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ANTIBIOTIC RESISTANCE

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Document purpose and destination

This document contains deliverable no. 3 of the project on Antibiotic Resistance: the final report. The contents are the outcome of the work of an interdisciplinary expert working group consisting of:

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The report draws on discussions with a range of other experts at an extended working group meeting in Copenhagen on June 27th and a workshop at the European Parliament on September 13th. The working group and the project management would like to thank everybody who has contributed to the report. The names of the participants in the two events can be seen in appendix 2.

Project details

Specific contract no.: IP/A/STOA/SC/2005-173

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Executive summary

The antibiotic resistance problem in brief

Since the discovery of penicillin in 1928 and the subsequent development of other antibiotics, it has been possible to treat previously life-threatening illnesses such as pneumonia and tuberculosis as well as a variety of common bacterial infections. Antibiotics have also enabled advances in surgery as the survival rate of patients is greatly improved by the treatment (prophylactic and otherwise) of surgery-related infections. However in recent decades it has become apparent that the use of these medicines is also the key to rendering them ineffective. Bacteria are becoming increasingly resistant to the drugs commonly used against them, creating an inability to treat multi-drug resistant bacteria. Without this ability the costs of treating infections rise, both in economic terms and in the quantity and quality of human life.

Inappropriate use of antibiotics is a serious contributor to antibiotic resistance. Inappropriate use may for example occur when antibiotics are used for viral and other infections where antibiotics have no effect, when antibiotics are sold without prescription and when self medication is carried out.

The need for immediate action to contain antibiotic resistance

We cannot wait any longer for the discovery of new antibiotic drugs. The research and development of these drugs is a long, expensive and arduous process which most large pharmaceutical companies no longer find to be profitable, and hence they are pulling out of the market. Even if profit could be assured, it is still by no means certain that new drug leads could be found and developed into useable antibiotics by the time they are needed. Containment of the development and spread of resistance must therefore be given first priority.

Action is required to tackle the overuse of antibiotics and the spread of infection, yet the causes of antibiotic overuse and infection spread are complex and related to many different factors including cultural beliefs, the organisation of health systems, political will and the incentives facing different stakeholders. Over the last 10 years this complexity has led a number of networks and organizations to develop frameworks comprising long lists of suggestions for dealing with the problem of antibiotic resistance. Yet still the problem remains.

The action plan

This report contains a suggestion for an action plan consisting of six policy options based on knowledge acquired from the most recent reports and initiatives occurring primarily within Europe. The term 'policy options' is used in a broad sense to include both options for immediate action and research activities. The six policy options are sharply focused on actions that can be initiated by the European Union within a short to medium time frame, and where the expected benefits are most likely to exceed the expected costs. The working group has selected four areas where the EU can contribute to the containment of resistance: coordination, standardisation, stimulation, and research. The six options are as follows:

Policy option 1 (coordination): Increase the role and scope of the ECDC in co-ordinating European strategy with respect to antibiotic resistance.

To further strengthen the coordinating role of the ECDC on behalf of the EU. Specifically:

- *to develop a portal* through which all EU policy and legislative documents relating to antimicrobial resistance can be obtained
- *to develop a database* of all national and European initiatives with regard to antimicrobial resistance, including both policy initiatives and research projects and both humans and animals
- *to co-ordinate an annual "European Antibiotic Resistance Day"* designed to increase awareness of this issue as a global health problem
- *to enable the ECDC to coordinate annual meetings with national authorities*, including liaison with veterinary and food safety colleagues at EU level
- *to further enable the ECDC to liaise with the WHO* with regard to policy on antimicrobial resistance
- *to further enable the ECDC to service and support the Member States*, particularly in relation to options 2, 3, 4 and 5 below.

Policy option 2 (standardisation): Further encouragement of 'prescription only' policies within Member States.

Humans: to further encourage the use of 'prescription only' across all Member States of the EU and to explore the use of policies that will encourage member country governments to enforce prescription only rules – one possibility might, for example, be to provide monetary disincentives for governments in countries where more than a certain percentage of antimicrobials are dispensed without prescription.

Animals: To develop and establish monitoring systems and encourage enforcement of the current Directives in relation to food producing animals; and to encourage the development of a prescription only system for all other animals.

Policy option 3 (standardisation): Europe-wide accreditation programme.

Develop a voluntary accreditation programme which incorporates and co-develops European and international standards for hygiene, health and day-care, and building standards.

Policy option 4 (stimulation): Encourage use of rapid diagnostics.

Explore the possibility of providing incentives to Member States to develop reimbursement systems that encourage the use of rapid diagnostic tests in general practice. These incentives could be via directive or by direct subsidisation, for example in countries with lower national incomes.

Policy option 5 (stimulation): Fund-matching programme for educational campaigns

Initiate the development of a matched funding policy, whereby the EU provides some matched proportion of the funding for national educational campaigns, with this matching determined in part by:

- the national income of the member country applying for funding (on equity grounds);
- the current extent of resistance (with greater resistance problems attracting a greater degree of funding). Although such a policy might "give out the wrong message" it would also enable funds to be targeted to areas where they will have greatest effect;
- the quality of the planned campaign (judged in a similar manner to research proposals, but concerned with clarity of objectives, clarity of methods, anticipated outcomes, adequacy of budget and so on).

Policy option 6 (research): Additional research funding to enhance containment of resistance.

To direct research funding towards the containment of antibiotic resistance, rather than towards new drug leads. More effort and funding needs to be directed toward the following areas: understanding cultural, contextual and behavioural aspects of antimicrobial usage; providing evidence about optimal methods of using different antimicrobial agents; developing methods to gather evidence and conduct analyses of the costs and benefits of containment strategies; conducting evaluations of the costs and benefits of initiatives to reduce antibiotic consumption and to limit transmission of infection; investigating the potential impacts of permits, guidelines, incentives, taxation, and accreditation as tools for containing antibiotic resistance; ensuring the rapid dissemination of results and coordinating research with policy initiatives.

No new drugs?

Previous reports on strategies for addressing the growing problem of antibiotic resistance have often advocated increased research into the discovery of new antibiotic drug leads and support to subsequent development of the leads into new antibiotic drugs. There is no question that without containing the further development of antibiotic resistance, these drugs will be direly needed. However, refilling today's thin pipeline with new discoveries and then developing these into new drugs will take time. The working group firmly believes that (1) resistance is currently outrunning antibacterial research and development, leading to a high risk situation that needs addressing urgently; (2) the lasting ability to treat infections of any new antibacterials, and hence their health impact, will be greatly reduced if factors leading to development of resistance are not contained by the time they reach the market; and (3) there is no guarantee that that these drugs will be discovered, nor developed in time. It is therefore the conviction of the working group that if additional resources are to be spent on addressing the antibiotic resistance problem, immediate and concerted action to combat further antibiotic resistance will be of much greater benefit to society than increased public investment in antibiotic R&D. Research on containment strategies to prevent further increases in antibiotic resistance has been prioritised in this report because we need *urgent* measures to counteract the rise of antibiotic resistance before it reaches a critical level. Immediate and concerted action to combat further antibiotic resistance will be of the greatest benefit to the society at the moment.

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Introduction

Antibiotic resistance – a highly underestimated problem

Antibiotic resistance is a highly underestimated problem. Not only among the European public but also among many politicians. This is most likely because there are still relatively few people from the developed world who experience and suffer from resistance in their everyday lives. And as long as there are still a few effective antibiotics around, doctors willing to prescribe them and others willing to sell them, it is difficult to make the world understand that it is moving towards a major catastrophe.

So far, only a relatively small number of Europeans have suffered and died from lack of effective antibiotics but think about what kind of place the world will be when there are no more effective antibiotics around; when people prefer to suffer than to undergo routine surgery because of the risk of fatal infection and when illnesses such as pneumonia or infections in the respiratory or urinary tract cannot be contained. Vulnerable groups like young children and old people will be particularly at risk.

Antibiotic resistance is the result of the use of antibiotics. Resistance develops through a natural process whereby susceptible bacteria are killed by the antibiotic and the small number of bacteria that are, by chance, resistant to the antibiotic are thus 'selected' and can grow in number. It is not possible to predict precisely where and when resistance will develop and indeed what new resistances will develop because the process depends on the chance mutation of bacteria to become resistant. Yet we know that any use of antibiotics will result in some resistance and that greater use of antibiotics increases the likelihood of developing resistance. Resistance can, however, be contained and the valuable resource of antibiotics maintained by careful use of antibiotics.

A major problem is that antibiotics are not, on the whole, being used carefully: there is inappropriate clinical use, inappropriate livestock practice and lack of surveillance. The problem is compounded by poor hygiene practices which allow resistant bacteria to spread from person to person and from animal to animal. And the uncertainty associated with the development of resistance and the long time scales over which the problem becomes apparent makes it easy to ignore.

The antibiotic resistance problem is not just difficult to comprehend, it is also complex to deal with. This is particularly so at the international level where specific problems will differ from locality to locality and where it may be beyond the power of international institutions to effectively impose and control legislation in all localities. Although containing antibiotic resistance is a viable possibility it demands political will at all levels.

And there are no simple solutions. Many strategies are required which may include complex and unpalatable changes: changes not only in social and cultural behaviour but also for example in livestock production methods, travelling habits and infrastructure.

It is tempting to suggest more research into, and development of, new antibiotics to replace those that are effectively becoming obsolete, yet since the 1970s few new antibiotics have been discovered and experts estimate that the chance of finding new antibiotics is small. This is partly because little research into new antibiotics is being conducted and partly, and perhaps more worryingly, because there may be few remaining effective antibiotics to be discovered[1].

The antibiotic resistance situation and the state of research within the last decade have been described in many reports. So have the causes and effects of the antibiotic resistance problem. A list of reports for further reading can be found in appendix 5. This project draws on several reports but two should be mentioned in particular, the report from the Strategic Council on Resistance in Europe (SCORE) called 'Resistance: A sensitive issue. The European roadmap to combat antimicrobial resistance' from 2004, and the report from the World Health Organization (WHO) called 'Antibacterial Drug Resistance: Options for Concerted Action' from 2005 (this report is produced as a part of a larger WHO report on 'Priority Medicines for Europe and the World' from 2005).

In these reports and others, valuable suggestions have been made about how to contain resistance and some of these suggestions have been turned into initiatives that have been conducted nationally, within the EU and beyond. Yet the problem of resistance remains and still, the effort to contain the problem is insufficient.

This report builds on the many valuable contributions from other projects. Many of these projects suggest strategies that involve long lists on important areas such as surveillance, consumption, transmission, research and international cooperation. This project, however, has taken as its point of departure that producing another long list of strategies would not be helpful. Instead it concentrates on identifying and expanding upon a small number of policies that the EU can be expected to drive and that can be expected to efficiently contribute to the containment of antibiotic resistance. They take into account the global nature of resistance and attempt to balance financial costs with the expected costs of human suffering.

Although the report provides a brief description of the current situation, since its main task has been to produce an action plan with policy options. Readers requiring a more detailed description of the problem are referred to these previous reports.

Please note that in the report the term 'policy options' is used in a broad sense to include both options for immediate action and research activity.

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[1] Becker, D. et al., 2006. 'Robust Salmonella metabolism limits possibilities for new antimicrobials', *Nature*, Volume 440, No. 7082, pp. 303-7.

Definitions

Antibiotics are pharmaceutical compounds, originally produced by bacteria or fungi but now often synthetically produced, which inhibit the growth of, or kill, bacteria. Compounds which act on fungi are called *antifungals*, similarly *antivirals* is the term used for those drugs acting on viruses. The term *antimicrobial* is used to cover all compounds acting on any of these microorganisms as well as parasites such as those causing malaria. For this document we will use the term antibiotic and focus on bacteria and resistance in these bacteria. This does not mean that antimicrobial resistance in viruses or fungi are not also a threat to society and are not therefore also important.

Antibiotics are lifesaving drugs, which **cure** infections without causing harm to the host. The advent of antibiotics completely changed the prognosis of lethal infections such as meningococcal meningitis, pneumococcal pneumonia and staphylococcal endocarditis, to mention a few.

Antibiotics administered as **prophylactic** drugs, i.e. before surgery or other means of implantation of foreign bodies, also improved the outcome of such therapeutic measures. Without prophylactic antibiotics a large part of modern surgery would be impossible due to the risk of postoperative infection.

Bacteria (procaryotes) are prevalent all over the environment as well as on the skin and on virtually all mucuous membranes of man. We live in symbiosis with bacteria, which are present in us as normal flora in numbers higher than the number of host (eucaryotic) cells.

Normal flora which inhabit us even as we, as newborns, leave the vaginal canal are beneficial for us in a number of ways: they protect the mucous membranes from unwanted pathogenic bacteria, prime the immune system to be able to recognize microbes, metabolise various nutritional and toxic substances and produce compounds such as hormones (e.g. vitamin K) which are taken up by and used by the host.

Resistance: Antibiotic resistance develops in bacteria, that become immune to the action of the compounds. This can happen in a number of ways, e.g. by mutation in the gene for the receptor, to which the antibiotic binds to exert its action, or by producing an enzyme that destroys the antibiotic. Most resistance develops by transfer of genes from a resistant to a susceptible bacterium – horizontal gene transfer – which then becomes resistant. Such transformation or conjugation easily takes place on the skin or in the gut, when these bacteria meet each other. Antibiotic resistance often occurs for several antibiotics concomitantly in the same bacterium rendering it **multi-resistant**.

Bacteria are biological entities, reacting against the use of antibiotics with mechanisms for survival and adaptation. The process of acquisition of antibiotic resistance is a bacterial phenomenon: when we speak about 'antibiotic resistance' we never refer to the patient, that is, the patient *never* becomes resistant to antibiotics, but the bacteria producing the infection within the patient can become resistant. It is possible to talk about a 'resistant infection' when referring to an infection caused by resistant bacteria.

Selection: the process by which the use of antibiotics results in increased resistance by removing the bacteria susceptible to the antibiotic and thereby promoting the growth of those bacteria resistant to the antibiotic. Unavoidably, during antibiotic therapy the drug will also act upon the normal flora removing the usually good susceptible bacteria, which are rapidly replaced with more resistant ones. When the treatment stops, the resistant intruders will usually be overgrown by the susceptible bugs. Therefore, the greater the antibiotic taken and the longer that is administered the lower is the chance of the resistant bacteria being replaced by the susceptible ones.

A member of this normal flora may become **pathogenic** to the host if the host's immune system breaks down allowing the bacteria to enter a tissue, fluid (e.g. blood) or organ, where its cell products act as so-called virulence factors, i.e. factors that allow the growth and spread of bacteria or their toxins. This can cause an **infection** which – depending on the ability of the immune system to cope with the intruders – can be cured by the host himself or lead to chronic infection or death.

The project

The scope of the project

The main scope of the project has been to develop an action plan with a set of clear policy options that can be undertaken by the European Union. A brief overview of the present situation and state of research has also been provided.

The interdisciplinary expert working group, who are the authors of this report, have been asked to take into consideration that antibiotic resistance is not only a European but a global problem. Other criteria are that the options suggested should be in line with, and build upon what is already being done by the European Community.

A possible action plan

The experts working group generally agrees with the policy options and recommendations that have been suggested in other reports. Among others these include the Copenhagen Recommendations[2], the SCORE report[3], reports from the WHO[4] and the Community Strategy Against Antimicrobial Resistance from the European Commission[5].

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[2] Rosdahl, V.T. and Pedersen, K.B., 1998. The Copenhagen Recommendations. Report from the Invitational EU Conference on The Microbial Threat, 9-10 September 1998, Copenhagen.

[3] Strategic Council on Resistance in Europe (SCORE), 2004. Resistance: A sensitive issue. The European roadmap to combat antimicrobial resistance.

[4] World Health Organization (WHO), 2005(a). Kaplan, W. and Laing R., (eds.). Priority Medicines for Europe and the World.
World Health Organization (WHO) 2005(b). A58/14: Report by secretariat: Improving the Containment of antimicrobial resistance, 7, April 2005.

However, the experts in this working group have developed their suggestion for an action plan on the premise that the policy options could be undertaken by the European Union. Further the group has taken as a point of departure that resources spent on containing antibiotic resistance should be used most efficiently (giving greatest value for the resources used) in respect of the fact that costs are not only financial but also include human suffering. Therefore this report suggests an action plan that is narrowly focused on a small number of policy options that can clearly be initiated at the EU level.

One result of using these criteria has been that no policy option actively supporting research into new antibiotics has been recommended. This is not because the working group is intrinsically against such support but rather because the action plan is focused on obtaining the greatest impact for the resources used. The options are thus focused on containment of resistance rather than its potential avoidance (or more realistically, its delay) through the continual development of new antibiotics.

The working group – in line with many other experts – point out that containment of antibiotic resistance starts at the political level. Strategies for containing resistance have been well known for some time and in the EU certain directives and recommendations have even been issued, but the increasing resistance particularly in some countries suggests that not only the consumers and general practitioners but also many national and local politicians have not fully understood the seriousness of the problem and their responsibility to contribute to its containment.

The method

The method for this project has been 'a fast working, interdisciplinary working group' consisting of five experts who were to compose an action plan. The working group started their work in March 2006 and have met five times. A draft version of the action plan was discussed with an additional four experts at an extended working group meeting in June. Based on these discussions the working group produced an interim report.

The interim report was presented at a workshop hosted by the STOA-Panel at the European Parliament in September. At the workshop members of Parliament, speakers and participants from relevant international organizations commented on the report.

World Health Organization (WHO), 2005(c). Critically Important Antibacterial Agents for Human Medicine for Risk Management Strategies of Non-Human Use. Report of a WHO working group consultation, 15-18 February, 2005, Canberra, Australia.
World Health Organization (WHO), 2005(d). Antibacterial Drug Resistance: Options for Concerted Action. Department of Medicines Policy and Standards, WHO.
World Health Organization (WHO), 2001. Global Strategy for Containment of Antimicrobial Resistance. WHO/CDS/CSR/DRS/2001.2a.

[5] European Commission, 2001. Community Strategy Against Antimicrobial Resistance.

In order to do an initial assessment of the potential attractiveness of antibiotic research and development incentives, a small round of interviews was carried out, with two large pharmaceutical companies and four small and medium sized firms.

A detailed description of the subjects discussed in the project can be found in appendix 1.

Brief biographies of the working group members and a list of other contributors to the project can be seen in appendix 2.

Chapter 1 The antibiotic resistance situation

1.1 The problem and the costs of antibiotic resistance

Currently the problem with antibiotic resistance is largely hidden. It is difficult to quantify precisely the total impact of antibiotic resistance in terms of mortality and morbidity because resistance is a problem additional to the initial infection. However, it is clear that patients are more likely to die if they are infected with an antibiotic resistant bacterium and will, if they do survive, have required more expensive therapy, have been sick for a longer time period and have been more likely to require hospitalisation. For MRSA, for example, a number of studies have shown that mortality is double that compared with non-resistant strains[6]; for other infections increased mortality has been shown, including *Salmonella*, *Campylobacter* and *Mycobacterium tuberculosis*.

