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Antibiotic resistance—action to promote new technologies: report of an EU Intergovernmental Conference held in Birmingham, UK, 12–13 December 2005

R. Finch[1]* and P. A. Hunter[2]

[1]Division of Microbiology & Infectious Diseases, Molecular Medical Sciences, Clinical Sciences Building, University of Nottingham & Nottingham University Hospitals NHS Trust City Hospital Campus, Nottingham NG5 1PB, UK; [2]Burnthouse, Burnthouse Lane, Cowfold, West Sussex RH13 8DH, UK

The increase in microorganisms that have developed resistance to currently available antimicrobial agents has become a major cause for concern worldwide. These organisms are widespread in hospitals but also occur increasingly in the community. Some of these strains are multiresistant and the agents available to treat infections caused by them are few and dwindling. Over recent years there have been a number of responses by national, international and professional bodies to this situation, many aimed at curbing this unprecedented growth in resistance, but there is an increasing recognition that a major problem in the management of infections caused by such organisms is the paucity of new drugs, vaccines and diagnostic aids.

A conference, organized by the Specialist Advisory Committee on Antimicrobial Resistance (SACAR) on behalf of the UK Department of Health and sponsored by the BSAC, was held in Birmingham in December 2005 with the aim of addressing these problems. Conference attendees included those from academia, industry, funding agencies, healthcare management, the European Medicines Agency (EMEA), the European Centre for Disease Prevention and Control (ECDC), European Directorates and representatives of EU governments. Following a number of keynote presentations which identified major issues, there were a series of workshops which addressed specific questions and produced a number of recommendations. These recommendations were discussed by all delegates.

The lack of new anti-infectives and the reasons for this were discussed in some detail. Major pharmaceutical companies no longer find this area as financially rewarding as other therapeutic areas while smaller biotechnology companies, who are seen as more innovative, are hampered by a lack of funding. In spite of a few marked successes, the use of vaccines has had minimal impact in the field of bacterial infections, and progress in this field also suffers from a lack of funding. Diagnostics could aid in the better use of antibacterials but need greater acceptance in the healthcare system, which does not generally appreciate their cost-efficacy.

The major recommendations were as follows:

(i) Increased efforts are needed to reduce the spread of resistant strains both in the environment and in hospitals—these include improved hygiene and decreased use of some antimicrobials.

(ii) Surveillance of resistance is a key factor and improved technology (e.g. IT systems) is needed to improve the potential for surveillance data to inform clinical practice.

(iii) Rapid, sensitive and specific diagnostics are urgently needed and the issue of reimbursement needs to be addressed.

(iv) More accurate estimates of the cost-efficacy of using anti-infectives and diagnostics are urgently needed.

(v) Vaccine technology is available but is underused for the prevention of bacterial infections, particularly those caused by organisms resistant to antimicrobials.

(vi) Incentives are required to encourage large pharmaceutical companies to partner small biotechnology companies, which are more innovative and have the potential to deliver the new drugs, diagnostics and vaccines.

*Corresponding author. Tel: +44-115-8231828; Fax: +44-115-8231943; E-mail: r.finch@nottingham.ac.uk

(vii) Modifications to the international regulatory requirements for drug licensing could have a major impact on the time and thus the costs of developing new agents.

Keywords: anti-infectives, antimicrobial agents, recommendations

Introduction

The major topics of this conference were the obstacles to the development of new agents and technologies aimed at combating antimicrobial resistance, and the identification of possible ways forward. An important target of the conference was to discuss why several large pharmaceutical companies have reduced their research and development (R&D) activity in the field of antimicrobial chemotherapy and to determine whether their place could be taken by smaller biotechnology companies or other research institutions.

The participants were from a range of backgrounds including academia, funding agencies, healthcare management, vaccine and diagnostic manufacturers, large pharmaceutical companies and biotechnology companies, as well as representatives of the European Medicines Agency (EMEA), the European Centre for Disease Prevention and Control (ECDC), EU Directorates and Member States.

What has gone before

The continuing increase in the incidence of microbes with resistance to an ever wider range of antimicrobials has been recognized for some years and there have been a number of national and international initiatives to deal with various aspects of this problem. While these initiatives have been well-intentioned and definite progress has been made in some areas, not all initiatives have produced the intended outcomes.

As long ago as 1995, a Task Force on antimicrobial resistance was set up by the American Society for Microbiology (ASM) in the United States (US). This Task Force recommended that surveillance systems should be implemented.[1] The Centers for Disease Control and Prevention (CDC) published their 'Guidelines for the Evaluation of Surveillance Systems' in 1998[2] and in June 2000, CDC [jointly with the Food and Drug Administration (FDA) and the National Institutes of Health] issued a Public Health Action Plan to combat Antimicrobial Resistance.[3]

In the UK the Select Committee on Science and Technology of the House of Lords considered the matter of resistance and in their excellent and comprehensive report one of the major recommendations was for more and better surveillance systems.[4] In response to this and to other important reports, the UK Department of Health issued an 'Antimicrobial Resistance Strategy and Action Plan' in June 2000.[5] Nevertheless, in spite of this, in March 2001, the Select Committee on Science and Technology issued a further report, stating that although the Government's response to the original report was extremely positive, with promises of action and expenditure, and that in some areas action was duly taken, concern was expressed over the time taken to implement a number of the recommendations. The report stated that the authors 'wonder whether our original report failed to convey the full seriousness of the situation. We repeat the main message: the inevitable rise and spread of resistance will render existing drugs progressively less useful. In the absence of new drugs, this leaves us at the mercy of infections'.[6]

A meeting held at the Royal Society of Medicine (London, UK) in March 2001 considered whether the needs of clinicians, microbiologists, public health specialists and policy makers with regard to surveillance were being met.[7] Included among the conclusions of the meeting were that the requirements of Government and of patients and clinicians differed and that some efforts at surveillance were not always well directed and often lacked denominator data. Education was considered key at many levels. Rapid detection of resistance was highlighted as now being possible but in need of funding. Moreover, there was recognition that the problems of resistance and surveillance were not just a national or European concern but a global problem, although no conclusions were reached as to what action should be taken and by whom.

The World Health Organization (WHO),[8] when considering the ability of microorganisms to develop resistance stated in 1998 that 'resistance is rapidly becoming a leading cause of concern for public health. In particular

- Resistant pathogens are emerging and spreading more rapidly than in previous decades.
- Resistance is a world problem, affecting developed and developing countries, and rapidly spreading through international travel.
- Treatment of infections caused by resistant microbes is increasingly hampered either by the prohibitive cost of existing 'new generation' agents or by a total lack of effective antimicrobial agents'.

The WHO concluded that the problem of resistance to antimicrobials was complex and that multiple solutions would be required. It identified surveillance and education as part of the solution together with regulation of the use of antimicrobials and research into the development of new agents.[8] This was followed up in June 2000 by a Press Release with the stark headline—'*Drug Resistance threatens to Reverse Medical Progress*'.[9] Furthermore its annual report on Infectious Diseases for 2000 entitled 'Overcoming Antimicrobial Resistance' reiterated concerns about the dearth of new agents emerging from the pharmaceutical industry.[10]

A conference of major importance in this area was held in Copenhagen in 1998.[11] It was entitled 'The Microbial Threat' and was initiated by Medical Officers of the European Union (EU). Major areas covered by the conference included the threat to human health posed by resistant organisms, the need to monitor the use of antimicrobial agents, and the need for surveillance systems. One of the recommendations was that a European surveillance system should be set up and this led to the formation of the European Antimicrobial Resistance Surveillance System (EARSS), an organization that has produced valuable findings.[12] A conference was held in Visby, Sweden in June 2001[13] to discuss what progress had been made as a consequence of the Copenhagen Conference. The conclusions were that much progress had been

made but 'the fact that resistance rates among common bacteria are still increasing emphasizes the urgent need for further efforts'. The EU also held a conference on 'The EU Strategy on Antimicrobial Resistance in Humans' in Brussels in November 2001.[14]

The Infectious Diseases Societies of America (IDSA) published a report in July 2004 entitled *'Bad Bugs, No Drugs: As Antibiotic Discovery Stagnates . . . A Public Health Crisis Brews'*.[15] This hard-hitting report used shock tactics to try and get the message across of what could happen. It paints a scenario reminiscent of a disaster movie, starting with two seemingly unrelated cases of gastrointestinal illness in different parts of the US. Both patients die of a multidrug-resistant *Salmonella* infection which spreads with great rapidity. By Day 5, 325 people are dead. Thousands—many of them children, the elderly and other vulnerable individuals—jam emergency rooms across the Northeast complaining of similar symptoms. By then the infection spreads and by Day 6, 1730 deaths and 220 000 illnesses occur in the United States. The effects of the epidemic spread to other countries. Canada, Mexico and Europe close their borders to food imports from the US, and travel initiated from the United States is banned around the globe. Economic losses to the US and global economies soon reach tens of billions of dollars. The FDA and CDC identify the source of the infections as a milk distribution facility located in New York State.

This report was designed to shock and was targeted in particular at the American Government. It highlighted the dramatic decline in effort in the pharmaceutical industry into R&D of anti-infective agents and urged the Federal Government to take action to halt this decline and give active encouragement to companies to undertake such work. Such a report was unusual for a scientific and medical Society who normally avoid emotive statements and it had been thought that it had a big impact. It is therefore disappointing to see that the IDSA felt it necessary to visit this area again in March of 2006. A press conference was held where the IDSA complained that Congress had still not passed the comprehensive legislation needed to stimulate the antimicrobial R&D called for in the previous report.[16] Funding has, however, been allocated to work on potential agents of bioterrorism but not on naturally occurring infections. The Director of Public Policy for the IDSA concluded that 'These bad bugs won't wait, neither should we'.

