worldwide to promote anti-infective research and innovation, and to translate these efforts into sustainable health benefits.

We agree with other recent recommendations that more can and should be done to contain the spread of resistance in hospitals and in the community by improved surveillance and control measures. However, in our view, this is not nearly sufficient. We now highlight the central importance of supporting research to identify and validate new targets and, at the same time, promoting the development of novel diagnostic and therapeutic agents. Achieving these priorities will require sustained commitment from both the public and private sectors, with the continuing challenge to identify and reward partnership initiatives. Effort must also continue to be made to clarify where there is still uncertainty and controversy about the proposed solutions.

The report is addressed to policy-makers in EU institutions and at Member State level, to research funders, professional and regulatory bodies, to companies, and to all interested parties. The recommended agenda for action requires both heightened awareness and effective coordination across a broad front, integrating work at the European and national levels and taking account of the relevant global developments.

Our objective, as in previous reports, is to provide the scientific evidence to inform and stimulate further debate on the opportunities and threats and to indicate some specific options for change, while welcoming what is already being achieved in Europe. I believe that this report does much to continue the tradition established by previous EASAC publications to provide an independent source of high-quality, expert advice at the European level about the scientific aspects of public policy issues. Furthermore, this report demonstrates again the growing capability of EASAC to serve as a means for the science academies of the EU to work together on policy issues and furnish policy-makers with the evidence base with which to inform their strategic actions.

The report, undertaken at EASAC's own initiative and expense, was prepared by a working group chaired by Professor Volker ter Meulen of the German Academy of Sciences Leopoldina and was independently reviewed following procedures established by the Council of EASAC, and approved for publication by the Council of EASAC. On behalf of EASAC, I again express my thanks to Professor ter Meulen and his colleagues for giving their time so generously.

EASAC will continue to address other issues within the broad domain of infectious disease policy and to build the links necessary to help take forward the present recommendations at European Union and Member State levels. I welcome feedback on any of the points raised in our report.

Professor David Spearman
Chairman, EASAC

Summary

Antimicrobial resistance is a global pandemic. The worldwide use of antimicrobial compounds to treat infection leads to the evolution of microbes resistant to these compounds. Beginning in the 1930s, antibiotics have had a near-miraculous impact on human and animal mortality and morbidity caused by bacterial infections. They have also been exploited for other uses, such as improved yields of meat from animals. The price of these dramatic benefits is that the prevalence of resistant microbes has dramatically increased to the point where, in some cases, antibiotics are no longer effective. Major problems are encountered for a growing number of pathogens including *Staphylococcus aureus*, *Clostridium difficile*, *Streptococcus pneumoniae*, *Escherichia coli*, *Acinetobacter baumannii* and *Mycobacterium tuberculosis*. The general trend to more widespread antibiotic resistance is relentless and, if it continues unabated, deaths from what were previously treatable infections will occur with increasing frequency.

Building on the findings of previous European Academies Science Advisory Council (EASAC) reports on infectious disease, and taking account both of the research and surveillance efforts already underway and of the recommendations previously made by various other bodies at national and international levels, the Working Group identified some major challenges and opportunities for policy development to tackle antibacterial drug resistance across a broad front. Policies that can be expected to have an impact in the relatively short term include: *heightening awareness* – measures to communicate, and quantify, the problem to policy-makers, health professionals and the general public; *improved and co-ordinated surveillance* – strategies to characterise the different types and degrees of bacterial resistance in both commensal and pathogenic bacteria across the European Union (EU); *prudent antibiotic use* – using evidence-based measures in both human and veterinary medicine; *containing the spread of resistance* – implementation of infection control methods in communities and hospitals; *co-ordination* – actions to build coherence in policies, data collection and intervention strategies among Member States. Co-ordinated action must address the veterinary as well as human health use of antibiotics. It is estimated that more than half of all antibiotics produced worldwide are used in animals: there is need to continue developing the evidence base to assess the risks to human health associated with the presence in food and feed of antibacterial-resistant micro-organisms.

However, these antibiotic reduction and resistance surveillance and containment measures alone are not enough. There is also need for commitment to research and development (R&D) to deliver new agents. This investment must be sustained for the longer term to realise the full consummation of research opportunities. The initiatives must be implemented now because the battle against antibiotic resistance is being lost: complacency and delay will have major detrimental effects on future European public health. We emphasise the importance to:

- *Develop novel rapid diagnostics*: standardised methodologies, sensitive, simple and cheap to use at point of care, able rapidly to differentiate between bacterial and viral infections, to identify specific pathogens and resistance profiles. Discussion on key priorities, resources and opportunities for collaborative effort requires companies and their trade bodies to engage further with the European Commission (particularly DG Sanco, DG research and DG Enterprise and Industry) as well as capitalising on current activities at Member State level.

- *Strengthen the science base*: including the relevant teaching and training, to facilitate, for example, antibacterial strategies through identification and characterisation of novel drug targets and the improved molecular epidemiological understanding of resistance mechanisms and their spread. There are also major opportunities for supporting translational clinical research and the economic assessment of disease burden and treatment. Broadly, the social sciences need to be more involved in studies concerning antibiotic usage and infection control. It is important for the scientific community to continue to work with DG Research and Member State funding agencies to identify the new approaches in basic research and to stimulate translational clinical research. It is also important for Members of the European Parliament to understand the great importance of sustained support for research in this area.

- *Support industry innovation in drug development*: the generation of new antibiotics is a lengthy, expensive and complex process. It is important to address the current impediments to innovation for both large pharmaceutical and smaller biotechnology companies by facilitating public–private partnerships and rationalising regulatory requirements so as to encourage development without compromise to safety and efficacy. The smaller company sector requires additional types of public support in seed-corn and later funding, at least up to the stage of pharmacological and therapeutic proofs of

concept. Recent pharmaceutical R&D investment has grown less in Europe than in the USA and there is need to consider new ways to provide support for industry R&D. Members of the European Parliament must also understand the importance of sustained support for innovation in this area. There is a broad array of tractable measures to address the current market failure in R&D in anti-infectives. These measures include policy development and legislative action by the European Commission and Member States, regulatory action by the European Medicines Agency (EMEA) and an increased surveillance function by the European Centre for Disease Prevention and Control (ECDC). The European Technology Platform Innovative Medicines Initiative has good potential to be a catalyst to stimulate collaboration across the public and private sectors and it is important for Member States to support the European Commission proposal to transform this Technology Platform into a Joint Technology Initiative with the independence and resources to make a real difference.

Our main message is that urgent action is needed to build the EU leadership position in efforts worldwide and in drawing on Member State activity, both in the short-term through co-ordinating surveillance, monitoring trends and containing the spread of antibiotic resistance, and in the longer-term through progressing the underpinning science to deliver innovative approaches to tackling drug resistance. These leadership roles are a major responsibility and of crucial importance for the European Commission and its agencies, the European Parliament and for private sector companies and their trade bodies.

1 Introduction

1.1 Pandemic of antibacterial resistance

Antimicrobial resistance – micro-organisms that have developed resistance to currently available microbial agents – has become a global pandemic. However, there is complacency about the necessary control measures and a relative lack of attention to the contribution that can be made by developments in new technology. As the World Health Organization (WHO) (2004) stated unambiguously, '*Today we are witnessing the emergence of drug resistance along with a decline in the discovery of new antibacterials . . . As a result, we are facing the possibility of a future without effective antibiotics. This would fundamentally change the way modern medicine is practised*.'

Infectious disease is the third leading cause of death in Europe, mostly in elderly and debilitated populations despite the existing therapies and vaccines (Vicente et al. 2006). Antibiotic resistance forms a prominent part of the challenge of tackling infectious diseases.

There has already been significant activity by national and international organisations to draw attention to the reasons for this growth in resistance. Some important changes have been made in some countries, for example in improving surveillance and infection control systems. However, the requirement to develop new therapeutic agents and vaccines remains urgent. Notwithstanding the difficulties in making progress in this area, EASAC judged that now is an important time to reinforce the messages about the threat of antibiotic resistance in the EU. It has done this to clarify what is tractable and to emphasise how the EU can take a leadership position in supporting research and innovation and the translation into improved clinical practice.

1.2 Previous EASAC work on infectious diseases

In an initial report, EASAC (2005) presented the general case for increased investment and coherence to support better responsiveness in infectious diseases with particular regard to: (i) disease surveillance and control systems; (ii) public health infrastructure to build national infrastructure and EU-wide co-ordination; (iii) development of novel applications in vaccines, diagnostics and therapeutics; and (iv) research and training in both basic and clinical science with concerted effort across human and veterinary sciences.

This EASAC (2005) report endorsed action for tackling antibiotic resistance:

- Supporting more research on the relation between antibiotic prescribing and development of resistance across Member States.

- Establishing the extent to which antibiotic use in farm animals contributes to resistance in humans.

- Understanding the scientific basis of the development of resistance, for example in terms of mechanisms of gene transfer.

- Providing support and incentives for private sector R&D to pursue new targets for anti-infective agents.

Concern about tackling antibiotic resistance was prominent in feedback to the EASAC (2005) report received from European opinion leaders. Respondents agreed that the national academies of science were well placed to advise on the scientific priorities and infrastructure needed to build a strong programme of European research on antibiotic resistance. Follow-up discussion emphasised that the growing problem of resistance will be compounded by demographic changes in an ageing population, increasing global infection rates and increasing numbers of immunocompromised patients. When EASAC published a report on vaccines in 2006, feedbackto that report welcomed the recommendations promoting R&D, manufacturing and uptake of vaccines as a potentially important contribution to reducing the frequency of infection and, in consequence, reducing antibiotic use and development of resistance.

1.3 EASAC project on antibacterial resistance

Following the feedback received, the EASAC Council agreed to constitute a new Working Group with a remit to cover in detail a range of policy issues relating to the opportunities and challenges for addressing antibiotic resistance, to include:

- Current clinical problems and EU vulnerability.

- Public health and the economic impact of antibiotic resistance.

- Novel scientific approaches – using life sciences to identify new targets and understand host susceptibility to infection.

- Expansion of research on social and behavioural issues related to infection control and prescribing.

- Issues for building public sector research infrastructure and partnership with private sector R&D.

- Innovative drug development – issues for building and supporting commitment by companies in the pharmaceutical and biotechnology sectors.

- Improving EU competitiveness by identifying and removing bottlenecks in R&D and innovation.