Box 1

Pneumococci cause the major part of upper (otitis media and sinusitis) and lower respiratory tract infection (pneumonia) and are natively susceptible to penicillin. Penicillin-resistance now occurs in up to 25-50% of isolates from Greece, Italy and Spain, which means that penicillin is obsolete in these countries. The rates are below 5-10% in northern Europe, where penicillin is still widely used[7].

Box 2

Staphylococcus aureus is the major bacterial pathogen causing some 30% of all bacterial infections. When they become Methicillin-resistant there are very few antibiotics left for treatment. High resistance rates are prevalent in Europe (see Figure 2): 25-50% in hospitals in the UK and most of southern Europe, 2-5% in northern Europe.

Changing treatment from oral oxacillin/dicloxacillin to the susceptible infections to intravenous vancomycin treatment to resistant infections increaes the cost with a factor 5-10. It has been calculated that if MRSA replace all susceptible S. aureus, the cost of intravenous antibiotic therapy will increase 100%[8].

[6] Cosgrove, S.E. et al., 2003. 'Comparison of Mortality Associated with Methicillin-Resistant and Methicillin-Susceptible Staphylococcus aureus Bacteremia: A Meta-analysis', *Clinical Infectious Diseases*, No. 36, pp. 53-59.

[7] http://www.rivm.nl/earss.

[8] Ibid.

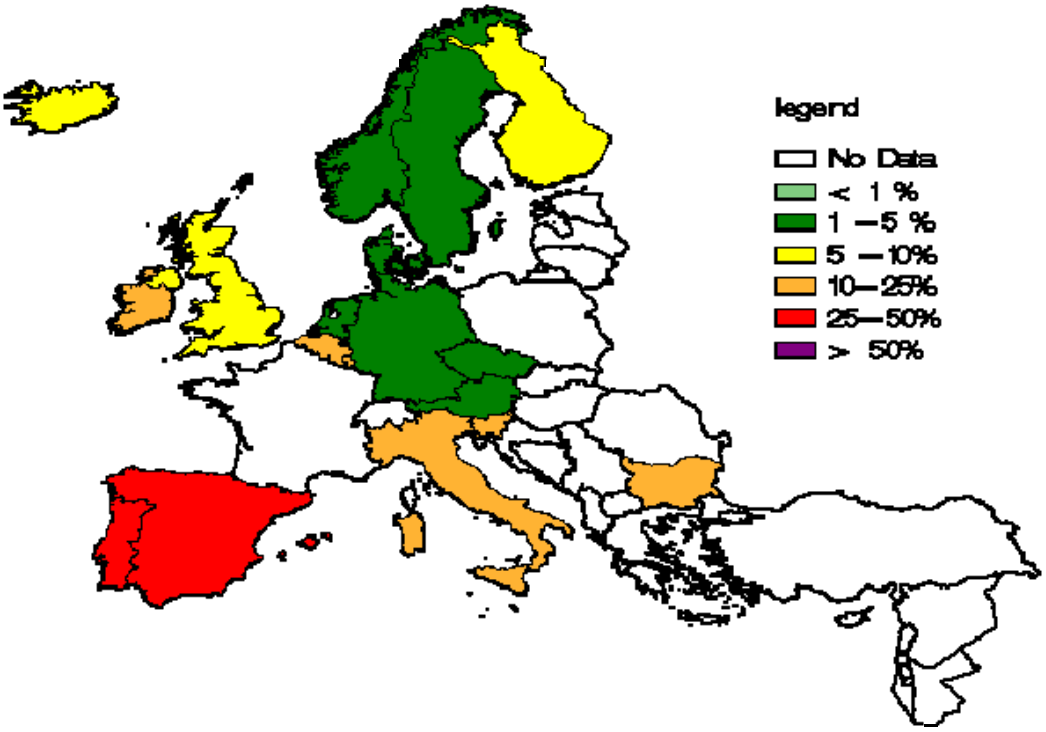

Figure 1: Proportion of Penicillin-Resistant Pneumococci in European countries in 2000[9].

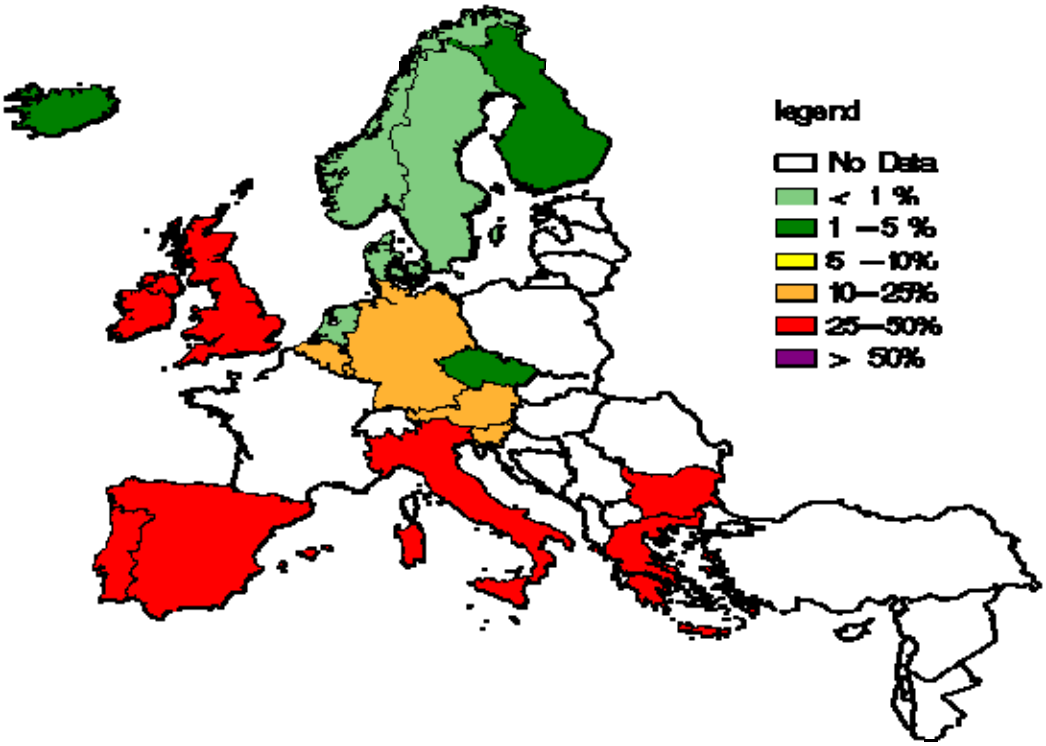

Figure 2: Proportion of Methicillin-Resistant Staphylococcus Aureus (MRSA) in European countries in 2000[10].

[9] Ibid.

As the current resistance levels are not yet catastrophic and as it can be hard to establish the precise contribution of resistance to mortality and morbidity, it is difficult to communicate the urgency with which action is required in this area. But consider the future: huge rises in infant mortality rates as resistant bacteria become widespread in the community; little possibility of chemotherapy for cancer because infection in the immune-compromised can no longer be dealt with by antimicrobials; little possibility of even routine surgery such as hip and knee replacement or tooth removal because so many now die of infection following the surgery that most people would rather suffer the pain; a dread of having to go into hospital because the risk of catching deadly infections is too high; and a much decreased life expectancy for all, as infection kills young and old.

Although this is a scenario of the future this future has already begun. Some countries, such as Greece, are already starting to report pan-resistant (resistant to all known available antibiotics) *Enterobacteriaceae*, e.g. *Klebsiella* sp. or *E. coli*. The increasing development of such pan-resistant organisms has the potential to become a worldwide catastrophe. Resistance is increasing rapidly, despite the focus by national and international bodies over recent years, but resistance levels are not even across the EU. As can be seen from the figures below the problem of resistance is much greater in southern Europe than in the north. This is likely to be due to differences in attitude to the control of use of antibiotics which may have a number of causes: it may be due to a difference in political will to grasp the problem; it may be differences in cultural perceptions about the relative benefits and harms of antibiotic use; it may be related to differences in national income and health systems, which allow some countries to deal with these problems more easily than others. Whatever the reason, these countries, where the control of use is much lower, are also a source of resistance for northern Europe as tourism attracts people to the south from the north. Compared to figures 1 and 2 on the previous pages, figures 3 and 4 below indicate the extent of this problem of transmission of antibiotic resistance from south to north.

[10] Ibid.

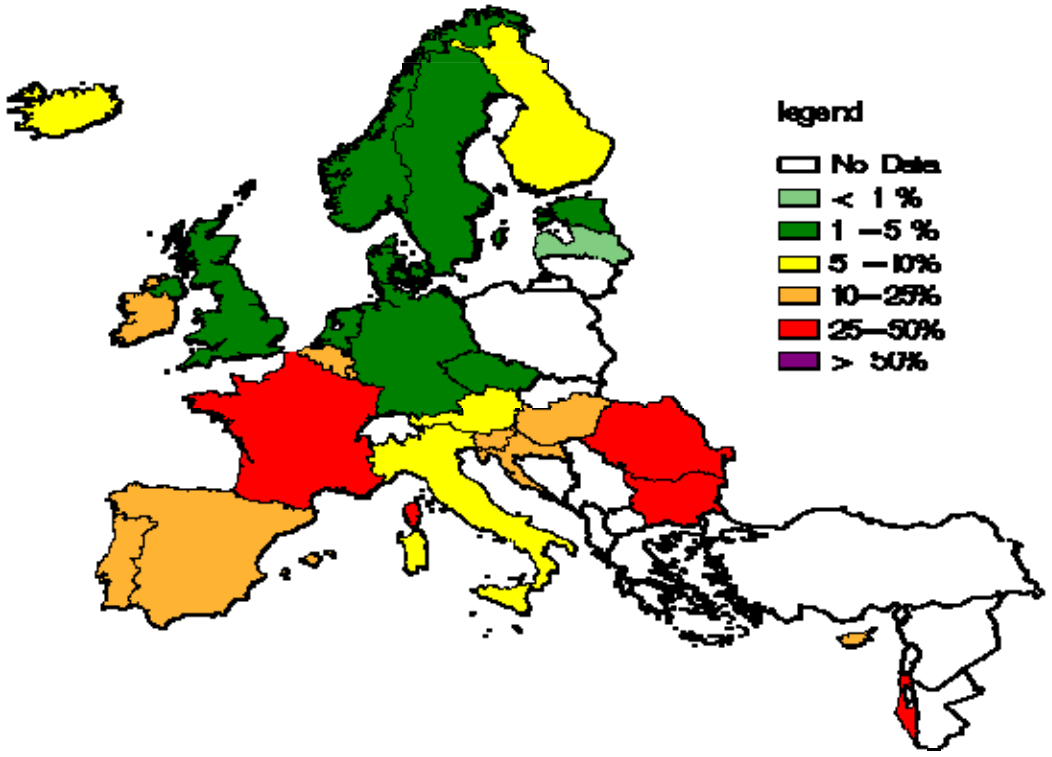

Figure 3: Proportion of Penicillin-resistant Pneumococci in European countries in 2005[11].

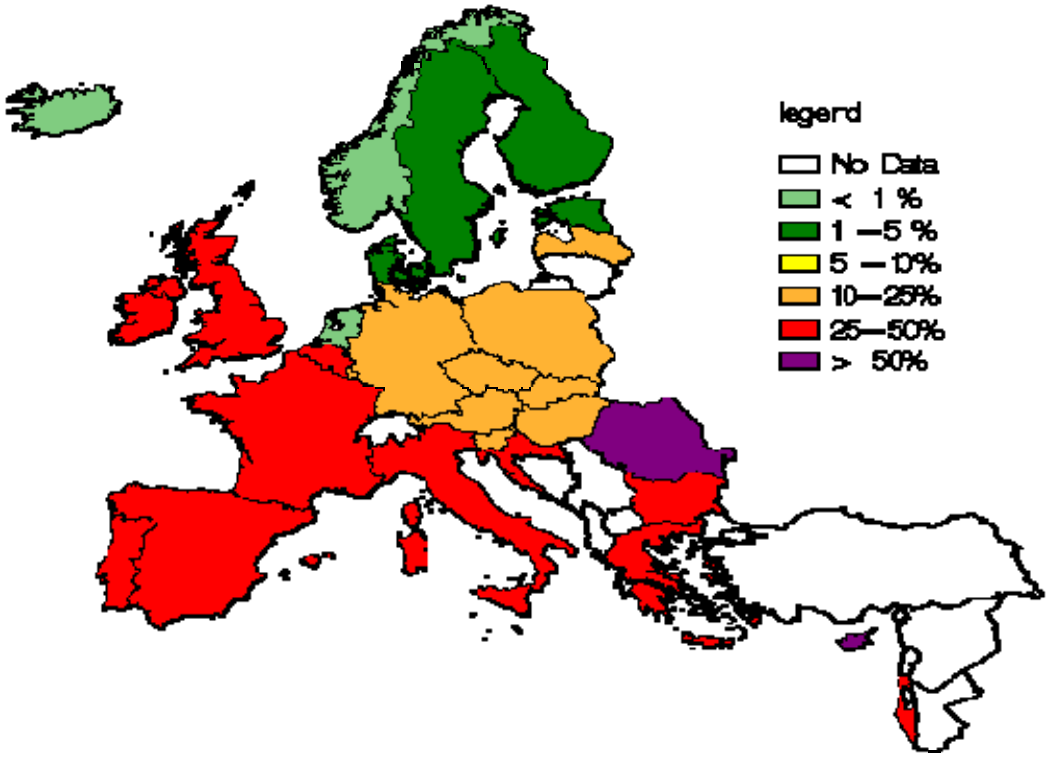

Figure 4: Proportion of Methicillin-resistant Staphylococcus aureus (MRSA) in European countries in 2005[12].

[11] Ibid.

As well as increases in morbidity and mortality and thereby human suffering, the increase in resistance has economic consequences. Because conventional therapy will not eradicate the resistant organism, there is a greater chance of spread to other patients or to friends and family of the patient. These increasing infections result in people being unable to work and thus impose economic costs in terms of lost productivity. Measures to contain resistance, such as hygiene measures to control the spread of antibiotic resistant bacteria, especially at hospitals, are costly and can be a major burden for many hospitals. A number of estimates of the costs associated with antibiotic resistance are given in the recent WHO report on *Antibacterial Drug Resistance*. These suggest high costs for resistance even back as far as 1995, with a US cost of over 4 billion US dollars in that year for the USA. Costs for Europe have been estimated more recently and suggest that the unrecognised cost associated with antibiotic consumption in 2001 was 9 billion Euros, excluding the costs associated with antibiotic prescription in hospitals[13]. This report also estimated costs associated with high levels of MRSA for which the greatest amount of data are available and found these to be in the order of 117 million Euros – exceeding the EU budget for research into all resistance for the years 1999-2002. Given continuing increases in resistance, these costs are undoubtedly increasing all the time. A list of the important negative effects associated with antibiotic resistance is given in Box 3.

[12] Ibid.

[13] Strategic Council on Resistance in Europe (SCORE), 2004.

Box 3

Negative effects associated with increasing antibiotic resistance

- Increase in clinical failure in the therapy of current and future bacterial infections.
- Sub-optimal recovery from current and future bacterial infections.
- Increase in metastatic (in other parts of the body) bacterial infections.
- Increase in recurrence rates and chronicity after bacterial acute infection.
- Increase in transmission rate of bacterial organisms to the familiar neighbourhood
- Increase in current or future opportunistic infections with resistant organisms.
- Increase in current or future bacterial complications of trauma, surgery, and therapeutic or pathological immuno-depression.
- Increase in super-infections by resistant organisms.
- Increase in para-bacterial diseases. An obvious example is the possibility of increase of infections like rheumatic fever or nephritis because of sub-optimal therapy of streptococcal infections.
- Treatment becomes more difficult and expensive, since the remaining active drugs are usually the newer, more expensive antibiotics (e.g. carbapenems or linezolid).
- Empiric therapy is more difficult, since it is increasingly difficult to predict resistance. The more that broad-spectrum antibiotics are used, the higher is the risk of selecting resistant bacteria (the vicious circle of resistance).

Increasingly complicated diseases and higher mortality; as has been shown for methicillin-resistant *Staphylococcus aureus* (MRSA), Salmonella spp and Campylobacter spp[14].

It should, of course, be remembered that antibiotics provide substantial benefits (a list of positive benefits from antibiotics is given in Box 4). The introduction of antibiotics in the 1940's was critical in allowing the modern advancement of medicine: antibiotics have permitted the introduction of advanced surgery, intensive care units, anticancer drugs, steroid therapy and transplantation. Without the antibiotic protection against microbes, these advancements cannot be imagined, and human life expectancy is likely to fall.

[14] Helms, M. et al., 2004. 'Quinolone Resistance Is Associated with Increased Risk of Invasive Illness or Death during Infection with *Salmonella* Serotype Typhimurium', *The Journal of Infectious Diseases*, Volume 190, No. 9, pp 1652-1654. Helms, M. et al., 2005. 'Adverse Health Events Associated with Antimicrobial Drug Resistance in *Campylobacter* Species: A Registry-Based Cohort Study', *The Journal of Infectious Diseases*, Volume 191, No. 7, pp. 1050-1055.

Because of these substantial benefits it is not possible to reduce resistance merely by avoiding use of antibiotics. Instead, the problem of resistance must be dealt with by a complex package of policies – this is the subject of chapter 3.

Box 4

Positive impact of antibiotics

- Increase in clinical cure or substantial recovery of a number of infections.
- Decrease in sick time due to infection, with increase in working productivity and/or quality of life.
- Decrease in the number of severe acute infections eventually complicating apparently mild infections (as meningococcal meningitis, or pneumococcal pneumonia).
- Decrease in sub-clinical infections with high health impact, as acne, caries, periodontitis, or subclinical urinary tract infections in young women.
- Decrease in chronicity after acute infection, or in the number of recurrences in chronic infections.
- Decrease in transmission of pathogenic or resistant bacteria to the close neighbourhood.
- Decrease in the number of meta-infective diseases, as rheumatic fever.
- Decrease in the number of para-microbial diseases eventually associated with acute or chronic disease.
- Decrease in carcinogenicity, or in central nervous system diseases (as with tetracyclines).

1.2 Causes of resistance

Resistant bacteria are those that cannot be killed or whose growth cannot be inhibited by antibiotics. Many bacteria that were susceptible in the past to antibiotics have evolved to become resistant. Antibiotics effectively become increasingly useless as bacteria become increasingly resistant.