In 2005, a document was published by a group called React, Action on Antibiotic Resistance, entitled '*The Antibiotic Innovation Study: Expert Voices on a Critical Need*'.[17] This document was drawn up from discussions with a number of opinion leaders in drug discovery and development, academia, the EMEA, the WHO and the UK National Institute of Clinical Excellence, among others, and covers much of the same ground as the current conference, namely why are there so few new antimicrobials and why is the pharmaceutical industry no longer investing in this area and again gave recommendations for action. React is an initiative of the Dag Hammarskjöld Foundation, the Swedish Strategic Programme for the Rational Use of Antimicrobial Agents (STRAMA) and the Division of International Health at the Karolinska Institute.

Why action is needed today

As is clear from the above, resolving the problems of the growth of resistance to antimicrobial agents is a complex issue, and not withstanding the excellent initiatives noted above, there is still a great need for positive action to encourage more work in this field. In spite of six decades of the use of antimicrobial agents, infectious diseases continue to have an impact both on human morbidity and mortality throughout the world and place a major burden on healthcare services. Roger Finch (UK), one of the keynote speakers, presented figures showing the burden of infectious diseases in terms of visits to General Practitioners in the UK in 2003. Over 12 000 visits per 100 000 population were for upper respiratory tract infections with a further nearly 8000 visits per 100 000 population for lower respiratory tract infections. This contrasts with ~5000 visits per 100 000 population for diabetes and 4000 visits per 100 000 population for asthma (Figure 1).[18] The total estimated economic costs to the healthcare system for infectious diseases in England were also presented by Roger Finch and these are shown in Table 1. Visits to GPs represented over 50% (£3.52 billion) of the total £6.07 billion spent.[18] Another keynote speaker, Otto Cars (Sweden), presented figures from the WHO which estimated that there were 4 million deaths caused by acute respiratory infections worldwide in 2002, with other major infectious diseases including HIV/AIDS, diarrhoea, tuberculosis and malaria accounting for a further 7 million deaths (Figure 2).[19]

Otto Cars also highlighted the problems caused by the increase seen in resistance to antimicrobial agents; not only has this led to major increases in healthcare costs but more patients are dying because of the lack of appropriate drugs. He quoted various authors who have estimated the additional costs for an episode of bloodstream infection caused by a methicillin-resistant *Staphylococcus aureus* (MRSA) as between 5300 and 9900 US dollars (Table 2).[20–23] An additional important point made was that antimicrobial treatment was frequently inadequate in critically ill patients, leading to an increased death rate (Table 3).[24]

Otto Cars presented data from EARSS showing the rise in resistance to fluoroquinolones among invasive isolates of *Escherichia coli* in various European countries between 1999 and 2004 (Figure 3). The figure shows that although the level of resistance differs between the countries, even in Sweden, where resistance is lowest, there has still been a rise each year.

The impact of resistance on the costs of treating patients was also highlighted by Roger Finch, who added that resistance complicated patient management with the result that the patient took longer to recover thus increasing hospital costs. He also pointed out that such problems undermine public confidence in healthcare services, as well as frustrate healthcare targets, and increasingly have medico-legal consequences. Over the years resistance has had a major impact already on prescribing practice with some of these changes listed in Table 4.

It was also pointed out that therapy is at best suboptimal for a number of serious diseases such as hepatitis B and C, many tropical diseases and tuberculosis. For an increasing number of species the growth of resistance means that there is a diminishing choice of therapies now available. These include MRSA, vancomycin-resistant enterococci, penicillin-resistant pneumococci, multidrug-resistant tuberculosis, malaria, diarrhoeal pathogens, extended-spectrum β-lactamase (ESBL)-producing Gram-negative bacteria and some strains of non-fermentable Gram-negatives (*Acinetobacter, Burkholderia* and *Pseudomonas* spp.). There are other infections for which there is no therapy available including variant Creutzfeld–Jacob disease, many gastrointestinal, central nervous system and respiratory viruses and Severe Acute Respiratory Syndrome (SARS).

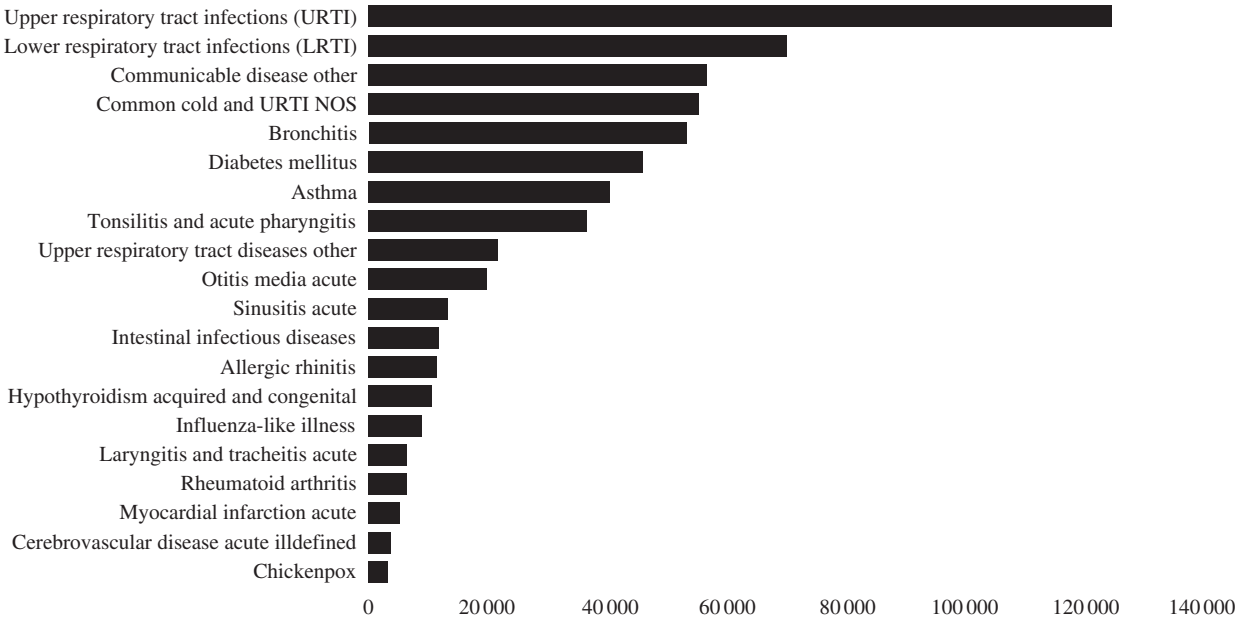

Figure 1. The UK burden of infection—GP consultations per 100 000 population (2003).[18]

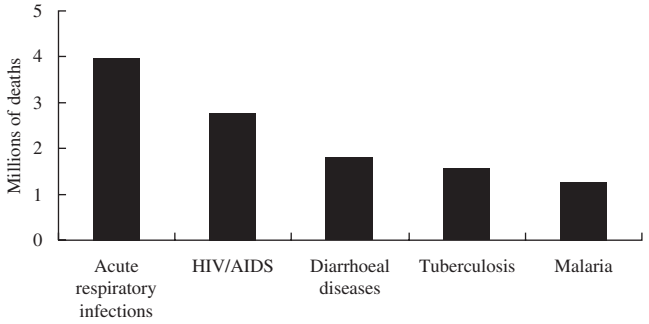

Figure 2. Global mortality in infectious diseases (extracted from WHO estimates for 2002).[19]

Table 1. Economic burden of infection in England[18]

	£ (in billions)
GP consultations	3.52
Hospital-acquired infections	1.39
Hospital admissions	0.89
HIV/AIDS treatment and care	0.27
Total	6.07

Otto Cars commented on an apparent complacency shown by most governments regarding this situation, which is not only difficult to understand but is also unacceptable. There is the paradox of an increasing burden of resistance coupled with a decreasing effort in drug development by the major pharmaceutical companies. This situation can be summed up by the phrase 'resistance leads to expenditure without benefit'. He highlighted the fact that only two new classes of antibacterial agents have been developed over the past few decades, in contrast with the period between the 1940s and the 1970s when many diverse classes of antimicrobial agents were introduced into clinical use (Table 5).

Table 2. Increase in costs for treating bloodstream infections caused by MRSA in comparison with MSSA

Authors of study	Increase in costs
Cosgrove *et al.*[20]	$7212
McHugh and Riley[22]	$5302
Lodise and McKinnon[21]	$9909
Reed *et al.*[23]	$7273–$8164

Table 3. Effect of inadequate antimicrobial therapy on the rate of mortality in critically ill patients[24]

	Inadequate therapy (22.5% of patients)	Adequate therapy
Mortality	42%	17.7%

Prospective study on 2000 patients in intensive care (655 patients with infections).

Why are there fewer new anti-infectives?

