Priority Medicines for Europe and the World

A Public Health Approach to Innovation

Antibacterial Drug Resistance

Per Nordberg[1] MD, Dominique L. Monnet[2] PharmD, Otto Cars[1] MD, PhD

ACKNOWLEDGEMENT:
This paper was orginally produced as a background document for the WHO project: Priority Medicines for Europe and the World "A Public Health Approach to Innovation." (for reference see: http://mednet3.who.int/prioritymeds/)

1. Swedish Strategic Programme for The Rational Use of Antimicrobial Agents and Surveillance of Resistance (STRAMA), Solna, Sweden

2. National Center for Antimicrobials and Infection Control, Copenhagen S, Denmark

Contact information

Per Nordberg, Otto Cars
Swedish Strategic Programme for The Rational Use of Antimicrobial Agents and Surveillance of Resistance (STRAMA)
Address: Swedish Institute of Infectious Disease Control, S-171 82 Solna, Sweden
Telephone: +46 8 457 23 67
Email: otto.cars@smi.ki.se, per.nordberg@sodersjukhuset.se

Dominique L. Monnet
National Center for Antimicrobials and Infection Control
Address: Artillerivej 5, DK-2300 Copenhagen S, Denmark
Telephone: +45 3268 3268
Email: dom@ssi.dk

Table of Content

Executive summary

A potential post-antibiotic era is threatening present and future medical advances. The current worldwide increase in resistant bacteria and, simultaneously, the downward trend in the development of new antibiotics have serious health and economic implications. Resistant bacteria dramatically reduce the possibilities of treating infectious diseases effectively and increase the risk of complications and fatal outcome for patients with severe infections. The current rising trends in antibiotic resistance suggest that the real problems are still ahead of us.

Globally there is an extensive overuse of antibiotics, e.g. use based on incorrect medical indications as well as misuse by using the wrong agent, administration route, dose and treatment duration. At the same time, there is a lack of access to effective antibiotics in some developing countries where the need for essential drugs is most immediate. In industrialized countries, around 80-90% of antibiotic use for humans occurs in the community and at least half of this is considered to be based on incorrect indications, mostly viral infections. Improved diagnostic tools to discriminate between viral and bacterial infections and to rapidly detect resistance in clinical samples would be important steps to reduce unnecessary antibiotic use in viral infections and to limit the use of broad-spectrum antibiotics. Development of new bacterial vaccines may also be necessary to control the spread of certain microorganisms between individuals and to reduce the number of carriers of these pathogens.

Failure of the initial antibiotic regimen due to resistant bacteria increases the risk of secondary complications and fatal outcome. In the case of methicillin-resistant Staphylococcus aureus (MRSA), studies repeatedly show the mortality in severe infections to be twice as high as in infections with non-resistant strains, after considering differences in severity of illness and underlying disease of affected patients. Besides the medical consequences for individuals, antibiotic resistance is associated with large societal costs. The previously continuous development of new antibiotics made it possible, in countries where new drugs are affordable, to change the therapy to new antibiotics. Because of the virtually empty pipeline of new drugs, clinicians are facing a situation where the likelihood of success from empiric antibiotic treatment is significantly reduced and where patients are sometimes infected with bacteria resistant to all available antibiotics.

The need for antibiotics will remain high and is expected to increase, with an ageing population, increased global infection rates, increasing numbers of immuno-compromised patients, who often require longer courses of antibiotic treatment, increasing bacterial resistance and increased specialized surgery, such as organ transplantation. For many years, society's medical needs for antibacterial drugs were met by the pharmaceutical industry. In the 1970s, innovative research to develop new antibiotics gradually waned, and the focus of research and development (R&D) shifted to modification of existing antibiotic classes. These modified antibiotics are basically using the same mechanism to attack bacteria as the preceding ones, making it easy for bacteria to develop resistance to the drugs.