The development of antibiotic resistance in bacteria is essentially a Darwinistic process of selection of the fittest. Just by chance (for instance genetic mutations leading to antibiotic resistance occurs at random with a low, but consistent probability in all bacteria) a small, very small number of bacteria is genetically resistant to a given antibiotic, among a huge majority of susceptible ones (for instance 1 cell for every 100,000,000 cells).

If the patient is treated with the antibiotic, every susceptible bacterium will die, but not the single one that was resistant by chance. These bacteria will survive and multiply, producing a resistant progeny: resistance is being *selected*. After a given period of time, the original susceptible population has been replaced by the resistant population. So, when people say that 'the bacteria have become resistant' what is really meant is that 'the resistant population has replaced the sensitive one'.

The capability of bacteria to adapt (to survive) to antibiotic challenge depends largely on the amount of antibiotic given in treatment and the number of bacteria that are being treated. The more bacteria that are challenged with an antibiotic, the greater the probability that resistant bacteria will emerge. The extremely high replication rate of bacteria (bacteria typically duplicate 17 times in a single day in a culture tube) means that there will be huge increases in the number of resistant bacteria.

Any human collective has an immense number of bacteria. Where use of antibiotics is very common resistant bacteria will inevitably emerge. Once resistant bacteria are selected and increase in number (as the sensitive ones tends to disappear) they can spread from the patient in whom selection took place into many others. This spread will be facilitated because of the ecological vacuum: resistant organisms will find 'empty niches' to colonize. These niches are the result of the elimination of susceptible bacteria by the antibiotic.

In a number of cases, resistant bacteria do not originate from random mutational events, but by the random acquisition (similar to mutation) of 'resistance genes'. Indeed the scientific community is convinced that there is a 'pool of resistance genes' both in our normal flora and present in soil, water and even in food. The bigger this pool, the greater is the possibility that these genes will be acquired by those bacteria that cause illness. If bacteria that have acquired the resistance gene are then selected by use of antibiotics, this will increase the possibility of emergence and spread of resistant bacteria. If bacteria are resistant to say two or three antibiotics, use of one of those antibiotics will select for all these resistances (known as co-selection).

The history of bacterial resistance probably began before antibiotics were first developed, possibly with resistance to heavy metals such as mercury, lead or cadmium. The same is likely to be true for other pollutants. A current concern is that industrial pollution might increase the pool of genes selecting for antibiotic resistance, by selecting those organisms that are resistant to both metal and antibiotic resistance.

So the two main causes of increasing antibiotic resistance are:

- *Selection by use of antibiotics*: the more antibiotics used, the higher the resistance rate; and
- Spread of resistant bacteria: the more wide-spread that resistant bacteria become, the higher is the risk of contamination and therefore the higher the risk of catching resistant infections.

Antibiotics are needed to fight infection and so there will always be some resistance. However, the inappropriate overuse of antibiotics has led to the potentially catastrophic rises in resistance that we see today. It should be noted that the vast majority of this antibiotic use is in the community rather than in hospitals (in the order of 90% to 10% respectively). There are a number of potential causes of this inappropriate overuse:

- Antibiotics tend to be given empirically, that is, without first diagnosing the cause of the illness. This means that antibiotics are often given by health practitioners where they will have no positive effects but only negative ones, because the cause of the illness is viral rather than bacterial. Because treatment is empirical, the antibiotic used may also be one that can be used for a number of illnesses (broad-spectrum antibiotics), rather than one that is targeted towards a specific cause.
- In some countries antibiotics are purchased directly by patients who have no knowledge about whether the infection is bacterial or viral. Again, a large proportion of antibiotics will be taken that have only negative effects.
- When farm animals or fish are treated the whole herd, flock or shoal will be treated rather than just the infected animal.

Where resistant bacteria are developing, their spread also becomes extremely important. The major cause of the spread in resistant bacteria, both in hospitals and in the community, is lack of infection control. This may be seen in a number of ways:

- poor hand hygiene;
- absence of isolation rooms in hospitals, poor compliance with rules for infection control,
- insufficient air circulation in environments where individuals are close together;
- importation of bacteria through imported animals and imported meat products.

Antibiotic resistance is closely connected with antibiotic consumption in the way that reduction of antibiotic use will also lead to reduction in antibiotic resistance. There are numerous examples of such correlations. Several appear in the DANMAP reports[15]. One obvious example from these reports is the reduction in resistance towards antibiotics used as growth promoters (e.g. avoparcin, streptogramins, tylosin) in animal production after the ban of growth promoters in the EU[16].

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[15] http://www.danmap.org

[16] In a few cases, resistance markers will not disappear in spite of reduction in antibiotic use. The gene for the mechanism behind streptomycin resistance in E. coli was incorporated into the chromosome of some E. coli strains already 20-30 years ago and the presence of the gene apparently does not induce any cost of resistance in these strains. There has therefore not been any influence of removal of the antibiotic on this resistance marker in E. coli; on the other hand, since streptomycin is not used for treatment and is not marketed anywhere in the World, this type of resistance has no clinical implication.

1.3 Inappropriate antibiotic use

Antibiotics should ideally be used to treat infections caused by bacteria susceptible towards the antibiotic in question, and only if the benefit of the treatment outweighs the risk of side-effects for the patient as well as the risk for society, i.e. the risk of resistance developing against the drug. Antibiotic prophylaxis, which covers the use of antibiotics not to treat but to prevent bacteria from causing infection, is also acceptable if used for a short period – preferably one dose – and if prospective randomized studies have shown reasonable effect. Any other use of antibiotics is inappropriate.

Antibiotic use should always be preceded by culture or other means of diagnosis and susceptibility test. But in serious infections antibiotic treatment is usually started before the culture results are known, which means that antibiotics will also be used for viral and other types of infections, where these drugs have no effect. Diagnosis of infection can only be performed where diagnostic microbiological laboratories are available. In most infections in general practice, even in most European countries, good and rapid clinical microbiology is not available in general practice but only in larger hospitals. In a few countries, e.g. Denmark, for many years efforts have been directed at improving the use of antibiotics by giving incentives to the general practitioner for performing the diagnostic workup locally. The Group A antigen test for streptococcal tonsillitis and microscopy and culture of urine samples for diagnosing urinary tract infection are such examples.

To what extent antibiotics are used inappropriately is not easy to monitor. Prevalence studies in hospitals have shown inappropriate use of antibiotics in up to 50% of those patients treated at any day[17]. The huge differences in consumption of antibiotics in Europe i.e. 3-4 times the amount used per inhabitant in southern Europe as compared to the consumption in Holland and Scandinavia must rest on a vast degree of inappropriate use since these drugs are used for the same infections in all countries, and there is no reason to believe, that the same degree of difference in the frequency of infections should be the explanation.

It is well known that in some places (within as well as outside the EU) patients can obtain antibiotics without prescription. A recent report from the Commission to the Council[18] indicates that selling antimicrobial agents without a prescription is considered a source of inappropriate human antimicrobial use in at least seven countries in the EU.

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[17] Erbay, A. et al., 2005. 'Evaluation of antibiotic use in intensive care units of a tertiary care hospital in Turkey', *Journal of Hospital Infection*, Volume 59, pp.53-61.
Ochoa, C. et al., 2001. 'Appropriateness of antibiotic prescriptions in community-acquired acute pediatric respiratory infections in Spanish emergency rooms', Spanish Study Group on Antibiotic Treatments, *Pediatric Infectious Disease Journal*, Voulume 20, pp. 751-8.

[18] European Commission, 2005. *Report from the Commission to the Council - On the basis of member states' reports on the implementation of the Council Recommendation (2002/77/EC) on the Prudent Use of Antimicrobial Agents in Human Medicine*.

The use of antibiotics often depends on the level of knowledge of the patient. The more the patient knows regarding the effect – and lack of effect on e.g. virus - of antibiotics and the risk of development of resistance the easier it will be for the physician to treat the patient correctly. When antibiotics are sold without prescription there is a substantial risk that the antibiotic will not be used appropriately. The EU funded Self medication and Antimicrobial Resistance (SAR) research project shows that self-medication with antimicrobials is a problem all over Europe[19] as do a number of other studies across Europe[20].

A contributing factor to this self-medication is the economic incentives faced by pharmacists, encouraging them to dispense without prescription. Every effort must be used to remove these economic incentives.

In animal husbandry there are numerous examples of inappropriate use of antibiotics. The use of antibiotics for growth promotion was completely inappropriate, since it had minor effect on growth of animals. The EU is now trying to stop this kind of inappropriate use by a Directive which became effective in the beginning of 2006. Flock feeding is another example of inappropriate use. This is the concept of treating the whole animal flock via the feed or the water since it is too time consuming (i.e. expensive) for the farmer to treat the individual sick animals. A third example is the policy of allowing the veterinarian to sell drugs directly to farmers thus giving him/her the financial incentive of maximising profit.

1.4 Distribution of antibiotic resistance

Geographic distribution

It should be noted that describing the distribution of resistance is not a simple task. Although the surveillance systems within the EU are much better than in other countries, even in the EU it can be difficult to obtain good data. Having said this, it is clear that antibiotic resistance is a problem throughout the world. The greatest problems are in the developing countries but there are also high levels of resistance in developed countries and newly industrialised countries in Asia, with particular problems in South Korea, China, Taiwan and Japan (for example *Streptococcus pyogenes* and macrolide resistance in Taiwan, *Streptococcus pneumoniae* and penicillin resistance in South Korea). These resistances are not only a problem for these countries, for Europe, since theys can be imported both through human travel and transportation of animals and foodstuffs.

Particular resistances can be local to different communities so, for example, the prevalence of multi-drug resistant tuberculosis is much higher in Russia and the Baltic states than in Western Europe. Within the EU, the greatest problems are in the Mediterranean countries. Data from Eastern Europe are scarce, but so far indicate that the levels of resistance are more similar to the northern states of the EU than to the south.

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[19] Ibid.

[20] Strategic Council on Resistance in Europe, (SCORE), 2004.

In relation to specific bacteria, in 2002 the proportion of penicillin resistant Streptococcus pneumoniae was over 25% in France, Poland, Romania and Spain (see Box 1); the proportion of E. Coli resistant to aminopenicillins was more than 30% for all countries in the EARSS study apart from Sweden and Finland was more than 30%; MRSA levels were around 40% in the UK, Ireland, Greece, Italy, Malta and Portugal (see Box 2) and the proportion of vancomycin resistant E. faecium was more than 10% in Ireland, Italy, Greece, Croatia and Romania[21].

Distribution between hospitals and community

Antibiotics are much more commonly used in the community than in hospitals, but in terms of antibiotic use per person, the use is much greater in hospitals. As antibiotic use selects for resistance, there will be more antibiotic resistance developed in hospitals than in the community because of the higher per person use (this can be seen even within the hospital environment where there is greatest use of antibiotics within intensive care units, increasing the likelihood of resistance). There is also likely to be greater transmission of resistance in a hospital environment where people are close together than in the community and also already have weakened immune systems through illness. Although there is undoubtedly greater resistance in the community, the problems associated with resistance appear much more clearly in the hospital environment.

1.5 Antibiotics in food animal production

Modern food animal production depends on the use of large amounts of antibiotics for disease control. These provide favourable conditions for selection, spread and persistence of antimicrobial-resistant bacteria capable of causing infections in animals and humans.

Because of worldwide trade (both in food animals and food of animal origin) these resistant bacteria become a problem across the globe. This emphasises the need for global initiatives and the establishment of common guidelines and systems for controlling resistance in all countries.

There are several cases in which multiple resistant bacterial clones have spread worldwide. In animal populations, examples have primarily included the international dissemination of different *Salmonella* clones[22]. One of the most striking examples has been the worldwide spread of multiple resistant *S.* Typhimurium DT104. During the late 1990's DT104 was reported from an increasing number of countries worldwide and can today probably be found in almost all countries. This special multiple resistant salmonella type has contributed to the prevalence of resistance reported in many countries.

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[21] World Health Organization (WHO), 2005(d).

[22] McDermott, P.D., 2006. 'Antimicrobial resistance in nontyphoidal salmonellae'. In: Aarestrup, F.M. (ed.). *Antimicrobial resistance in bacteria of animal origin*. ASM Press, Washington DC, USA, pp. 293-314 (ISBN 1-55581-306-2).

The mode of transmission is not definitively known but is probably related to trade with breeding animals, travelling and international sale of food products.

Beside salmonella, a large number of different resistance genes have also emerged worldwide in the food animal population from where they constitute a reservoir of resistance genes that may transfer to and cause problems for humans. A recent example is the worldwide emergence of extended β-lactamases such as CMY- and CTX-enzymes, which have emerged and spread worldwide within the last few decades including the animal reservoir[23].

Antimicrobial resistant bacteria can have human health consequences both due to the occurrence of infections that would otherwise not have occurred or due to treatment failures and increased severity of infections. **However, it should be noted that most of the resistance problems in human medicine are caused by human usage and over usage of antimicrobial agents for therapy and prophylaxis.**

Use of antibiotics in food animal production

In modern food animal production antimicrobial agents are normally used in one of four different ways:

- **Therapy**: treatment of infections in clinical sick animals, preferably with a bacteriological diagnosis.
- **Metaphylactics**: treatment of clinical healthy animals belonging to the same flock or pen as animals with clinical signs. In this way infections may be treated before they become clinical visible and the entire treatment period may thereby be shortened. In addition, this can, because of the modern productions systems, often be the only way to treat large broiler flocks with water medication.
- **Prophylactics**: treatment of healthy animals in a period where they are stressed to prevent disease (e.g. medicated early weaning). This use of antimicrobial agents can be signs of management problems, and it is in most countries not legal or considered imprudent.
- **Growth promotion**: inclusion of antimicrobial agents continuously in animal feed to improve growth. This usage has been banned in the EU.

It is difficult to obtain good information about the consumption of antimicrobial agents for medical and growth promoting purposes. Exact figures are very rare and estimates are only available for a few countries. However, the data that are available show major differences between countries with in some cases more than a factor of 10 in the consumption of antibiotics per produced kilogram of meat.

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[23] Bauernfeind, A., Chong, Y. and Lee, K., 1998. 'Plasmid-encoded AmpC beta-lactamases: how far have we gone 10 years after the discovery?', *Yonsei Medical Journal*, Volume 39, No. 6, December, pp. 520-5. Cantón, R. and Coque, T.M., 2006. 'The CTX-M β-lactamase pandemic', *Current Opinion in Microbiology,* Volume 9, pp. 466-475.

Thus, the European Agency for the Evaluation of Medical Products[24] estimated the amounts of antimicrobial agents used for treatment and growth promotion for food animals in the different EU countries in 1997. The average usage was approximately 65 mg of antibiotics used to produce one kilogram of meat, but this differed from less than 10 mg/kg to more than 140 mg/kg between the member states. Even though there may be some problems in the validity of the data and there are differences in production in different countries, it is obvious that there are major differences in the amounts of antimicrobial agents used in different countries to produce the same amount of meat, which provides room for major reductions in some countries. Another example is provided by the USA, where the consumption of antimicrobial agents increased tremendously from 1950 to 1978[25]. In 1951 a total of 110 tonnes was produced for addition to animal feed and other application, whereas 580 tonnes was produced for medical use in humans and animals. In 1978 5,580 tonnes was produced as feed additives, whereas 6,080 tonnes was produced for medical use in humans and animals. Thus a 50 and 10 times increase, respectively.

Spread from animals to humans

A zoonosis is an infection or infectious disease that under normal conditions are transmissible from vertebrate animals to man[26]. Well-known food borne zoonotic agents are *Salmonella*, *Campylobacter*, *Yersinia*, *Listeria* and enterohaemorrhagic *E. coli*.

The importance of meat and eggs in the direct transmission of pathogenic zoonotic bacteria, including antimicrobial resistant once, from animals to humans is well documented in numerous studies. This direct transmission is quantitatively the most important mode of transmission of antimicrobial resistant bacteria and resistance genes from the farmhouse to the consumer.

One of the most pronounced examples in recent years of emergence of antimicrobial resistance among food animals and subsequently spread of resistant zoonotic bacteria to humans is resistance to fluoroquinolones. In several countries fluoroquinolones are the drug of choice for treatment of gastrointestinal infections in man caused by zoonotic organisms such as *Salmonella* and *Campylobacter* and the emergence of resistance among zoonotic organisms such as *Salmonella* and *Campylobacter* is a matter of increasing concern.

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[24] European Agency for the Evaluation of Medical Products (EMEA), 1999. *Antibiotic resistance in the European Union associated with therapeutic use of veterinary medicines. Report and qualitative risk assessment by the Committee for Veterinary Medical Products*.

[25] Black, W. D., 1984. The use of antimicrobial drugs in agriculture, *Canadian Jounal of Physiology and Pharmacology*, Volume 62, pp. 1044-1048.

[26] Acha, P. N. and Szyfres, B, 1994. *Zoonoses and communicable diseases common to man and animals*. 2nd Ed. Pan American Health Organisation, Pan American Sanitary Bureau, regional office of the World Health Organization, Washington D. C., USA.

The first reported study was from The Netherlands where water medication with the fluoroquinolone enrofloxacin in the poultry production was followed by an emergence of fluoroquinolone resistant *Campylobacter* species among both poultry and humans[27]. Since then several studies worldwide have documented an increase in the occurrence of resistance to fluoroquinolones among *Campylobacter* and *Salmonella* from food animals and humans following the introduction of fluoroquinolones for the treatment of infections in food animals[28].

Antimicrobial resistance genes are not only present in the pathogenic bacteria, but also prevalent in the normal commensal flora that makes up the major part of the gastrointestinal flora. These bacteria may function as a reservoir of resistance genes that can transfer to pathogenic bacteria. Several studies have also documented that resistance genes might be selected for in the animal reservoir and thereafter transferred to bacteria causing infections in humans. The importance of this gene transfer is very difficult to quantify, but it is expected to contribute to the overall problem with antimicrobial resistance.

Antimicrobial resistant bacteria may also transfer from animals to humans through direct contact. This is also the case for companion animals, where it has been shown for example that humans may become colonized with *S. intermedius* from dogs. Food animal transfer may occur to the farmer or other humans in contact with the animals. This has been shown for vancomycin and streptogramin resistant enterococci as well as methicillin resistant *Staphylococcus aureus*.

Human health consequences resulting from resistant zoonotic bacteria

Antimicrobial resistant bacteria can have human health consequences both due to the occurrence of infections that would otherwise not have occurred or due to treatment failures and increased severity of infections[29].

The use of antimicrobial agents in humans disturbs the intestinal microflora. Individuals taking an antimicrobial agent for e.g. respiratory infections etc. are therefore at increased risk of becoming infected with intestinal pathogens resistant to that agent. It has been estimated that in the USA resistance to antimicrobial agents result annually in an additional 29,379 Salmonella infections, leading to 342 hospitalisations and 12 deaths, and an additional 17,668 *Campylobacter jejuni* infections, leading to 95 hospitalisations[30].