Traditionally the source of new anti-infectives has been the major pharmaceutical companies but there are now few of these companies with significant research efforts on antibacterials and antifungals, although there is more effort still ongoing in the field of antiviral research, particularly on HIV. The reasons for this

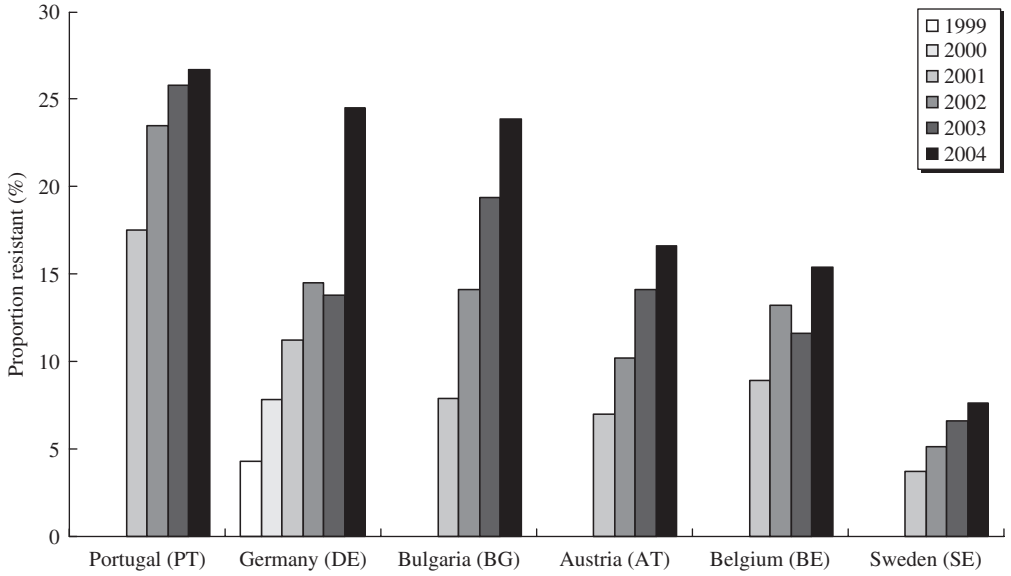

Figure 3. Fluoroquinolone resistance among invasive isolates of *Escherichia coli* between 1999 and 2004. Data extracted from the European Antimicrobial Resistance Surveillance Scheme (EARSS).[12]

Table 4. Impact of resistance on prescribing practice

Infection/pathogen	Changing regimen
Urinary	sulphonamide to trimethoprim to quinolone
Meningitis	chloramphenicol to ampicillin to ceftriaxone
Gall bladder	ampicillin to cephalosporins
Typhoid fever	chloramphenicol to ampicillin to quinolone
Gonorrhoea	penicillin to quinolone to ceftriaxone/cefixime
Staphylococci	penicillin to flucloxacillin to vancomycin

Table 5. Introduction of new classes of antibacterials

Decade of introduction	Class of antibacterial
1930s	sulphonamides
1940s	penicillins
	aminoglycosides
1950s	chloramphenicol
	tetracyclines
	macrolides
	glycopeptides
1960s	streptogramins
	quinolones
	lincosamides
1970s	trimethoprim
1980s	
1990s	
2000s	oxazolidinones
	lipopeptides

reduction in effort have been discussed in many recent conferences and have been summarized by Projan.[25]

Andrew Witty (GlaxoSmithKline, UK) presented a number of these reasons at the conference, the major one being that companies no longer find the area of anti-infectives financially attractive. The costs of progressing anti-infectives are no less than for other classes of pharmacologically active agents, but patients only take an anti-infective drug for days rather than years (or life!). Many companies thus prefer to put more effort into areas such as heart disease, cholesterol-lowering agents, anti-inflammatories, diabetes mellitus or Alzheimer's disease, where drugs are taken for prolonged periods and they can thus recover their expenditure on the development. The only way to recoup the expenditure for a drug used for short course of therapy would be to charge an unacceptably high cost, an anathema in the current era of cost-consciousness.

Stewart Adkins (Lehman Brothers, UK) emphasized this point and presented figures to show that branded sales of anti-infectives (annual sales worth nearly $20 billion) which used to lead the field are now in third place, with drugs for hypertension and angina topping the list (annual sales of ~$33 billion) followed by lipid lowering agents (annual sales of ~$27 billion) (Figure 4). A more useful economic analysis is to express the value of a therapeutic area as the Net Present Value (NPV), a figure used in the pharmaceutical industry to project future expenses and revenues and which discounts the potential investment value of the money spent on the project. This NPV may also be 'risk-adjusted', a greater risk being associated with earlier stages of development. Using the NPV, anti-infectives become even less attractive than when judged solely on sales.

Another point made by Stewart Adkins was that although anti-infectives have been extremely successful, with several products giving high lifetime sales and profits, there is a wide spread of branded products, with the top 10 representing only 40% of the group (Figure 5). The compounds giving the highest lifetime sales and profits are co-amoxiclav (~$25 billion), ciprofloxacin (~$19 billion), ceftriaxone (~$17 billion) and azithromycin (~$16 billion). Many older agents are still sold quite widely and are mostly generic, giving reduced profits for the original

company. Major compounds for which the patents have either expired or will soon are co-amoxiclav (2001), ciprofloxacin (2004), clarithromycin, azithromycin and ceftriaxone (2005) and levofloxacin (2007). Figure 6 shows a list of 'Blockbuster' drugs illustrating that these are now rarely found among anti-infectives. The field is again led by drugs for hypertension/angina, with anti-infectives ranking ninth.

J. Todd Weber (CDC, US), another keynote speaker, also outlined the reasons for large pharmaceutical companies now finding the field of anti-infective R&D difficult and less rewarding than other areas of drug development, emphasizing that a major factor was the lack of success at the drug discovery phase. He presented figures showing that there had been a decrease in the submission of New Chemical Entities (NCEs) to the FDA in the US over the past decade, but spending on research had increased over the same period. He made reference, as did others, to the fact that there was a 'golden period' in the 1950s and 1960s when many new antimicrobials from a range of novel classes were approved, but since the 1970s, this flow of compounds has slowed dramatically. In the past 2 decades only two new classes of antibacterials have been approved (Table 5). Other agents licensed during this period were all modifications of existing classes and it is to be expected that resistance will develop more rapidly to such agents. He noted as Stewart Adkins had, that what he referred to as the 'blockbuster' mentality was a particular problem for large companies. In the US the best selling antibacterial agent made $2.01 billion, whereas in contrast the best selling lipid lowering agent made $9.23 billion.

The current requirement is for less broad-spectrum agents and more drugs targeted against specific infections/diseases, which reduces the potential sales even more. Although it may be desirable from a clinical/scientific viewpoint, it is difficult to see how industry could view such an approach as being cost-effective, since sales could not possibly compensate for development costs. Added to this is the dilemma between a fair return on investment and the current view that anti-infectives must be used 'prudently', which often means limiting their use in specific situations, for example avoiding their use in upper respiratory tract infections when it is suspected that the infection has a viral origin.

The problem of resistance is unique to anti-infectives and limits the value of all products sooner or later, no matter how carefully they are used. Andrew Witty also noted the problem in conducting clinical trials on drugs targeted at resistant strains—it is extremely difficult to recruit sufficient patients for such trials and extends the time considerably. He also stated that pharmaceuticals are not a 'free market' as the costs are often state controlled, a further complicating factor.

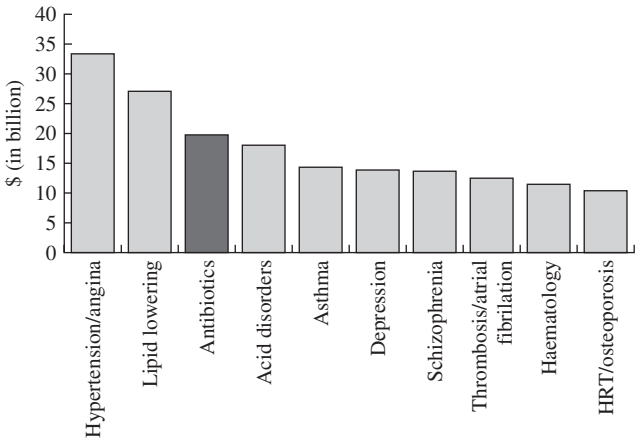

Figure 4. Top selling groups of pharmaceuticals.

What is needed

Many of the Conference speakers and workshop participants reiterated the point previously highlighted in the published reports

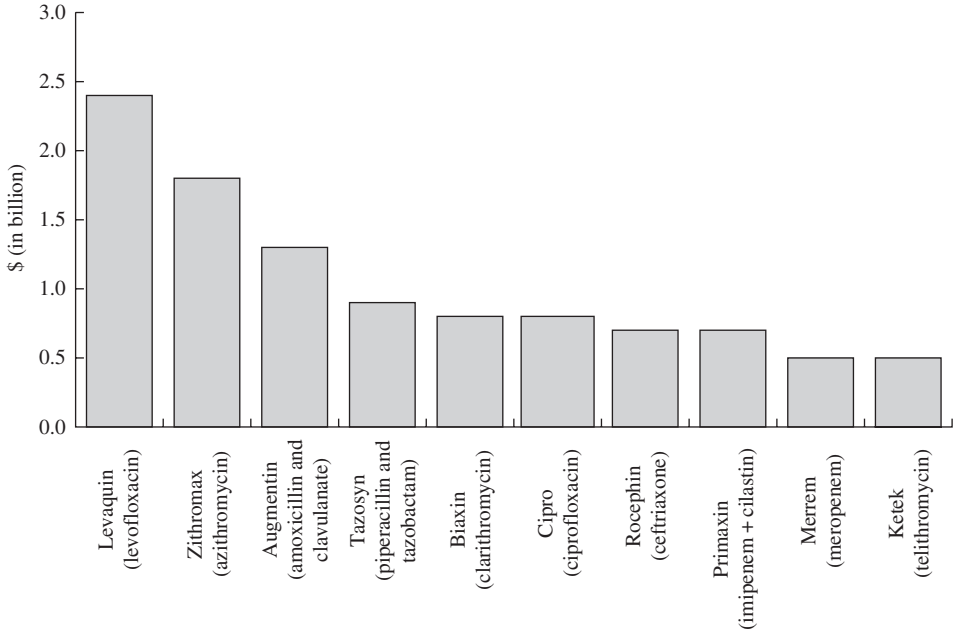

Figure 5. Top selling antibacterials.

