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Healthcare-associated infections: the view from EASAC

Foreword

Healthcare-associated infections are an increasing problem for the European Union. Many Member States are spending a substantial proportion of their healthcare budget on these infections, which affect about 7% of patients in acute care hospitals. The problem is compounded by the decreasing clinical effectiveness of antibiotics because of the spread of bacterial resistance.

This report is the latest in a series published by the European Academies Science Advisory Council (EASAC, www.easac.eu) on issues that policy-makers need to take into account when addressing public health challenges associated with infectious disease. Our previous publications in this series are as follows:

1. 'Infectious diseases – importance of co-ordinated activity in Europe', Report, May 2005.
2. 'Vaccines: innovation and human health', Report, May 2006.
3. 'Tackling antibacterial resistance in Europe', Report, June 2007.
4. 'Impact of migration on infectious diseases in Europe', Statement, August 2007.
5. 'Combating the threat of zoonotic infections', Report, May 2008.
6. 'Drug-resistant tuberculosis: challenges, consequences and strategies for control', Report, March 2009.

EASAC welcomes the current activity by the European Commission and national health services in developing improved approaches to the safety of patients by strengthening surveillance, implementing standardised infection control procedures, developing a skilled workforce and informing patients. However, EASAC emphasises that these relatively short-term actions are not sufficient. It is also essential to pursue longer-term objectives for research and innovation in order to understand epidemiology and pathogenesis, and develop new diagnostics, drugs and vaccines.

This report was prepared by EASAC following a scientific discussion meeting in Berlin in 2008, organised by the German Academy of Sciences Leopoldina together with the Royal Society (UK), the Academie des Sciences (France), the Royal Swedish Academy of Sciences and the Royal Netherlands Academy of Arts and Sciences. In addition, EASAC recommendations draw on the published work of individual academies, particularly the Royal Netherlands Academy of Arts and Sciences and the Royal Society. The latter publication ('Innovative mechanisms for tackling antibacterial resistance', Royal Society, 2008) is itself based on a meeting organised to follow up on the initial EASAC report on antibacterial resistance. I thank the experts who contributed to these meetings and I thank my colleagues on the Council of EASAC, who were responsible for organising the independent review of the draft report and its approval for publication.

I welcome further discussion on any of the points raised in our report.

Professor Volker ter Meulen
Chairman of EASAC

Summary

Healthcare-associated infections (HAIs) are those infections occurring after admission to hospital or exposure to other healthcare interventions. They are caused by a wide range of pathogens, many of which are becoming increasingly resistant to standard antimicrobial agents. Vulnerable patients become colonised and infected by these resistant, nosocomial micro-organisms through contact with healthcare workers, patients, visitors and other colonised sources. About 7% of patients in acute care hospitals in the European Union (EU) experience HAIs, resulting in a considerable public health burden, with about 37,000 directly attributable deaths per year and perhaps three times as many partly attributable deaths.

A recent European Commission Communication and Recommendation outlines approaches to improving the safety of patients by containing HAIs, strengthening surveillance systems, improving workforce training and increasing the information supplied to patients. These objectives are welcome and there is an important translational medicine agenda to be pursued in measuring, understanding and containing the transmission of pathogens as part of the consistent implementation of standardised infection control procedures. However, these relatively short-term actions are not enough. Assessment of the available evidence by EASAC leads to the conclusion that it is also essential to commit to longer-term objectives for research and innovation, to provide the improved products and services that will detect, monitor, prevent and treat HAIs. There are important roles for the European Commission, Parliament and successive Presidencies to act across a broad front in addressing these significant problems for all Member States.

At the research level, it is necessary to understand better the behaviour of both human and microbial populations, by integrating research priorities for epidemiology, social sciences, clinical translational research and the basic biomedical sciences, so as to provide the primary resource to tackle antibiotic resistance and pathogen virulence. There is continuing need to connect the research advances with innovatory capacity to discover and develop new diagnostics, drugs and vaccines, and to use these new tools in new ways, for example to target therapy in personalised medicine. There is concomitant need to devise new incentives for the private sector to invest; there are opportunities for public–private partnerships to share risks and rewards in discovering and validating the novel targets, supported by new centres of excellence to help train the next generation of experts.