At present, the industry's ventures are shifting from therapy for acute conditions towards long-term treatment of chronic diseases. Prospective investments in antibiotics compete with drugs for musculoskeletal and neurological diseases with 10 or 15 times greater 'net present value', a measure used by the industry to predict the potential success of

products. In 1991, approximately 50% of large pharmaceutical companies had ended, or seriously decreased, their funding of antibiotic research programmes because of the unfavourable financial prospects. Although potential new antibiotic targets are still being discovered, the question is whether these will be developed into drugs and marketed. The financial motives for the pharmaceutical industry to bring a new antibiotic compound through the stages of drug development are not convincing enough. Consequently, we are facing a paradoxical situation with increased levels of resistant bacteria along with a downward trend in antibiotic development.

Incentives for the development of antibacterial drugs with new mechanisms of action are essential. To get out of this impasse, the industry must be sufficiently attracted to return to investing in new antibiotics. This requires concrete measures, including reducing the costs of R&D as well as securing the longer use of products. There may be a need for a special regulatory regime for antibiotics in situations where a great public health need exists, e.g. to treat infections due to multidrug-resistant microorganisms where little or no alternative treatment is available. The ways in which the public sector can constructively intervene in the industrial value chain of antibacterial drug R&D should be thoroughly explored as the pharmaceutical industry continues to show little interest. When new drugs are developed, systems must be in place to secure their appropriate use to reduce emergence of resistance.

Antibiotic resistance does not rank high on the lists of priorities for funding. Nevertheless, Europe has recently started to make preparations for research in this area and some funding for basic and applied research for the development of new antibacterial drugs and diagnostic tests is available. Although there are several antibacterial drugs in the pipeline most of them do not represent true innovation.

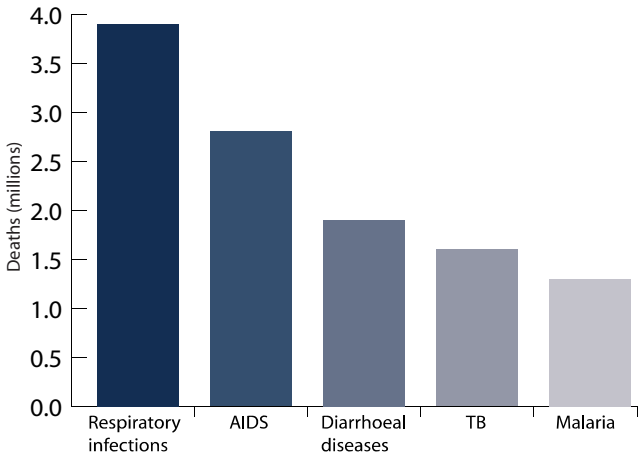
The alarming spread of resistant bacteria has attracted academic interest for the last 30 years, but a concerted and powerful public health response has been lacking. Policy documents and recommendations from the World Health Organization (WHO), North America and the European Union (EU) and others have been produced. However, as responsibility for health remains predominantly national, there is a potentially significant disparity between the problems and potential solutions associated with antibiotic resistance and the institutions and mechanisms to deal with them. The vagueness of the international response and the failure to translate existing knowledge into concrete action are serious problems. This complacency on the part of global society needs to be replaced by concerted action to reduce the present and future consequences of antibiotic resistance.

Introduction

A potential post-antibiotic era is threatening present and future medical advances. The current worldwide increase in resistant bacteria and, simultaneously, the downward trend in the development of new antibiotics have serious implications. Resistant bacteria dramatically reduce the possibilities of treating infectious diseases effectively and increase the risk of complications and fatal outcome for patients with severe infections. Most vulnerable are young children and the elderly with high susceptibility to infections and reduced immune response. Other risk groups are people with compromised immune defences, such as cancer patients and people who are HIV-positive, for whom adequate antibiotic therapy to prevent and treat severe infections is necessary for their survival. In addition, antibiotic resistance jeopardizes advanced medical procedures such as organ transplants and implants of prostheses, where antibiotics are crucial for patient safety and to avoid complications.

Mortality as a result of infectious diseases represents one fifth of global deaths.[1] Respiratory infections are the leading killer, causing nearly four million deaths annually (Figure 1).