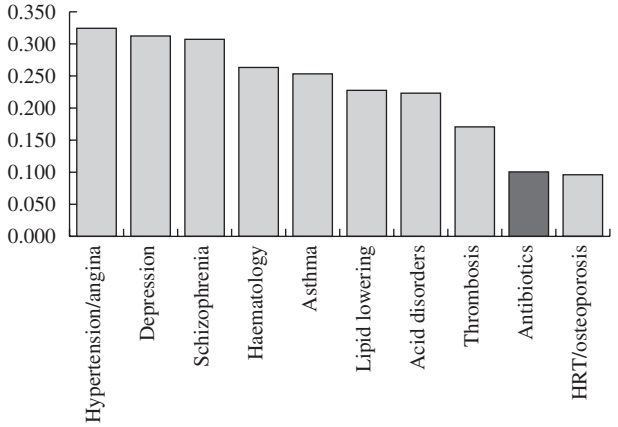

Figure 6. 'Blockbuster' drugs per billion dollar sales.

referred to above, namely that the problem of resistance to antimicrobials is a complex one with no one clear answer. The problems thus need to be attacked on several fronts. A number of areas of particular importance emerged, most of which are dealt with in more detail in subsequent sections.

(i) A major point made was that it was essential to reduce the growth of resistance and the spread of resistant strains in the environment. This involves better, and in some cases, reduced use of some antimicrobials and improved hospital hygiene to curb the spread of resistant strains in the hospital environment.

(ii) Surveillance of resistance to antimicrobials was identified as a key factor. This has been addressed in many previous reports and is one area where some progress has been made. There is no room, however, for complacency as much still needs to be done.

(iii) More and better diagnostics are urgently needed as these were seen by all as having the potential to play a major role in providing the clinician with guidance to selecting the most appropriate antimicrobial. In some instances, for example a simple test to distinguish between viral and non-viral infections in general practice, this could indicate when antimicrobials should or should not be used. In the hospital setting rapid diagnosis of when an infection is caused by a resistant strain is essential.

(iv) Vaccines, once seen as a major way forward in preventing infectious diseases, are now a relatively neglected area. Vaccines have tended to be regarded as predominantly of use for major 'pandemic' and very serious infections such as smallpox, cholera, polio, hepatitis and influenza, but of less importance for the types of infections we are now having to confront and which previously were adequately dealt with by antimicrobial therapy. In this new era of reducing value of antimicrobials, vaccines could play a far more important role.

As has been noted, there are many good reasons why the major pharmaceutical companies are reducing or already have reduced their effort in R&D of antimicrobial chemotherapy (with the possible exception of anti-HIV research). Ways need to be explored for encouraging these companies to reinvest in R&D. Various suggestions were made and discussed (see below). Small biotechnology companies were seen by many as highly innovative with the potential to provide a source of new ideas, chemical entities or technologies. A major stumbling block for these companies, however, is to obtain further funding after the initial 'seed' funding. The problem is particularly acute at the stage of development before the compound has progressed far enough to interest larger companies. There was a general consensus that this is a critical area that has to be addressed.

Table 6. ECDC work programme for 2006

- Coordinate surveillance networks
- Establish scientific committees
  - antimicrobial resistance
  - immunizations
- Build up a web-site for AMR
- Convene a working group for the assessment/discussion tool
- Produce scientifically based information to public
- Localize contact points in Member States
- Start country visits

It was considered that it would be beneficial to raise the awareness of both the public and governments of the threats from infectious diseases and encourage a strategic response. Many noted the excellent document from IDSA (quoted above) entitled 'Bad bugs, no drugs'.[15] Many governments seem to appreciate the risks from bioterrorism, and some have spent large sums on this, but there is a lack of appreciation that equal or even greater risks could accrue from seemingly 'ordinary' infections.

One of the problems in getting across to governments the importance of antimicrobials lies in our current inability to identify the true costs of infection to healthcare systems. Instead anti-infective agents are frequently primarily perceived as a major source of expenditure both in hospitals and in general practice with little appreciation of their actual value in containing overall healthcare costs. Although some attempts have been made to address this issue these appear to have had little impact.

It was noted that much of the problem of resistance resides in hospitals and a major factor is overcrowding. Hospitals with lower bed occupancy have a greater chance of preventing and controlling resistant infections. Such facts have to be conveyed to governments. A much-repeated theme was funding. This was perceived as a problem in almost all areas.

Technological support for the surveillance of resistance

Progress has been made in expanding and improving existing surveillance systems. The ECDC is now established, and Peet Tull (ECDC) outlined the planned programme of work for 2006 (Table 6). Priority has been given to the implementation of coordinated surveillance schemes which should provide a good indication of the emergence and spread of resistance. EARSS has been providing valuable data on the incidence of resistance in Europe for some years now, such as that quoted by Otto Cars (Figure 3) on the incidence of fluoroquinolone resistance among invasive isolates of *E. coli* between 1999 and 2004. Peet Tull said that the challenges for the ECDC were to decide what data are needed on a European level and how these data are to be interpreted and establishing whether they can be used for benchmarking. One target was to try to ensure the use of the same methods of surveillance between countries so that data would be

comparable. He commented that the epidemiological spread of resistant strains needs to be evaluated in relation to prevalence studies. Data from individual countries could only be an indicator for further analysis.

Dr Tull also stated that one limitation of current surveillance systems is that they do not improve the ability to inform clinical practice. For this, information is needed on the incidence of illnesses, patient demographics and clinical features of disease. In addition, there is a need for high quality validation of microbiological testing in reference laboratories, systematic sampling, and linkage of datasets including those for prescribing and resistance data in both primary and secondary care.

The most urgent needs identified in this area, noted by Peet Tull and others, include various technological approaches such as better statistical tools (IT) to analyse the data collected, novel techniques to track emerging resistances and local collation and analysis of data to guide therapy. The results of surveillance are, however, inevitably retrospective and David Livermore (Health Protection Agency, UK) expressed a note of caution, pointing out that too much emphasis on the precision was probably not worthwhile since surveillance studies could not reveal a rapidly emerging novel type of resistance. Furthermore, some of these resistances can emerge far quicker than the ability of the industry to develop a new drug.

Diagnostics

Roger Finch (UK) emphasized the need for diagnostics, which many participants agreed are an essential part of improving the use of current antimicrobials. To date diagnostic tests for infections are little used in community practice, where therapy is frequently empirical. In particular, a diagnostic test to distinguish between bacterial and viral respiratory infections is required since this is difficult on clinical grounds alone and thus antimicrobial therapy is often given unnecessarily. Moreover, with the diagnostic tools currently available for testing clinical samples there are inherent delays and it can take up to 48 h before results are available. In hospital practice fewer than 35% of supposed infections are confirmed microbiologically and again there are delays before results are available to the clinician. This lack of rapid reliable diagnostics frustrates targeted treatment and perpetuates empiricism, broad-spectrum therapy and encourages the widespread overuse of antimicrobials. If sensitive and specific rapid diagnostic kits were more widely available, it is believed that their use could help reduce the increase in resistance by ensuring that the correct drug is used.

Diagnostics need to be targeted carefully to the correct user, who may be in general practice, on the hospital ward or in the clinical laboratory. Ragnar Norrby (Swedish Institute for Infectious Disease Control Sweden) emphasized that if they are for what is termed 'near-patient' or general practice use, they need to be cheap, simple to use, accurate, and able to be used and interpreted not only by doctors but by other relevant staff also, such as practice nurses. Although it is desirable for obvious reasons that diagnostic kits, especially 'near-patient' ones, should be cheap, even more costly diagnostics may none the less often be cost-effective. This is an area, however, where cost-efficacy studies are badly needed since authorities may need to be convinced of the value of various diagnostic tests.

A number of other possible problems or barriers to the acceptability of using diagnostic kits in the healthcare system were highlighted. If, for example, the kit, no matter how good, extends the consultancy time significantly, it may be unpopular. Some noted that there may be a barrier to the acceptance of kits involving novel technology and the medical profession may need to be persuaded to use such kits.

Reimbursement, at several levels, was seen as a major barrier to the increased use of diagnostics. Some diagnostics with a high initial price may become cheaper when they are used more widely but this is not necessarily true for all diagnostics. If the technology used is patented, as is the case for PCR, then costs may not reduce with increased use. Only when there is more competition will some of these diagnostics become more cost-effective.

Vaccines and immunotherapy

Vaccines have proved their value for controlling and, in the case of smallpox, eliminating a number of serious infectious diseases. Historically, effort has been concentrated on those diseases for which no therapy was or is available. Vaccines were identified by a number of speakers as having an unrealized potential for preventing a range of infectious diseases caused by strains of microbes resistant to anti-infective agents. Roger Finch said that vaccines could be valuable in the control of MRSA infections and reduce the burden of respiratory viral infections, which might reduce unnecessary prescribing of antibacterials. He also pointed out that there had been unexpected additional benefits from the use of the pneumococcal vaccine. As well as the expected reduction in pneumococcal disease among the vaccination age group, a reduction was also seen in other age groups (Figure 7). A reduction was also seen in the incidence of macrolide resistance (Figure 8).[26] More recent evidence has shown a reduction in the incidence of drug-resistant pneumococcal infections by ~50% again in both the target population and in the elderly.[27] The ever-widening number of diseases caused by microbes with resistance to antimicrobial agents suggests that these should also be candidates for control by vaccination. In addition, the use of vaccines could make transplantation and cancer chemotherapy safer.