EASAC also emphasises that the issues for HAIs should not be considered in isolation from other policy issues; nor should the issues for the EU be considered in isolation from the rest of the world. It is important to develop more coherent and co-ordinated policy to ensure that health services take account of the best evidence on what works in reducing HAIs, recognising that incentives and training for them may be more effective than financial penalties and that there should be better integration between the human health and veterinary health sectors. It is also vital for the EU to support wider international efforts, in particular to help build the necessary epidemiological databases to clarify HAI disease burden, risk factors and emerging pathogens, as part of a global commitment to tackle antimicrobial resistance.

What are healthcare-associated infections?

Hospital-acquired, or nosocomial, infections are among the most common adverse events associated with healthcare. The connection between hospitalisation and risk of infection can be attributed to various factors[1]. For example:

- The underlying illness may increase vulnerability to infection or impair the immune response; drug treatments may weaken the immune system.
- Invasive surgical or other procedures may facilitate pathogen entry.
- The use of antibiotics to treat infection can encourage other pathogens to colonise the patient. Poor infection control practices may encourage antibiotic resistance.
- Organisational factors, such as high bed occupancy, sub-optimal staffing levels, poor governance practices or poor compliance with recommended hygiene standards, provide opportunities for pathogen transmission between patients.

[1] Health Protection Agency, 'Healthcare Associated Infections – General Information' on www.hpa.org.uk. The ECDC (2008), in clarifying the definition of HAIs, notes that difficulties arise in developing a common European terminology because of differences in health and social service provision.

Studies of the prevalence of nosocomial infections in Europe indicate that the main infection sites are urinary tract (27%), lower respiratory tract (24%), surgical sites (17%), bloodstream infection (11%), with other sites including gastro-intestinal, skin and soft tissues, and the central nervous system (European Centre of Disease Prevention and Control (ECDC) 2008). HAIs are frequently associated with specific hospital procedures: for example, bloodstream infection with intravenous devices, respiratory infection with artificial ventilation, wound infection with surgery. Infections are caused by a broad range of micro-organisms: in European prevalence surveys, *Escherichia coli* is the most common, followed by *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Enterococcus* species, coagulase-negative *Staphylococci*, and *Candida* species, with smaller numerical contributions from *Klebsiella*, *Proteus*, *Enterobacter* and *Acinetobacter* species. More recently, *Clostridium difficile* has become a much more prominent problem in some EU Member States. A somewhat different perspective is obtained from the major reported nosocomial outbreaks, where the most frequently documented organisms were *S. aureus*, *P. aeruginosa* and *Klebsiella pneumoniae* but others were *Legionella pneumophila*, *Aspergillus* species, hepatitis virus and norovirus, the last being a frequent cause of closure of affected medical departments.

Multi-drug resistance may be responsible for half of all deaths from HAIs in some EU Member States (Watson 2008): major antibiotic-resistant organisms include methicillin-reistant *S. aureus* (MRSA), multi-resistant *Acinetobacter* and extended-spectrum beta-lactamase (ESBL)-producing *E. coli*.

Public health and economic burden

About 7% of patients in acute care hospitals in Europe experience an HAI. The documented range is 3–10% across Member States, although the quality of the surveillance data is not consistently high (ECDC 2008). The annual number of HAIs in the EU has been calculated to be about 4.5 million.

Estimating the impact of HAIs requires several assumptions about the quality and comparability of prevalence data, and hospital practices and costs. The mortality directly attributable to nosocomial infections is estimated to be about 37,000 in the EU (compared with 90,000 in the USA and perhaps 3 million in developing countries), but they also contribute to other deaths, perhaps 110,000 in the EU. The total annual healthcare costs of such infections for the EU was estimated to be 7 billion euros (ECDC 2008), but this probably grossly underestimates direct costs. For example, the data for sepsis alone in Germany (estimated in a recent meeting, Appendix 1) may be nearly 2 billion euros per year. Indirect and post-hospital costs of nosocomial infections, including those related to loss of income, are probably at least threefold higher than the direct costs.