The Working Group focused on bacterial resistance as the priority problem but it is important to note that increasing resistance is also becoming a problem for other microbes. In reviewing the present status of antibacterial drug resistance in Europe, taking account of other recent recommendations and drawing on the expertise of the scientific community, this EASAC report emphasises the importance of knowledge creation – the necessity of research to underpin science-based prescribing for public health and to deliver new concepts, new drugs and diagnostics.

2   Current status of policy and research activity

2.1 Priority to focus on innovation

The WHO report 'Priority Medicines for Europe and the World' (2004) assesses antibacterial drug resistance to be the most important global health challenge and recommends co-ordinated international action:

- Reducing inappropriate use of antibiotics in man by implementing evidence-based public health interventions, improving prescribing and dispensing practices.

- Conducting surveillance of resistance and antibiotic consumption in hospitals and the community.

- Investing in basic and applied research and innovation on antibacterial drugs to arrest the decline in development of new agents.

There is already considerable activity by individual Member States and the European Commission, especially to address issues of antibiotic resistance surveillance and antibiotic use. There have been several important strategy documents from European Institutions, for example the EU Council Recommendation on prudent use of antimicrobial agents in human medicine in 2001 (2002/77/EC). This Recommendation was followed by a report from the Commission to Council in 2005 (COM (2005) 0684) supplemented by a detailed analysis (SEC (2005) 1746) describing how Member States reported their implementation of the Recommendation in terms of their national strategies, surveillance systems for antimicrobial use and antimicrobial resistance, control and preventive measures, research, education and training. Although this Commission summary of Member State self-reporting is valuable, it now needs to be supplemented by independent, evidence-based bench-marking to validate and ensure comparability of the assessments made at national level.

Progress has been made in developing and – to an extent – sharing good practice in infection control measures (screening and isolating patients, better hygiene). The launch of the ECDC provides a major opportunity for creation of a coherent EU-wide surveillance system to link antibiotic resistance surveillance, monitoring of drug consumption and prescribing practices, and the application of interventions to prevent emergence of resistance. However, there are problems of standardising and collecting data and potential ethical constraints in linking and using data. We welcome the current activity of the ECDC in addressing antimicrobial resistance as a priority topic and support their plan to review the ability of Member States to tackle the issues; we will discuss subsequently the options for further co-ordination.

The Commission's analysis document (SEC (2005) 1746) identifies current implementation gaps and, in the view of the EASAC Working Group, there is much more still to be done to develop consistent, high-quality infection control strategies and to support prudent use of therapy: for example by developing evidence-based guidelines at the EU level for disease management and by using computer-assisted selection of therapies as part of decision-making protocols.

Science and Technology Options Assessment (STOA) Report

A major recent report commissioned by the European Parliament provides a useful summary of various issues relating to antibiotic resistance in Europe and recommends an increasing focus on the containment of resistance (Box 1).

Box 1 Report commissioned by the European Parliament on antibiotic resistance

The report recommends applying resources in the containment of resistance rather than the development of new therapeutic approaches:

'We cannot wait any longer for the discovery of new antibiotic drugs . . . Containment of the development and spread of resistance must therefore be given first priority. Action is required to tackle the over-use of antibiotics and the spread of infection.'

The proposed action plan includes:

- *Co-ordination*: to increase the role and scope of the ECDC in co-ordinating European strategy with respect to antimicrobial resistance.

- *Standardisation*: to encourage 'prescription only' policies within Member States, and to develop Europe-wide accreditation programmes covering hygiene, health, day-care and building standards.

- *Stimulation*: to encourage use of rapid diagnostics and to provide fund-matching schemes for educational campaigns.

- *Research*: on ways to contain resistance.

European Technology Assessment Group for STOA, January 2007, IP/A/STOA/ST/2006–4

The EASAC Working Group agrees with these recommendations for short-term policy actions to rationalise the use of antibiotics and reduce the spread of antibiotic resistant organisms. To be credible, and to achieve these recommended objectives, there is further

work to be done in (i) building the evidence base to substantiate the proposed actions and (ii) clarifying the roles for those identified as responsible for the actions. Such clarification is needed to determine what can already be accomplished under current mandates and what requires new mandates or the development of new policy advisory roles.

However, the EASAC Working Group was not optimistic that the proposed action plan (Box 1) could achieve the level of desired effects. There is doubt about the current ability of all Member States to comply with the reduction and surveillance measures. Furthermore, antibiotic selection pressures will still drive resistance even if consumption is reduced and the reversibility of resistance can be very slow. Therefore, the EASAC Working Group disagreed strongly with the conclusion in the European Parliament report that sustained investment in R&D to deliver new antibiotics has less priority than the short-term objective of containing resistance. Containment will not be enough and a longer-term vision is vital. Although the European Parliament report itself does not entirely dismiss the longer-term opportunities in support of innovation, the accompanying press release conveys the unfortunate impression that the search for new drugs does not merit additional resources.[1]

This goal, to deliver new drugs, is tractable – advances in fundamental research are bringing new opportunities within range – but the goal cannot be accomplished without reinforcing commitment to building research infrastructure, human resources and partnership. The lack of new anti-infective drugs in prospect was discussed at the EU InterGovernmental Conference (Finch & Hunter 2006) held during the UK's Presidency of the European Council in 2005. The need to provide new support to companies and to collaboration has also been discussed extensively in the USA, notably in response to the initiative by the Infectious Diseases Society of America (IDSA, 2004). In this respect, the purpose of the present report is to clarify some of the issues for the EU and to explore how innovation capacity can be built by partnership across the public and private research sectors.

2.2 European research support

The European Commission has provided financial support for research on infectious diseases, particularly in human

immunodeficiency virus (HIV) and other specific areas, and for networking activities between leading research groups through the Framework Programmes.[2] A comprehensive strategy for research on antimicrobial resistance was supported by Framework Programme 5 within the Quality of Life Programme, and details of all relevant projects, approximately 80, were published by DG Research (Lonnroth 2003).

While a broad range of research was supported in Framework Programme 5, some of the most interesting initiatives in the context of the current report were aimed at setting up new surveillance networks and databases, some of which are listed in Table 1 as background to further discussion of the current clinical situation in Europe in the next chapter. This research by large collaborative projects is a vital resource for evidence-based policy-making in Europe. However, there has been less funding allocated at the national level, with the consequence that the performance of national surveillance networks is very varied. Furthermore, we advise that it is important to extend EU surveillance network development initiatives to include non-EU countries – which may require EU funding – and, as discussed subsequently, to ensure appropriate standardisation of methodologies to support connectivity between EU and other (particularly US) databases.

Framework Programme 6 is also now funding a broad range of research on resistance surveillance, genetic elements and mechanisms of dissemination of resistance genes, identification of new therapeutic targets and support for rapid diagnosis, some of which will be referred to subsequently.

For Framework Programme 7 (started 2007), there will also be considerable coverage of antimicrobial drug resistance within the overall health theme of translational research in major infectious diseases, combining basic research on molecular mechanisms of resistance, microbial ecology and host–pathogen interactions with clinical research towards new interventions to reduce the emergence and spread of multi-drug resistance. We will discuss subsequently priority topics for Framework Programme 7 and the link with the proposed European Technology Platform on Innovative Medicines (www.imi-europe.org).

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[1] Press release 24 January 2007 includes the statement: 'Previous reports on antibiotic resistance have frequently advocated increased research into the development of new antibiotic drugs, but this approach is rejected in this latest report.'

[2] There is also relevant research funded by individual Member States. In the context of taking the pan-European perspective on developments, mention should also be made of the National Research Program 'Antibiotic Resistance' in Switzerland (Swiss National Science Foundation 2003), which is of particular interest in funding a multidisciplinary strategy to cover a wide range of issues: (i) develop scientific strategies and new methods for resistance surveillance; (ii) analyse resistance in Switzerland in human and animal populations and the environment; (iii) determine the spread of resistant bacteria and resistance genes and assess the risk; (iv) promote molecular studies for the development of new antibiotics and diagnostics; and (v) evaluate social, legal, ethical and economic consequences of resistance.

***Table 1 Antimicrobial resistance research
supported by the European Commission: examples
of surveillance networks, databases and strategy
development***

Project acronym	Description	Link
Gene	Framework Programme 5 (FP5) Network for automated bacterial strain fingerprinting	www.ewi.med.uu.nl/gene
ARPAC	FP5 Development of strategies for control and prevention of resistance in hospitals	www.abdn.ac.uk/arpac
ESAC	Funded by ECDC; Scientific evaluation on use of antimicrobial agents in human therapy	www.esac.ua.ac.be
ARMed	FP5 Antibiotic resistance surveillance and control in Mediterranean region	www.slh.gov.mt/armed/ overview.asp
EARSS	Funded by ECDC; European antimicrobial resistance surveillance system	www.rivm.nl/earss/about
HELICS	Funded by ECDC; European network of nosocomial infections	http://helics.univ-lyon1.fr/ipsehome.htm
EUCAST	Funded by ECDC; European Committee on Antimicrobial Susceptibility Testing	www.eucast.org

3   Quantifying clinical challenges in Europe

Historically, the public health applications of infectious disease epidemiology have often come much later than the discovery of the microbial causes; this is also true for antimicrobial resistance epidemiology. If this epidemiology is now to occupy a central role in public health science, then it is necessary to integrate research findings from several levels: from analysis at the societal, individual and cellular levels, in order to understand the origins of resistance.

Frequency of antibacterial drug resistance varies considerably between Member States, explained to a significant extent by national differences in antibiotic use and resistance control policies (WHO 2004). There is increasing concern about the problem of resistance in the community as well as in hospital settings. Work in the USA, for example, has found that resistance is an increasing problem in long-term care facilities, but this problem has been relatively poorly studied in Europe. The Working Group noted the valuable impact of the European Commission decision to develop an EMEA crisis management plan for pandemic influenza (EMEA/214301/06) and the public health tools mobilised rapidly in response to the threat of severe acute respiratory syndrome (SARS). In extending the previous EU Council Recommendation described in the chapter 2, we recommend introducing an analogous contingency plan and network for antibiotic-resistant organisms. EU and Member State plans should be scrutinised by the Health Security Committee of DG Sanco and the ECDC, and implementation should be monitored.

3.1 Surveillance data

ESAC (Table 1) is a European network of national surveillance systems aiming to provide comparable antibiotic consumption data; the accumulating evidence base will facilitate further exploration at the local level on the relation between antibiotic consumption and development of resistance. A recent series of papers provides data up to 2003 on trends of use and seasonal variation in hospitals and by outpatients for antibiotics including cephalosporin, macrolide/lincosamide/streptogramin and quinolones. Outpatient antibiotic use varies more than threefold between EU countries. In general, countries in southern and eastern Europe consume more antibiotics than countries in northern Europe (Goossens et al. 2005). There is need for further quantification in several areas: for example, to determine the extent to which broad-spectrum antibiotics are promoted for minor infections and the extent of self-medication in the misuse of antibiotics (Grigoryan et al. 2006).