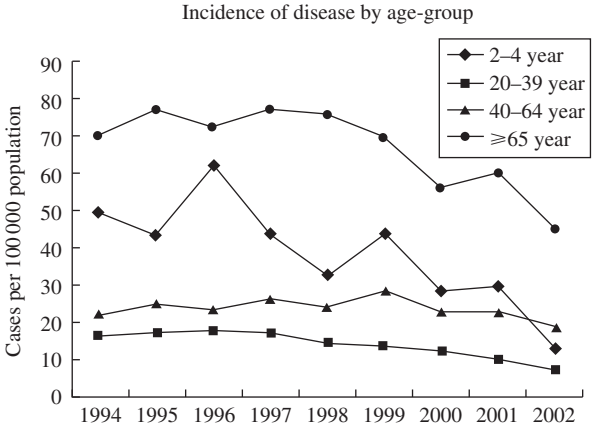

Figure 7. Impact of pneumococcal conjugate vaccine on incidence of disease (reprinted from *The Lancet* 2005; **365**: 855–63 with permission from Elsevier).[26]

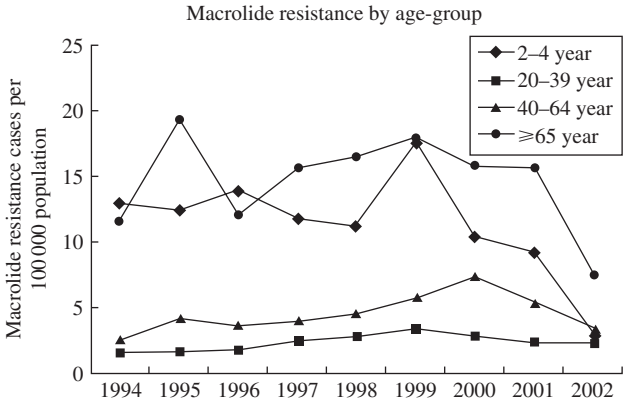

Figure 8. Impact of pneumococcal conjugate vaccine on incidence of macrolide resistance (reprinted from *The Lancet* 2005; **365**: 855–63 with permission from Elsevier).[26]

Table 7. Bridging the gap between discovery and clinical trials

Factors affecting progress of drug development	Spin-out/start-up (discovery phase)	Pre-clinical development	Clinical trials
Market proximity	far	medium	near
Technology	untested but novel	well characterized	well characterized
Compound attrition	inconsequential	high	low
Funding required	low (£1s M)	high (£10s M)	higher (£25s M)
Risk	high	high	lower
Investor appetite	yes	no	yes

Gerd Zettlmeissl (Intercell, Austria) said that although vaccine technology is proven, there are still very few new antibacterial vaccines. This is in spite of the obvious success of, for example, the vaccine for *Haemophilus influenzae* type B, which has drastically reduced the incidence of meningitis through the 1990s following its introduction. In addition a conjugate pneumococcal vaccine (Prevenar, Wyeth) has been marketed recently and is proving highly successful. Apart from these two vaccines the pipeline for new antibacterial vaccines is relatively thin. In the field of hospital-acquired infections it currently amounts to an anti-*S. aureus* vaccine (Merck/Intercell, Phase I) and an anti-*Pseudomonas aeruginosa* vaccine (Berna, Phase III).

There are now technologies available for the development of vaccines, in particular recombinant DNA technology, which allow better target selection and characterization. Human monoclonal antibodies have proved successful in the cancer field but have not as yet been used as antibacterials. It is difficult to see why this should be. However, the recent sad events with the trials of a human monoclonal antibody targeting CD28 are unlikely to be a positive factor in this area.[28]

Most innovative approaches in this field are taking place in smaller biotechnology companies such as Intercell who have already developed new prophylactic and therapeutic vaccines for Japanese encephalitis (Phase III) and hepatitis C (Phase II). The company uses a novel anti-genome technology which can identify novel targets. They have a number of ongoing projects against bacterial targets, the most developed of which are those against *S. aureus* (partnered with Merck, Phase I) or *Streptococcus pneumoniae* and *Streptococcus pyogenes* which have progressed to validation of the antigen target in *in vivo* models. They have a range of other potential vaccines at earlier stages of development including those for *Helicobacter pylori, Shigella flexneri, Enterococcus faecalis, Klebsiella pneumoniae, Chlamydia pneumoniae* and enteropathogenic *E. coli*.

This illustrates well the potential for innovation in small companies. Gerd Zettlmeissl pointed out that they have the possibility of a faster and more cost-effective route to 'proof of concept' and are willing to work outside the 'billion dollar indication'. An essential part of this approach is to become a partner for major pharmaceutical companies at the later stages of development. Funding is however a problem, as discussed below.

Funding and new drug development

In one of the Workshops, Sir Richard Sykes (Imperial College, UK) said that 'Industry plus academia can deliver anything—provided there is a need (market), and there is reimbursement'. This comment was reiterated numerous times by various speakers. The general opinion was that the barriers to producing new drugs, diagnostics and vaccines are not technological—all the targets and the technology are there. In addition, as highlighted by Jeff Errington (University of Oxford and Prolysis), the pathways from an initial 'hit' to a drug candidate are also well characterized. Most of the barriers for progress in small companies were related to funding.

As noted above for vaccines, the small biotechnology companies were seen by participants as having the capability of greater innovation than the large pharmaceutical companies, who require a potential drug or approach to be capable of producing billions of dollars profit. Jeff Errington illustrated the funding problem in this area (Table 7). Funding is often available for the start-up of a project even though the risk level is high and the technology may be untested. When a drug has proved itself in early pre-clinical or discovery phase tests it is then also relatively easy to interest potential investors, often large pharmaceutical companies. The real problem lies in the later pre-clinical stage where larger sums are required than at start-up and the area has yet to prove its worth. There is still a considerable financial risk attached to this stage, with a high attrition rate for potential candidate compounds. In addition the funds required are far greater than at start-up and venture capitalists and other investors are generally reluctant to provide funding at the level required. This was seen as a major barrier to progress in drug development, vaccines and diagnostics since much of this work takes place in smaller biotechnology companies.

There were a number of suggestions concerning this dilemma. Incentives are needed to persuade large pharmaceutical companies to partner small companies at an earlier stage. Hedge funding, LINK schemes with government funding via Research Councils/Department of Trade and Industry and charities such as the Wellcome Trust and the Bill Gates Foundation were all mentioned. Although Public Private Partnerships (PPP) have been successful in the malaria field, they were not seen as relevant for most anti-infectives and have become branded with third world

and neglected disease initiatives. Nevertheless co-operative ventures between private and public partners may still be of value.

Stuart Adkins summarized the various means currently used to fund R&D and said that established pharmaceutical companies with a background of anti-infective experience will constantly weigh up the commercial opportunities for each therapeutic area (antimicrobial and non-antimicrobial) and make go/no-go decisions as each clinical milestone is reached. If resources are constrained the projects with the greatest commercial potential will usually receive the greatest funding. New companies set up with venture capital money and spin-outs from large pharmaceutical companies will be judged by progress made towards the original objective and the extent to which each company is building value.

Most companies changed their approach to drug discovery in the 1980s to a target-based approach using genomics (and subsequently proteomics), together with combinatorial chemistry and high-throughput screening. This was extremely expensive and while it has been of value in some therapeutic areas, to date, it has proved a major disappointment in infectious diseases. The exceptions are in the HIV area and in the development of the peptide deformylases.[25] This low return on expenditure has not encouraged large companies to continue research in this area.

A neglected approach raised by one of the workshops was that of natural products as a source of new compounds. This tried and tested area, which gave us so many of the chemotherapeutic agents still in use today, was dropped by most companies as being too time consuming and inefficient compared with genomics, combinatorial chemistry and rapid throughput screening, which were seen as far more 'cutting edge'. The timing was unfortunate as new technologies were just being developed for isolating and identifying compounds without recourse to large-scale fermentation. Antibiotic databases make it possible to determine whether activity detected from a culture is from a known compound or not, using very small amounts of partially purified samples from fermentation broths. These techniques make the process of discovering drugs from natural sources far more efficient, particularly when coupled with some of the rapid throughput screens.

The regulatory process

The regulatory process is currently different in the US, Japan and the EU. The general opinion was that international harmonization is needed between these authorities as this could reduce the costs and the time taken for the licensing of a new agent or diagnostic test. This is especially urgent for developing diagnostics. Goran Ando (Novexel, UK) pointed out that harmonization could help smaller companies to develop products on a global scale. There was also a call for a simplification of the current requirements. The main suggestions made are listed in Table 8.

Other points noted were that surrogate markers are not accepted by the FDA and that there was a need for the authorities to accept validated markers. Comments were made that a fast formulary review system could help in the development of products for areas of a high medical need. The general opinion was that orphan drug status was unlikely to be of value for most anti-infectives as currently the prevalence of the disease should not exceed 5 cases per 10 000.

Table 8. Improvements to the regulatory process suggested by various workshops and speakers

Suggested improvements to the regulatory process
• Reduce the need for full development for each indication and/or microbial species. Currently this is major burden and is seen by many as unnecessary, especially in relation to the variation in international regulatory requirements. If extrapolation of results was allowed this could decrease the requirement for separate trials for each indication
• Evaluation in children and the elderly needs to remain flexible according to the drug, target indications and safety considerations and could be left to the initial post-licensing stage
• Clear guidance should be developed by regulators in agreement with industry regarding the criteria for choosing an appropriate margin of non-inferiority in active comparative studies.
• Greater use of 'fast tracking' is needed. This could result in earlier licensing and longer patent protection, which would be an important encouragement for companies to continue with R&D.
• The allowance of initial marketing authorization on more limited data for the more serious infections. It is usually difficult to recruit sufficient patients with serious and less common infections short term, which can substantially extend the time taken for patient recruitment.
• A true 'fast track' is needed which would leave much of the documentation to Phase IV. This could result in earlier licensing and longer patent protection, which could be an important encouragement for companies to continue with R&D, but is not without risk
• Consider uncontrolled studies in special circumstances
• Companies should be encouraged to consult with regulators throughout the development process

Opinions varied with regard to the possibility of replacing classic efficacy trials with pharmacokinetic and pharmacodynamic (PK/PD) studies. These studies can provide valuable information but if the drug is of a new class there is no background information on which to validate the studies. They can, however, be of use in supporting licensing indications and guiding dosing regimens.