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[27] Endtz, H. P. et al., 1991. 'Quinolone resistance in campylobacter isolated from man and poultry following the introduction of fluoroquinolones in veterinary medicine', *Journal of Antimicrobial Chemotherapy*, Volume 27, pp. 199-208.

[28] Engberg, J. et al., 2001. 'Quinolone and macrolide resistance in *Campylobacter jejuni* and *coli*: A review of mechanisms and trends over time of resistance profiles in human isolates' *Emerging Infectious Diseases*, Volume 7, pp. 24-34.

[29] Mølbak, K., 2006. 'The clinical importance of animal-related resistance'. In: Aarestrup, F.M. (ed.). *Antimicrobial resistance in bacteria of animal origin*. ASM Press, Washington DC, USA, pp. 329-338 (ISBN 1-55581-306-2).

[30] Barza, M. and Travers, K., 2002. 'Excess infections due to antimicrobial resistance: the "Attributable Fraction"', *Clinical Infectious Diseases*, Volume 34, pp. 126-130.

Several studies have shown that infections with resistant *Salmonella* and *Campylobacter* are associated with a higher death rates and longer durations of illness than infections with susceptible isolates[31]. Resistance to some antimicrobial agents are more critical that resistance to other agents. Thus, resistance to the drugs of choice for treatment of the infection caused by the zoonotic agent in question must be considered most important. Currently this would be resistance to quinolones and cephalosporins in *Salmonella* and resistance to quinolones and macrolides in *Campylobacter*. However, the increased rate of infections caused by resistant bacteria disregarding the drug of choice should also be remembered.

The frequent occurrence of methicillin resistant *S. aureus* (MRSA), penicillin-resistant *S. pneumoniae*, multiple resistance in *P. aeruginosa*, glycopeptide resistant enterococci (GRE) and resistance to cephalosporins in *E. coli* and other Gram-negative bacteria have been mentioned as some of the main problems for treatment of infections in humans. The problems with antimicrobial resistance in non-typhoid salmonella and campylobacter are mainly caused by the use of antimicrobial agents for food animals. A potential link between use of avoparcin for growth promotion in food animals and GRE in humans has been suggested and as a consequence the use of avoparcin for food animals banned[32]. No link has been suggested for penicillin-resistant *S. pneumoniae* and multiple resistance in *P. aeruginosa*. It has until now been the general belief that *E. coli* from animals and humans mainly makes up different populations and that besides *E. coli* O157:H7, *E.* coli isolated from the normal intestinal flora in food animals will not cause invasive infections in humans. However, recent studies have indicated that antimicrobial resistant *E. coli* causing infections in humans might have a reservoir in food animals[33]. Recently, MRSA have emerged from being mainly a hospital pathogen to also be a major cause of infection in the community and this bacterium have now also emerged in the food animals reservoir from where it has spread back to humans. The importance of the animals reservoir for human infections with MRSA is at present not entirely clear.

[31] Mølbak, K., 2006. pp. 329-338..

[32] Aarestrup, F.M., 2000. 'Occurrence, selection and spread of resistance to antimicrobial agents used for growth promotion in Denmark', *APMIS*, Volume 108, suppl. 101, pp. 1-48.

[33] Johnson, J.R. et al., 2005. 'Antimicrobial-resistant and extraintestinal pathogenic Escherichia coli in retail foods', *Journal of Infectious Diseases*, Volume 191, pp. 1040-9.

1.6 Current initiatives[34]

Numerous networks, organisations, and institutions are working to survey, monitor, and contain the phenomena of antibiotic resistance. The most common form of Inter-European initiatives have been established with start-up co-financing from the European Commission, particularly from the public health and research sectors; formalized as networks of cooperating member states, generally and gradually becoming more reliant on national public health funding.

Nearly all of the EU member states' health services have drafted national strategy plans for antibiotic resistance, and many have similarly established national laboratories for the monitoring and reporting of bacteria outbreaks and levels of drug resistance[35].

Other forms of action networks include NGO's and professional societies that arrange semi-annual workshops and meetings, often sponsored by national health services. These organizations and networks are reliant on medical, veterinary and research professionals donating their time and/or results from projects conducted at research laboratories, national health institutes and universities.

By looking at the wealth of reports and number of activities on antibiotic resistance it is clear that what is lacking is not necessarily knowledge or advice, but rather coordination between the various institutions, organizations and networks. A new agency, the European Centre for Disease Prevention and Control (ECDC) established by EU Parliament and Council in 2004 should, given the right level of funding and responsibility, be able help to improve the coordination between national and international organizations. Recently the Commission have also appointed a Community Reference Laboratory for Antimicrobial Resistance among bacteria from food and food animals.

Since antibiotic resistance is a global matter it is important that containment of antibiotic resistance is handled at a global level. And this can only happen if knowledge is shared and strategies are coordinated. The World Health Organization (WHO) is an important collaborator for the EU on health matters and co-operation on antibiotic resistance could be strengthened through ECDC.

Some important actors and their activities are mentioned below. The initiatives vary in kind and size and cover several aspects such as surveillance, education, coordination and research[36].

It is important to note that although there are countries that in some cases have managed to contain antibiotic resistance, the over all picture is that the many good initiatives have not contained the resistance problem sufficiently neither in Europe nor worldwide.

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[34] We would like to thank the presenters and discussants at the workshop at the European Parliament on Sept. 13th 2006 for their useful comments and input to this section.

[35] National action plans for the containment of antibiotic resistance can be found on the majority of national health agency websites.

[36] A list of past European initiatives, small-scale projects, and industry based projects can be seen in Strategic Council of Resistance in Europe (SCORE), 2004.

Activities initiated by the European Union

Since 2001, the European Commission, Council, and Parliament have implemented numerous activities with the aim of reducing antibiotic consumption and resistance, monitoring the use of antibiotics in humans and animals, monitoring the spread of resistant bacteria, among other aspects of disease control and prevention. In a joint-effort in 2001, the EU parliament and council established a network committee on infections diseases to be under the auspices of the Directorate-General SANCO (public health). Through the network committee framework over 25 networks and projects were set up for improving hygiene practices, education and training, encouraging the prudent use of antibiotic drugs, monitoring the use of antibiotics and the spread of antibiotic resistance since 2000. Projects under this programme were financed up to 70 % by the European Commission, and co-financed by other organisations such as research centres, hospitals, national health authorities, and universities. While some projects became more formalized structures in the antibiotic resistance landscape, others were discontinued after their original contracts expired.

In 2002, the European Commission published recommendations on the prudent use of antibiotics, to define clear guidelines for the use of antibiotics in humans that could help reduce resistance. And in 2005, the Commission composed a review of their activities to be delivered to the council, where their projects were assessed and recommendations were made for further harmonization and improvement of the activities[37].

Current projects under DG SANCO network committee

(*Projects are listed in no particular order)*

European Antimicrobial Resistance Surveillance System

European Antimicrobial Resistance Surveillance System (EARSS) is a network of national monitoring boards that collects resistance data following common protocols from laboratories in 28 countries with the aim being to monitor resistance levels throughout the network to target interventions and assess national intervention programmes.

European Surveillance on Antimicrobial Consumption

European Surveillance on Antimicrobial Consumption (ESAC) is a data collection system based on a common register of available antibiotic products. National data are collected in a database to enable comparison of antibiotic use with resistance patterns, socio-economic variables and health indicators. Funding from 2001-2007 came from national institutes and laboratories responsible for surveillance activities and DG SANCO.

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[37] European Council, 1999. *Council Resolution of 8 June 1999 on antibiotic resistance: a strategy against the microbial threat.* http://europa.eu.int/scadplus/leg/en/cha/c11561.htm
European Commission, 2001. *Communication of 20 June 2001, Community strategy against antimicrobial resistance.* http://europa.eu.int/scadplus/leg/en/cha/c11568.htm
European Council, 2001. *Council Recommendation of 20 June 2001, Prudent use of antimicrobial agents in human medicine.* http://europa.eu.int/scadplus/leg/en/cha/c11569.htm

EUCAST

The European Committee on Antimicrobial Susceptibility Testing (EUCAST) is a standing committee jointly organised by ESCMID and European national breakpoint committees. It was set up to standardise antibiotic breakpoints and susceptibility testing in Europe so that comparable results are produced. EUCAST is co-financed by ESCMID, the National Breakpoint Committees represented on the Steering Committee and through a grant (2004 – 2007) from DG SANCO of the European Union. Furthermore, EUCAST, in cooperation with a number of other stakeholders, helped draft a common methodology and definitions for determining resistance thresholds and standardized reference methods.

Similarly, *ESGARS, European Study Group for Antimicrobial Resistance Surveillance:* another committee under ESCMID has published a key-document on Methodology of Surveillance of Antibiotic Resistance in Europe[38].

Improving Patient Safety in Europe

Improving Patient Safety in Europe (IPSE) is the predecessor to HELICS, a network that includes the WHO, the European Society of Clinical Microbiology and Infectious Diseases (ESCMID), and various national public health institutes and EU-supported networks aiming to resolve persisting differences in the variability of preventive practices and outcomes with respect to nosocomial infection and antibiotic resistance in Europe.

EURO TB

EURO TB has coordinated the surveillance of tuberculosis (TB) in the 52 countries of the WHO European Region since 1996. Its overall goal is to improve the contribution of epidemiological surveillance to TB control in Europe. It is a collaboration centre of the WHO and is funded by DG SANCO.

ENTER-Net

ENTER-net is an international surveillance network for gastrointestinal infections in humans. The participants include microbiologists from national reference laboratories responsible for investigating salmonella and *E. coli* infections, and epidemiologists responsible for the national surveillance of these diseases. The network is funded by the European Commission DG SANCO, and conducts surveillance of salmonellas and *Escherichia coli*, including antimicrobial resistance.

[38] Cornaglia, G. et al., 2004.'Report from the European Conference on the Role of Research in combating antibiotic resistance', *Clinical Microbiology and Infection*, Vol. 10, No. 5.

The European Union Invasive Bacterial Infections Surveillance Network

The European Union Invasive Bacterial Infections Surveillance Network (EU-IBIS) began in 1999 based on decision No 2119/98/EC on setting up a network for the epidemiological surveillance and control of communicable diseases in the EU stated as a priority "Diseases prevented by vaccination". It established surveillance networks within the EU for invasive *H influenzae* and *N meningitidis* disease. The overall aims of the project are to improve epidemiological information and laboratory capacity to characterise isolates of these two invasive bacterial infections within the EU. The EU-IBIS project received further funding from DG-SANCO in 2003.

DIVINE-Net

DIVINE-Net aims to improve the prevention of emerging food-borne enteric viral infections through diagnosis, viability testing, networking and epidemiology. DIVINE-Net is a collaboration between national health and food safety agencies and ministries, the European Food Safety Administration (EFSA) and the European Centre for Disease Control (ECDC). The project is co-financed by DG SANCO and participating countries.

The European Surveillance Scheme for Travel Associated Legionnaires' Disease

The European Surveillance Scheme for Travel Associated Legionnaires' Disease (EWGLINET) is one of the components of the European Working Group for Legionella Infections (EWGLI). EWGLINET is supported as a European Union Disease Specific Network (DSN) under Decision 2119/98/EC of the European Parliament and Council for setting up a network for the epidemiological surveillance and control of communicable diseases in the community.

European Surveillance of Sexually Transmitted Infections

European Surveillance of Sexually Transmitted Infections (ESSTI) is a network and a working collaboration between sexually transmitted infections (STI) surveillance heads and microbiologists of 22 EU member states and Iceland, Norway and Turkey. Established in 2001, the ESSTI network aims to improve collaboration between and within agencies, build capacity, and facilitate the dissemination of information on STIs to inform public health policy and planning across European Union partners. This project receives funding from DG SANCO.

BASIC Surveillance Network

The Basic Surveillance Network (BSN) is funded by the European Commission and administered by the Swedish Institute for Infectious Disease Control. The purpose of BSN is not to collect detailed information only on one disease, but rather to collect basic data on approximately 40 different diseases. The legal background to the BSN can also be found in Decision No 2119/98/EC. Basic data includes information on the reporting country, the date when the case was reported, age and sex of the case as well as a case identifier. On some diseases an additional data set can also be found, including information on country of infection, the origin of an implicated food source, mode of disease transmission and immunisation status.

Directorate General for Research[39] *– Framework Platforms 5, 6, 7*

The Directorate-General for research, through the fifth and sixth framework programmes, has committed over €20 million annually to activities that are related to antibiotics and antibiotic resistance focusing on numerous small projects in FP5, and fewer large projects in FP6. The FP6 portfolio consists primarily of genomics-based approaches to discovering new drug leads, alternative target medicines, developing diagnostic tests, as well as some translational research. The FP7 agenda is expected to continue basic research in the genomics approach, while building upon the research of FP6 through more science-to-innovation translational research; in short, developing tools, drugs, and procedures from the research conducted in FP6.

EU research: FP5

Starting with the 5th Framework Programme (1999-2002), research funding was primarily dedicated to building basic knowledge in a broad range of aspects of the antibiotic resistance problem in humans and animals. The projects focused on discovering new leads for antibiotic drugs and alternative treatments, development of diagnostic tests, mechanisms of resistance, intervention studies, and resistance epidemiology. Projects were small-to-medium sized, usually 1-2 million € for a period of 3 years with 4-8 participating laboratories. The total sum invested in FP5 amounted to approximately 100 million € distributed over 80 projects[40].

[39] The description of the activities in the Framework Programmes builds to a large extend on the presentation of the paper 'The European Commission's research policy on antibiotic resistance' presented at the STOA workshop at the European Parliament, Sept. 13th 2006, by Anna Lönnroth, Head of Sector for Emerging Infectious Diseases at the European Commission's Directorate General. The reference is Lönnroth, A., 2006. 'The European Commission's research policy on antibiotic resistance', *Background document for the STOA Workshop on Antibiotic Resistance, 13 September, 2006.* STOA-Panel, The European Parliament, pp. 63-66.

[40] Project descriptions are available at: http://www.cordis.lu/lifescihealth/major/drugs.htm.

EU research: FP6

The Sixth Framework Programme (2003-2006), was characterized by a focus on priority areas, genomics research in life sciences in particular, and the number of projects were reduced in exchange for fewer projects with broader objectives to be achieved through Networks of Excellence. One of the priority areas was antimicrobial drug resistance relevant to human health. Particular emphasis was placed on translational research to stimulate the flow from basic to applied research.

Translational research in FP6

One very recent initiative in the drug resistance project portfolio of FP6 is the GRACE network launched in early 2006. GRACE establishes a research platform for coordinated translational research ranging from microbial and human genomics, through clinical research down to health economics in an area that suffers from a huge lack of evidence for current medical practices, namely the management of lower respiratory tract infections (LRTI), where a large share of all antibiotic prescriptions are taking place. The network includes academic research centres, biotech firms, hospitals, European professional societies and primary care networks. This strategy is often called a vertical strategy, meaning one pathogen or group of pathogens is singled out for intervention on all fronts including research, medical practices, treatments, and education and training. A second project called MOSAR, will address drug resistance in hospital-acquired infections through an analogous approach, but where the emphasis instead lies in development and implementation of diagnostic tests into the clinical setting.

Research into new antimicrobial drugs in FP6

Considering that the FP6 research programme has a strong focus on genomics, basic research into the discovery of targets for new classes of antimicrobial drugs was therefore a component of the FP6 funding strategy. As an example of this approach, Eur-Intafar is an Integrated Project that aims to address unexplored enzymatic steps in the bacterial cell wall biosynthesis in order to identify novel potential targets. Bacterial genomics can also be used to capture naturally produced antibiotics by bacterial strains that have previously not been possible to culture in the laboratory. The ActinoGEN Integrated Project is an example of this approach.

Beyond, translational research or novel drug targets, most of the smaller-to-medium sized research projects of FP6, so called STREP projects, aim towards knowledge generation, while others have more specific objectives, in particular the so called SME-STREPs, where biotech companies play a prominent role. Projects in this area address basic molecular mechanisms of horizontal gene transfer (CORANIX, DRESP2), resistance to inhibitors of cell wall synthesis (COBRA), development of alternatives to antibacterial drugs (PNEUMOPEP, AMIS, NPARI), molecular ecology of specific resistant strains (PREVIS), evolutionary aspects of resistance and its possible reversibility (EAR, StaphDynamics, ACE), development of diagnostic tests (MagRSA, EACCAD) and control of anti-fungal resistance (EURESFUN, MANASP).

Towards FP7

At the time of writing, the Commission is preparing the Seventh Framework Programme (2007-2013). Antimicrobial drug resistance will continue to be a priority and many of the instruments launched in FP6 will continue to be used. More emphasis will be placed on translational research, building on models elaborated in FP6. The validation and implementation of diagnostic tests into the clinical setting is being prioritised for such a translational approach. Various priorities also include research into novel molecular targets for Gram-negative bacteria as well as a study to quantify the health and economic burden posed by antimicrobial drug resistance in different parts of the world.

The European Centre for Disease Prevention and Control

The European Centre for Disease Prevention and Control (ECDC) was established by the European Parliament and Council, as seen in Regulation 851/2004 of 21 April 2004, as an independent institution to identify, assess and communicate current and emerging threats to human health from communicable disease. Its budget is established by the EU parliament, and the it reports to a management board consisting of a representative form each member state, 2 members of the EU parliament, and 3 members of the European Commission.

The ECDC is organized in four units: Scientific Advice, Surveillance and Communication, Preparedness and Response and Administration. Across these units there are programs that encompass all units. At present these programs address influenza, HIV, vaccine issues and antimicrobial resistance (AMR).

Its primary aims with in the AMR sector are to coordinate, increase the knowledge base and establish international commitments on the following initiatives:

- Monitoring antibiotic usage, and resistance patterns,
- Decreasing the need for antibiotics via hindering the spread of bacteria
- Improving the prudent use of antibiotics by encouraging the use of diagnostics and proper prescribing behaviour
- Improving the non-medical use of antibiotics in the environment, foodstuffs, and animals.

At the current time, the ECDC works to accomplish these goals through its cooperation with member states, existing surveillance networks, the EFSA, and the WHO. As the scope of the ECDC continues to expand, it is expected that some of the above-mentioned networks such as EARSS and IPSE, may have more formal roles within the ECDC itself.

The European Food Safety Authority

The European Parliament established EFSA in 2002, following a series of food scares in the 1990s, which undermined consumer confidence in the safety of the food chain. It is an independent institution that reports to a management board selected by the European Council and consisting of 14 representatives of member states and one member of the European Commission. It is entirely funded by the European Community. EFSA's two main areas of work are risk assessment and communication. Its main activities in relation to containing antibiotic resistance include the investigating and reporting on the risks associated with using antibiotics in the production of food and livestock.