What should be the objective for reducing the public health and economic burden? It is not plausible to aim for no HAIs; the objective should be to avoid preventable infections by implementing consistently good clinical practice. This requires, however, better diagnostic and therapeutic tools as well as the prudent use of the tools already available.

What are the EU policy issues? The European Commission proposal for a Council Recommendation

A recent European Commission Communication[2] recommends a comprehensive approach to improving patient safety whereby Member States are encouraged to introduce plans to reduce the incidence of adverse events in all healthcare settings. Action on patient safety is seen as increasingly important for health systems because of the ageing population, rising public expectations, and advances in medical procedures, together with the increasing threat posed by antimicrobial resistance. As the Communication notes, '*Although the problem of patient safety is primarily the responsibility of Member States, the European Union can encourage cooperation between Member States and support their actions in areas where EU interventions can have an added value*'. The Commission proposal includes a specific focus on HAIs, with a range of recommendations: to support the containment of HAIs; strengthen surveillance systems; foster education and training of healthcare workers in infection prevention and control; and improve the information given to patients. However, the Communication makes relatively little mention of the necessary research agenda, suggesting only

[2] 15 December 2008, Communication from the Commission to the European Parliament and Council, COM (2008) 836 final. This follows the identification in the Commission's Health Strategy White Paper (2007) of patient safety as a priority area for action, with objectives to address the issues for nosocomial infection and antibiotic resistance.

a '*programme on patient safety*'. The accompanying Council Recommendation[3] provides slightly more information on what is seen as the research priorities, primarily for the social sciences, although there is brief mention made of research to include '*new preventive and therapeutic technologies and interventions and cost-effectiveness of prevention and control*'.

In the view of EASAC, there is an urgent need to increase commitment to biomedical research and innovation because, without that, the battle against antibiotic resistance will be lost. There is no doubt, of course, that much can be done to contain the spread of resistance – for example, by improving hospital hygiene and prudent prescribing – and the ECDC has made a strong case for strengthening active surveillance systems (Box 1).

However, in previous work by EASAC (2007), we have warned that better surveillance, heightened awareness and containment measures, although highly important, are not enough. The accumulating evidence on the threat posed by HAIs reinforces our previous conclusion that there must be a commitment to research and development (R&D) to generate new diagnostics, therapeutics and vaccines, to increase our ability to detect, control and prevent infection: this requires new forms of partnership and the provision of new incentives to encourage R&D.

Tackling the challenge of HAIs: recommendations from the European Science Academies

A scientific discussion (Appendix 1) organised by the German Academy of Sciences Leopoldina, together with the Royal Society (UK), the Academie des Sciences (France), the Royal Swedish Academy of Sciences and the Royal Netherlands Academy of Arts and Sciences, evaluated new information and perspectives on nosocomial infection, covering the main public health challenges and the relationship between hospital- and community-associated infections. The meeting explored priorities both for the short-term, about how scientific evidence can better inform clinical practice, and for the longer term, about how scientific advances can be connected to the development of novel diagnostic, therapeutic and preventive strategies.

EASAC's conclusion based on this work of the academies can be summarised in six main themes.

Box 1 Issues for surveillance of HAIs in Europe

- Surveillance currently involves case finding, usually by infection control teams, uses clinical definitions, sometimes without microbiological confirmation, and may not identify infection source.
- As national priorities in infection control vary, so different surveillance protocols have emerged. Comparison of infection rates between hospitals may be difficult and requires risk adjustment to correct for case mix variability.
- In addition to variation in case definitions and surveillance methodologies, interpretation of differences between institutions and countries is confounded by the reluctance of some institutions to publicise their data.
- Therefore, insufficient data are currently available to allow meaningful comparisons between institutions by surveillance networks, to monitor the epidemiology and to evaluate and guide policies in prevention and control. The Commission Recommendation proposes that surveillance systems should be established or strengthened at the national and regional levels.
- The EU-funded HELICS (Hospitals in Europe Link for Infection Control through Surveillance) project has attempted to standardise surveillance protocols. ECDC recommends that to access and improve the quality of data, a European validation study based on standardised methodology should be progressed accompanied by development of indicators to evaluate the implementation of infection control measures.
- Further challenges emerge in the extension of European surveillance of HAIs to all Member States and in the wider application of electronic data collection. Furthermore, consideration must now be given to extension of surveillance to other pathogens, such as *C. difficile*, and new variants of old pathogens, such as MRSA, which require molecular typing data. There is need for real-time surveillance of clusters of particular pathogens and strains.