Figure 1. Mortality graph of infectious diseases, millions of deaths, worldwide, all ages.[1]



These deaths are to some extent regarded as preventable with increased access to health care and medicines. However, the global emergence and spread of bacteria that resist antibiotics is raising the question as to whether this is still the case, especially in parts of the world where second and third line antibiotics, still effective to treat these infections, are unavailable.

Despite a pressing need for new antibiotics to meet the threat of resistant bacteria, industrial research in this area is declining. New products have faced the inevitable emergence of resistance and the potentially short durability of antibiotics is one of the reasons why the development of new products is decelerating. As resistance has accelerated, national and international drug policies have been developed to contain resistance, aiming towards restricted and rationalized antibiotic use. Increased demands from regulatory bodies have raised the development cost of new medicines, and prioritizing measures to secure optimal return on investment have driven the industry into other pharmaceutical areas with bigger and safer markets, e.g. long-term treatment or prevention of chronic diseases.

Considering the increasing knowledge of the medical, economic and ecological consequences of antibiotic resistance among medical professionals and political actors, the inertia surrounding the issue is difficult to explain. The alarming spread of resistant bacteria has attracted academic interest for the last 30 years, but a concerted and powerful public health response has been lacking. Policy documents and recommendations from WHO, North America and the EU and others have been produced, but to a large extent failed to reach out to individual countries. The vagueness of the international response and the failure to translate existing knowledge into concrete action are serious problems. Society's complacency needs to be replaced by urgent concerted action to reduce the present and future consequences of antibiotic resistance.

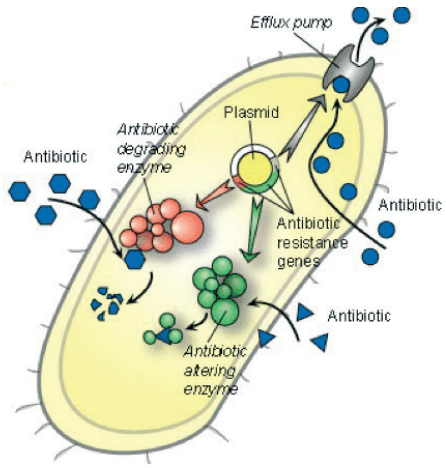
What is the nature and extent of antibacterial drug resistance?

Use of antibacterial drugs over the last 60 years has triggered a combination of genetic and biochemical mechanisms within the bacteria to secure their survival in environments where antibiotics are present.[2,3] Bacterial clones with natural and acquired resistance have continuously been selected as an evolutionary response to the use of antibiotics. Resistance can be acquired as a result of genetic events causing alterations in the pre-existing bacterial genome, such as point mutations and gene amplifications. The other major mechanism is horizontal gene transfer between bacteria both within and between species, where transposons, integrons or plasmids are introduced into an organism. The introduction of new antibiotics has resulted in accumulation of genetic elements coding for resistance mechanisms that can be transferred between microbes and create clones with multiresistant properties.[4,5]

The genetic alterations in bacteria cause resistance to antibiotics in one or more of four principal ways, as shown in Figure 2: the target molecules are structurally altered to prevent antibiotic binding; antibiotics are excluded from cell entry; they are inactivated, e.g. through enzymatic degradation; or they are or pumped out of the cell (efflux).[6]

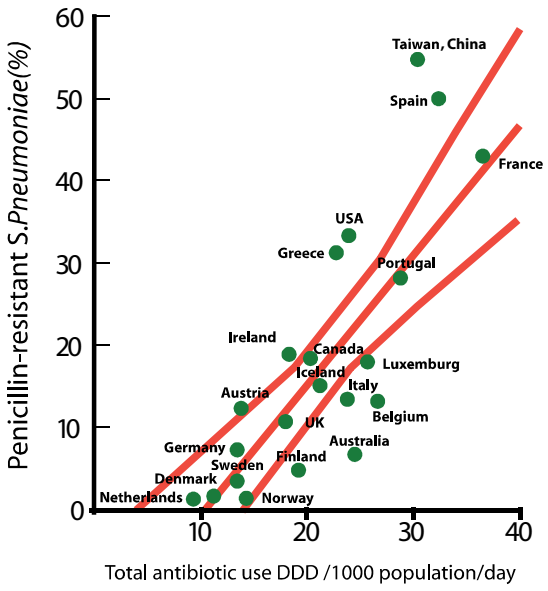
Bacterial resistance can be defined either genotypically (the bacteria carry certain resistance elements); phenotypically (the bacteria can survive and grow above a certain level of antibiotic in the laboratory) or clinically (the bacteria are able to multiply in humans in the presence of drug concentrations achievable during therapy).[7]