The European Antimicrobial Resistance Surveillance System (EARSS) (Table 1) maintains a comprehensive surveillance and information system linking national networks to provide comparable, validated data on prevalence and spread of antimicrobial resistance. EARSS collects routine data on the indicator pathogens *Streptococcus pneumoniae*, *Staphyloccus aureus*, *Enterococcus faecalis*, *Enterococcus faecium*, *Escherichia coli*, *Klebsiella pneumoniae* and *Pseudomonas aeruginosa* from 1200 hospitals in 30 European centres. We advise that it is important to continue to build the pan-European approach to comparing standardised datasets in specific settings and key micro-organisms and endeavouring to incorporate denominator data, so that resistance can be characterised according to community and region to define local variations. An international database for tracking strains of several species, using multilocus sequence typing of metabolic genes, is also now available (www.mlst.net) and will help to clarify origins and routes of transmission of resistant clones. This application of molecular epidemiological techniques offers huge potential for detailing resistance at the genotypic rather than traditional phenotypic level. Furthermore, robust datasets can now be used for predicting trends using mathematical modelling.

In industrialised countries, over half of all hospital-acquired infections are caused by drug-resistant micro-organisms (Vicente et al. 2006). Consider the data from just one Member State: in the UK, hospital-acquired infections are estimated to affect more than 300,000 patients every year (9% of patients have an acquired infection at any one time) and account for 5,000 deaths per year (Parliamentary Office of Science and Technology (POST) 2005; however, these estimates are based on data that are a decade old). At the EU level, there are probably more than two million hospitalised patients with nosocomial infections and perhaps 175,000 deaths from infection each year (European Science Foundation 2004). Moreover, resistant pathogens, including methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant and intermediate-resistant *Staphylococcus aureus* and Enterococci are no longer confined to hospitals but are also found in community settings (where more than 80% of antibiotic prescribing occurs).

For the present report, a few indicative points are emphasised for pathogens of particular interest.[3]

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[3] In addition to the sources already mentioned, the publication by the study group of the Paul Ehrlich Gesellschaft provides a comprehensive summary of the situation in Europe (Kresken et al. 2004).

Streptococcus pneumoniae

There is a north–south gradient in Europe for non-susceptibility to penicillin. In Spain and France in 2001, more than 50% of strains were not susceptible to penicillin compared with less than 5% for the UK, Germany and Sweden (Vicente et al. 2006). Resistance is also a significant problem in eastern Europe (for example in Romania it is greater than 25%), USA and southeast Asia, probably as a result of more community prescribing and selection pressure. Resistance to the macrolide erythromycin has also been increasing in Europe with a similar geographical pattern; newer fluoroquinolone resistance rates are comparatively low, but rising fast in some settings (Global Advisory on Antibiotic Resistance Data (GAARD) 2005).

The GRACE Framework Programme 6 project (genomics to combat resistance, www.grace-lrti.org) has initiated a major study of lower respiratory tract illnesses, the most common condition treated in primary care in Europe (and by 2020 it is predicted that chronic obstructive pulmonary disease (COPD),[4] will be the third most common cause of death in Europe). COPD and community-acquired pneumonia will be characterised in terms of the contribution made by antibiotic resistance in *Streptococcus pneumoniae* and *Haemophilus influenzae*. Strains of *H. influenzae* in Europe show small but increasing numbers of isolates with reduced susceptibility to the fluoroquinolones, and the broader pattern of resistance may mimic *Streptococcus pneumoniae*.

Staphylococcus aureus

Some Member States have experienced a dramatic increase in blood culture isolates of MRSA, for example in the UK from less than 5% to more than 50% of infections within the decade 1992–2002. The frequency in the UK now appears to have peaked but recent data show that 25% of patients with MRSA had the disease on admission to hospital (Health Protection Agency 2006). By contrast, in the Netherlands, the prevalence of MRSA has historically been kept very low; only about 2% in unselected hospital departments in 2005 (up to 4% in intensive care units). Eleven percent of patients with MRSA in the Netherlands acquired MRSA abroad (National Institute of Public Health and the Environment (NETHMAP) 2006).

Another cause for concern is the emergence of highly virulent MRSA in the community, causing soft tissue and skin infections as well as severe necrotising pneumonia in immunocompromised individuals. This community-acquired MRSA (CA-MRSA), which carries the genetic information for a highly potent toxin along with various resistant traits, occurs worldwide and already poses a major challenge for the public health sector in some regions of the USA. In Europe, CA-MRSA has been detected in numerous countries,[5] including Sweden, Switzerland, Germany, the Netherlands, Croatia and Serbia. According to the German National Reference Centre for Staphylococci at the Robert Koch Institute, in 2003–2004 the percentage of CA-MRSA among all *Staphylococcus aureus* isolates analysed was 1.4% in Germany, whereas in the Netherlands 8% was recorded (W. Witte, personal communication). It can be expected that these numbers will rise in the near future and that CA-MRSA might gain further in importance when it is transmitted to hospital settings where it could merge with the highly resistant resident MRSA microflora. CA-MRSA infections represent a major challenge for the future, requiring a co-ordinated programme of contact tracing, education and treatment of infected and colonised contacts (Aramburu et al. 2006). In addition, there is increasing concern about CA-MRSA emanating from pig farmers (see Huijsdens et al. 2006) because of the ease of transmission between pigs and humans.

Enterococci

The problem of resistance to glycopeptides, mostly in *Enterococcus faecium*, is a major resistance challenge, causing infections of the bloodstream and heart with resistance rates of 70% among high-risk groups. Initially emerging in the USA, high resistance rates have been reported in several European countries according to data from EARSS.

Pathogenic *Escherichia coli*

According to data from EARSS, in 2004 the overall resistance of *Escherichia coli* to common aminopenicillin antibiotics reached 50% across Europe (with greater than 20% for resistance to fluoroquinolone). Pathogenic *Escherichia coli* strains causing extraintestinal infections are an increasing problem for human health, involved in a diverse spectrum of diseases including urinary tract infections, newborn meningitis and abdominal sepsis and septicaemia (Vicente et al. 2006). The contribution to resistance by extended-spectrum beta-lactamases (ESBLs) is becoming increasingly

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[4] However, evidence from good prescribing practice (for example, in the Netherlands) indicates only a limited need for antibiotic treatment in COPD. Other commonly prescribed infections such as acute otitis media, sinusitis, pharyngitis and acute bronchitis may also not be considered as definitive indications for antibiotic treatment according to experience in the Netherlands.

[5] There is a rapidly growing European literature documenting the nature of the challenge: for example, Salid-Salim et al. 2003; Berglund et al. 2005; Aramburu et al. 2006. A recent summary from US Centers for Disease Control and Prevention (CDC) experts (Gorwitz et al. 2006) reviews strategies for the clinical management of MRSA in the community.

important for *Escherichia coli* and for *Klebsiella pneumoniae* and *Proteus mirabilis*; up to 30% of *Escherichia coli* strains tested in eastern Europe may be ESBL producers (compared with 15% in southern Europe and 5% in northern Europe; GAARD 2005).

Mycobacterium tuberculosis

The emergence of multi-drug resistant tuberculosis (TB) has forced the use of second-line drugs that are 100-fold more expensive, less effective and more toxic than traditional therapies. The third report from the Global Project on Drug Resistance Surveillance for TB provides data from 1999–2002 that shows significantly increased prevalence of multi-drug resistant TB in Estonia, Latvia, Poland and the countries of the former Soviet Union although most other northern, western and central European countries see only a few cases each year (for example, the Netherlands, less than 1% in 2005; NETHMAP 2006).

In 2006, a joint report from the US Centers for Disease Control and Prevention (CDC) and the WHO expressed deep concern about the emergence of XDR-TB (extensive drug-resistant TB), resistant not only to first-line but also to second-line drugs (CDC 2006). XDR-TB has been identified in all regions of the world but is most frequent in the countries of the former Soviet Union and in Asia. Data from South Africa highlighted the deadly association of XDR-TB and HIV infection. According to the WHO, these findings raise the possibility that epidemics of virtually untreatable TB may develop (WHO 2006). It seems likely that XDR strains have emerged on many separate occasions in separate locations (Anon. 2006a) and there is concern that the ease of international travel will enable rapid movement from the place of origin.

Acinetobacter baumannii

There is a particular problem with this Gram-negative bacterium in intensive care; it has become progressively more resistant to all antibiotics including carbapenems, which were the last good line of defence (Levy & Marshall 2004). US data indicate that *Acinetobacter baumannii* incurs 20–50% mortality rates as a cause of hospital-acquired pneumonia and is a growing problem for soldiers returning from Iraq and Afghanistan with highly resistant wound infections (Talbot et al. 2006). In the European experience it has been found that *Acinetobacter baumannii* typically spreads under conditions of high antibiotic pressure and inadequate hospital hygiene (van den Broek et al. 2006).

Klebsiella pneumoniae

Multiple-drug-resistant strains (resistant to carbapenems) are appearing worldwide, notably in

Greece according to data from EARSS, with the risk of spreading to other Member States.

Other pathogens

In a recent follow-up to the Infectious Diseases Society of America (IDSA) 2004 report (Talbot et al. 2006), a 'hit list' of six priority drug-resistant microbes was compiled. Particular potential for concern was defined in terms of a lack of appropriate drug in development – highlighting the mismatch between current R&D and unmet clinical needs. In addition to MRSA (where there are some drug leads), ESBL-producing *Escherichia coli* and *Klebsiella* species, *Enterococcus faecium* and *Acinetobacter baumannii*, the hit list included *Pseudomonas aeruginosa*, causing invasive Gram-negative hospital infections, sometimes resistant to all or most antibiotics, and a particular problem worldwide in intensive care units and in immunocompromised patients and in children with cystic fibrosis.

In addition, resistant *Clostridium difficile* is an increasing problem (Kuipjer et al. 2006) both in hospitals and the community: the recent spread of a highly virulent strain is linked to use of quinolones, third-generation cephalosporins and aminopenicillins and to over-use of proton pump inhibitors. In one Member State, the UK (according to data from the Office for National Statistics in February 2007), the number of hospital deaths linked to *Clostridium difficile* as a contributing factor has now outstripped those linked to MRSA. This linking to *Clostridium difficile* increased by 69% between 2004–2005 and 2005–2006 although it reflects improved recording as well as changed incidence.