From ECDC (2008) and the HELICs project on http://helics.univ-lyon1.fr/frtitle.htm

1 *Building the evidence base in public health for decision-making*. Efforts in disease surveillance across Europe must do better in adopting standardised methods for data collection and in sharing these data. Public health responsiveness must achieve better co-ordination in national and regional plans to use

[3] Annex 2 in the Proposal for a Council Recommendation on patient safety, including the prevention and control of healthcare associated infections, COM (2008) 837 final.

the available evidence base, to develop good practice guidelines and to use those guidelines already promulgated.

2 *Engaging with patients and the public-at-large*. There is a responsibility for the health services and the wider scientific community to understand public attitudes, expectations and behaviour better, and to inform the public better about the problem of antibiotic resistance.

There is an extensive translational medicine agenda associated with measuring and understanding the transmission of the most clinically relevant pathogens, with the building and use of databases to enhance surveillance capacity, the routine implementation of standardised infection control measures and the creation of a well-trained workforce. Investments in hospital hygiene must be a priority. The potential for vulnerable patients to be infected by healthcare workers, other patients and visitors (and vice versa) highlights the importance of raising awareness and rapid diagnosis to enable early preventative action. For these, EASAC endorses the objectives and plans outlined in the recent European Commission Communication and Recommendation. In addition, however, EASAC emphasises the need to fund and progress the longer-term strategic agenda for tackling HAIs.

3 *Strengthening capabilities in fundamental science*. There is a research need to understand the behaviour of both microbial and human populations. Significant new opportunities to inform policy are now becoming possible in consequence of advances in both the social sciences and basic biomedical science. However, there must be better integration of the research agenda to cover epidemiology, social and basic biomedical sciences and clinical translational research. There are important issues to resolve in the level of research funding in Europe, the selection of research priorities, and in improving the use of research in policy development and in innovation for improved healthcare.

Social science research can be expected to aid understanding of the determinants of antibiotic resistance and to target behavioural modification in the health services to improve rational antibiotic prescribing, compliance with guidelines and promotion of hospital hygiene. Epidemiological research is vital to provide the sound basis for public health strategic analysis and action. In addition to the broad surveillance needs (Box 1), there is particular value in collecting time-series data to measure the effects of intervention and in using the available data for economic assessment to quantify the attributable costs for hospitals and society and, thereby, to determine the cost-effectiveness of intervention. Advances in biomedical research, to increase understanding of antibiotic resistance, virulence and host-defence mechanisms, provide the discovery resource for new and better diagnostics, therapeutics and vaccines.

4 *Health and wealth creation*. Addressing the currently unmet medical needs requires better connectivity between the research advances in genomics and other fundamental science and the development of new products, and their use in new ways, for example diagnostic–therapeutic combinations in personalised medicine.

Uncertainty in diagnosis is a major reason for excessive use of antibiotics in both developed and developing countries. Therefore investment in better diagnosis to identify causative pathogens and their resistance profile can be expected to be both advantageous to public health and cost-effective. However, although there is now a realistic prospect for using new diagnostics to target therapy, there are obstacles:

- Translational research: most of the current research studies are small. It can be difficult for academia and small companies to fund the bigger, prospective, studies needed to confirm initial findings and provide clinical validation.
- Standard setting: there may be disparity in the molecular signatures discovered by different research laboratories. This problem can be reduced by shared training and information exchange.
- Infrastructure: prospects for clinical application are weakened by the increasing tendency to separate microbiology laboratories from hospitals.
- Education: there is continuing need to train medical professionals to be responsive to laboratory information on diagnosis and to issues of hospital hygiene and antibiotic stewardship.
- Healthcare budgets: current cost structures can make it difficult to show that increased spending on diagnosis and prevention will be cost-effective by sparing cost of therapy and improving clinical outcomes.