Figure 2. Mechanisms of resistance



The antibiotic used to treat an infection should be active against the most probable pathogen causing the infection. Besides killing the causative pathogen, the use of this antibiotic will give advantage to bacteria that naturally can withstand the antibiotic chosen. It will also favour the growth of resistant subpopulations, e.g. bacterial clones, of the causative pathogen over susceptible ones.[8] The selection and enrichment of bacteria with natural resistance that follows any antibiotic use will affect the balance in the microflora of any environment both at the community and the individual level. The magnitude of this selection will be determined by the total consumption of antibiotics within the setting.[5,9,10,11] Generally, the consumption of antibiotics per patient is greatest in hospitals, especially in intensive care units (ICUs) where patients are critically ill and highly susceptible to infections and the use of invasive procedures, and lower in the community. The levels of resistant bacteria follow the same pattern with the highest proportions of resistance in the critical care area.[12] This correlation is also seen on a larger scale, as the frequency of resistant bacteria is considerably higher in countries with high antibiotic consumption (Figure 3).

Figure 3. Correlation between penicillin-resistant (non-susceptible) pneumococci and outpatient antibiotic use (with 95% confidence intervals).[13]



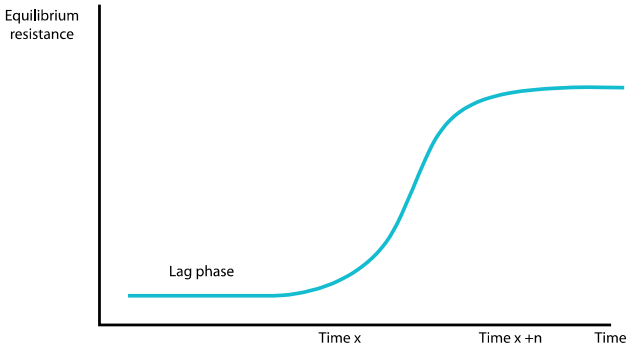
However, determining the relative risk of resistance development in the case of any specific antibiotic or dosage regimen is complicated. Influential factors are the antibacterial spectrum of the drug and its pharmacokinetics, such as the building up of concentrations in the gastrointestinal tract, skin and saliva. These factors will influence the extent of impact on the body's normal bacterial flora.[14] Poor patient compliance with dosage regimens and the use of substandard antibiotics lead to sub-optimal concentrations that fail to control the infection and may promote growth of resistant bacterial populations. Thus, underuse, through lack of access to effective antibiotics, and their irrational use may play as important a role in driving resistance as overuse.[15] At present we lack detailed knowledge on the pharmacokinetic/pharmacodynamic relationships required to use antibiotics in an optimal manner that minimizes resistance development. However, experimental studies indicate that certain concentrations may prevent outgrowth of existing resistant bacterial sub-populations.[16]