World Health Organization

At its annual assembly in 1998 the WHO passed a resolution on Antimicrobial Resistance and published its *Global Strategy for Containment of Antimicrobial Resistance* in 2001. A follow-up resolution in 2005, resolution WHA58.27, called for WHO members to step up their efforts in developing and implementing strategies to contain antibiotic resistance. In collaboration with the Swedish NGO Action on Antibiotic Resistance (ReAct), the WHO released a report in 2004 titled "Priority Medicines for Europe and the World", which included a chapter on the need for new medicines to treat resistant bacteria and highlighting the lack of drugs in the pipeline.

In the arena of surveillance, communication and training programs, the WHO has made the following worldwide initiatives in collaboration with member countries:

- WHONET 5, is a program developed by the WHO for managing data and analysis of antimicrobial susceptibility test results. It is now used by hundreds of laboratories worldwide.
- Educational tools for improving the use of antimicrobials and infection control.
- Drug and Therapeutic Committees, (DTC) have been promoted throughout the developing world through the development of an international training course and accompanying materials in collaboration with Management Sciences for Health (MSH).
- Operational research to develop standard methodology for surveillance of antimicrobial use and resistance and to identify effective interventions to promote rational antimicrobial use.
- WHO has worked with collaborative partners to identify effective interventions to promote the rational use of medicines in developing countries.
- WHO has in 2000 appointed a Collaborating Centre for Antimicrobial Resistance among food borne bacteria.
- Together with the Collaborating Centre and several other institutions the WHO has established Global Salm Surv with the overall aim to reduce the global burden of Food borne infections including antibiotic resistance.

NGO's

Action on Antibiotic Resistance

Action on Antibiotic Resistance (REACT) is non-profit organization founded and hosted by the Dag Hammarskjöld Foundation, the Swedish Strategic Programme for the Rational Use of Antimicrobial Agents (Strama), and the Division of International Health at Karolinska Institut (IHCAR). React was started in 2004 and is an independent global initiative consisting of a number of networks, institutions, and individuals including, some 60 people from 23 countries around the world. React works to address the problem of antibiotic resistance in three ways: 1) by communicating the need for urgent action to confront bacterial resistance, 2) by promoting concerted action to achieve the rational use of antibiotics and to contain antibacterial resistance, and 3) by promoting the development of new antibacterial agents and other technologies to ensure effective treatment of bacterial infections[41].

The members of React include practising physicians, microbiologists, health systems researchers, regulatory authorities, pharmaceutical industry and NGO's working on the subject. In 2005, React published a study built on interviews with experts on the likelihood of bringing innovative, affordable and appropriately used antibiotics to market in the face of growing resistance.

Alliance for the Prudent Use of Antibiotics

Since its founding in 1981, the Alliance for the Prudent Use of Antibiotics (APUA) has developed into an international network consisting of national chapters and health agencies, international agencies and trade associations, with the common aim to stop the development of antibiotic resistance.

[41] Action on Antibiotic Resistance (ReAct), 2005. *The Antibiotic Innovation Study: Expert Voices on a Critical Need*, Uppsala, Sweden, p.10.

Chapter 2 The state of research into new drugs

2.1 The antibiotic research and development pipeline is drying up

In order to outwit drug resistant bacteria, new narrow spectrum and gram-negative antibiotics with novel mechanisms of action are needed, in particular for acute hospital infections. And if further development of resistance is to be limited, use of these new drugs should be restricted to last resort (a list of the needs for research into new antibiotics can be seen in appendix 3). However, these needs are not being met.

Until the mid-seventies new antimicrobial drugs appeared with reasonable frequency, countering the problems of resistance in many pathogens. During the last 20 years this pipeline has dried out, however, with few new antibiotics being registered (only 5-10 new drugs currently listed for registration, with most of these being copy drugs) . The prospect of seeing the antibiotic pipeline refilling has been further dented by a pull-out by several large pharmaceutical corporations since 2000, as illustrated in box 5 below.

Box 5

The disengagement of large pharmaceutical companies from anti-infectives	
2000	Roche spins off its anti-infective division (creation of Basilea)
2002	Bristol Myers Squibb Company, Abbott laboratories, Eli Lilly and Company, and Wyeth all halt or substantially reduce their anti-infective discovery efforts
2004	Aventis spins off its anti-infective unit (creation of Novexel) Procter& Gamble and Bayer withdraw from antibiotic R&D

The reasons for the general loss of interest in antibiotic R&D are multiple. The chief ones among these are that science has become increasingly difficult and that antibiotics are not big money-makers, especially if their use is limited by resistance.

2.2 A great scientific challenge

It has become increasingly difficult to find new targets or new antibiotics for old targets. Whilst the development of genomics and use of large number of DNA-sequences have been seen as a promising approach they have not, to date, resulted in any significant new products. New discovery techniques, such as combinatorial chemistry or X-ray crystallography have not been very successful either at identifying new antibiotics and, although basic research is being carried out by academia, little of this is being translated into "druggable" drug leads. Overall the consensus is that there is a need for more early research to provide credible leads. New targets, or novel mechanisms of action against existing targets, are needed, if the problem of combating resistance is to be solved through the development of new drugs.

Some recent studies have suggested that all the targets in some bacteria species may have already been used, meaning that it is simply not possible to find new drugs that will not at the same time cause unacceptable secondary effects on the patients.

Are we at the end of antibiotic discovery? If that is the case, the only chance to fight antibiotic resistance in the future will be to assure that the 'potency' of current drugs is not eroded by overuse, although there is no guarantee that 'appropriate use' will be enough to stop the evolution towards resistance.

Some scientists, including companies interviewed as part of this project, still believe in a future of efficient discovery of antibiotics but new drugs or forms of treatments of higher complexity are needed. The simple notion "one-target - one-drug" is probably exhausted. This is particularly true as many pharmaceutical companies are no longer willing to invest expensive resources in developing novel antibiotic molecules that are not "extremely active", "extremely stable", and "extremely safe" (see section 2.3 below).

2.3 A shrinking antibiotic market

The antibiotic market is too small to stir R&D of new products and justify spiralling R&D costs, last estimated to be above $1 billion per new drug[42]. The problem has been further exacerbated by the consolidation of the pharmaceutical industry over the past decade, with ever larger firms chasing ever more profitable markets and focussing on cash cow areas such as chronic diseases. The antibiotic market, in contrast, has been increasingly tightened by health authorities pushing for a reduction in antibiotic use for resistance containment purposes. Resistance in itself has been an additional limit to profitability, as it reduces the efficacy, and hence the market value, of the drug over time. And even though drug resistant diseases are emerging, there are still enough treatments available that any new antibiotic has a very small market.

[42] Adams, C. and Brantner, V., 2006. 'Estimating the cost of new drug development: is it really $802m?', *Health Affairs*, Volume 25, No. 2, pp. 420–428.

This is especially true since many doctors only use new drugs as a last resort for fear of creating even more drug resistant bacteria.

As a result, many large pharmaceutical firms have withdrawn from the field of anti-infectives or substantially reduced their operations (see box 5 above). Still, a number of smaller biotechnology and pharmaceutical firms, which have a lower cost structure and hence a lower profitability bottom line than large pharma, remain interested in developing antibiotics,. But most have no history of successful drug development and face difficulties in finding interested large pharmaceutical partners to help with clinical development and regulatory approval, which require both experience and large financial resources. While some will be successful, the business model whereby smaller, less experienced firms are increasingly left with the responsibility of shouldering the entire antibiotic development pipeline, carries a high degree of risk which further reduces the prospect of seeing new antibiotics reach the market.

When market-driven antibiotic R&D occurs, the products developed very often fail to address the areas of highest public need. For instance, research into new drugs to control severe sepsis by Gram-negative agents, which address relatively tiny markets in terms of number of patients (most of them confined to hospitals), is virtually non-existent. Being by nature profit-maximizing entities, companies developing antibiotics tend to focus instead on broad spectrum agents and promote their use outside the hospital setting and across a wide range of indications (a strategy at odds with resistance containment measures). Last, the limited nature of the market also means that in order to maximise return on investment, firms tend to engage in lower cost/lower risk "adaptive" R&D, such as improving formulations or developing variations of existing antibiotics. Between 1998 and 2004, only 10 new antibiotics were approved by the FDA, and of these only 2 were truly novel[43].

The expert working group behind this project have not included policies on research into new antibiotics in their action plan. Research into new antibiotics and incentives for such research are subjects that have been discussed carefully and for the interested reader a list of possible research incentives for the pharmaceutical industry can be found in appendix 4.

2.4 Current and future research projects in antibiotic resistance under the European Commission

The 6th Framework Programme includes a number of important research projects to fight antibiotic resistance that can be summarised in three main groups.

[43] Infectious Disease Society of America (IDSA), 2004. *Bad Drugs, No Bugs. As Antibiotic Discovery Stagnates… A Public Health Crisis Brews.*

The first and more extensive group mostly includes projects focused on research in the **molecular bases of antibiotic resistance, in order to provide the bases for adopting appropriate strategies to reduce and or rationalise the use of antibiotics.** Bridging the gap between basic and applied science, a number of research objectives might be really important, among them those that are listed below:

- Evidence-based practice changes in antibiotic prescription and resistance (GRACE)
- Development of new diagnostic tests for community-acquired lower respiratory infections (GRACE)
- Genetic differences in host-susceptibility in bacterial-virulence and epidemicity in respiratory tract infections (GRACE)
- Molecular mechanisms of resistance to beta-lactam antibiotics, and particularly genetics of beta-lactamases (COBRA)
- Molecular epidemiology of antibiotic resistance: characterization of multiresistant clones (COBRA)
- Structural bases for the discovery of new agents active on bacterial cell wall or inhibitors of beta-lactamases (COBRA)
- Molecular bases for the spread of particular clones of respiratory pathogenic bacteria, particularly in long-term care facilities (PREVIS)
- How ecological factors influence antibiotic resistance (EAR)
- Reversibility of antibiotic resistance in the absence of antibiotic use and selection (EAR)
- Possibility of designing antibiotics that will not develop resistance (EAR)
- Factors influencing the spread of genes involved in resistance of Gram-negative bacteria (CORANIX)
- Genetic elements mobilizing antibiotic resistance genes: looking at the environment (metagenomics) as a source of tools for antibiotic resistance (DRESP2)
- Molecular bases of staphylococcal virulence, resistance, and dissemination (STAPHDYNAMICS)
- Molecular bases of resistance to antifungal agents (EURESFUN)
- Alternative immunotherapy in deep fungal infections (MANASP)
- Rapid diagnostic tests for detecting resistant staphylococci (MagRSA)
- Development of new point-of-care diagnostic tests to combat *Clostridium difficile* diarrhoea (EACCAD)
- Audit registration research to evaluate rapid diagnostic tools in respiratory tract infections, and its influence on antibiotic prescribing (HAPPY AUDIT)

- Changing behaviour of health care professionals and the general public towards a more prudent use of anti-microbial agents (CHAMP)

The second group of research projects is more focused on **epidemiology of resistant microbes**, and a number of its research objectives are:

- How to dimensionate, control and prevent spread of resistant organisms generated or selected in the hospital to the surrounding community compartment (MOSAR)
- How to control the spread of dangerous multi-resistant clones of the genus *Enterococcus*, with emphasis in normal flora as a reservoir (ACE)
- Surveillance of antiviral drug resistance (VIRGIL)

The third group of research projects deal with **new ways of treating infections**. A number of its research objectives are:

- New antimicrobials based on "natural antibiotics" of the innate immune system of humans (AMIS) (NPARI)
- Novel vaccination strategies for encapsulated bacteria (REBAVAC)
- New targets in the bacterial cell envelope for new antibiotics (EUR-INTAFAR)
- Genomic tools in exploring natural antibiotic producing fungi, able to produce novel antibiotic candidates (AntinoGEN)
- New peptides directed against virulence determinants in *S. pneumoniae* (PNEUMOPEP)

Among the preliminary topics that are being explored for suggesting priorities in the **next EU Work Programme (FP7)**, and only as an indication of the type of research that might have implications for combating antibiotic-resistance, the following should be mentioned:

Projects related with ameliorating the ability of pharmaceutical companies to develop new drugs less expensively and with higher efficiency:

- Alternative testing strategies for pharmaceutical discovery
- Safety without animal testing
- Quantitative structure-activity relationship for toxicology
- Alternative testing strategies for nanoparticle-based diagnostics
- In-silico simulation models for pharma compounds
- Novel targets for drugs acting on Gram-negative bacteria

Projects dealing with the complexity of host-bacteria interactions:

- Preparing for future challenges in Systems Biology
- Host-pathogen interactions

Projects specifically directed to antibiotic resistance:

- Epidemiology of multi-drug-resistant pathogens
- Point-of-care diagnostic devices for microbial detection and antibiotic susceptibility testing
- Health and economic cost of antibiotic-resistance

The major achievements obtained during the 6th Framework Programme should constitute stepping stones to design new projects and applications to fight against antibiotic resistance.

2.5 Synergy between research strategies

The optimum research strategy on containing antibiotic resistance contains a set of strategies that involve research focused on containment of antibiotic resistance and research focused on innovative tools in therapy and prevention of infections caused by resistant bacteria.

Research on containment strategies to prevent further increases in antibiotic resistance has been prioritised in this report because we need *urgent measures* to counteract the rise of antibiotic resistance before it reaches a critical level that compromises the patients. It is important to note that in these years we are faced with a dangerous spread of novel resistances that affect all known antibiotics, including glycopeptides, third-generation cephalosporins, fluoroquinolones, or carbapenems. The maintenance of current protocols in haematology, cancer, intensive care units, advanced surgery, or transplantation depends on the *preservation of currently acceptable levels* of antibiotic susceptibility. Additionally, without an effective resistance containment strategy in place by the time newly developed antibacterials reach the market, their lasting ability to treat infections, and hence their health impact, will be greatly diminished. So in order to address today's pressing needs most effectively and establish a solid base for tomorrow, the working group recommends that the EU invest additional resources in containment strategies as a matter of urgency before considering expanding its support to research into new innovative drugs. The policy options suggested in this report will therefore focus on the former, rather than the latter.

The working group recognises that containment strategies are not expected to *solve* the problem of antibiotic resistance. Containment is a strategy that should assure that the problems of antibiotic resistance remain manageable until they can hopefully be counteracted with strategies directed particularly at the resistance mechanism. Such strategies could be the result of long-term research programmes focused on new antibiotics drugs, eventually unable to develop resistance, or antimicrobials or vaccines acting only on *resistant* organisms, for instance on particular widespread clones, that is selecting for susceptibility. Research could also include the development of "eco-drugs", not necessarily acting (inhibiting) bacteria, but just given to patients to impede the building-up of the resistance mechanisms associated with antibiotic resistance, for instance, anti-integrases, or anti-plasmid replication or transfer drugs.

Though, a huge amount of research is needed to develop these concepts, but today the world does not have time to wait for these solutions. Moreover, in the best of the future worlds, appropriate and well-validated containment measures will still be needed, because the ability of the microbial world to counteract any human initiative will go on in any case.

Chapter 3 An action plan

3.1 Introduction

The speed at which levels of antibiotic resistance are rising has long surpassed the speed at which new drugs are appearing. There is now an urgent need to contain the problems of antibiotic resistance. There are three main options for containing antibiotic resistance. The first is to reduce the use of antibiotics and the second is to reduce transmission of resistant bacteria. The third option for dealing with resistance is to develop new, alternative antibiotics.

Within the first option it is possible to consider policies to reduce the selective pressure of antibiotics by reducing their overall use. Such policies include: to reduce inappropriate use of antibiotics, to alter dosages, to develop and improve the use of rapid diagnostics, to improve use of vaccination, to improve rules and regulations, to improve education and awareness. The second option concerns reducing the spread or transmission of resistant bacteria, incorporating infection control both in and outside of hospitals. The third option is to try to increase the development of new antimicrobials. There are a number of reasons why the pharmaceutical industry may not be interested in targeting the antibiotic market as described in chapter 2.

A number of previous documents contain comprehensive lists of recommendations in all these areas and these are not duplicated here. This working group has taken as its point of departure that an action plan should be based on a realistic number of clear, targeted options for action and research, over and above what is already being achieved in the area of the containment of antibiotic resistance. These options therefore necessarily assume that additional resources will be targeted towards resistance.

The options have been chosen on the basis of four criteria:

Focused on what the European Union can do

The policy options developed here are based on the premise that antibiotic resistance is not an isolated European problem, but a global problem. Nevertheless, the options focus on what can most efficiently be influenced by the EU, either directly or indirectly, although the effects would be expected to be felt at a number of levels, including at local level within the EU as well as globally. Policies which operate ***primarily*** at country or local (for example hospital) levels are not included here because the EU can most effectively help in the fight to contain resistance by the conduct of activities at the European level where it has greatest power and influence. At the EU level, there is clear potential for policies in four areas: co-ordination; standardisation; stimulation and research, and the policies described below are classified according to these headings.

Avoiding repetition

The policy options attempt to build on and extend current work already being done by the EU, WHO and others. There is little point in ignoring the many good initiatives already taking place, and none in setting up competing structures. What is important is to ensure the sustainability of many of these initiatives, and that what is learnt from these initiatives goes on to inform future work in this area.

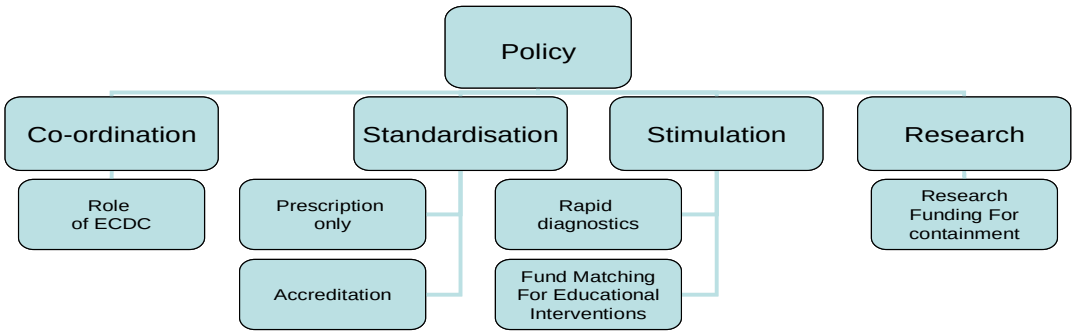
Likely benefits must exceed likely costs

The anticipated benefits of the policy options must exceed the anticipated costs, where costs do not include just financial costs, but also the costs of human suffering. A number of policy options have been rejected by the working group on the grounds that the costs that would be imposed by these policies could not, currently, be justified by the expected benefits even given the potentially catastrophic implications of antimicrobial resistance. Such policies included restrictions on extensive international travel – which would reduce the likelihood of transmission of resistant bacteria, but would also have heavy economic and personal costs. They also included restrictions on the trade in animals which again was not seen as feasible due to the large costs that would be imposed, despite their potential benefits in terms of reducing the potential dangers of resistance.