Commensal bacteria

Non-pathogenic, commensal bacteria can act as a reservoir for resistance genes, which may then be transferred to pathogens when the latter colonise a host. Thus, in order to be in a position to detect resistance before it emerges in pathogenic strains and to take measures to avoid such transfers, it would be highly advisable also to monitor commensal micro-organisms. The study of commensal flora as model organisms can also help to quantify the impact of antibiotics in selecting antibiotic resistance as illustrated by a recent randomised, double-blind, placebo controlled trial of different macrolide antibiotics on commensal streptococcal flora in a healthy population (see Malhotra-Kumar et al. 2006).

Global vulnerability

Drug-resistant bacteria are not only a local problem: they can spread rapidly throughout the world in humans, animals, vectors and food (Heymann 2006). In developing countries, in addition to the pathogens

already mentioned, other enteric pathogens demonstrate multiple drug resistance (for example, *Salmonella typhimurium*, *Shigella flexneri* and *Vibrio cholerae*; Levy & Marshall 2004); there are no antibiotics being developed to tackle drug-resistant dysentery. Data collected by the WHO (Heymann 2006) indicate antimicrobial resistance rates in developing countries of up to 98% for gonorrhoea (penicillin), 82% for malaria (chloroquine), 70% for pneumonia, bacterial meningitis and for hospital infections (penicillin) and 17% for TB (primary multi-drug resistance).

Europe is not immune from the global spread of disease, as exemplified by recent concerns over SARS (EASAC 2005) and pandemic influenza (EASAC 2006). Preliminary results from the ARMed project (Table 1) (www.eurosurveillance.org/em/v11n07/1107–226.asp) support the previous sporadic reports suggesting high antibiotic resistance in non-EU countries in the Mediterranean region (rates in EU countries in this region are already generally higher than northern European Member States). The ARMed report notes some of the implications for the EU in consequence of the high human mobility in the region from both tourism and migration. The importation of multi-resistant organisms to European hospitals from the Mediterranean region is well documented and can stimulate intra-hospital spread of resistance.

3.2 Economic burden of antibacterial resistance

An important deficiency in the present knowledge is the limited amount of data defining the impact of resistance on clinical outcomes of infection and the associated economic burden both in the community and hospital setting. Much of the current data associating mortality, morbidity and economic costs have been obtained in US settings (for example, Cosgrave 2006). A co-ordinated European effort addressing this point is crucial to improve the quality of clinical care, to launch the EU political process to drive change and to convince Member State health authorities to invest in intervention to control resistance.

The burden of resistance in terms of morbidity and mortality was discussed in detail at the EU InterGovernmental conference in 2005 (Finch & Hunter 2006) and it was estimated that the direct economic burden of infectious disease in England, calculated from cost of primary care, hospital admission and hospital-acquired infection, is up to €10 billion annually. The commitment by DG Sanco and DG Research to support additional public health economic research is highly welcome in order to provide the foundation for new efforts in impact analysis to steer policy development.[6] There is a need to assess and model both direct costs (use of more expensive drugs) plus costs of illness and disability associated with resistance (including costs of lost work days and post-hospital care) plus the economic implications of deaths caused by the inability to cure formerly treatable diseases. Use of the correct antibiotic, even if more costly for the drug budget, will result in lower total costs if the problem of resistance (and its consequence of extended in-patient treatment) is then avoided. Determining the current economic costs of antibiotic resistance would also provide a rational basis for selecting economic-based incentives to develop testing and surveillance systems for public health purposes.

US data on resistance indicate that costs for hospitalised patients are as much as $20,000 higher per patient with resistant bacteria than for susceptible strains (GAARD 2005). Fear of resistance leads doctors to prescribe more costly drugs for initial treatment of infection – the extra costs for treatment of ear infection in the USA were estimated at more than $20 million annually. The 1998 Institute of Medicine report estimated that the total cost to US society of antimicrobial resistance was at least $5 billion annually.

According to WHO analysis (2004), the annual cost of MRSA bloodstream infections alone in Europe exceeded the entire EU budget for antibacterial research in Framework Programme 6 for the period 1999–2002. Various published estimates indicate that the additional costs for an episode of bloodstream infection caused by MRSA range from $5,000 to $10,000 (Finch & Hunter 2006; Cosgrave 2006). Recent analysis of data (Wernitz 2005, using 2001 data) on the cost of MRSA estimated a total annual impact of up to €350 million for Germany (covering hospital and community infections and counting cost of lost working time of nursing staff and patients as well as direct treatment costs but excluding costs of surveillance, screening and rehabilitation). Although Member States will vary in the pharmacoeconomic impact according to local clinical practice, it seems clear that the total cost of antimicrobial resistance in the EU is now well in excess of the 1998 estimate made for the USA.

3.3 Improving co-ordination of surveillance

There is a role for new research in the social sciences to understand the current differences between Member States in their consumption of antibiotics and their

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[6] For example, the second Call of the Framework Programme 7 Health theme provides funding for studies to assess the health and economic cost of antimicrobial resistance. Work is encouraged to model the future burden for a range of possibilities according to alternative assumptions about the emergence and transmission of resistance and about the current implementation of strategies to fight resistance.

patterns of antibiotic resistance, and to interpret the changing landscape. Sections 3.1 and 3.2 highlighted specific pathogens to exemplify the issues for constructing the epidemiological framework that needs to be in place rather than, necessarily, identifying the specific priorities for surveillance. There is need for Member States to collect representative surveillance data, systematically across locations (in the community as well as in hospitals), and to collect antibiotic consumption data according to location and clinical indication.[7]

There is an additional obstacle to developing co-ordinated European surveillance activity, because different Member States have had different laboratory procedures for testing antibacterial resistance, and this technical issue creates a clinical problem of incomparable data (with potential for bias). Clarification of what are the current gaps in our knowledge about antimicrobial resistance is confounded by the uncertainty in the estimates. The ECDC-funded European Committee on Antimicrobial Testing (EUCAST) initiative (Table 1) is important in co-ordinating antimicrobial susceptibility testing (in a model for harmonising breakpoints) but, in the view of the EASAC Working Group, the effort needs to expand to consider the issues for current as well as future methodologies across all the Member States, to address the issues for current as well as new drugs and to progress opportunities for co-ordinating EU efforts with other international activity, particularly in the USA. We recommend that the EU develops guidelines for a standardised platform of microbiological susceptibility testing in order to generate and report homogenous data and that phenotypic data are complemented by collection of data on mechanisms. Increasing standardisation of methods will facilitate the global sharing of data and, potentially, the better correlative analysis of resistance surveillance data in terms of antibiotic consumption, thus also allowing better linkage with intervention initiatives.

However, EU guidelines will not succeed if Member States are not uniformly capable of tackling the technical challenges and if sustained funding is not forthcoming to support an integrated system. The immediate priority for standardisation is in phenotyping; the routine introduction of common methodology across all Member States is feasible in the judgement of the Working Group. Standardisation of definitive genotyping methodologies will be harder to attain and can be viewed as the longer-term objective for a research strategy:

probably best delivered by a centralised, reference laboratory function linked to national sample collection efforts and building on current best practice.[8] In common with phenotypic data, these centralised research facilities are envisaged as providing real-time laboratory data to the ECDC, and this raises issues for data management, improved IT systems (Finch & Hunter 2006) and the provision of advice back from the ECDC to Member States on management of resistance to inform clinical practice. The choice of pathogens for the advanced surveillance work requires further discussion on relative clinical importance but, undoubtedly, there is a key co-ordinating, training and enabling role for a well-resourced ECDC.

3.4 Use of antibiotics in farm animals: developing evidence-based strategies

It is estimated that more than half of all antibiotics produced worldwide are used in animals. Chronic use of sub-therapeutic amounts of antibiotics for growth promotion has been banned in the EU since the end of 2005 (Regulation (EC) No. 1831/2003) and it is important to collect the data (by testing animals and feed stocks) to determine if compliance with the ban is effective. Information from Switzerland, where such use was banned in 1999, indicates that the ban did not lead to increases in the amount of prescribed veterinary antibiotics (Arnold et al. 2007).

Evidence shows that low-level application selects determinants mediating high-level clinically relevant resistance (Levy & Marshall 2004; Molback 2004). This is particularly so for enteric organisms (*Salmonella*, *Campylobacter*, *Listeria*, *Escherichia coli*).[9] A series of registry-based studies in Denmark determined the mortality associated with gastrointestinal infections (*Salmonella typhimurium*), demonstrating that patients with a resistant strain had up to 13-fold higher mortality than the general population (Molback 2004). Further experience in Denmark, which banned the use of antibiotic growth promoters in 2000, shows a rapid decline in occurrence of resistance in animals and food after withdrawal of use, without significant negative impact on food production (Wegener 2005). However, an example of persistence of glycopeptide resistance through transfer of plasmid borne genes between animal and human populations of Enterococci was observed in Norway (Johnsen et al. 2005).

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[7] It is also necessary for some Member States to collect better data on use of antibiotics in animal husbandry and veterinary medicine: see section 3.4.

[8] A co-ordinated effort is now required in bacteriology analogous to that already developed in virology for genotyping HIV.

[9] The European Food Safety Authority (EFSA) analysed information submitted on antimicrobial resistance in zoonotic bacteria for the year 2004 (EFSA 2005). These data indicated that animals, and food of animal origin, might serve as reservoirs for resistant bacteria, with the risk of direct or indirect transfer of bacteria to humans. EFSA has now published a proposal for a harmonised monitoring scheme of antimicrobial resistance in *Salmonella* in poultry and pigs and *Campylobacter jejuni* and *Escherichia coli* in broiler chickens and turkeys (www.efsa.europa.eu/en/science/monitoring_zoonoses/reports/ej96_amr1.html).