In developing new therapeutics, it is now generally agreed that Gram-negative pathogens present a particular challenge to health systems because of the lack of drugs under research and development. No new drugs are further forward than phase I, by contrast, for example, with several new therapies for *S. aureus* in phases II–III. The European Medicines Agency (EMEA) is currently engaged in a 'gap analysis' on antimicrobials to identify pathogen priorities for the pharmaceutical sector: it is expected that EMEA will publish its priorities in 2009 to encourage the development of novel antimicrobials. Drug development is a lengthy, expensive and complex process; recommendations from the previous work of EASAC and individual academies are summarised in Box 2.

EASAC also emphasises that the issues for tackling HAIs should not be segregated from other relevant policy issues, and that the issues for the EU should not be considered in isolation from the rest of the world.

5 *Strategic coherence*. The different policy-making groups must be better co-ordinated across functions in national governments and at the EU level in order to integrate the scientific, economic and political aspects of the challenges faced for HAIs. In particular:

(1) There is need to connect activity between the human health and veterinary health sectors to foster the concept of one health.

(2) The improvement of the worst-affected hospitals may require a range of support mechanisms and incentives. Experience indicates that legal sanctions are unlikely to be the most effective mechanism. The imposition of financial penalties is controversial, although these are likely to be increasingly used in Member States[4]. It is possible that the recent US legislation denying Medicare payment to hospitals for some HAIs (Anon 2008) may be counterproductive in its unintended consequences if it encourages the hospitals to over-prescribe antibiotics and deters the admission of high-risk patients. The reporting of infections may also be adversely affected if doctors are then tempted to classify infections as community acquired rather than hospital acquired.

(3) The importance of considering the inter-sectorality of policy development is also exemplified by the emergence of antifungal resistance in healthcare facilities. Tackling this problem requires sharing of information and options across the public policy-making and regulatory departments concerned with health, agriculture and manufacturing.

6 *Global leadership*. There are growing opportunities for the EU to provide active

Box 2 Innovative mechanisms for tackling HAIs

- Existing antibiotics must be used prudently to slow down the development of resistance.
- It is vital to develop antibacterial agents that act in novel ways, for example by targeting bacterial adherence and virulence, inhibiting efflux pumps and destroying bacterial cell walls in an unconventional manner.
- Some public- and private-sector research funders have been deterred by the apparent low early success rate for genomics research in identifying targets. This disappointment is premature, but the problem is compounded by perceptions of low return on investment and excessive barriers to innovation in infectious disease therapeutics.
- The private sector needs to be encouraged to invest, by market pull mechanisms and other incentives and by simplification of regulatory hurdles without compromise to product quality, efficacy and safety.
- There are significant opportunities for promoting public–private partnership between industry and academia, to share risks and rewards, with the aim of discovering new targets, clarifying resistance determinants and reaching proof of concept for the new pharmacological approaches. The Joint Technology Initiative in Innovative Medicine, part of Framework Programme 7, represents a great opportunity for industry and academia to tackle bottlenecks in R&D.
- New centres of excellence are required to develop the various skills needed for the complex R&D programmes and to train the next generation of experts in antimicrobial therapeutics and related disciplines.

Conclusions drawn from the publications of the Royal Netherlands Academy of Arts and Sciences (2005), EASAC (2007) and the Royal Society (2008).

[4] For example the UK where the 2008-9 NHS contract for acute services introduces financial penalties for failing to reduce hospital acquired *C. difficile* in accordance with national targets (Walker et al., 2008).

support and leadership for strategic activities at the global level, for example in building a high-quality research database as a resource for systematic review, to clarify disease burden and risk factors, and to inform World Health Organization (WHO) activity in tackling antibiotic resistance. There is no such thing as fortress Europe in this context, and the trans-national nature of infectious disease makes the reduction of resistance a global public good.

Further details on these key issues are provided in Appendix 1.