Focused on both current and future strategies

Finally, the aim here has been to provide some policy options to fight antibiotic resistance, whilst at the same time being mindful of the poverty of the evidence base upon which to make such options. There is little understanding, for example, of the determinants of antimicrobial usage in different cultures and contexts, little knowledge about which clinical interventions are likely to produce the most gain at lowest cost, and almost no research into policy stratagems that may be valuable in containing resistance. The recommendations therefore seek a balance between active current options and the urgent need for research so that future options and recommendations can be more effectively targeted. There are a number of potentially promising strategies for which the evidence base is not sufficiently strong to recommend their use currently, but which are recommended here via the vehicle of research.

Following extensive discussion among the working group members and with those participating in the external workshop, a total of six policy options are made here. Figure 5 below shows a schematic representation of the policy options made by the working group.



Funding the development of new antibiotic drugs

It should be noted here that the option for additional resources to be targeted at the development of new drugs does not appear within these six options and it is felt that some justification of this decision may be required. Although an obvious possibility for dealing with the resistance problem is to develop new antimicrobials which could, in theory, effectively remove the resistance problem, the working group thinks that at present it will solve no problem to suggest that additional resources should be prioritised for research into new drugs at the expense of other options. The reasons for that are stated below.

First, although many classes of antimicrobial agents have been reported since protosil was discovered in 1928, recent developments have tended to result from modification of existing compounds rather than the development of new classes of antimicrobials. The last twenty years of research have provided very few insights into novel families of drugs, and indeed there is concern among many commentators that there may not be new antimicrobials to be discovered. To maximise the chances of finding new drugs, new research strategies will be required. Although some such strategies are already technically available, even if they were implemented today, it would still be 10 to 15 years before new drugs arrive onto the market. In the simplest terms, the uncertain development of such novel drugs cannot be relied upon to counteract the threat of antibiotic resistance.

Second, currently, there are few bacterial multiresistant organisms that cannot be treated at all with any of the available compounds. The efficacy of these compounds needs to be guaranteed by ensuring better early diagnosis and better targeting of antimicrobials. Again, the objective of the action plan provided here is to maintain the efficacy of the currently available antimicrobial agents into the future.

Third, and most importantly, however, developing new antimicrobials without an effective containment strategy will delay the problems associated with resistance by only a short time frame. The development of new antimicrobials at this time, and without the existence of an effective containment strategy will result almost immediately in the squandering of this new resource. The absolute requirement is therefore for effective containment strategies to protect the antibiotics we currently have and those that are developed in the future.

It is also noted that the EU already supports efforts in the search for new antimicrobials through the FP6 and FP7 research programmes. Although putting even more resources into drug development could yield benefits, the uncertainty associated with such development and the potentially large costs involved, have led this working group to avoid this as a recommendation, believing that EU resources could be better targeted elsewhere both in relation to policy and research. In consequence, development of new drugs does not appear as a priority in the policy options described below.

As part of the work process of the working group, a range of incentives to encourage the pharmaceutical industry to develop new antibiotics were originally explored, and a small sample of companies consulted. For the interested reader, a summary of this work and ensuing (deprioritized) recommendations can be found in appendix 4.

3.2 Action plan

Policy option 1 (coordination): Increase the role and scope of the ECDC in co-ordinating European strategy with respect to antimicrobial resistance

Problem

Antimicrobial resistance is a complex and multi-faceted problem and its containment requires complex and multi-faceted approaches. Many different agencies both within the EU and outside develop policies which are either intended to contain resistance or which indirectly impact on resistance: an example from another agency which was provided during this work was that of the maternal and child health section promoting antimicrobial use whilst at the same time the arm of that agency concerned with resistance was advocating that antimicrobials should not be used. During the writing of this report there was no single place to turn to, to find out about the legislation and initiatives already promoted through the EU and, indeed, the very existence of this working group on behalf of STOA did not clearly link into any of the existing European networks.

Recently, the ECDC has been given an important co-ordinating function for the EU in its response to the problems of containing antimicrobial resistance. Its role is to coordinate concerted actions within the Community, to initiate technical activities and to give technical support to EU Member States in implementing the recommendations of Council. It potentially has a vital role in coordinating the existing surveillance networks (for both antibiotic resistance and antibiotic consumption) and ensuring that the data obtained via these networks can be harmonised and communicated rapidly, particularly where important emerging strains of bacteria are identified. It also has an important coordinating role in initiating meetings between National Coordinating Groups, and improving collaboration of the human side of resistance with veterinary and food safety colleagues concerned about use of antimicrobials. This coordinating role has become particularly important in view of the dwindling level of global coordination in this area provided by WHO.

Policy option

To further strengthen the coordinating role of the ECDC on behalf of the EU. Specifically:

- ***to develop a portal*** through which all EU policy and legislative documents relating to antimicrobial resistance can be obtained and which links to the European Region of WHO;
- ***to develop a database*** of all national and European initiatives with regard to antimicrobial resistance, including both policy initiatives and research projects. This could be achieved by asking all project co-ordinators to complete a structured summary of their programmes incorporating aspects such as objective, methods, outcome measures, budget, funding organisation, contact details and so on;
- ***to co-ordinate an annual "European Antibiotic Resistance Day"*** designed to increase awareness of this issue as a global health problem. This Day could include specific targeted actions each year, be used to release new data and information, be used as the start date of public campaigns, and be used to highlight advances in prevention, diagnosis and treatment. It is expected that the Day would be supported by a number of European research groups and organisations, including ESCMID, GRACE, MOSAR, ESAC, EUBug project and BURDEN. It is anticipated that such a Day would be held in the autumn, prior to the period of the heaviest consumption of antibiotics for minor self-limiting illness.
- ***to enable the ECDC to coordinate annual meetings with national authorities***, including liaison with veterinary and food safety colleagues at EU level;
- ***to further enable the ECDC to liaise with the WHO*** with regard to policy on antimicrobial resistance;
- ***to further enable the ECDC to service and support the Member States***, particularly in relation to policy options 2, 3, 4 and 5 below.

Main stakeholders

European and global agencies with a role in containing resistance; EU funded surveillance networks; European Parliament.

Level at which option operates

EU.

Potential obstacles

The possibility that existing groups and networks will be reluctant to relinquish their power in this area to a single coordinating authority.

Likely outcome/benefit

There are many individual attempts to contain resistance. With better coordination and understanding of the strategies being undertaken, there is potential for avoidance of similar agencies trying to achieve the same ends by possibly conflicting means, the possibility of better targeting of policies towards clear gaps in provision and the potential to learn from best practice.

Likely costs

The ECDC already receives funding to coordinate antimicrobial resistance policy. It is suggested here that a modest increase in funding could enable ECDC to undertake these additional activities and thus achieve substantial benefits.

Policy option 2 (standardisation): Further encouragement of 'prescription only' policies within Member States

Problem

Despite good work by the EU in providing for Member States to use 'prescription only' for both humans and animals, there are still problems associated with the enforcement of these 'prescription only' policies.

Humans: The recent *Report from the Commission to the Council – On the basis of member states' reports on the implementation of the Council Recommendation (2002/77/EC) on the Prudent Use of Antimicrobial Agents in Human Medicine* indicates that selling antimicrobial agents without a prescription is still considered a source of inappropriate human antimicrobial use in at least seven countries in the EU[44]. Further the EU funded Self medication and Antimicrobial Resistance (SAR) research project shows that self-medication with antimicrobials is a problem all over Europe[45] as do a number of other studies across Europe[46]. This is despite the *Council Recommendation (2002/77/EC) on the Prudent Use of Antimicrobial Agents in Human Medicine and the Community pharmaceutical legislation on medicinal products for human use*[47] which provides for individual countries to have in place measures to enforce regulations for prescription only use of systemic antimicrobial agents. The lack of impact of these measures suggests that further encouragement of Member States, possibly using particular incentive and disincentive mechanisms, would be appropriate.

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[44] European Commission, 2005. Report from the Commission to the Council – On the basis of member states' reports on the implementation of the Council Recommendation (2002/77/EC) on the Prudent Use of Antimicrobial Agents in Human Medicine, Brussels, 22 December 2005, COM (2005) 0684.

[45] Ibid.

[46] Strategic Council on Resistance in Europe, 2004.

[47] European Union, 2004(a). *Directive 2001/83/EC as amended by Directive 2004/27/EC.*

Animals: There are wide variations in how antimicrobials are obtained and used for animals although an EU directive will ensure that by the end of 2006 all antimicrobials for food-producing animals will be prescription only[48]. Currently, dispensing may require a prescription, but equally there are vets employed by pharmaceutical companies who may have little incentive not to prescribe, and systems where farmers are effectively able to dispense their own medicines. In addition, many veterinarians make a profit out of selling the antibiotics they are prescribing. The monitoring of a prescription only system is here vital in ensuring that antimicrobials are not misused. Further, the EU may also want to take into account antimicrobials used in non-food producing animals.

Policy option

Humans: to further encourage the use of 'prescription only' across all Member States of the EU and to explore the use of policies that will encourage member country governments to enforce prescription only rules – one possibility might, for example, be to provide monetary disincentives for governments in countries where more than a certain percentage of antimicrobials are dispensed without prescription. Such exploration might also form a part of policy option 6 (research).

Animals: To develop monitoring systems and encourage enforcement of the current Directives in relation to food producing animals; and to encourage the development of a prescription only system for all other animals.

Main stakeholders

Doctors, patients, pharmacists, vets, farmers, pet-owners, pharmaceutical companies and any others who profit from dispensing antimicrobials.

Level at which option operates

Encouragement from EU level, but with monitoring and enforcement at local and national levels.

[48] European Union, 2004(b). *Directive 2001/82/EG as amended by Directive 2004/28/EG*.

Potential obstacles

1. To alter current national systems where 'prescription only' is not in operation such that all antibiotics medications can only be obtained via prescription is likely to be a large problem in some countries and much less problematic in others.
2. There may be countries for whom the cost and practicalities of developing a prescription only system may be prohibitive given current levels of organisation and national income levels. These countries will need to be assisted.
3. To obtain data on the proportion of drugs that are dispensed without prescription for the purposes of monitoring is difficult.
4. There is a need for putting in place the required legislative framework for ensuring compliance if incentive or disincentive mechanisms are considered appropriate following exploration by the Commission.
5. It is a challenge to avoid possible consequences of a prescription only system such as the potential for a black market to develop (in which antimicrobials are shipped and sold by their chemical name rather than as medicines, or the internet is used to illegally obtain antimicrobials). To date, such a possibility does not seem large.

Likely outcome/benefit

There is clear evidence from a number of studies that restricting use of antimicrobials reduces the rise of resistance and, in for some resistances but not all, a decline in resistance can result where restrictions on antibiotic use are put in place[49]. There is also some evidence that having a prescription only system reduces inappropriate use of antimicrobials. One study, for example, suggested that reducing restrictions on antimicrobials (as opposed to increasing restrictions as recommended here) for Urinary Tract Infection and placing these treatments on an over-the-counter basis, would result in an overall increase in resistance because of the likelihood of incorrect self-diagnosis[50]. Further encouragement by the EU to increase the proportion of antibiotics across Europe that is dispensed via prescription could be expected to reduce further inappropriate use of antibiotics and thus reduce further rises in resistance.

[49] Strategic Council on Resistance in Europe, 2004.

[50] Ruben N. and Foxman, B., 1996. 'The cost-effectiveness of placing urinary tract infection treatment over the counter', *Journal of Clinical Epidemiology*, Volume 49, pp. 1315-1321.

Likely costs

Costs to some health services in achieving system change; costs to some agricultural/veterinary services in achieving system change; costs to EU/national governments in terms of monitoring; potential costs of pain and suffering for patients no longer receiving treatment; additional costs to patients, doctors and vets, in terms of time required for obtaining prescriptions.

Policy option 3 (standardisation): Europe-wide accreditation programme

Problem

The direct, indirect, and airborne spread of bacteria is necessary to limit the spread of infection. Three factors have demonstrated a close link with the spread of bacteria and infection: hygiene, the proximity of occupants in a room or building, and ventilation. Though these factors affect any and every human environment, the places where they become most problematic are places where there is a high concentration of people who are generally more susceptible to infection. In particular, these factors affect the hospital environment, day care for young children (nurseries, kindergartens, pre-school), and residential homes for older people. The *Council Recommendation (2002/77/EC) on the Prudent Use of Antimicrobial Agents in Human Medicine and the Community pharmaceutical legislation on medicinal products for human use*[51] provides for Member States to implement hygiene and infection control standards in such organisations, but only in fourteen Member States are there accreditation procedures in place for hospitals, with even fewer for nursing homes[52].

Hospitals: It has been known for decades that the spread of antimicrobial resistant bacteria within hospitals is a major problem for human health. Hospitals harbour excellent conditions for creating major health problems – a large use of antimicrobials, including the newest and most broad spectrum, vectors (nurses and doctors) transmitting resistant bacteria between patients and a large susceptible population of patients with impaired immunity. Much knowledge has been generated in this area and it is generally accepted that one of the most important interventions is to improve hygiene. This has however, been extremely difficult to achieve as evidenced by the transmission of MRSA.

Day care for young children: Young children are unsurprisingly among those citizens who receive the highest number of antibiotic treatments. Young children enrolled in day-care centres have been shown to have a greater occurrence of bacterial illnesses (i.e. ear, eye, and throat infections) than those cared for at home. Poor hygiene, both among day-care workers and children, mean that these institutions can be a source of rapid dissemination of bacteria.

[51] European Union, 2004(a).

[52] European Commission, 2005.

Studies in the Copenhagen area have shown significant gains from hand washing by children and employees[53]. A further variable that has shown a negative correlation with the spread of bacteria in day care centres is the space in terms of square metres per child. In Denmark, one intervention study showed that an 11% drop in the occurrence of illness was gained for every additional square metre per child, and other studies have shown that the amount of time spent out of doors influences the extent of transmission of infection.

Residential homes for older people: Similar problems can also be seen in residential homes for older people as, again, people with greater susceptibility to illness are concentrated in a limited space. Even where occupants have their own room or small apartment, care workers going from one location to another to distribute food, medicine and care, can spread illness. Again, hygiene is a problem, particularly because employees may not be highly educated but instead have undergone only short-term training programmes without a stringent focus on hygiene and sterilization techniques. There are, however, two issues that distinguish residential homes for older people. First, illnesses tend more often to be viral than bacterial, particularly norovirus and influenza, which contribute to a lowering of the immune system and an increased susceptibility to infection. Second, residents may be in and out of hospitals to receive treatment, thereby acting as carriers of multi-resistant bacteria that are typically only found in the hospital environment, for example, MRSA and Community Acquired Pneumonia.

Policy option

One strategy to address these problems is to develop a voluntary accreditation programme which incorporates and co-develops European and international standards for hygiene, health and day-care, and building standards. Such a voluntary programme would be akin to the notion of "Baby friendly hospitals" or the UK's "Investors in People" scheme with no compulsion for institutions to take part, but with the award of accreditation being seen as a positive step by the institution, creating for them a competitive advantage. The creation of European and international standards will have two particular advantages over leaving the creation of such standards to Member States. First, it enables clarification and standardisation of best practice across the EU; second, and perhaps more importantly, it enables institutions in countries without their own accreditation programmes to be able to pursue such standards as part of the competitive dynamic, thus reducing transmission of infection.

To create a competitive dynamic in the accreditation programmes, there would be both basic level accreditation and higher levels of accreditation so that institutions that improve their results on various factors can improve their accreditation ranking in a manner that that would be observable to stakeholders.

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[53] Collet, J.P. et al. 1994. 'Risk of infectious diseases in children attending different types of day-care setting', Epicreche Research Group, *Respiration,* Volume 61, Suppl. 1, pp. 16-9.
Louhiala, P.J. et al. 1995. 'Form of day care and respiratory infections among Finnish children', *American Journal of Public Health,* Volume 85, pp. 1109-12.

Through constant improvement and upgrading of the standards, these programmes will contribute to the gradual, but steady, improvement of institutions with regard to control of infection, without leaving institutions in less economically well-off countries without the possibility of obtaining any form of accreditation.

Programmes would include provisions for

- personal hygiene;
- hygiene regarding objects such as medical instruments, toys, serving trays, and so on;
- an increase in the amount of space per person in these institutions;
- improved ventilation and air exchange.

To ensure effectiveness, institutions that choose to take part in the accreditation scheme will require adherence enforced through monitoring, regular evaluation, and reporting or ranking of institutions. The programmes, though similar in their basic premise, will need to be tailored to their specific areas:

Hospitals: In the European Union, EU legislative harmonization could, in cooperation with the European Centre for Standardization, develop frameworks for each of the three types of institutions. Long-term aims could include coordination with the International Standards Organisation (ISO) ISO 9000, and IWA 1:2005 standards, as well as the Joint Commission for accrediting health care institutions.

Day care for young children: A number of countries have already developed national accreditation programmes for day-care centres. These programmes, however, are generally concerned with the curricula and activities for the children rather than hygiene and cleanliness. Accreditation programmes here would be concerned with hygiene of workers, premises, toys and objects, and children. The programme could potentially also be concerned with building and ventilation standards and space per child (minimum 3 m^2 per child, while 8-10 m^2 per child is optimal).

Residential homes for older people: Here it would be important for shared spaces such as cafeterias and common rooms to reach standards of air exchange and personal space, as well as requirements for hygiene and attendance at hygiene and sterilization courses for employees.

Main Stakeholders

Doctors, health care professionals, employees working in day care centres for young children and residential homes for older people, owners of day care centres for young children and residential homes for older people, patients, older people and children.

Level at which option operates

The development and harmonization of standards would be conducted at the EU and international levels, whilst the accreditation programmes themselves would operate at the national and institutional level. At the EU level, the EU parliament would work to harmonize legislation for health care standards and building codes in coordination with the European Committee for Standardization (CEN) whilst CEN and ISO could further develop provisions for international standards. It is envisaged that the work of administering the accreditation programmes would either be carried out by the national standards institute, the ministry of health, or by a private accreditation institute (c.f. the Joint Committee).

Potential Obstacles

1. The implementation of standards such as ISO or CEN in general takes around three to five years and requires the agreement of a variety of stakeholders. Without immediate action, the adoption and harmonization of standards may be a lengthy process.
2. Achieving adherence to the standards of the accreditation programmes may be difficult. Research may be required into the best methods for achieving internalisation of these standards within institutions.
3. Stricter standards on space and mechanical ventilation may pose economic obstacles to many institutions and some costs are likely to be faced by private individuals.