Clinical therapeutic use in animals is justified. However, there is a practical problem with large-scale animal farming, in that individual treatment is not feasible and the difference between mass prophylaxis and therapeutic treatment may be poorly defined (Soulsby 2005). It is noteworthy that fluoroquinolone-resistant *Campylobacter* arose from large-scale use of enrofloxacin for prevention of infection, not for growth promotion. There is continuing controversy as to the net health risks of transfer of antibiotic resistance from animals to humans when set against the increased production costs (particularly for pigs, chickens and fish) and food prices–a trade off between public health and economic benefits. In material received in response to the Working Group's call for evidence, it was observed that it is difficult to assess risk and establish the economic case for use of antibiotics in animals. An increased production cost as a result of abstaining from the use of antibiotics as growth promoters has been reported for pork production in Denmark (Verseput 2000). The uncertainties in defining cost–benefit could be resolved by collecting linked data at the farm-level on the relations between antimicrobial usage, disease, animal productivity and consumer response (Miller et al. 2006). Better data would help to inform evidence-based policy intending to regulate the global trade of animals and animal products. The announcement by the FAO–WHO Codex Alimentarius Commission (2006) to establish an Intergovernmental Task Force on Antimicrobial Resistance is welcome. We recommend that the European Commission should consider the options for assisting further in this assessment of the risks to human health associated with the presence in food and feed of antimicrobial resistant micro-organisms.

3.5 Development of novel diagnostics

Diagnostic tests for infection are used relatively rarely in community practice (Finch & Hunter 2006). There is a major need for developing improved diagnostics and for establishing their clinical cost–efficacy status as new scientific opportunities come into range. There is also need for research to understand why many clinicians do not use the tests that are already available.

It will be important to provide guidance to the clinician to select the best antimicrobial agent by using:

- Standardised diagnostic systems based on common technology platforms, sensitive, simple and cheap to use at the point of care.

- Rapid diagnostics to differentiate bacterial from viral respiratory infection.

- Rapid diagnostics for identification of a specific pathogen and its resistance profile.

- Diagnosis to profile the immune status of a patient so as to target immunomodulatory drugs.

- Diagnostics to investigate susceptibility to infectious agents.

4 Strengthening the science base for infectious diseases research in Europe: scientific opportunities and infrastructure

4.1 Generating scientific knowledge and rebuilding previous expertise

Europe has a history of excellence in scientific research on infectious disease. But there is no room for complacency. According to an analysis of publications on infectious disease over the period 1995–2002 (Bliziotis et al. 2005), western Europe[10] generated slightly fewer publications than the USA (38.5% versus 41.3% of the world total). Although there is some indication that western Europe was increasing its relative proportion of publications over that period (so that in 2002, western Europe exceeded the US share, 38.6% versus 37.8%), the relative impact factor for US publications was consistently higher (average 3.4 versus 2.8 for 1995–2002).[11] Eastern Europe contributed 2.4% of the world's publications on infectious disease in 2002, significantly and consistently increasing over the period, from 1.0% in 1995.

When the Working Group analysed the number of papers cited in the ISI Web of Science, the quantitative contribution by European laboratories to publications dealing with antibiotic resistance was equivalent to US laboratories over the period 2001–2004 (2058 EU publications, 2054 US publications). There is some evidence of a relative decline in the EU more recently by this measure (for the period 2005–2006, 874 EU publications, 1042 US publications). Most of these papers describe clinical resistance cases and resistance mechanisms, although EU research has also provided a remarkable contribution to current knowledge of resistance and the mechanisms involved in the evolution, transfer and dissemination of resistance genes. This scientific area is rapidly developing, and support to sustain and reinforce the EU research capacity is needed to maintain leadership.

The Working Group concluded that European research on resistance also needs more specific support in two other areas. First, in structural studies: there is relatively little research on antibiotic-modifying enzymes apart from the beta-lactamases. For example, none of the antibiotic esterases and RNA methylases involved in resistance development have been crystallised. Secondly, more is required from cell culture and animal studies: for example,

an exploration of the mechanisms involved in the discrepancy (and lack of predictability) between *in vitro* and *in vivo* effects. The scientific value of exploring such mechanisms was illustrated by the recent publication on *Listeria* (Scortti et al. 2006) demonstrating differential expression of bacterial determinants of antibiotic susceptibility.

Broadly, there is a need for more basic research to provide information on the functions of conserved essential genes identified by functional genomics. Basic research on model organisms must be supported as the most rapid means to access targets, using inhibitor screens that are sensitive, specific and robust.

4.2 Scientific opportunities for target selection coming into range

It is not the purpose of the present report to review in detail current research leads or future directions. Outlines of what infectious disease research is now coming into range or is still uncertain were provided in the previous EASAC report (2005) and in the European Science Foundation review (2004). We agree that there is still a significant amount of research required to understand mechanisms and origin of resistance, the phase of the microbe and its susceptibility, the ecology and dynamics of transmission of resistance between individuals and different bacterial species, the interplay of resistance and virulence, and the environmental factors influencing resistance development and persistence.

The Working Group emphasised several key strategic points about the selection of targets for novel therapeutic approaches:

(i) New therapeutic targets emerging from pathogen genomics research may, perhaps, provide the resources for a new era of antibiotic therapy. A genomics search comparing the genomes of *Haemophilus influenzae*, *Streptococcus pneumoniae* and *Staphylococcus aureus* revealed more than 350 bacterial genes as possible targets (Payne 2004). The scientific complexity inherent in confronting the

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[10] Using the United Nations' definitions of regions (Bliziotis et al. 2005).

[11] Broadly considered, the contribution by western Europe relative to the USA is less when publication on any topic in leading biomedical journals is compared over the same period (Soteriades et al. 2005), when articles published from the USA constituted two thirds of all papers, and from Europe one quarter. A similar conclusion emerges from a comparison of total scientific publications (between 1993 and 2002; King 2004) where the number published is approximately similar for the EU-15 and the USA (37% versus 34% of world publications) but US publications were more frequently cited (49% versus 39% of world citations). The US also has a much higher share of the top 1% of highly cited publications. Analysing disciplines, the EU-15 was found to be a little stronger than the USA in physical sciences and engineering – where the EU-15 caught up with the USA to close the gap that existed before 1993 – but still lags in life and medical sciences.

challenges of antibacterial discovery should not be underestimated; in particular, serious difficulties have been encountered in improving on compound leads, and chemical libraries may not be sufficiently diverse to address new targets successfully (Payne et al. 2007). However, knowledge of genomics is important for tracing the epidemiology of resistance and for finding susceptibility in already resistant pathogens as well as for discovering new ways to prevent resistance arising. Genomic mode of action studies are also important in re-examining older compounds with demonstrable efficacy but unknown mechanisms of action in order to provide new leads for chemistry to develop improved compounds.

(ii)   It is no longer sufficient to consider anti-infective endpoints solely in terms of killing microbes in standard experimental models – increasing attention must be given to virulence and host–pathogen relationships.

(iii)   Many novel targets have already been identified and tested without yielding good results. It is important not to over-value expectations from genome sequencing although functional genomics does have an important role in understanding and validating targets. Elucidation of target function and the development of assay methodology (with the exploration of target modulation in animal models) are essential for drug discovery. Genes involved in metabolic functions tend to make good targets for new antibiotics, particularly if equivalent metabolic pathways are not found in the host (thereby minimising the potential for adverse effects in man).

The requirements for a validated target are summarised in Box 2.

The question arises then as to whether recent microbial genomic efforts failed to deliver good targets or whether most such targets have already been discovered. Clearly, the number of genes that provide good targets for antibiotics will be limited but a single target can provide a wide array of product opportunities.[12]

The opportunities provided by genomics both in identifying determinants of established pathways and by underpinning new intervention approaches (for example mediated by lipid and carbohydrate metabolism and innate immunity) were reviewed by Ziebuhr et al. (2004), who emphasised the importance

Box 2 Requirements for a validated target for a broad-spectrum antibiotic
• Presence in several relevant pathogens.
• No human or experimental animal homologue.
• Represents a gene/protein essential for bacterial viability and multiplication within the infected host.
• Function confirmed in animal infection models and other experimental studies.
• Biochemical function characterised.
• Assay available and, preferably, amenable to high throughput screening.
• Protein structure solved.
• Druggable.
Adapted from presentation by Koller to ERA-Net on PathoGenoMics, July 2005.
Requirements are similar for narrow-spectrum targets except for presence in multiple pathogens.

of taking a system-based perspective, regarding all interactions between host, pathogen and environment in combating the development of resistance.[13]

There are also alternative strategies that focus on inhibiting expression of virulence factors. In addition to the need to continue basic research on conventional, essential gene targets noted in section 4.1, there is potential value in pursuing more speculative approaches. For example, targeting pathways that are implicated in the behaviour of microbial communities such as quorum sensing, or co-operative behaviour essential to infection of tissues may also create novel therapeutic approaches. In contrast to the classic resistance mechanisms of individual bacterial cells, such as mutational alteration of a penicillin-binding protein, targeting functions that characterise the fitness of a bacterial community (such as formation of a biofilm) would be much less susceptible to the emergence of resistance because such functions depend on communication and co-operation and are, therefore, not a phenotypic property of each individual cell in the bacterial community. The challenge for bridging the current gap between untested research in academia and industry priorities will be discussed in chapter 5.

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[12]   For example, the discovery of the penicillin-binding protein family as a target led to several generations of products (including penicillins, cephalosporins, carbapenems).

[13]   It is also now realised that low, residual levels of antibiotic found in sewage and wastewater systems, and previously characterised as 'sub-inhibitory' concentrations, do have major effects on virulence gene expression. More research is required to characterise these 'sub-inhibitory' impacts and the potential link with development of resistance.

Expression profiling of host tissues during infection could provide important leads for identifying immunomodulatory signals that target bacterial molecules as well as for providing an indication as to whether a lead compound might have an adverse effect on host cells. In developing radical new strategies to fight infectious diseases, we reiterate that there is need to develop much better understanding of host–pathogen interactions at the molecular level. As observed in a recent *Nature* editorial (Anon 2006b): '*Rather than seeking ways to kill bacteria, for example, molecules that slow their growth or spread may be enough to let the host microbiota and immune system out-compete them, particularly if ways can be found to stimulate or modulate either*.' New research areas are opening up to understand and modulate human microbiota ecology and the molecular basis of the host immune system regulatory pathways, as discussed in recent workshops organised by the US National Research Council (Committee on New Directions in the Study of Antimicrobial Therapeutics 2006). There is a great opportunity for Framework Programme 7 to support research on the human microbial metagenome, to characterise endogenous microbial communities, their response to medication and interaction with pathogens. Although immunomodulation has not been very successful yet clinically, bringing together the research areas that target the disease-causing agent and enhance the immune response may create new selective approaches, for example by developing pro-drug antibiotics that could be selectively activated through interaction with the mediators used by the immune system to signal damage.