Bo Aronsson from the EMEA emphasized that the Agency was conscious of the problems and was aware that resistance to antimicrobials was a top priority for the WHO. He acknowledged the need for both speeding up the regulatory process and to be flexible. There is already an acceptance of uncertainties in oncology and for products for HIV. The EMEA seems now to accept that drugs being developed for treating infections caused by multiresistant bacteria, where there were few therapeutic options, might need greater latitude with regard to the regulatory criteria for their approval. Their current thinking had already included, or planned to include, several of the points highlighted by the participants and noted in Table 8. Points of agreement included extrapolation, the use of PK/PD, a larger delta and uncontrolled studies or placebo controlled studies. A trial design suggested was for an initial marketing authorization based on limited data when the drug was for a serious infection with few therapeutic options. Finally, the issue of international harmonization is regularly addressed and progress is being made.

Table 9. Possible incentives from governments suggested by various workshops and speakers

Possible actions by governments
• The use of incentives, for example in the form of tax credits and public subsidy for R&D costs
• Other public funding initiatives, especially for vaccine work
• The removal of taxes and penalties on launch and promotion costs
• The guarantee of premium prices for low volume products. It was also pointed out that a high price could be a way of restricting the use of a valuable new drug
• An extension of the patent life to restore the time lost during the review process
• Give consideration to the use of the 'Wild card' patent extension currently used in the US

Table 10. Factors affecting industry, governments and funders

What causes industry to act
• profitability (easy)
• public good (special cases)
What causes governments to act
• crises (easy)
• media campaigns
• mounting public opinion (slow)
What causes funders to act
• evidence of need
• clear-cut proposal
• convincing proponents

What can governments do?

There were many suggestions as to how governments could give positive help but it was accepted that most of these were likely to be unpalatable since they involved expenditure and until governments could be convinced of the importance and urgency of the situation, suggestions for increased expenditure were not likely to be welcome. The point was made that economic restraints tend to lead to 'penny wise pound foolish' attitudes but that changing this would be difficult. The main suggestions made are listed in Table 9. In an interesting presentation Ted Bianco (Wellcome Trust, UK) summed up succinctly the factors that affected the willingness of industry, governments and funders to act. These are listed in Table 10.

The wider picture

The EU market is complex and most decisions are made at the national level, which makes it difficult to have any overall European leadership. Member States tend to have different national strategies for controlling resistance; some lack a policy at all and others have stringent control and preventative measures. The approaches to the preventative measures for restricting the spread of MRSA are an example of the wide variability seen between Member States. In some Member States hospitals have screening programmes, single rooms are available for nursing colonized or infected patients to limit the spread of infection, nose decolonization is carried out and blood cultures are routinely taken. This is not the case in all Member States and these differences no doubt contribute to the variation seen in the incidence of MRSA.

In the discussion it was revealed that the 6th Framework, a source of funds for small companies, was perceived by many to be too complex and restrictive. The 7th Framework is due to start in 2007, but it will need to have a simpler structure and to be more geared towards encouraging smaller companies. It is still not clear what level of funding will be available for the 7th Framework. Other possible sources of funds include the Innovative Medicines Initiative and the Joint Technology Initiatives in Medicine (JTI).

Much of the discussion centred on how to get governments and funders to act (Table 10). In addition, Ted Bianco said that those trying to persuade the various sources of funds needed well-defined proposals and had to persuade the funders that there was a clinical need. The creation of higher value 'smart' products could be a way forward. Governments would always act in a crisis but were otherwise slow to respond. Media campaigns could be valuable especially if they increase public opinion but this approach is slow. He also provided examples of the types of approaches for 'seeding' drug discovery that Wellcome found helpful. These are detailed in Table 11. Stewart Adkins noted that potentially public policy has a significant role to play to tip the balance in favour of reinvigorating investment in the development of antimicrobials.

Table 11. Seeding drug discovery for early stage R&D

Aim at projects that
• address an unmet need (i.e. non-redundant)
• spring from novelty in understanding or approach
• are likely to attract third-party 'take-up'
Use an approach that adds value
• by contracting missing know-how & resources
• by making available technical advisors
• by facilitating project management & controls

Comment

Anti-infective chemotherapy is a relatively new area of medicine, being ~60 years old. It is quite unlike all other areas of medicine since the agents are not designed to affect a pharmacological target in the host but to attack an invading microorganism. Microbes will invariably develop resistance sooner or later to virtually any drug even when the drugs are used in a 'prudent' fashion. Discovering new targets and new classes of drugs will still not avoid resistance but it might slow up the time taken for microbes to evolve or acquire multiple mechanisms of resistance resulting in infections which are untreatable.

Most of the measures discussed at the conference will not prevent the development or spread of resistance; that is probably impossible. At best we may be able to delay the inevitable, curb the spread of resistant isolates and perhaps allow existing drugs and those under development to have a longer life. This may possibly allow the statement in the React report,[17] quoted by

Otto Cars, to be fulfilled, namely that 'current and future generations of people around the globe should have access to effective treatment of bacterial infections'.

An interesting question raised in the discussion was are attempts to deliver more and more antimicrobials sustainable in the long term? Some felt that it may not be. But that emphasizes the importance of alternative approaches, such as vaccines and immunotherapeutics. Diagnostics are clearly still essential to allow the antimicrobials that are available to be used correctly and only when necessary.

Transparency declarations

RF: Professor Finch is a Non-Executive Member of the UK Department of Health Specialist Advisory Committee on Antibiotic Resistance as well as Education Secretary to the British Society for Antimicrobial Chemotherapy, which collaborated in the organization of the EU Conference on which this publication is based. In addition he holds consultancy agreements with Astellas, Bayer, Chiron, Cubist, GlaxoSmithKline, Mayne Pharma, Novartis and Prolysis. Neither the content of his presentation nor these published proceedings contain any reference to the products or research activities of these companies. This information is provided solely in the interests of transparency.

PH: None to declare.

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APPENDIX 1

WORKSHOP ONE

Linking surveillance to identify unmet needs and define the research agenda

Chair: Herman Goossens

Rapporteur: Chris Butler

What is the purpose of surveillance and to what extent has it achieved its goals?

There have been several achievements such as raising awareness of the problems of resistance and informing policy, and national actions have flowed from existing surveillance systems.

Recommendations

Existing data cannot improve the capacity to inform clinical practice. For this we need data at individual level on the following:

- Demographics.
- Incidence of illness.
- Clinical features to allow judgement of case mix.
- Clinical, economic and healthcare related outcomes.

In addition the following developments are required:

- Linkage of datasets that include prescribing, clinical and resistance data in both primary and secondary care.
- Data should be validated and reliable, include appropriate denominators and should be derived using systematic sampling in carefully managed, pragmatic environments.
- High quality validation of microbiological testing by reference laboratories.

It is important that this opportunity is not lost during the developments new IT programmes (e.g. National Programme for IT in UK).

What type of information should be collected to improve antibiotic prescribing, to contain resistance and how?

There is a major gap in EU-wide guidelines on antibiotic management in primary care. There is a lack of aetiological and outcome data for many antibiotic-treated conditions and there have been insufficient large clinical studies to identify which subgroups will and will not benefit from antibiotic treatment. Existing datasets have few clinical outcomes and often lack denominator information.

Recommendations

There is a need for:

- Better statistical tools for combining and interpreting studies.
- Better diagnostics, especially near-patient tests (NPTs) that are acceptably sensitive, specific, and have a reasonable 'shelf life' and are compatible with everyday care, as well as being appropriately supported in terms of funding, training, recording of results and IT.
- Translation of technology (e.g. for the rapid identification of agents of bioterrorism) so that it is relevant to clinical use.
- The cost-effectiveness of new interventions should be established and must include the size of the target population, the level of uptake and the effect on future consulting behaviour.
- To support this adoption of new technology, research into how to change physician and patient behaviour should be promoted and supported.
- The next decade should be the 'golden age' of diagnostics! With better NPTs, fewer antimicrobials could be prescribed; narrow spectrum agents are likely to be used more often with improved outcomes for patients and, in turn, less resistance.

What should be the roadmap for future research?

The quality of data and its analysis should be improved.

Recommendations

We need to:

- Make data as similar as possible between and within countries.
- Standardize methodology.
- Design surveillance around defined goals.
- Ensure that prescribing data and clinical data are reliable and validated.
- Resolve ethical issues (particularly those relating to consent and linkage of data) that frustrate clinical and epidemiological research.
- Enhance understanding of the microbial epidemiology of resistance by using novel genetic and molecular techniques to characterize detect and map emergent strains (e.g. Spa typing and *S. aureus*).

EU funding in the next round (FP7) presents considerable opportunities under the 'Genomics and biotechnology for health' to improve the outcome for patients by its emphasis on:

- Translational research in infectious disease.
- Biotechnology: opportunities for diagnostics.
- Translating clinical research into practice – better use of medicines.
- Child health and health of the elderly where infection plays a major role in disease.
- Innovative medicine initiative including opportunities with joint technology initiatives.

WORKSHOP TWO

Can a more holistic approach to healthcare budgeting facilitate the adoption of new technologies? The pros and cons of sustaining a culture of cost containment and therapeutic empiricism

Chair: Roger Finch

Rapporteur: Kathleen Holloway

What technologies do healthcare systems need: diagnostics

Recommendations

There is a need for rapid, near-patient clinically-relevant discriminatory tests that address problems such as:

- Infection versus non-infection.
- Bacterial versus viral infection.
- Distinguishing between susceptible and resistant pathogens (e.g. MRSA versus MSSA).
- Acute pharyngitis—*Streptococcus pyogenes* detected or undetected.
- Distinguishing between infected and non-infected specimens from UTIs.
- TB test which distinguishes drug-resistant strains from drug-susceptible strains.

There should be more automation in diagnostic microbiology laboratories to improve turn-around-times and reduce technician workload without compromising the quality of investigations or the appropriate interpretation of the results.