Likely Outcome / Benefit

Improving hygiene and building space have been shown to be beneficial in research studies. Thorough hygiene and sterilization programmes in hospitals, day care centres for young children, and residential homes for older people have all been shown to reduce the transmission of infection by up to 40-50% [54]. This can significantly reduce the number of sick days for these populations. In many cases, the employment of a hygiene specialist in a hospital wing or care centre has been proven to more than pay for itself in the reduction in costs associated with infection. More space per child has been shown in one study to provide a reduction in the number of sick days per child of 11% per additional square metres[55]. This in turn would result in less health care spending and prescription of antimicrobials for children.

The competitive element of an accreditation programme would both provide an incentive for these institutions to meet the relevant hygiene standards, and ultimately will help to generate consumer demand for a higher quality of service, thus spreading the benefits of the programmes via market mechanisms, as opposed to the implementation of regulations.

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[54] Kotch, J.B. et al. 1994. 'Evaluation of an hygienic intervention in child day-care centers', *Pediatrics*, Volume 94, No. 6, pp. 991-994.

[55] Uldall, P., 1990. 'Pasningsformer og børns infektioner. 1. Forekomst og årsagsfaktorer', *Ugeskrift for Læger*, Volume 152, pp. 2345-2348.

Likely costs

Initial costs to the EU would include the development, harmonization and implementation of new standards, and the development of coherent accreditation programmes for the three types of institution. In taking part in the accreditation programmes, institutions are likely to face additional costs which may include elements such as additional training programmes, or the employment of a hygiene supervisor. Higher amounts of space per person and ventilation systems may represent high costs in renovations or in the construction of larger and technically advanced buildings.

Policy option 4 (stimulation): Encourage use of rapid diagnostics

Problem

For most common infections such as otitis media, sinusitis, tonsillitis and others it is impossible for the physician to tell whether the aetiology is viral with no antibiotic needed (most infections) or bacterial, where antibiotics may have an effect. For many of these illnesses it has been possible to test in the long-term but, practically, treatment has been required before the results of the tests have been available. Doctors have therefore often prescribed antibiotics just in case the infection is bacterial.

Now, for many of these illnesses, rapid diagnostic tests are starting to become available. These tests are extremely important, as they can be used to determine the aetiology of the infection while the patient is waiting in the clinic and thus the decision about whether to prescribe antibiotics or not can be made based upon the appropriate evidence. Currently a small number of these tests are available for use in general practice, for example, the streptococcal antigen test, which detects haemolytic group A streptococci (the most important bacterial aetiology for tonsillitis) from a throat swab in 10 minutes and which, when used, can reduce antibiotic treatment by up to 70% by targeting penicillin at only those patients who can benefit from it. Other tests remain to be developed for use in this context. For example, it may be possible to detect the bacterial aetiology of otitis media, especially *Streptococcus pneumoniae*, which is the main and most virulent bacterial aetiology in upper – (and lower) respiratory tract infections. When causing infection the remnants of these bacteria can be found in the urine of patients, and the so-called pneumococcal urinary antigen test is already used as a diagnostic aid for pneumonia in hospitals. Further development of the test might also make it useful for use in general practice and further development of the method might enable the development of tests for several other respiratory tract pathogens such as Chlamydia, mycoplasma and so on.

The development of rapid diagnostic tests is promising, but there is a problem in that the market is failing to provide sufficient incentive for the development and use of these tests. The financial cost of the test is greater than the financial cost of empirical treatment with antibiotics and, of course, individual hospitals, doctors and patients do not have to account for the societal cost imposed by their use of antibiotics, meaning that use of antibiotics (empirically) appears to be the least costly policy option.

Policy option

The EU should explore the possibility of providing incentives to Member States to develop reimbursement systems that encourage the use of rapid diagnostic tests in general practice. These incentives could be via directive or by direct subsidisation, for example in countries with lower national incomes. It is probable that this exploration will require some preparatory research in the following areas:

- To determine obstacles facing health care systems in terms of reimbursing these tests (including social, ethical, environmental, economic and political factors);
- To define a strategy for integrating rapid diagnostic tests into health care systems;
- To ensure that reimbursed diagnostic tests have been subject to proper evaluation in well-designed clinical studies.

It is not suggested that the EU directly attempt to work with companies developing diagnostic tests, because if the market failure is dealt with, the incentive to develop and market affordable tests will exist.

Main stakeholders

Doctors, patients, hospitals, national governments, companies developing and producing diagnostic tests.

Level at which option operates

EU and national level.

Possible obstacles to solutions

1. Possible lack of influence of the EU over Member States in being able to provide strong incentives;
2. Cost of direct subsidisation.

Likely outcome/benefits

The effect of rapid diagnostic tests on antibiotic consumption has been shown in practice. Further, subsidisation of rapid diagnostic testing has been shown to increase the use of these tests in Denmark. Whilst different methods of subsidisation might be explored by the EU, the success in Denmark does suggest that the use of incentives can be an efficient way to contain resistance, whilst also improving the quality of prescribing.

Likely costs (including evaluation, follow up, monitoring)

The major costs will be in the increased use of rapid diagnostic tests, which will be offset to some extent, but not completely, by reduced costs associated with prescription of antibiotics. Costs of subsidising the tests will either be borne by the EU or by national governments.

Policy option 5 (stimulation): Fund-matching scheme for educational campaigns

Problem

The recent *Report from the Commission to the Council – On the Basis of member states' reports on the implementation of the Council Recommendation (2002/77/EC) on the Prudent Use of Antimicrobial Agents in Human Medicine* indicates that there has been some success in encouraging educational campaigns by member states[56]. All but six countries have conducted some form of campaign in the five years up to 2005, but these have most often addressed health professionals[57]. Neglected groups have been pharmacists (who may be particularly important where antibiotics are bought directly over the counter) and the general public. (It is also noted that many campaigns have been sponsored by the pharmaceutical industry which may not be appropriate given the potentially conflicting interests of these stakeholders.) Indeed, the main neglected target group with regard to containing resistance is the consumer – of health care and veterinary products. This is an expensive group to target, but campaigns addressing the public are key in at least three ways.

First, there is the suggestion that it is the demands of patients for antimicrobials that result in their over-prescription for minor self-limiting conditions and for infections with a viral rather than bacterial cause, leading to increases in resistance and the development of new resistances. Second, where antimicrobials are sold over the counter, patients and the public are directly responsible for the inappropriate use of antimicrobials. Even where health professionals prescribe, there is evidence that doctors over-prescribe antimicrobials because of patient demand, particularly for minor self-limiting conditions and for infections with a viral rather than bacterial cause, leading to increases in resistance and the development of new resistances. Third, there continues to be potential for educational campaigns for the public concentrating on issues of hygiene and transmission given that reducing transmission of resistant infection is likely to be important in the fight against resistance.

Ultimately, as with the environment, there is a need to create a paradigm shift in which antibiotics are understood to be much more valuable than is currently the case, thus leading to behaviour change. It may be particularly important to bear in mind that different groups will perceive the risks associated with resistance differently and that this will bear on their actions.

[56] European Commission, 2005.
[57] Ibid.

Policy option

To initiate the development of a matched funding policy, whereby the EU provides some matched proportion of the funding for national educational campaigns, with this matching determined in part by:

- the national income of the member country applying for funding (on grounds of equity);
- the current extent of resistance (with greater resistance problems attracting a greater degree of funding). Although such a policy might "give out the wrong message" it would also enable funds to be targeted to areas where they will have greatest effect;
- the quality of the planned campaign (judged in a similar manner to research proposals, but concerned with clarity of objectives, clarity of methods, anticipated outcomes, adequacy of budget and so on).

Such an initiative could also be expected to have the side-effect of enabling best practice in educational campaigns to be shared and disseminated through this source of funding. Although research evidence suggests that such campaigns are effective (see below), there are many detailed questions which remain to be researched and which could in part be answered alongside this initiative. These detailed questions might include, for example: which groups of people are most effectively targeted? How often do campaigns need to be repeated to retain effectiveness? Which forms of campaign are most cost-effective?

Campaigns should be encouraged to be focused towards the particular culture and context for which they are intended (and again, evidence about the effectiveness and cost-effectiveness of different types of campaign for different cultures and contexts could be a valuable by-product of this initiative). Innovative use of different media should also be explored and encouraged, as for example with recent UK campaigns that have targeted women's magazines and the primary school curriculum.

Main stakeholders

Patients, public, pharmacists, national governments, doctors and other health professionals.

Level at which option operates

EU.

Potential obstacles

1. Patients and health professionals may ignore educational advice about inappropriate use of antimicrobials as their incentive is that the patient gets better from their illness (that is, the intervention may not be effective, particularly in the long-term); they may also ignore educational advice regarding hygiene and transmission.
2. Budgetary cost to EU and national states.

Likely outcome/benefit

There is evidence from one randomizied controlled trial (RCT) where education to patients and professionals was combined, that prescribing reduced from 74% to 48% in the short term following an educational intervention including education and practice profiling[58]. Recent evidence from the EU also suggests that educational campaigns among the public are of value[59]. If best practice is pursued in this area, with educational interventions being targeted to the particular culture and context in which they are undertaken, such interventions offer the greatest long-term hope of altering behaviour, as appropriate use of antimicrobials becomes culturally the norm.

Likely costs

Costs to EU in providing matched funding. Plus costs to member states in developing and implementing intervention (including costs of trainers, educational and campaign materials, media); potential costs of pain and suffering for patients no longer receiving treatment (although in the RCT above there were no apparent differences in health outcome); possible time costs for doctors BUT there may be cost savings in relation to reduction in prescription of antimicrobials.

Policy option 6 (research): Additional research funding to enhance containment of resistance

Problem

The Commission's Directorate General for Research has been strongly committed to research into antimicrobial resistance through its Framework Programmes for Research and Technological Development, with an annual budget of at least 20 million Euros devoted to this topic since 2000. In FP5 (1999-2002) research was largely concerned with capacity building and knowledge generation, with around one quarter of funding concerned with antibiotic usage, and just over one third of funding spent on research on each of transmission and the development of new antibiotic therapies. In FP6 (2003-2006) this focus has changed slightly such that the majority of funding, over 40% now goes towards research concerned with antibiotic usage, with the remainder split equally between research into reducing transmission and developing new antibiotic therapies. For FP7 (2007-2013) it is anticipated that there will be an emphasis on translational research as well as the conduct of studies looking at the health and economic burden of resistance.

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[58] Gonzales et al, 1999) Gonzales, R. et al., 1999. 'Decreasing antibiotic use in ambulatory practice. Impact of a multidimensional intervention on the treatment of uncomplicated acute bronchitis in adults', *JAMA*, No. 281, pp. 1512-1519.

[59] Goossens, H. et al., 2006. 'National campaigns to improve antibiotic use', *European Journal of Clinical Pharmacology*, Volume 62, pp. 373-380.

The promise of finding a new antimicrobial to 'solve' the problem of resistance is, in many respects, more attractive than the prospect of having to implement containment solutions that might mean the possibility of increased morbidity and mortality among the current patient population, or the prospect of increased costs associated with these containment strategies. Yet, in reality, these containment strategies are likely to be the major means for containing resistance, at least in the short term, given the current promise of new antimicrobials. Such strategies are also vital if any new antimicrobials that are developed are not to be squandered as soon as they emerge onto the market.

The evidence base from which to draw in taking decisions about the containment strategies that will offer greatest benefit at least cost, and thus which strategies and interventions to pursue is poor at best, with extraordinarily few robust studies[60]. Indeed in developing the policy options contained within this report, the working group was hampered hugely by a lack of robust evidence upon which to make the options, and policy option 4 and 5 both contain clear links to future research as well as to current policy making. The lack of evidence was clear both at the level of particular clinical interventions in terms of what works well and what does not, but also at the policy level, so that, for example, possibilities such as the use of resistance permits (in a similar way to the Kyoto system of environmental permits) are currently effectively no more than suggestions in the literature[61].

In conducting research in this area there are considerable methodological challenges in improving the robustness of future studies which have, in the past, been largely ignored. There are also complexities associated with the need for cultural and behavioural change, given the many and diverse cultures within the EU. One example that was brought up within the extended expert work group meeting in June may be helpful in explicating this issue. One participant at the meeting was strongly in favour of guidelines which he felt were a valuable tool in changing behaviour in his country. Others at the meeting felt that in their own contexts guidelines were largely ignored and thus pointless. This suggests that much more attention needs to be paid to the potential generalisability of possible containment strategies to specific contexts. Indeed, there is no lack of frameworks for containing antimicrobial resistance but almost no guidance on how these frameworks should be implemented in different contexts. Even now, there is little understanding of the socio-economic determinants of differential antimicrobial usage or the current incentives and disincentives that operate in different health care systems, and little knowledge about how to change that usage via either education or incentive mechanisms.

Research on how best to contain resistance also provides a vital contribution to countries outside the EU, particularly developing countries and the newly industrialised countries that may not have resources to invest in research about how to contain resistance.

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[60] Smith, R.D. et al., 2001. Interventions against antimicrobial resistance. A review of the literature and exploration of modelling cost-effectiveness. Global Forum for Health Research, Geneva.

[61] Coast, J., Smith, R.D. and Millar, M.R., 1998. 'An economic perspective on policy to reduce antimicrobial resistance', *Social Science and Medicine*, Volume 46, pp. 29-38.

These countries can hugely benefit from research that is, effectively, a public resource once conducted and will particularly benefit where the impact of different cultural contexts is taken account of during the research.

Policy option

To ensure that additional EU funding is provided in the area of antimicrobial resistance research, and that this additional funding is focused on methods of containing resistance by focusing on research that aims to:

1. enhance understanding of the cultural, contextual and behavioural aspects of antimicrobial usage, thus generating possibilities for interventions to reduce usage.
2. provide robust evidence about the optimal methods of using antimicrobial agents to ensure efficient treatment and at the some time reduce the selection of resistance. This should include studies on the benefits and consequences of using different types of antimicrobial agents for different diseases and in different reservoirs and strategies for usage including dosage and time.
3. conduct sophisticated translational research to ensure that scientific results already generated are developed into successful interventions for managing infectious disease and reducing antibiotic resistance, within medical practice and patient care.
4. develop methods for providing robust evidence whilst dealing with the challenges of assessing the costs and benefits associated with resistance and its avoidance/reduction. These challenges include:
    - identifying diffuse impacts;
    - generational and intergenerational time preference (i.e. how we weight current health and life compared to future health and life);
    - uncertainty; and
    - measuring and valuing impact.
5. provide robust evidence about the relative costs and benefits of interventions designed to reduce use of antimicrobials (including, for example, educational interventions, rapid diagnostic tests and so on) and interventions designed to reduce transmission of resistance
    - in a manner which acknowledges that the challenges may be greater for studies designed to reduce antimicrobial use than for studies intending to reduce transmission;
    - using, as far as possible, study designs that are high in the hierarchy of evidence;
    - but supplemented, where necessary, with modelling to allow extrapolation of effects and costs to a relevant timescale.

6. disseminate and implement study findings in a timely manner, using notions of 'best practice', guidelines and systematic reviews, and by linking with research on incentives and policy development.
7. develop funding streams focusing on policy research and incentive mechanisms in relation to the containment of antimicrobial resistance, including particularly:
    - taxations systems;
    - use of permits;
    - use of subsidies;
    - use of accreditation systems.

    For example, one issue that could be usefully studied would be whether it is possible for the EU to provide an incentive at the national level for countries to reduce their antimicrobial use by taxing countries on their use of antimicrobials. Potential barriers include that (1) it may be difficult to agree a tax level that has the required effects on all countries. Tax levels may need to be set on the basis of (a) any differences in population that would be expected to influence appropriate antimicrobial usage (b) national income levels; (2) reduction in antimicrobial use will only be achieved if it is (a) possible and (b) less costly for countries to reduce antimicrobial use than to pay the tax; and (3) that all antimicrobial use through whatever means of reaching the consumer would need to be monitored which is likely to be extremely costly.

Main stakeholders

EU research funding; research community.

Level at which option operates

EU.

Potential obstacles

1. Budgetary cost to EU.
2. It may be difficult to ensure that these different aspects of research are all included somewhere among the various EU budgets. This is quite true of research issues such as understanding the determinants of antibiotic usage which in topic are concerned with a medical area but in methodological terms are more related to the social sciences. Such topics can easily fall outside both funding areas and it is important that this is avoided.
3. The need for innovative and sustained work in this area suggests that funding individual projects may not be the most efficient way to achieve the goals suggested here. One alternative option might be to provide core funding that allows promising leads to be pursued on an ongoing basis.

Likely outcome/benefit

Better understanding about the influences on antimicrobial use, evidence about which interventions are most likely to be successful in containing resistance and evidence about which policies might impact most strongly on resistance at least cost. Ultimately this will ensure that the EU is successful in containing the problems of resistance and that, where new drugs are eventually developed, they will not be squandered in a very short time.

Likely costs

Costs to EU in funding additional research in antimicrobial resistance.

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Links

http://www.danmap.org

http://www.rivm.nl/earss

http://www.cordis.lu/lifescihealth/major/drugs.htm

Appendixes

Appendix 1 – Subjects discussed in the project

The project has been informed by the following questions:

Which regulations are necessary to reduce the unwarranted use of antibiotics for humans as well as for animals?

Which initiatives, aside from regulations, may contribute to a reduction in the use of antibiotics?

How is it possible to ensure research in new, narrow-spectrum antibiotics or other technologies for anti-bacterial treatment?

The background for the selected policy options (chapter 3) is a number of oral discussions of current and future needs and possible solutions. In the first phase of the project the expert working group made a list of subjects to be taken into consideration when working out the policy options in the action plan. The list follows below and shows the subjects that have been discussed in the group before working out the action plan.