In addition to advances in genomics and cognate biosciences, progress in anti-infective drug discovery relies on advances in medicinal chemistry to deliver lead compounds with appropriate properties to access micro-organisms and be tolerated by the host. Many conventional chemical libraries of compounds are now considered to lack diversity, but advances in combinatorial synthetic chemistry are generating the resources to underpin the search for new potency, specificity and safety. Industry issues will be considered further in the next chapter but improved library preparation is an opportunity for collaboration between academia and industry. If industry provided an inventory for access to promising, but discontinued, compounds these could emerge as promising leads in other research and could promote collaboration in either the public or private sectors. A shared chemical library would also help to compensate for the fact that existing libraries tend to focus on chemicals that bind human

receptors or enzymes, and these are likely to be of limited use as antibacterials, because of the potential for side effects (Tickell 2005). Public sector support for building open access chemical libraries should also be encouraged.

4.3 Strengthening research infrastructure in Europe

To capitalise on the exciting range of research opportunities, the research infrastructure in Europe must be augmented. Moreover, an improved capacity for research must be accompanied by improved resources for teaching, training and career development, particularly in academic microbiology. Similar general points have been made in the previous reports (EASAC 2005, 2006), summarised in Box 3.

Although progress has been made in some of these areas, there is no room for complacency. What is needed is a coherent, integrated programme to improve the infrastructure for basic, applied microbiological and

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Box 3 Priorities in developing infrastructure for research and training in infectious diseases

Summary of points from EASAC (2005, 2006):

- Longer-term planning for training greater number of both basic and clinical scientists in microbiology.[14]

- Tackling weaknesses in EU public sector-funded clinical trial capabilities.

- Increasing support for multi-disciplinary research centres.

- Integrating strategies for human and veterinary science agendas.

- Co-ordinating laboratory containment facilities for safe handling of microbes across Member States and enabling access by other researchers.

- Addressing particular problems in newer Member States in consequence of structural reorganisation and consolidation of laboratories at time of accession.

- Using Structural Funds (convergence funding) to build research infrastructure in less developed regions as well as support knowledge transfer.[15]

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[14] Further details of specific proposals in one Member State for generating a trained workforce in academic medical bacteriology are exemplified by the UK Academy of Medical Sciences report (2001) with recommendations covering undergraduate education, speciality training and clinical career pathways.

[15] Investment of European Regional Development Fund; European Commission Press Release, February 2006.

infectious disease research in Europe. Investment for an improved science base will, in turn, attract and support private sector commitment to innovation as discussed in the next chapter.

In summary, strengthening the life sciences research infrastructure must address the following priorities:

- Basic science to understand and exploit essential genes.

- Microbial population biology and ecology of resistance for better understanding of mechanisms of resistance development.

- Epidemiology of antibiotic resistance and its spread in the EU.

- Exploiting new technologies for identification and validation of new molecular targets and new drug discovery.

- Clinical research to evaluate impact and outcome of infections.

- Integrating microbiological, epidemiological and ecological research for control of antibiotic resistance.

- Translating new knowledge on resistance into novel solutions.

- Improving and expanding training, including continuing training of health personnel.

In addition to reinforcing the points made previously (Box 3), the Working Group suggested some specific ways to build research capabilities:

Adding value to medical microbiology infrastructure

There is already an infrastructure of medical microbiology within the many hospitals throughout Europe, although the performance of hospital-based microbiology and the associated public health links are extremely variable, ranging from world class to poor. The clinical microbiological services could be the focus for catalysing an improved infrastructure for research, teaching and training. Most of the good, even the excellent, microbiology services in Europe lack the resources and staff to be able to use their existing infrastructure for research but they enjoy potentially good links (some in need of strengthening) to their associated universities. The strategic aim would be to build added value into these existing service centres. We propose that EU-funded studentships, fellowships and research projects should be awarded to universities that can make competitive

applications that explicitly involve collaborative programmes with their associated hospital microbiology services. In addition to the scientific credibility of the proposal, such applications must demonstrate how the training or research will further knowledge on antimicrobial resistance, how the investigator will ensure commitment of their time to the stated aims, how the university infrastructure and microbiology service will interact and how the funding will bring added value to existing programmes. Such funding could be used to build new bridges between functions but preference might be given to applications in which the links already demonstrably exist. The portfolio of research activities funded should be sufficiently broad in the area of resistance to encourage inquiry on basic mechanisms, molecular and classical epidemiology, target discovery, improved screening assays, improved diagnostics, data management and modelling. Priority should be given to applications that encourage the recruitment of young scientists (medical or non-medical) into structured career pathways where the university makes a reasonable, conditional commitment to the individual after the fellowship is completed.

Focused networking for compiling the evidence base

We also propose that the European Commission fund a series of relatively small, focused workshops on specific aspects of drug resistance. Each meeting would produce a report and set of recommendations which, after approval, could be posted on a dedicated website. A scientific committee would be responsible for awarding the funds, for providing a representative at each meeting and for taking forward recommendations. Such meetings should aim to attract and include younger, as well as experienced, scientists.

Informing about drug discovery and development

Industry scientists, responding to the Working Group's call for evidence, observed that relatively few researchers in academia know what it takes to discover and deliver drugs. Although we do not suggest that academia should strive to do what industry is far better placed to accomplish, it is important collectively to identify those areas where research in academia is most likely to facilitate the discovery of novel drugs. We recommend that industry researchers take the initiative to organise events (perhaps as part of the activity described in the preceding paragraph) for academic researchers and those involved in supporting technology transfer to share perspectives on what is needed in discovery research and in generating candidate drugs for

development, as a basis for helping to build new partnerships.[16]

In addition to collective discussion, there is also significant opportunity for industry consortia to fund and support professorial and other research appointments in universities in microbiology and infectious disease research to help take forward key research areas. EU initiatives for collaboration between academia and industry will be considered further in the next chapter.

4.4 The human factor

The use of antibiotics promotes the emergence of antibiotic resistance. Antibiotics are misused if treatment is given when there is no benefit for the patient or when treatments given are not in accordance with developed guidelines. In many instances there is a false public expectation of what antibiotics can and cannot do. Guidelines for infection control are now available for most healthcare settings. However, compliance with these guidelines is often proven to be low.

Many attempts have been made to improve the adherence to antibiotic usage and infection control guidelines. In some instances these attempts were successful but little of this experience has been documented. There is a need to do better in collecting information on the impact of interventions at the national level, to co-ordinate this information, and to share good practice between Member States. There is also

continuing need for well-designed studies of interventions to try to evaluate what particular factors are influential in practice (see, for example, a recent publication by one of the members of the Working Group, Van der Meer & Grol 2007). Such research studies need to incorporate expertise from the disciplines of sociology, anthropology and psychology as well as the medical sciences.

In many cases, behaviour change is triggered by economic incentives, but the mechanisms require more analysis. Thus, in what ways do different economic and organisational systems influence prescription habits and the usage of antibiotics? Similar issues are applicable for the study of infection control practices and there is a need for more health economics studies. Legal interventions have also been used in different countries to steer drug usage and infection control but, again, the effect of legal rules has been little studied systematically and new research methodologies are required.

Thus, there are many fields of expertise, including the social sciences, currently outside the medical community that need to be more involved in studying the issue of antimicrobial resistance. If there is continuing imprudent use of antibiotics and poor adherence to infection control practices, then development of new antibiotics will not solve the challenges in infectious disease. Creating consistent, evidence-based conditions for the clinical use of drugs can, in turn, provide a more rational basis for developing new diagnostics and therapeutics.

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[16] One example of an initiative that provides general support for interaction between academia and industry scientists in biomedical R&D is the UK Academy of Medical Sciences Forum. Recent Forum activities have included a symposium on Experimental Medicine exploring issues for building public sector research infrastructure to support industry innovation (www.acmedsci.ac.uk/images/ event/Emsummar.pdf) and a review from industry (www.acmedsci.ac.uk/images/event/Annualle.pdf) on pharmaceutical opportunities and the human genome, including issues for novel lead generation in HIV infection. The US Institute of Medicine (www.iom. edu) also supports a Forum on Drug Discovery, Development and Translation that aims to enhance mutual understanding of research processes and foster partnership.

5 Supporting industry innovation: drug development and European competitiveness

5.1 After the decline: facilitating a renewal in industry activity

There is urgent need for new drugs and vaccines: the EU must redouble efforts to attract and support industry R&D. What then are the current weaknesses and bottlenecks?

The average cost of bringing a new drug to market, including the cost of failed investments for the pharmaceutical sector, is estimated to be greater than €800 million (Vicente et al. 2006). There is good evidence that, since the 1990s, some major pharmaceutical companies have withdrawn from R&D on infectious diseases (IDSA 2004; Spellberg 2004; WHO 2004). Although many smaller companies have entered this research area, there is concern that they have inadequate funding, R&D infrastructure and partnering opportunities with larger companies, such that it is difficult for their products to reach the market (Talbot et al. 2006). Industry respondents to the call for evidence noted that the anti-infective area is scientifically challenging–perhaps more so than other therapeutic areas. The success rate from high-throughput screening has been relatively low and the development lifecycle has not appreciably shortened. Activity against the target must be combined with drug properties enabling access to the pathogen, with maintenance of a high blood level that is safe for the patient. Furthermore, as described previously, current compound libraries may lack appropriate chemical diversity.

Various factors render antimicrobial agents less economically attractive targets for companies than other drug classes (Spellberg et al. 2004). The ageing of populations has encouraged drug discovery initiatives towards agents that treat chronic medical conditions and must be prescribed long-term (in contrast with short-term use of antibacterials). The large number of cheap generic antibiotics available creates a challenging marketing environment for new agents (even though the older agents may now be ineffective in some patients), a challenge compounded by the public health need to limit use of novel broad-spectrum antibiotics ('reserve status') so as to minimise the pressures driving onset of resistance. The number of antimicrobial agents receiving US regulatory approval has decreased by 56% over the past two decades. Projecting future development, new antibacterial agents constitute only 6 of 506 drugs disclosed in the pipelines of the largest pharmaceutical and biotechnology companies (Spellberg et al. 2004), compared with 67 new drugs for cancer, 33 for inflammation/pain, 34 for metabolic/endocrine disorders and 32 for pulmonary disease.

The lack of ongoing R&D is particularly problematic for some of the pathogens identified as of most societal concern, because of significant resistance, in the IDSA 'hit list' (Talbot et al. 2006). This predominantly US analysis of current and future paucity of compounds is now reinforced by European analysis from the work of the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) (Norrby et al. 2005), from a recent report of an initiative by the Dag Hammarskjöld Foundation together with the Swedish Strategic Programme for the Rational Use of Antimicrobial Agents and the Karolinska Institute (the React Consortium; Tickell 2005), by discussion at the EU InterGovernmental Conference in the UK and by the work of the Federation of European Microbiological Societies (Vicente et al. 2006) highlighted in the response to the call for evidence by the Working Group. A gap has been confirmed in the R&D pipeline for anti-infective agents with particular unmet needs for Gram-negative pathogens, for community-acquired resistant infections and for diseases that occur predominantly in developing countries, such as TB (where there is a major EU interest).