In conclusion, a European programme on patient safety, to include rational prescribing, improved hospital hygiene and attention to other best practices in infection control, is important in managing HAIs and slowing antibiotic resistance. However, a longer-term vision is vital to build sustained commitment to R&D in order to strengthen the science base, develop novel diagnostics and support innovation in drug and vaccine development. EASAC asks that the European Commission now considers what needs to be done in research and innovation policy as well as in health policy to tackle the growing concerns expressed in this paper. We welcome the increasing political commitment, manifested by successive Council Presidencies, and we look to both the public and private sector research functions to capitalise on the scientific opportunities in tackling the major problem of infections associated with healthcare.

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Appendix 1: Summary of points from the Berlin Inter-Academy meeting 'Nosocomial Infections and Host Susceptibility', September 2008

The importance of understanding current medical practice and collecting sound epidemiological data

There is a broad agenda of priorities for social science research aimed at understanding and influencing the behaviour of individual medical professionals in using antibiotics and, thereby, improving the aggregate performance of healthcare systems. There are three dimensions for targeting behaviour:

(1) socio-cultural determinants (partly accounting for differences in practice between Member States);

(2) organisational variation (partly accounting for differences between institutions within Member States);

(3) professional practice (differences in behaviour of individual doctors).

Integrating interventions at all three levels should help to improve rational antibiotic use. Evidence suggests that use of more restrictive prescribing measures may be expected to be more effective than merely providing advice to prescribers, but greater restriction on antibiotic availability could be counter-productive for those clinical indications, such as sepsis and pneumonia, where early treatment is critical. Uncertainty in diagnosis may be a major reason for the excessive use of antibiotics: increasing investment in better diagnosis would be both advantageous to public health and cost-effective.

Higher-quality data on the consequences of antibiotic use in agriculture are also needed. However, it would be prudent to assume that veterinary use may impact on public health use: there is need both to develop better guidelines for animal health and better co-ordination in policy-making between animal health and public health departments.

Given the degree of cultural differences between Member States, and their retained responsibilities for

healthcare delivery, more work is required to determine the appropriate form of EU/international guidelines on antibiotic use that would allow the flexibility to adapt to local circumstances.

Detailed statistics are available in some Member States for priority pathogens, in particular MRSA which accounts for about 20% of *S. aureus* and *C. difficile*, a rapidly increasing problem. Among some of the emerging policy needs for infection control are:

- Regional networks to communicate consensus in healthcare principles and increase implementation of best practices on a local level, particularly when involving more than one Member State.
- Good practice guidelines should cover a wide range of topics, including hygiene measures, prudent use of antibiotics, standardised surveillance procedures and reporting systems, access to reference laboratories. Guidance on provision of information to patients is also important, especially as some hospitals may not willingly disclose poor performance.
- Resolution of resource problems that may limit compliance with guidelines, such as the shortage of trained staff, particularly nurses. There are lessons to be learnt from sharing good practice about the appropriate level of resources to commit to infection control.

The EU has experienced historical problems in generating consistently high-quality epidemiological data, although the situation should improve now that the ECDC is consolidating the previous multitude of individual surveillance networks. However, there are continuing issues for data comparability in the supply from heterogeneous Member State surveillance systems (Box 1). In consequence, the measured rates of HAIs across the EU are influenced not just by differences in clinical practice (case mix, extent of invasive procedures, length of hospital stay) but also by methodological differences in diagnosis, differing interpretations of standardised definitions, differences in case finding (such as whether surveillance is continued after hospital discharge) and differences in disclosure.

The new ECDC surveillance system is addressing these variabilities by instituting a standardised reporting system with a data warehouse approach used to evaluate diverse data. There is much still to be done by the ECDC, together with the Member States, not least in strengthening some national systems. Unlike the US Centers for Disease Control and Prevention (CDC), the ECDC does not have its own laboratories; some think that it should have. In this regard, the ECDC sees its role as collaborating at Member State level with the reference laboratories to support training, capacity building and quality assurance.