What technologies do healthcare systems need: IT

Recommendations

There is a need for IT which supports clinical management. This should include:

- Prescribing decision support systems which link diagnosis, surveillance, guidelines, antibiotic usage and outcomes data.
- IT systems that are timely, user-friendly and cost-effective.

IT systems are needed to support surveillance of antibiotic prescribing by site of care e.g. hospitals, community, by prescribing healthcare professionals and those purchased without prescription (over-the-counter).

IT systems are also needed to inform the economics of healthcare planning and to support targets in the area of healthcare associated, and community, infections.

E-learning should be developed to support education, training, revalidation and CPD (continuous professional development) relevant to antimicrobial use.

What is optimal financial planning and how should this be designed with regard to drugs, vaccines and diagnostics?

Recommendations

The budgeting process for the purchase of technologies should be reviewed to take account of the following issues:

- The current diverse approaches should be more strategic.
- Validated cost-effective analyses should be used in purchasing technologies.
- The budget framework should be workload sensitive and relevant to identifiable healthcare gains and targets.
- The budget should be calculated according to past expenditure versus need and measured performance.
- Best practices across different healthcare systems should be promoted and adopted.

What is required for coordinated and joined-up healthcare planning which avoid conflicts between short term effectiveness versus longer term public health gain of containing antimicrobial resistance?

Recommendations

- Improved links are required between information bases on surveillance of infection, antibiotic resistance and the use of antimicrobials in relation to patient outcome to better inform clinical practice and healthcare planning.
- Better linkage is needed of the public health benefit of technologies and clinical practice: this should include diagnostics as well as drugs and vaccines.
- The likely impact on antimicrobial resistance of healthcare policy and interventions should be considered prior to implementation and monitored (e.g. bed occupancy and antimicrobial resistance rates).

What are the priorities for the control of the burden of infection in healthcare and how should these be decided?

Recommendations

- Establish robust methods to measure the burden, both health and economic, of infections including those caused by resistant organisms.
- Improve the evidence-base for measuring the cost-effectiveness of new technologies.
- Establish effective modelling systems that can prioritize interventions by their cost-effectiveness using suitable measures of healthcare gain.
- Local, national and international strategies are needed to control healthcare-associated infections (e.g. nosocomial and chronic patients such as those on dialysis) and resistance to antimicrobials and monitoring should be undertaken to determine implementation of these strategies.

WORKSHOP THREE

The commercial reality of new drugs, vaccines and diagnostics innovation—which medical needs will be met by the market, and which will not and why?

Chair: Sir Richard Sykes

Rapporteur: Sandy Primrose

What industrial models are most likely to deliver technologies?

Small companies are more innovative and are the best source of new ideas BUT they find it difficult to get funding from major pharmaceutical companies until they have a potential product. Solutions to this dilemma are required.

Recommendation

- Small companies need in-house expertise for pre-clinical validation of targets and development to get the interest of major pharmaceutical companies.
- Natural products have historically provided the greatest chemical diversity. Natural product screening is an area that could be resurrected since modern technology allows for far more effective and rapid screening.
- The development of a good cell-based screen is essential.
- Modern genetics facilitates pharmacophore manipulation to produce a wider range of antibiotics.
- The possible place of hedge funds should be considered.

What are the obstacles to developing narrow spectrum, cost-effective medicines?

- The current financial return is unlikely to be sufficient, even for drugs targeting Gram-positive pathogens (other than very active anti-MRSA compounds).
- For infections due to Gram-negative pathogens, a narrow spectrum agent is likely to be prohibitively expensive and technically challenging.
- Clinical assessment of narrow spectrum agents, including antifungals, is a major obstacle.
- There are problems in finding sufficient patients in the desired disease area which are compounded by the current requirement for comparative trials. Furthermore, the FDA does not accept surrogate markers of infection or response.

Recommendation

- Consideration should be given to conducting Phase IIIb trials post-licensing as is the case for antiretroviral agents.

How can the time & cost of developing new technologies be reduced while increasing the success rate?

Recommendations

- The clinical assessment should streamlined. Regulatory Authorities need to develop rules which allow easier assessment, especially in the design of trials.
- Caution is necessary with the use of PK/PD; mostly this has been applied to compounds in known classes, but it may not be of such predictive value with compounds based on novel structures.
- Regulatory authorities need to be persuaded to accept validated biomarkers of infection and response.

What technology-based healthcare needs can be delivered by industry and what cannot?

Recommendations

- Industry plus academia can deliver ANYTHING, provided there is a clearly defined need and appropriate reimbursement.

- Diagnostics should be developed but not just by major pharmaceutical companies; to support this development, it is essential to tackle the problem of reimbursement.
- Diagnostics will have to be targeted carefully so that they are used correctly and in the appropriate context (hospital, community practice).
- Barriers to the use of diagnostics need to be overcome which include resistance by some specialist groups to non-cultural techniques.
- There is a need for appropriately trained and supportive clinical microbiologists to co-operate in the testing and application of new technologies.
- There is a need to raise the profile of antibacterial research, since it is currently less popular than other areas in the pharmaceutical industry.
- There is a great need for collaboration between academia, major pharmaceutical companies, small companies with governmental support especially in the development of diagnostics.

WORKSHOP FOUR

European regulatory opportunities—facilitating innovation without compromising safety

Chair: Ragnar Norrby

Rapporteur: Javier Garau

What is the current record for licensing novel technologies for infection in Europe?

i. Anti-infectives

New antibiotics introduced since 2000 have included:

- Linezolid (oxazolidinone)—new class (Gram-positive activity).
- Daptomycin (lipopeptide)—parenteral agent from a new class but with similarities to glycopeptides (Gram-positive activity).
- Tigecycline—parenteral tetracycline derivative but with enhanced spectrum and activity against resistant staphylococci (Gram-positive and Gram-negative).
- Telithromycin (Ketolide)—a macrolide derivative (Gram-positive activity).

Very few of the above have significant anti-Gram-negative activity and only linezolid and telithromycin are available for oral administration.

New antifungals have included:

- Caspofungin (echinocandin)—a new class.
- Voriconazole—an azole derivative.

Recommendations

- In view of restricted range of new antibiotics active against Gram-negative pathogens, new agents are needed for treating these organisms.
- A greater choice of oral therapies, preferably with cidal activity, is needed for MRSA.
- New antifungal agents should be developed that treat opportunist mould infections. Oral antifungals, particularly cidal agents, are required.
- Many antiretroviral agents have been developed but there is a need for agents active against a wider spectrum of viral pathogens particularly influenza and the many respiratory viruses.

ii. New vaccines

New conjugated pneumococcal vaccines have proved highly effective at preventing invasive disease and have resulted in a reduction in pneumococcal infections among non-recipients.

Recommendations

- A wider range of pneumococcal serotypes need to be covered to reduce the risk of invasive infection and contain antibiotic resistance.
- There is a need for accelerated regulatory approval of new pneumococcal vaccines, which should adopt surrogate markers of immunity.
- There are few other vaccines against bacterial infections. An effective vaccine against *S. aureus* remains a desirable goal.

iii. Diagnostic tests

Recommendations

- New rapid diagnostic tests are needed especially to distinguish between viral and bacterial pathogens. This would facilitate more targeted therapy in the early management of infection, especially in relation to community-acquired infections e.g. urinary antigen tests in pneumonia.
- Better bacteria-specific diagnostics are also needed in the hospital and specialist care setting.

What are the obstacles to speedy licensing?

i. Anti-infective drugs

There are too many separate indications for antibacterials and extrapolation of data to related conditions should be considered e.g. otitis and sinusitis, surgical abdominal and gynaecological infections.

Recommendations

- The costs of clinical trials for new antimicrobial agents are increasingly prohibitive, frustrate drug development and should be reduced. Systems other than RCTs should be explored.
- Current clinical trial guidelines should be reviewed. A single study per indication should be considered if supported by improved trial design. Where drugs seek multiple indications, single studies per indication should be considered acceptable, provided individual studies were multicentre and the same trend was seen at all centres.
- Consideration should be given to the replacement of clinical trials by surrogate methods of evaluation and extrapolation between study populations.
- Greater use of novel diagnostic tools in clinical trials should be considered with a view to improving the evaluability of study populations.
- Greater cooperation between industry and regulatory authorities is desirable to improve the efficiency of drug development and assessment.
- Common international guidelines are urgently required to reduce the current complexity of drug development programmes.
- Consideration should be given to moving the safety evaluation to Phase IV supported by the monitored release of drugs and continued documentation of safety. Although controversial, this might be appropriate for serious infections where the need for a new drug is urgent.
- Consideration should be given to extrapolating efficacy in selected indications to other infections to accelerate drug development and licensing.

ii. Vaccines

Recommendations

- There is a need to work rapidly towards international harmonization of immunization schedules and standards for licensing.
- A global view of pricing should be negotiated so that countries needing them most can afford them.

How effective are the criteria for fast tracking, earlier licensing and/or orphan drug regulation?

i. Fast tracking

This has proved useful by reducing the time to licensing and hereby increasing time on the market with patent protection.

Recommendations

- The revenue costs of drug development could be reduced if earlier licensing could be facilitated with further documentation of safety and efficacy being undertaken post-licensing.
- Consideration should be given to determining if there are special niche indications for differing durations of patent protection?

ii. Orphan drug regulation

This has had limited usefulness in developing new anti-infectives since the prevalence rate of disease should not usually exceed 5/10 000. An exception is tuberculosis where countries with low prevalence rates have been selected.

Recommendations

- The cost advantages of orphan drug development are attractive to small companies and deserve wider consideration in developing new drugs to manage uncommon infections.

How successful have been the efforts towards international harmonization of licensing requirements?

There has been limited success in the international harmonization for antimicrobials. There are still major differences between licensing requirements of the FDA and the EMEA and neither are harmonized with those of the regulatory authorities in Japan.