Industry respondents to the call for evidence agreed that there are problems both for large and small companies engaging in infectious disease R&D. However, experience within the Working Group indicates that some larger companies are beginning to return to the area with the renewal of research leads. It is still too early to ascertain the extent to which new growth in the R&D pipeline will be sustained or can be attributed to entirely novel classes of agent. What is clear, and where there is consensus across the industry sector, is that further support is needed.

The specific problems facing industry R&D in Europe into anti-infectives are amplified by a relative decline overall in the pharmaceutical sector R&D performance in Europe compared with the USA (Table 2).

Recent pharmaceutical R&D investment has grown less in Europe than in the USA; there are now fewer pharmaceutical companies based in Europe; fewer medicines originated in Europe during the past five years. However, European R&D performance was relatively good in 2005 in terms of the total number of drugs approved. Furthermore, when comparative anti-infective R&D performance in Europe and the USA was analysed by the Working Group, according to the number of compounds currently in late development (late phase II clinical trials onwards) or recently launched, the number of anti-infective compounds that had been discovered in Europe and the USA was found to be the same (nine each; six by Japan). Some of the other estimates made

Table 2 Comparison of European and US pharmaceutical sectors

Data covering all therapeutic areas are obtained from 'The Pharmaceutical Industry in Figures' (EFPIA 2006 on www.efpia.org).

Metric	Europe[17]	USA
Growth in R&D investment 1990–2005[18]	2.8-fold	4.6-fold
Origin of top 40 companies by R&D investment, 2004–2005	12	16
Origin of top 30 medicines by worldwide sales, 2004	8	21
Origin of drugs launched worldwide, 2001–2005	51	61
Origin of drugs launched worldwide, 2005	13	9
Number of public biotech companies, 2005	122	329
Number of private biotech companies, 2005	1,491	1,086

elsewhere of comparative performance in innovation have been confounded by a tendency for some compounds, discovered in Europe, to be acquired by US companies for development.[19]

5.2 Providing new support for industry R&D

IDSA (2004) proposed an array of measures to reverse the decline in US pharmaceutical anti-infective R&D, addressed to Congressional leaders, regulators at the FDA, policy-makers involved in funding academic research and in surveillance (CDC). In discussing lessons that the EU can learn from the US debate on addressing market failure and stimulating anti-infectives R&D, the Working Group reviewed literature that proposed three distinct models for tackling the problem (Nathan and Goldberg 2005):

(i)   Government guarantees purchase of products from private sector: this 'pull' model may work particularly well for vaccines (EASAC 2006) or responding to the national priorities for bioterrorism preparedness (EASAC 2005).

(ii)   Government provides funding for combining not-for-profit discovery research with private sector development: this model is already progressing as various Public–Private Partnerships for developing country diseases.

(iii)   Government provides tax or other incentives for the private sector to invest in its own R&D.

Although these models are conceptually distinct (Nathan and Goldberg 2005), it would also be possible to combine elements from each model to develop a broader strategy for support, applicable to the EU context. Taken together with the recommendations from the React study (Tickell 2005), the IDSA recommendations can be translated into a framework that provides options from which European institutions can select (Box 4).

Box 4 Addressing market failure: promoting European innovation to tackle antimicrobial resistance (and other anti-infective goals)

Examples of options adapted from IDSA (2004), Norrby et al. (2005), Tickell (2005) together with discussion at EU InterGovernmental Conference in 2005:

Proposals for legislative action (European Commission and Member States)

• Supplemental intellectual property protections (for example 'wild-card' patent extension; extended market exclusivity).

• Tax incentives for R&D.

• Guaranteed market.

• Liability protections.

• SME-specific support.

• Establish and empower independent body to prioritise discovery research objectives, to target incentives.

Proposals for regulatory authority action (EMEA)

• Update guidelines for clinical trials and encourage innovative trial design (for example surrogate markers; alternative statistical analysis).

(Box 4 *continues*)

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[17]   Including Switzerland.

[18]   In 2004, the pharmaceutical industry invested €21 bilion in R&D in Europe, and the biotech sector invested about €2.5 billion. In 2005, the pharmaceutical industry employed 615,000 in Europe, of whom 103,000 were in R&D (some data are not available from smaller EU countries).

[19]   For example, Ceftobiprole medocaril and Ramoplanin oral formulation in Phase III and Dalbavancin in pre-registration Phase were all discovered in Europe but then acquired by US companies.

- Greater harmonisation and simplification of regulatory requirements.

- Encourage use of novel animal models and *in vitro* technologies to reduce clinical efficacy studies required for additional indications.

- Accelerated priority review status: mechanisms for conditional approval when high medical need (based on Phase II data plus commitment to post-marketing studies).

- Introducing culture of company-regulatory agency partnership for development.

Proposals for funding agency action (European Commission and Member States)

- Stimulate research on basic studies in model microbes for exploitation in access to targets and better understanding of pathogen biology.

- Promote translational research and clinical trials (bench to bedside).

- Significantly increase funding in key areas of resistance R&D and diagnosis.

- Progress new funding models for collaboration with industry for technology and tools, drug discovery and early stage development.

- Support research to quantify economic and public health burden of resistance as evidence for setting priorities for drug discovery.

Proposals for surveillance action (ECDC)

- Build in-house antimicrobial resistance programmes, build links with academic researchers and take enabling role in standardising surveillance methodologies.

- Increase horizon scanning to prepare for future needs.

Some of these possibilities (for example, for regulatory agency reform, for liability protection, for improved surveillance networks and for improved clinical trial design) have been discussed in detail in the previous EASAC reports (2005, 2006); we agree that action across a broad front is needed.

Our main message, however, is the need to ensure sustainable R&D infrastructure – as vital for the private sector as it is for the public sector. In underlining the points listed in Box 3 about the priorities for research funding, we emphasise the opportunities for partnership, in particular for companies to collaborate with academia to help build the science base as described in the previous chapter. The recently proposed European Technology Platform/Joint Technology Initiative on Innovative

Medicines is an exciting opportunity for pharmaceutical and biotechnology companies to lead collective research on infectious diseases and, if successful, the suggested Strategic Research Agenda of collaborative work on predictive toxicology, in standardising tools and biomarkers, can be expected to shorten clinical development time and improve compound attrition rate.

Industry members of the Working Group proposed several critical success factors for academia if it is to attract interest from industry in pursuing research leads through linkage across the public-private sectors (Box 5).

Box 5 What scientific information attracts industry interest in academic research?

- Validated protein targets, mechanisms and assays.

- Protein structure determination for target.

- Extensive biochemical and genetic information.

- Genomic mode of action studies for active compounds.

- Predictive animal models.

- Identification of hits through screening of natural products or chemicals.

- Information on compound structure–activity relations.

The primary requirement is validated targets, reinforcing the earlier analysis (Box 2), but academic research does not usually deliver this level of information. There is a potential new role for public funding streams to provide support across a broad front in target assay, validation and development, structural biology, animal experimentation and medicinal chemistry in order to bridge the current gap between academia and industry.

5.3 Biotechnology sector

Even though the number of privately owned biotechnology companies is now greater in Europe than the USA (Table 2), the sector is much less mature and there are far fewer public companies. In the experience of members of the Working Group, there is a considerable problem for smaller companies in the anti-infectives area, both in obtaining seed money at the initial stage of research and then sustained funding for scientific work from the stage of discovery through to clinical development, including proof of concept. Evidence contributed by witnesses during the consultation, confirmed that smaller companies lack critical mass in key discovery disciplines (for example, drug metabolism and pharmacokinetics), as well as lacking funding to proceed

to clinical trials. In consequence, companies may close or merge and this often results in a movement of talented scientists out of antimicrobial drug discovery.

In the Working Group's experience, European venture capitalists usually find this early R&D too risky to support, by contrast with attitudes in the USA. This discrepancy is substantiated by the detailed EU–US biotechnology company comparison compiled by Critical I (2006) for EuropaBio, the European association of bioindustries. Thus, fewer EU companies receive venture capital; those that do, receive less than in the USA.[20] The Critical I report notes the implication for EU policy-makers who have become preoccupied with multiple technology transfer initiatives or seed funding schemes, '*Any strategic approach to building a biotechnology sector in Europe . . . ought to give at least as much consideration to the rapid growth of existing companies as to the propulsion of fragile start-ups into a highly competitive environment*.'

Although there is evidence for growing global sophistication in capital markets, we emphasise that more needs to be done to make new sources of money available. For example, there is a role for using EU funds to match venture capital and to provide financial and tax support to incentivise investors to support new technologies. EU Member States might also learn from the success of the US Small Business Innovation Research Program (SBIR) scheme whereby US Government agencies are mandated to procure R&D from smaller companies. Therefore, the recent revision by the European Commission of state aid guidelines to promote risk capital investment in the small- and medium-sized enterprises (SMEs) (European Commission 2006) is welcome, especially as this approach requires that 50% of capital comes from private sources so that funds will be managed on a commercial basis. The recent announcement that the Commission aims to triple SME funding in the forthcoming Competitiveness and Innovation Framework Programme (to run 2007–2013) is also highly relevant in focusing on the instrument of risk capital.

SMEs and framework programmes

The Working Group agreed with the objectives of the European Commission in encouraging SMEs to become more involved in the Framework Programmes of research support. However, analysis by the Working Group indicated that the relatively extended timetable for the initial phases in project assessment coupled with the perception of relatively low success rates deters SMEs. For Framework Programme 6, the average interval between the project application deadline and evaluation meeting is five months and the average time between evaluation decision and contract finalisation is nine months. These delays must be decreased significantly, and the Working Group recommends an overall goal of six months for the period between application deadline and contract. The calls for bids are also relatively inflexible: it would be better to schedule broader-based calls more frequently (perhaps twice a year) to attract consortia at the time that is most appropriate for them. Notwithstanding the points discussed previously about the collective value of consortial multidisciplinary activity and pre-competitive research, in evidence provided to the Working Group, SMEs emphasised that they would be most attracted to participate in projects that were stringently focused with clear direction and leadership; where SMEs could own project intellectual property and product rights so that they could then secure venture capital investment; and where there were prospects of developing new therapies within a reasonable timescale.