The prevalence of persons infected or colonised with antibiotic resistant bacteria present in healthcare settings outside of the hospital inpatient facility, for example in long-term care and other community facilities, is also an increasing problem. For example, 50% or more of MRSA-positive patients in German hospitals are already colonised on admission, according to the national nosocomial infection surveillance system database. The multiple challenges inherent in HAI necessitate a broad agenda for data collection and research to inform decision-making:

- time-series data to measure the effects of intervention;
- economic data to assess attributable costs for hospitals and society and determine cost-effectiveness of interventions;
- interdisciplinary research including social sciences, to understand the determinants of antibiotic resistance;
- mandatory reporting of public health data in all Member States;
- close co-operation between human and veterinary research agendas;
- proactive work to target emerging pathogens.

The HAI disease burden in developing countries is much less well quantified and communicated than those other major infections (HIV, tuberculosis, malaria) that have formed the traditional infectious disease priorities for the WHO. There is much for policy-makers to do to raise global awareness, mobilise national resources and support improvement in healthcare settings. A lack of standardised methods for definition, surveillance and assessment has limited the collection of reliable data worldwide; the risk of HAI is assumed to be 2- to

20-fold greater in developing than developed countries, because of very limited resources, unsafe practices and social deprivation. There is only a relatively small high-quality research database available and there is need for more, better-standardised, epidemiological research worldwide. The issue of diagnostic uncertainty leading to overuse of antibiotics can also be a problem for developing as for developed countries: there is broad opportunity for better diagnosis in cost-effective healthcare delivery. However, best practice in infection control procedures may be difficult to implement uniformly. For example, use of alcohol hand-rubs as a hygiene measure may be unwelcome in some countries for religious as well as for cost reasons. The WHO-designated initial HAI priority for hand-hygiene promotion is being followed by initiatives on safer surgery and on tackling antimicrobial resistance.

Progress on biomedical research priorities

Significant progress in biochemistry is accompanying the resurgence in epidemiology. Case studies of pathogens of particular importance illustrate current and emerging public health threats; however, they also show where scientific advances are helping to provide new interpretation of pathogen behaviour, characterising differences from commensals. A continuing challenge is to determine the extent to which the present problems in public health can be addressed by better clinical management of resources already available or where novel therapies are needed:

- Discussion highlighted the importance of the emerging virulent lineage of enterococci in hospital infections. The observation that enterococci have a particularly wide range of hosts (including insects) may provide insight into the origins of antibiotic resistance in higher animals. Detailed biochemical study that follows initial case finding is beginning to clarify the role of enterococci in transmitting vancomycin resistance to staphylococci, a key event in the developing threat of HAIs.

- Case-study analysis of *C. difficile* has been aided by recent elucidation of genome sequences coupled with development of animal models to provide the scientific basis to understand the emergence of hypervirulence and, thus, to discover new approaches to treatment.

- Until recently, *E. coli* had not been judged a major problem in infectious disease. However, after the control of other pathogens in the twentieth century, *E. coli* has occupied a more prominent role as a cause of urinary tract infection, neonatal meningitis, intra-abdominal infections and septicaemia. Work in model systems is beginning to clarify the mechanisms that enable systemic infection by extra-intestinal *E. coli* strains. Variation in the host response has an important role as a driving force in the adaptation of *E. coli* to its environment; this increased understanding may provide a basis for developing new therapeutic strategies, for example for urinary tract infection.

- There has been a dramatic increase in resistance by Gram-negative bacteria to cephalosporins (particularly in southeast Europe and Turkey) and there is now detailed epidemiological data available from German hospitals to track the emergence and dissemination of resistance to the newer generation cephalosporins and carbapenems as a basis for clarifying the determinants of resistance.

- The clinical emergence of azole resistance in the opportunistic mould Aspergillus fumigatus is of growing importance in some Member States. Development of resistance seen in healthcare facilities can be attributed, in part, to the prevalence of environmental exposure. Azole fungicides are used extensively for protection of plants and in manufacturing – it may be that resistance has emerged recently as a clinical problem because of the introduction of newer fungicides with broad-spectrum activity.