Recommendations

- These differences add to the cost of drug development and should be resolved.
- For diagnostics, international harmonization on performance and standardization should be developed.
- The regulation of generics needs to be considered, and ideally licensing should be based on current patterns of susceptibility. It is inappropriate to grant a license for historical indications in the absence of current data.
- Consideration should be given to the regulated withdrawal of agents whose efficacy has been eroded e.g. by high rates of resistance.

What is the position for PK/PD studies as replacements for classical efficacy trials?

Recommendations

- To some extent these could be applied to drugs within established classes of antibiotic. Extrapolation from different infection sites and PK/PD evidence could provide evidence to support licensing indications, including dosing regimens.
- The severity of infection also needs to be considered in drug evaluation and not simply the diagnostic indications. How far can PK/PD information be used in this way? Most clinical trials have not used the most 'rational' doses for all cases evaluated, so perhaps the regulatory authorities need to be more ready to accept uncertainties as well as PK/PD information more readily.

How can balancing support for technological innovation against managing risk and safety be improved?

Recommendations

- Consider more Phase IV studies with enhanced pharmacovigilance assessment.

- There should be greater adoption of pharmacogenomics to identify those at risk of reduced efficacy or increased toxicity. Risk management plans will need to be developed to support this approach.
- Consideration should be given to increasing drug prices to allow manufacturers to recoup costs sooner and support safety assessment.
- Consideration should be given to controlling the availability and use of outpatient medications except for agents with robust evidence to support safety and efficacy.

How important are 'wild cards' and staggered approval of indications in encouraging product development?

Recommendations

- 'Wild card' could increase the willingness of industry to invest in new antimicrobials and should be considered.
- Staggered approval could reduce developmental costs and should be discussed with the regulatory agencies.

WORKSHOP FIVE

Leadership, strategy and policies to remove barriers to innovation and create a sustainable environment for technology-based solutions

Chair: Thomas Sørensen

Rapporteur: Sophia Tickell

What are the strengths and weaknesses of current R&D and funding approaches?

Recommendations

- The major industrial strengths in the technical development of new compounds needs to be supported by more effective mapping of the technology gaps by governments and the EU.
- Greater investment in point of care diagnostics will require a 'market' to ensure an acceptable volume-price trade off.
- The high attrition rate of 'hit' compounds and unpredictable negative development effects, such as toxicity, emphasize the importance of adequate financial support for early drug development.

Are public/private partnerships (PPPs) the right way forward and do they work?

Current PPPs have been directed at malaria and tuberculosis and have been premised on the lack of an end market. This is complicated for antibacterials and a bifurcated model would be needed to meet the needs of both developed and developing countries.

Recommendations

- Pre-competitive models could be considered for early research. However this needs defining to ensure authentic collaboration and is commercially complicated.
- An advocacy PPP is more appropriate for antibiotics in order to create awareness, rather than for promoting R&D.

What new funding approaches should be considered?

Recommendations

- A greater acceptance of the need to pay more for true rather than incremental innovation is required.
- Pharmacoeconomic analyses should be performed on low volume secondary care products to persuade governments to:
  - Streamline the regulatory process to give a longer product cycle before patent expiry.
  - Increase Net Present Value (NPV) by considering public subsidies and tax credits.
  - Identify public policies which would permit premium pricing of relevant technologies.
  - Link the use of diagnostics to disease management. Healthcare savings should be considered as a potential incentive for the manufacturer.

How could changes in patent registration and regulatory approval realistically facilitate technology development?

Recommendations

- It is important to consider whether drug development and licensing can be facilitated and expedited. The possibility that improved diagnostics might reduce patient numbers should be investigated. In addition, the use of surrogate endpoints which give appropriate data which satisfy the requirements for quality, safety and efficacy should be encouraged.
- Scientifically plausible and ethically acceptable means of reassessing risk-benefit analyses should be developed in order to achieve improvements in the regulatory approval process.

How important are emerging markets in influencing investment in novel technologies?

Currently, these are not big enough to offer incentives that are likely to influence investment decisions compared to the major US, Japanese and European markets.

How are social, ethical and commercial needs viewed by the financial sector?

Social and ethical needs are not considered by investors.

Recommendation

- Utilize concerns regarding corporate reputation as a potential incentive to participate in PPPs.

What are the primary barriers to innovation?

The complexity of the EU market is a significant obstacle to innovation. Most public sector R&D decisions continue to be made at the national level.

Politicians currently have little incentive to support technology-based solutions in the absence of any lay articulation of the clinical need or economic consequences of the technology gap.

The absence of any clear means of identifying the value of antimicrobials in terms of overall healthcare expenditure, welfare funding and employment needs resolution.

A lack of leadership which catalyses and unites in a common agenda.

Recommendations

The consequences of the technological innovation gap, both for the present and future, need to be clearly articulated in order to provoke a coordinated European and international approach.

The economic costs of infection and the technology gaps need to be quantified, and brought to the attention of Member States. A clear process for prioritization of R&D needs to be developed by the EU and its agencies.

There is a need to identify leaders, champions and advocates to communicate the issues to government, the public, academia and industry.

APPENDIX 2

Keynote speakers

Dr Stewart Adkins
Lehman Brothers, UK
25 Bank Street
London E14 5LE, UK
stadkins@lehman.com

Professor Otto Cars
Swedish Institute for Infectious Disease Control
S-171 82 Solna, Sweden
otto.cars@smi.ki.se

Professor Roger Finch
University of Nottingham & Nottingham University Hospitals NHS Trust
Division of Microbiology & Infectious Diseases, Molecular Medical Sciences
Clinical Sciences Building
Nottingham NG5 1PB, UK
r.finch@nottingham.ac.uk

Dr J. Todd Weber
Centers for Disease Control & Prevention
1600 Clifton Road, Atlanta
GA 30333, USA
jtw5@cdc.gov

Mr Andrew Witty
GlaxoSmithKline plc
980 Great West Road
Brentford, Middlesex TW8 9GS, UK
Theresa.f.tres@gsk.com

Mr Gerd Zettlmeissl
Intercell AG
Headquarters
Campus Vienna Biocentre 2
Austria
gzettlmeissl@intercell.com

Workshop Chairs and Rapporteurs

Workshop 1

Chair: Professor Herman Goossens
Department of Medical Microbiology
University of Antwerp
Wilrijkstraatb 10
BE 2650 Edegem, Belgium
Herman.Goossens@uza.be
Rapporteur: Professor Chris Butler
Department of Primary Care Medicine
Cardiff University
Llanedeyrn Health Centre
Llanedeyrn, Cardiff CF23 9PN, UK
butlerCC@cardiff.ac.uk

Workshop 2

Chair: Professor Roger Finch
University of Nottingham & Nottingham University Hospitals NHS Trust
Division of Microbiology & Infectious Diseases, Molecular Medical Sciences
Clinical Sciences Building
Nottingham NG5 1PB, UK
r.finch@nottingham.ac.uk
Rapporteur: Dr Kathleen Holloway
World Health Organisation
Department of Medicines, Policy & Standards
Geneva, Switzerland
hollowayk@who.int

Workshop 3

Chair: Sir Richard Sykes
Imperial College London
South Kensington

London SW7 2AZ, UK
c.young@imperial.ac.uk
Rapporteur: Professor Sandy Primrose
Business & Technology Management
21 Amersham Road
High Wycombe
Bucks HP13 6QS, UK
primrose@webstar.co.uk

Workshop 4
Chair: Professor Ragnar Norrby
Swedish Institute for Infectious Disease Control
SE 17182 Solna, Sweden
Ragnar.Norrby@smi.ki.se
Rapporteur: Professor Javier Garau
Department of Medicine
Hospital Mutua Terrasa
Barcelona, Spain
jgarau@garmar.e.telefonica.net

Workshop 5
Chair: Dr Thomas Sørensen
Clinical Unit of Health Promotion
Bispebjerg Bakke 23, DK 2400,
Kobenhavn NV, Denmark
tls01@bbh.hosp.dk
Rapporteur: Ms Sophia Tickell
20-22 Bedford Row
London WC1R 4EB, UK
sophia.tickell@btopenworld.com

Conference Discussants

Dr Goran Ando
Novexel
Parc Biocitech
102, route de Noisy
93230 Romainville, France
goran.ando@ukonline.co.uk

Dr Bo Aronsson
European Medicines Agency
7 Westferry Circus
Canary Wharf
London E14 4HB, UK
bo.aronsson@emea.eu.int

Dr Ted Bianco
Wellcome Trust
Gibbs Building
215 Euston Road
London NW1 2BE, UK
t.bianco@wellcome.ac.uk

Dr Stephan Bronswaer
European Commission
Public Health Threats
Jean Monnet Building, Office C3-21A,
Rue A de Gasperi
Luxembourg
Stef.Bronzwaer@cec.eu.int

Professor Jeff Errington
University of Oxford
Sir William Dunn School of Pathology
South Parks Road
Oxford OX1 3RE, UK
jeff.errington@path.ox.ac.uk

Professor Ragnar Norrby
Swedish Institute for Infectious Disease Control
SE 17182 Solna, Sweden
Ragnar.Norrby@smi.ki.se

Dr Peter Potter-Lesage
Medicines for Malaria Venture
PO Box 1826
20 rte de Pré-Bois
1215 Geneva 15, Switzerland
potter-lesagep@mmv.org

Dr Octavio Quintana-Trias
European Commission
Directorate F—Health
DG Research
B-1049 Brussels
Belgium
octavi.quintana-trias@cec.eu.int

Dr Peet Tull
European Centre for Disease Control
171 83 Stockholm, Sweden
Peet.Tull@ecdc.eu.int

Mr Bart Wijnberg
Ministry of Health, Welfare & Sport
Department of Pharmaceutical Affairs & Medical Technology
PO Box 20350
NL-2500 EJ, The Netherlands
b.wijnberg@minvws.nl