1 Consumption

- Appropriate and inappropriate use
- Humans (drugs, hygiene, foods, surroundings, hospitals)
- Animals (drugs, livestock practices, antibiotic growth promoters)
- Agriculture (biocides, herbicides, manure, fertilizers)
- Soaps and other items with anti-bacteria
- Studies of how to use antibiotics for maximum positive effect and minimum risk of resistance

2 Bacterial flows – how to reduce?

- Working/living/school environments
- Nurseries, kindergartens and residential homes for elderly people
- Hospitals
- Pollution, sewage, ground water (farming)
- Other modes of circulation

3 Ecology / bio-restoration / bio-remediation / flora / alternative treatments

- Eco drugs, flora restoration, weak antibiotics, strain activated drugs
- Vaccinations
- Wait out the illness

4 Infrastructures and engineering as solutions

- Schools
- Waste treatment
- Buildings and infrastructure
- Hospitals

5 Social patterns – incentives and methods to change behaviour

- Consumer
- Education and awareness
- Medical and veterinary practices
- Regulatory framework - subsidies / incentives / taxes, regulation vs. liberal freedom
- Research programs
- Unintended effects of policy
- Politicians
- International implications

6 Research and innovation

- New antibiotics
- Diagnostics (rapid diagnostics – cheap and fast tests for general practice, handheld diagnostics)
- Other drugs
- Bionanotechnology
- Genomics
- Needs for basic research
- Needs for focused research (what do we know / not know, mild antibiotics, successful networks, narrow spectrum drugs, understanding resistance, when to share knowledge)
- Funding and policy issues
- Public private partnerships (PPP)
- Extended patents

Appendix 2 - Contributors

The expert working group and authors of this report

Fernando Baquero (Spanish nationality) is the Director of the Department of Microbiology at the Ramón y Cajal University Hospital, Madrid, Spain. Ex President of the Spanish Society of Microbiology, he promoted and contributed to the establishment of teaching and training programmes for specialization in Microbiology (1973) and Infectious Diseases (1977) in Spain. He has been interested essentially in the elucidation of the mechanisms of antibiotic resistance, the selective processes leading to the spread of resistant organisms, and, in recent years, in the understanding of antibiotic resistance as a process of evolutionary biology. Founder member of the Alliance for Prudent Use of Antibiotics, he was received as member of the American Academy of Microbiology (2000). In 2002 Fernando Baquero received the highest award in the field of antibiotic research and chemotherapy (Aventis Award) of the American Society of Microbiology, and in 2004 the Award of Excellence of the European Society of Microbiology and Infectious Diseases. He has more than 325 published research papers mentioned in NCBI-PubMed.

Joanna Coast (British nationality) is a professor of health economics with a degree in social medicine. She works with decision making in health care and takes a special interest in the economics of antimicrobial resistance. She is based at the University of Birmingham. Joanna Coast has published widely in a number of areas of health economics. She currently leads an MRC programme on Effective and cost-effective care for older people (ICEPOP) as well as contributing to a number of other research projects. She is doing work on economics of antimicrobial resistance, including (1) an HTA project incorporating an economic evaluation to look at molecular diagnosis in central venous catheter infections and (2) Economics of resistance as part of an EU programme on antimicrobial resistance in lower respiratory tract infections (GRACE).

Niels Frimodt-Møller (Danish nationality) is a doctor of medical science and a professor of in clinical microbiology. He is working at the National Center for Antimicrobials and Infection Control at Statens Serum Institut, Copenhagen, department of antimicrobial resistance and hospital hygiene, where he is the head of antibiotic research. The center is the national referral center for antimicrobial resistance and functions as the monitoring center for antibiotic resistance among human pathogens in the DANMAP project (Danish Integrated Antimicrobial Resistance Monitoring and Research Programme). The department participates in a number of European and other international networks e.g. EARSS and ESAC, as well as being partner in various research programmes and collaborations funded by the EU (FP5 and -6) and other funds.

Anne-Laure Ropars (French nationality) is a senior policy analyst (BSc, MSc., MA in Political Economy and International Relations) at the Pharmaceutical R&D Policy Project (PRPP) at the George Institute for International Health. After completing a Masters degree in Political Economy and International Relations at the University of Chicago, she worked for a number of years as a consultant, specialising in European and developing country health systems and policies.

Her clients have included the EU-based pharmaceutical industry, philanthropic organisations and government bodies. She joined the PRPP at its creation in 2004, where she has managed research on the pharmaceutical industry's involvement in neglected diseases and worked on developing incentive proposals. She is now heading the London-based research team.

Frank Aarestrup (Danish nationality) is research professor in antimicrobial resistance at the Danish Institute for Food and Veterinary Research which is a WHO Collaborating Centre for Antimicrobial Resistance in Bacteria from Food and Food of Animal Origin. During the last nine years most of his work has been within different aspects in relation to antimicrobial resistance, mainly among bacteria from animals. This includes evaluation of methodologies for susceptibility testing, epidemiological investigations, determinations of the occurrence of resistance among different bacterial groups, and molecular studies on the identification and characterisation of resistance mechanisms, transposons and plasmids in different Gram-negative and Gram-positive bacterial species. Frank Aarestrup's main interests are national and international monitoring of antimicrobial resistance and evolution of antimicrobial resistance as a consequence of usage of antimicrobial agents in the food animal production and the public health consequences thereof.

Participants at the extended working group meeting June 16, 2006

From the working group

- Joanna Coast , professor of health economics, University of Birmingham
- Niels Frimodt-Møller, professor of microbiology, Statens Serum Institute, Copenhagen
- Anne-Laure Ropars, senior policy analyst, The George Institute for International Health, London

Invited experts

- Christina Greko, Dr. in veterinary medicine, Swedish National Veterinary Institute, Stockholm
- Patrice Nordmann, MD in microbiology, Hospital Bicêtre South-Paris Medical School, Paris
- Richard Smith, Dr. in health economics, University of East Anglia, Norwich
- Henri A. Verbrugh, MD in clinical microbiology, Erasmus University, Rotterdam

STOA, European Parliament

- Marcelo Sosa-Iudicissa, Department of Scientific Policies

Participants at the workshop in Brussels September 13, 2006

From the working group

- Fernando Baquero, Director of the Department of Microbiology at the Ramón y Cajal University Hospital, Madrid
- Joanna Coast, professor of health economics, University of Birmingham
- Niels Frimodt-Møller, professor of microbiology, Statens Serum Institute, Copenhagen
- Anne-Laure Ropars, senior policy analyst, The George Institute for International Health, London

Invited speakers

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- Theo Karapiperis, STOA, DG Internal Policies, European Parliament
- Christian Meseth, DG INFO, European Parliament
- Stephan Miran, Internal Policies, European Parliament
- Ragnar Norrby, Swedish Institute for Infectious Diseases
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- Nathalie Seignoret, European Medicines Agency (EMEA)
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Project management

- Benjamin Michael Hope, project assistant, the Danish Board of Technology
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Appendix 3 - Needs for new antibiotics

Research on more sensitive antibacterial assays for natural compounds, combining both novel cell-based screening tests and interaction with molecular targets will be needed to increase the platform of potential new drugs. Obviously the "chemical-empirical" approach using combinations of organic compounds in the hope of finding something useful has not been harvested, as probably we need to use in these combinations more and more "scaffold architectures" based on chemical modules that we have identified previously as biologically active. Unfortunately, many of these approaches are based on the exploration of "large landscapes of candidate activities" that should be refined in the process of development, that will require considerable expenses and technology. Probably a way of facing such strategic difficulty is by enlarging cooperation between academic basic research laboratories and the large pharmaceutical industry. To facilitate such a process of joint-discovery and development small enterprises could eventually be created to favour the "intermediate stages" of research, too cumbersome both for the academy and the big pharmaceutical companies.

Needs for new antibiotics include:

In terms of antibacterial activity:

- Antibacterials, alone or in combination, with much higher intrinsic activity, able to kill all offending organisms, optimally after single exposure to the drug; reducing such a way undesirable effects on resistance, as prolonged exposures expands the influence of antibiotics on non-target organisms;

Antibacterials with activity on slow-growing and stationary-phase bacteria;

Antibacterials directed to particular clones; in many cases, the more aggressive and resistant organisms are found in a limited number of clones (Clones and clonal complexes: particular "families" of closely related bacteria within a given bacterial species) that should be identified as the real targets of chemotherapeutic action.

In terms of type of target illnesses:

- "Weak-Cheap" antimicrobials to be used in self-limited infections, only to assure a prompt recovery, a limitation of the symptoms, or reduction in human-to-human transmission. Many pharmaceutical industries discover dozens of molecules with weak activity, that are never converted into "leads" for further research. Indeed pharma companies almost exclusively do research on antibiotics targeted to threat the more aggressive, multi-resistant, mostly hospital-based infections. On the contrary, most infections that might benefit from antibiotic therapy, particularly in the community (and therefore, most of the antibiotic pressure selecting for resistance) only requires safe (low undesirable effects) drugs that might reduce the growth rate of offending organisms, giving time to immunity to develop. The costs of development of "weak-cheap" drugs will be compensated by the high number of potential prescriptions. Note that the need for these drugs is a priority in developing countries.

- “Strong-Expensive” antimicrobials to be used in life-threatening infections. If death is an issue of a particular infection (for instance, death rates due to the infection exceeding 10-20% of the affected people) any cost should be allowable to treat these patients, and a relatively high risk for toxicity might be acceptable. Many pharmaceutical companies are rejecting to develop compounds because the expectations of high costs in production and/or toxicity. But if the society has these needs (as in the case of expensive HAART therapy in AIDS, or transplantation procedures), these costs should be assumed.

In terms of biorestoration (bioremediation) of antibiotic activity.

- Antibiotics targeted to specifically suppress antibiotic-resistant organisms, to be promoted as “cleaners” of resistance in particular areas, or to combine with more conventional antibiotics. The net result will be “selection for susceptibility”. For instance:

  - Antibiotics whose activity is triggered by specific mechanisms of antibiotic resistance, particularly those enzymatically-driven
  - Antibiotics increasing the “biological cost” associated with the expression of resistance
  - Antibiotics inactivating resistance mechanisms.

Appendix 4 - Possible research incentives for the pharmaceutical industry

Below is a description of three possible research incentives to encourage the pharmaceutical industry to engage in the research and development of new antibiotics. Although the working group behind this report has not included an option for increased R&D of new antibiotics, they have discussed a range of possible incentives for the pharmaceutical industry. The working group has found the incentives described below to be interesting and have therefore described them using the same template as the policy options in chapter three.

The incentives proposed here expound, in part, upon the findings of a previous study concerning how to incentivise the pharmaceutical industry to conduct R&D in drugs for neglected diseases[62]. In that study, ten out the top thirteen companies and numerous small and medium-sized enterprises (SMEs) were interviewed for a better understanding of the motivations of the few that were already involved in R&D for neglected diseases, and of what would encourage all others to engage in the field.

The incentives below also follow from discussions with a small sample of firms (two large pharmaceutical companies and four small and medium firms) interviewed for this project, and where a range of potential incentives were assessed. If one of the proposals were to be further considered, obviously a larger consultation would be needed with all stakeholders involved.

Establishment of an antibiotic R&D Public-Private partnership (PPP)

Problem

- The market is generally too small to stir sufficient R&D activity. "The unresolved problem is that you want drug companies to produce more drugs but you don't want them used too much. Simply stated, that's the economic dilemma"[63].
- For the small group of companies for which the antibiotic market is of interest, higher revenue drivers, and hence direction of R&D efforts, are usually drugs targeting multiple infections and marketed as widely as possible. In contrast, most urgent needs are for gram negative, narrow spectrum agents targeting small (generally hospitalised) patient populations - and use of these drugs should be as last resort for resistance containment purposes.

Please refer to chapter 2, section 2.3, on "A shrinking market", for more detail.

Policy option

Drug development PPPs for neglected diseases have successfully catalysed activity by private sector partners. An antibiotic PPP – i.e. a not-for-profit organisation that drives antibiotic R&D projects in collaboration with public groups and industry - could achieve similar outcomes for developing antibiotics with the smallest markets (e.g. gram-negatives).

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[62] Pharmaceutical R&D Policy Project, 2005. *The New Landscape of Neglected Disease Drug Development*, LSE/Wellcome Trust (now at the George Institute).

[63] Hadley, C. 2004. 'Overcoming Resistance', *EMBO Reports*. Volume 5, No. 6, pp. 550–552.

The premise underlying the creation of an antibiotic PPP is a recognition that, in order to get the drugs needed and to control their distribution:

- The public sector needs to take the lead and replace the market "pull" mechanism for antibiotic R&D (for the reasons explained above).
- Cost-efficient and effective drug development cannot happen without industry skills and expertise. (This premise was unequivocally validated in an empirical study of 80 + drug development projects for neglected diseases undertaken between 1975 and 2004[64]).

The PPP will not conduct in-house drug development. It will secure funds from the public and possibly private sectors; review the field of promising projects and R&D leads; and then work with an Expert Scientific Committee to select, fund and manage the best projects from a public health perspective. An initial focus could be the smaller market of gram negative hospital infections.

The PPP will incentivise involvement by private partners in various ways:

- **Large pharmaceutical firms** with anti-bacterial expertise may be motivated to develop drugs with uninteresting commercial prospects if the PPP subsidises their direct project costs (current favoured approach for neglected disease R&D). The partnership may offer large firms a low cost opportunity to fulfil strategic interests, such as managing reputational risk in the light of highly publicized cases of incurable *e coli* or MRSA infections, or synergies with other technologies or markets. The PPP could also provide an opportunity for industry experts, who are otherwise focussed on developing antibiotics for the more lucrative markets (e.g. upper respiratory infection), to provide support to the PPP projects (e.g. secondment programmes).

- A PPP is also likely to be attractive to **small firms** that are developing antibiotics and need funding and expertise for clinical development and registration of their products. The conditions for PPP support would be some degree of public control over the marketing of the drug (e.g. to pre-agreed types of infection and settings). Other alternatives could include the PPP paying the company and providing support to develop the product, including paying subsequent royalties, in exchange for exclusive distribution rights if the drug is successfully registered. Unlike large firms, small biotechs or pharmaceutical companies cannot afford to work on a not-for-profit basis, and their engagement in a funding partnership will be dependent on a satisfactory return on investment (i.e. balance between the opportunity to receive immediate funding and help versus the possibility of forgoing some future revenues from the resulting product).

- In order to incentivise early research and feed its pipeline, the PPP could act as a **central fund to purchase drug leads** at early stages. Small firms may be particularly attracted by this immediate source of revenues.

[64] Ibid.

The availability of an "exit" route for leads is also likely to make private groups more willing to come forward with shelved compounds and as a result put more leads in the public domain. The PPP would then choose the optimal development route for these compounds, either using contract research organisations, partnering with a large firm, or pay the originator group to complete the development (e.g. initial payment plus milestone payments at each phase of development up to registration of the product).

Main stakeholders

Large and small pharmaceutical and biotechnology firms, public R&D groups, EU

Level at which option operates

EU + possibly funding by all non EU countries, as the antibiotics developed through the PPP mechanism would likely benefit all patients around the world.

Potential obstacles

- Large pharmaceutical companies that are already involved in neglected disease R&D may not be willing to extend their not-for-profit activities to antibiotic R&D. Large interviewed companies also stated that for antibiotics with applications for relatively larger markets such as, for instance, upper respiratory infections, they would want to keep development in house.
- If the partner company expects to derive revenues from the end product (as is likely the case for small firms), a contractual agreement limiting its marketing rights to PPP-recommended therapeutic areas may be difficult to reach. One way of addressing this could be to include price considerations in the agreement.
- Opportunity costs associated with funding development of new antimicrobials rather than intervention studies.

Likely outcome / benefits

More innovative products targeting drug-resistant infections will be registered in the medium to long term, and distribution of these will be more consistent with public health needs.

Likely costs

- Industry interviews carried out in the frame of the previous study on neglected disease R&D have indicated that the cost of purchasing leads with low commercial potential from a company has consistently been in the order of €5 million per lead – and sometimes has been free.
- The extent to which the PPP would cover the cost of development of the antibiotic candidates it selects will depend on the type of partnerships it enters. Long term funding will be needed to carry forward the portfolio of selected projects.
- Cost to health systems of paying for new drugs that may otherwise not be developed.

Stimulating early research and translation with the creation of a pairing academia/industry fund

Problem

Interviewed companies all agreed that there was a big gap in the provision of "druggable" leads, despite a host of basic research by academia.

Policy option

With these considerations in mind, a new fund could be established to encourage the translation of basic research into credible drug candidates, by funding multidisciplinary teams of academics paired up with industry partners. The special programme could fund discovery projects planned up to and including lead optimization stage, encouraging translation of basic research into drug candidates. Industry skills, such as project management and chemistry, would complement academic scientific skills. The funded research would be expected to progress to a point where private or public organisations (such as the antibiotic Public-Private Partnership), find the lead attractive and worthy of further development. This fund could possibly sit within the Innovative Medicines Initiative, a new European public and private sector collaboration, proposed to be funded under the EU's 7th Framework Programme. The IMI aims "to support the faster discovery and development of better medicines for patients and enhance Europe's competitiveness by ensuring that its biopharmaceutical sector remains a dynamic high-technology sector"[65].

Main stakeholders

Pharmaceutical and biotechnology industry, public research groups, EU.

Level at which option operates

EU.

Potential obstacles

Obtaining the funds needed.

Likely outcome/benefit

New leads will start re-filling the pipeline and will be taken forward by the antibiotic PPP or industry.

Likely costs

Cost to FP7 of supporting a portfolio of discovery projects.

[65] Innovative Medicines Initiative (IMI), 2006. *Strategic Research Agenda*, EFPIA/IMI, 15 September (version 2.0). IMI.

Re-evaluate regulatory requirements for antibiotics

Problem

Regulatory requirements are a major driver of the cost and length of antibiotic development. Clinical trials are the most expensive element of a drug development programme and involve hundreds of patients. These trials can be especially difficult for companies developing antibiotics as there is a lack of rapid diagnostic methods to help identifying eligible patients, and enrolling enough patients can sometimes take years depending of the type of infection studied.

Policy option

The scientific committee (CHMP) of the EMEA has already provided guidance[66] that discussed the possibility of an initial marketing authorisation based on limited clinical data especially for drugs active against resistant organisms and/or for use in life threatening infections. It is further recommended that:

- The CHMP should keep this under review and revise its recommendations as appropriate.
- Innovative regulatory approaches that would reduce the trial burden should be explored, e,g,: improving statistical methods, or using PK/PD studies as support to extrapolation between indications.
- The CHMP should consider packaging its various regulatory tools aiming to ease and accelerate development of new drugs (e.g conditional approval, accelerated procedure, risk management plan, free and early scientific advice) into one single "fast-track" type mechanism for companies developing "priority" antibiotics (and in fact for all companies developing medical products for life threatening conditions).

Main stakeholders

Pharmaceutical and biotechnology industry, EU, European Medicines Agency (EMEA).

Level at which option operates

EU.

Potential obstacles

- This measure may face political and public resistance. Since the withdrawal of Vioxx from the global market over drug safety issues, the trend is for more, rather than less, regulatory requirements.

[66] European Agency for the Evaluation of Medical Products (EMEA), Scientific Committee, 2004. *CPMP/EWP/558/9. Note for Guidance on Evaluation of Medicinal Products Indicated for Treatment of Bacterial Infections (CPMP adopted April 2004).* EMEA.

- Higher risk that unexpected effects may be discovered post-registration, but this should be seen in the light of the benefit of making a potentially life-saving drug available to critically ill patients.

Likely outcome/benefit

More antimicrobials will be developed for patients infected with multi-drug resistant organisms and or with life threatening infections.

Likely costs

Cost to health systems of paying for new drugs that may otherwise not be developed.

Appendix 5 - Further reading

Alliance for the Prudent Use of Antibiotics, (APUA), 2005. *The GAARD Report: Global Antimicrobial Resistance Alerts and Public Health Implications.* APUA.

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