The EU SME funding challenges are not specific to the biotechnology sector, nor to anti-infectives research. However, the various European SME initiatives may be of value for such companies in obtaining funding to validate proof of concept and to progress with clinical trials. In addition, there is potential to consider new instruments to create incentives for R&D for those areas where there is no perceived profitable market. The current Orphan Drug legislation provides incentives mainly for development/marketing activities rather than for the research stage, and new European incentives for neglected research areas might be contemplated as part of a globally co-ordinated initiative (for example with WHO and endowed foundations), analogous to the current support on TB.

In summary, the conclusions from the EASAC Working Group analysis of large and small companies and of the public research sector provide a common theme. Thus, there are opportunities for the EU to take a leadership position both in terms of the fundamental science and in support for industry innovation. Although tackling the problem of antibacterial drug resistance requires urgent action across a broad front, in improved understanding of the emergence, transmission and evolution of resistance, in better case management and tracing of contacts, in surveillance of populations and in the various actions recommended by other bodies to attempt to contain the spread of resistance, there is also need for a longer-term vision. Europe must encourage sustained R&D commitment to deliver new diagnostics and therapeutics.

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[20]   Therefore, some EU companies access US capital markets by relocating to the USA (for example BioVex from the UK) or by merging with US companies, for example UK Cyclacel with Xcyte, French IDM with Epimmune, German Micromet with Cancervax, Danish Nordic Bone with Osteologix, Italian BioSearch with Versicor. The EU still requires a strategy to make it easier for SMEs to raise the capital they need at home. Removal of obstacles to cross-border investment within the EU would help to create the European investment market, involving banks as well as venture capital providers.

6 Recommendations

The range of necessary activities must involve global as well as European collaboration. There is some room for optimism, as research advances are beginning to clarify the gaps in our knowledge and to bring within range opportunities for improved surveillance and novel healthcare products.

One urgent issue is to raise awareness of the importance of antibacterial drug resistance for individuals, public health systems and the economy in the EU. We recognise that the European Commission is already active. The recent publication of the STOA report for the European Parliament brings the prospect of increasing visibility for the issues at the political level–although we are concerned at the lack of emphasis accorded by that report to biomedical research and novel drug development.

We also endorse the aspirations whereby European policy-makers continue to build collaboration at the global level, both to clarify the threats and to capitalise on the opportunities for collective action. The continuing commitment shown by the G8 science academies to highlighting the problems of infectious disease provides significant impetus to policy-making at a global level, which the EU should actively support.

Our specific recommendations, summarised from the previous chapters, are the following.

Surveillance

Good scientific data are essential for effective public health policy and the current scientific deficits need to be addressed. Significant progress has already been made in co-ordination, in particular in terms of the follow-up to the EU Council Recommendation in 2001 and the EUCAST initiative. The further development of a coherent strategy for the surveillance of antibacterial drug resistance in the EU requires a staged approach to building the evidence base by agreement of standardised guidelines on testing, identification of priorities for established and emerging pathogen monitoring and management, and creation of uniform databases that will facilitate the global sharing of data. The first step is to introduce a common methodology for phenotyping in Member States to generate homogenous data on microbiological susceptibility testing for different locations (community as well as hospital). There will need to be monitoring of resistance in commensal bacteria as well as pathogens. A longer-term objective is the standardisation of definitive genotyping methodology, probably centralised in reference laboratories, drawing on the national sample collection efforts. In each case, real-time data should be provided to the ECDC and we strongly advise that the ECDC be given the necessary resources to build its key benchmarking, co-ordinating,

enabling and training roles in antimicrobial resistance surveillance.

The collection of improved data on mapping of resistance will serve as a research as well as a public health resource and will facilitate robust analysis of the relationship between antibiotic consumption and development of resistance in different settings. It will also provide the high-quality evidence base needed to support policy-making to tackle antibiotic drug resistance as a pandemic. One critical objective for improved surveillance and policy-making is to assess the range of possible scenarios for the impacts of future migration into the EU and the expansion of the EU on the development of resistance in Member States.

Animal health and food supplies

There is also a need in the short-term to collect better data on the therapeutic use of antibiotics and development of resistance in animal husbandry and veterinary medicine, with in-depth genetic analysis for comparison of animal and human isolates, in a consistent manner across Member States, and to analyse these data to determine cost–benefit considerations. We welcome the growing interest of the EFSA in data collection and analysis. The European Commission should now consider how best to support the proposed work by the Codex Alimentarius Commission at the global level.

Novel rapid diagnostics

New diagnostics are strategically important to improve prudent antibiotic prescribing and treatment outcomes. Improved surveillance capacity will help to inform the priorities for developing novel rapid diagnostic agents. Broadly, there is an urgent need for improved diagnosis in clinical practice: standardised methodologies, sensitive, simple and cheap to use at point of care, able rapidly to differentiate between bacterial and viral infections, to identify specific pathogens and resistance profiles. This requires R&D for highly innovative approaches based on the resolving power and rapidity of molecular analysis. We look to leadership by trade bodies in the diagnostics sector to work with the European Commission to build strategic links across the relevant Directorates General (in particular, Sanco, Enterprise and Industry, and Research). In the short term, stakeholders should determine the roadmap to identify priorities, resources and opportunities for collaborative effort, involving academia, companies and with Member State governmental as well as Commission support. We suggest that an excellent starting point for this collective effort is the output from the EU Intergovernmental conference in 2005 (Finch & Hunter 2006).

Strengthening the science base

We endorse previous EASAC reports on the importance of strengthening the public sector science base, in both basic and clinical research. There is a key challenge to face in rebuilding European capability in academic bacteriology. We suggest that there is a particular opportunity both for Member States and the European Commission to add value to medical microbiology and clinical infectious disease infrastructure in improved research, teaching and training by funding collaboration between universities and their associated hospital microbiology services. Furthermore, behavioural, health economics and other social sciences need to be more involved with studies concerning antibiotic usage and infection control. There have been insufficient studies as antimicrobial resistance has, until now, been seen as a purely medical issue. This needs to be changed.

Therefore, in terms of the opportunities afforded by European research (funded by the Commission and by Member States), we identify a wide range of priorities for research on antimicrobial resistance:

- Basic research on the function of essential genes in pathogens.

- Structural biology on proteins involved in the development of resistance.

- Study of mechanisms of transfer and dissemination of resistance genes.

- Study of host–pathogen relations.

- Skill development in cell culture and animal studies of resistance.

- Identification of new opportunities emerging from more speculative approaches, for example the properties of microbial communities and immunomodulatory signals.

- Anti-infective drug discovery target identification.

- Synthesis of open access chemical libraries.

- Economic and other social sciences analysis of the burden of infectious disease, development of resistance and cost-effectiveness of treatments.

A significant amount of research in these areas will be funded in Framework Programme 7 in consequence of previous discussions between DG Research and the scientific community and we recommend continuing joint efforts to identify priorities.

In addition to the funding of new research projects, support for priority topics could include organisation of an integrated series of workshops as networking events to develop recommendations on specific aspects of drug resistance. We also recommend initiating activities utilising industry practitioners to inform academic scientists about what is involved in the discovery and development of novel therapeutic agents.

Support for industry innovation

We vigorously support previous EASAC recommendations to promote vaccine innovation and uptake and strongly recommend increasing effort to develop new therapeutic agents.

There is a broad array of tractable measures to address the current market failure in anti-infectives R&D: encompassing legislative actions by the European Commission and Member States and regulatory action by EMEA as well as the increased surveillance functions of the ECDC and the leadership role of the Commission in stimulating basic and translational clinical research.

The European Technology Platform Innovative Medicines Initiative has good potential to be a catalyst to stimulate both consortial work between companies and collaboration across the public and private research sectors in anti-infective drug predictive toxicology. It is important, therefore, for Member States to support the European Commission proposal to transform this Technology Platform into a Joint Technology Initiative, viable to attract new sources of funding. We welcome the continuing leadership displayed on this initiative by the European Federation of Pharmaceutical Industries and Associations (EFPIA), and its member national trade associations; this initiative has been slow to progress but we discern the real prospect of impact on innovation in the medium term. We urge companies to persist in their efforts to create an attractive environment for innovation in Europe in the face of increasing competition from new regions, in particular Asia.

It is now vital for the European Commission and Member States to support research in academia that can be of potential value to companies, for example by helping to validate new targets and generate lead compounds as anti-infective agents, to serve as the basis for building new linkages between the public and private research sectors. The SME sector requires additional support in provision of initial and follow-on funding (at least to proof of concept stage) from public sector sources. The options for introducing new incentives for R&D of potential societal value, that is otherwise deemed commercially unattractive, should also be considered further.

List of abbreviations

ARMed	Antibiotic Resistance Surveillance and Control in the Mediterranean Region
CA-MRSA	Community-acquired methicillin-resistant *Staphylococcus aureus*
CDC	Centers for Disease Control and Prevention
COPD	Chronic obstructive pulmonary disease
DG Sanco	Directorate-General for Health and Consumer Protection
EARSS	European Antimicrobial Resistance Surveillance System
EASAC	European Academies Science Advisory Council
ECDC	European Centre for Disease Prevention and Control
EFPIA	European Federation of Pharmaceutical Industries and Associations
EFSA	European Food Safety Agency
EMEA	European Medicines Evaluation Agency
ESAC	European Surveillance of Antibiotic Consumption
ESBL	Extended-spectrum beta-lactamase
ESCMID	European Society of Clinical Microbiology and Infectious Diseases
EU	European Union
EUCAST	European Committee on Antimicrobial Susceptibility Testing
FP5	Framework Programme 5
GAARD	Global Advisory on Antibiotic Resistance Data
HIV	Human immunodeficiency virus
IDSA	Infectious Diseases Society of America
MRSA	Methicillin-resistant *Staphylococcus aureus*
NETHMAP	The Netherlands National Institute of Public Health and the Environment
NIAID	National Institute of Allergy and Infectious Diseases
R&D	Research and development
SARS	Severe Acute Respiratory Syndrome
SBIR	Small Business Innovation Research Program
SME	Small and Medium Enterprise
STOA	Science and Technology Options Assessment
TB	Tuberculosis
XDR-TB	Extensive drug-resistant tuberculosis
WHO	World Health Organization

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Appendix: Expert consultation

This report was prepared by consultation with a Working Group of experts acting in an individual capacity, and was reviewed and approved by EASAC Council. We are grateful to all who contributed:

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A late draft of the Working Group output was discussed with Anna Lonnroth (DG Research), Stefan Schreck (DG Sanco) and Peet Tull (ECDC) and we are grateful for their comments.