Developing novel diagnostics, therapeutics and vaccines

Diagnosis

There is the prospect of new approaches to molecular diagnosis of sepsis – a major clinical challenge – where the history of therapeutic failure can be attributed, at least in part, to the problem of delayed and imprecise diagnosis using current procedures. Considerable scientific progress is being achieved in identifying sepsis markers (in particular, procalcitonin); in using transcriptomic fingerprinting to accomplish earlier, differential diagnosis and to monitor the disease process; and in whole genome association screens to explore predisposition to sepsis.

Diagnostic 'theranostic' biochips may become part of personalised medicine for HAIs (and other infections).

Multiplex chip assays are being developed to measure simultaneously pathogen genotypes (species, antibiotic resistance and virulence factors), host genotype (predisposition to disease, xenobiotic metabolism) and host response (to infection and to therapy). Proof-of-concept studies have been accomplished and cost–benefit studies are starting for a range of pathogens.

Vaccinology
There are also novel approaches to vaccine antigen discovery based on genomic insight, exemplified by work on extra-intestinal *E. coli.* Subtractive reverse vaccinology, comparing pathogenic and non-pathogenic strains, may be able to overcome some of the limitations of conventional vaccinology by focusing on non-conserved regions and identifying novel antigens. It is anticipated that a highly immunogenic polyvalent vaccine can be prepared from a combination of antigens, although the final formulation may be a compromise because of manufacturing complexity and cost.

Novel antibody therapy-based strategies are also being proposed to tackle *S. aureus* infection, an area where there has again been a history of disappointment in clinical development, perhaps because of the limited number of antigen targets previously identified. New results for monoclonal antibodies in animal models provide encouragement to develop additional targets to explore the therapeutic options for monoclonal as well as polyclonal antibodies.

Therapeutics
The broader issues for tackling the current obstacles to R&D for novel antibacterial drugs are summarised in Box 2. One example of the novel approaches in prospect is the use of phage lytic enzymes as an alternative approach to controlling pathogens before the onset of the clinical problem. That is, removing pathogens from their colonising reservoir without affecting commensals. If successful, this targeted approach could be used in a range of settings, such as nursing homes and day-care centres to decolonise high-risk subjects.

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EASAC

EASAC – the European Academies Science Advisory Council – is formed by the national science academies of the EU Member States to enable them to collaborate with each other in providing advice to European policy-makers. It thus provides a means for the collective voice of European science to be heard.

Its mission reflects the view of academies that science is central to many aspects of modern life and that an appreciation of the scientific dimension is a pre-requisite to wise policy-making. This view already underpins the work of many academies at national level. With the growing importance of the European Union as an arena for policy, academies recognise that the scope of their advisory functions needs to extend beyond the national to cover also the European level. Here it is often the case that a trans-European grouping can be more effective than a body from a single country. The academies of Europe have therefore formed EASAC so that they can speak with a common voice with the goal of building science into policy at EU level.

Through EASAC, the academies work together to provide independent, expert, evidence-based advice about the scientific aspects of public policy to those who make or influence policy within the European institutions. Drawing on the memberships and networks of the academies, EASAC accesses the best of European science in carrying out its work. Its views are vigorously independent of commercial or political bias, and it is open and transparent in its processes. EASAC aims to deliver advice that is comprehensible, relevant and timely.

EASAC covers all scientific and technical disciplines, and its experts are drawn from all the countries of the European Union. It is funded by the member academies and by contracts with interested bodies. The expert members of project groups give their time free of charge. EASAC has no commercial or business sponsors.

EASAC's activities include substantive studies of the scientific aspects of policy issues, reviews and advice about policy documents, workshops aimed at identifying current scientific thinking about major policy issues or at briefing policy-makers, and short, timely statements on topical subjects.

The EASAC Council has 26 individual members – highly experienced scientists nominated one each by the national science academies of every EU Member State that has one, the Academia Europaea and ALLEA. It is supported by a professional secretariat based at the Royal Society in London. The Council agrees the initiation of projects, appoints members of project groups, reviews drafts and approves reports for publication.

To find out more about EASAC, visit the website – www.easac.eu – or contact EASAC Secretariat at e-mail: easac@royalsociety.org

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