When a patient is treated with antibiotics, both the causative pathogen and the normal non-pathogenic microflora in the body will be affected. The indigenous microflora make up a complex ecological system of great importance for human health. Besides being essential for the digestion of food and to metabolize drugs, they also produce essential vitamins and are important for the activation and maintenance of the immune system in the gut. Ideally, antibiotics should effectively kill the pathogen responsible for infections and, simultaneously, cause as little disturbance as possible to the microflora of the individual. At present, the ideal antibiotic does not exist and the overuse of broad spectrum agents in respiratory infections and diarrhoeal diseases consequently drives resistance development in pathogenic bacteria as well as in the normal bacterial reservoir of the patient. This makes antibiotic-treated patients potential carriers of resistant microbes that might be harmful to themselves and to other patients. The resistance mechanisms in the gut can be transferred to more virulent pathogens passing through the body and be spread to other individuals. Furthermore, the bacteria that are carrying resistance mechanisms will disappear very slowly, if at all, even if exposure to antibiotics is removed.[17]

The window of opportunity

The development of resistance appears to follow a sigmoid distribution (Figure 4), with a lag phase before resistance appears, then a relatively rapid increase in the proportion of resistant bacteria, followed by a third phase in which this proportion reaches an equilibrium.[18] This equilibrium level is determined by the relative fitness of resistant and sensitive strains including transmission ability, the genetic basis and stability of resistance, and the magnitude of the antibiotic selection pressure. When this level of resistance has been reached, measures to contain or potentially reverse the trend seem very difficult.[19] This suggests that to achieve containment of resistance it is vital to act early e.g. in the lag phase, rather than to wait until resistance has begun to emerge. To take actions within this 'window of opportunity' appears to be fundamental for any strategy to limit resistance development.

Figure 4. The development of antibiotic resistance over time.[26]



The potential reversibility of resistance is a debatable issue, and the chances of success differ greatly between the hospital setting and the community. The rationale for reversibility is that resistant bacteria will have a disadvantage over susceptible strains in environments without antibiotics, as most resistance mechanisms will confer a reduction in bacterial fitness e.g. a slower growth rate, reduced virulence or transmission rate. Thus, a decreased volume of antibiotic use should lead to lower selection pressure and a reduction in the proportion of bacteria resistant to a certain antibiotic. Thereby resistant organisms will be replaced by susceptible ones.

However, this picture is complicated by the fact that bacteria may reduce the biological costs associated with resistance through compensatory evolution.[3,20,21] The role of compensatory mutations that maintain the fitness of resistant strains is now well established and increasing levels of biologically competitive resistant bacteria are detected in the community, with no decrease in vitality compared to non-resistant strains. Thus, in the community where antibiotic pressure is lower or absent, resistance levels may be slow to reverse and sometimes appear to be irreversible.[19] In addition, genetic

linkage between resistance genes will result in co-selection of the genes. Multiple resistance genes are frequently found on plasmids and transposons and the use of one antibiotic will result in selection for that specific resistance gene as well as all the other linked genes. This phenomenon will also contribute to irreversibility. Consequently, when bacteria have developed resistance towards several antibiotics, even a substantial reduction of one drug may be ineffective in reducing resistance.[22]

In hospital settings the rate and extent of reversibility of antibiotic resistance are much higher than in communities, as shown by both clinical intervention studies and by theoretical models.[23] The reason for this difference is that the main driving force for reversibility in hospitals, in contrast to communities, is not the biological cost of resistance. Instead, in hospitals a 'dilution effect' is observed as incoming patients are in most cases bringing susceptible bacteria into clinical wards and therefore affect the levels of resistant bacteria. Thus, models predict that rapid reversibility can occur in hospitals in response to reduced antibiotic use as long as the frequency of resistance is lower in the community than it is in the hospital.

Transmission of resistant bacteria

Many human pathogens are characterized by a limited number of successful clonal lineages, which share genetic elements involved in pathogenicity and resistance to antibiotics.[24] Once resistant clones are selected, their spread is promoted by factors such as overcrowding and poor hygiene. One example is day care centres, which provide ample opportunities for the transmission of infectious diseases and, in particular, the emergence of resistant Streptococcus pneumoniae. The combination of the presence of young, susceptible children suffering from recurrent infections and the use of multiple, often broad-spectrum antibiotics makes such environments ideal for the carriage and transmission of these bacteria.[25] Another example is the spread of multi-drug resistant tuberculosis (TB) in Russian prisons. In the hospital setting where the antibiotic pressure is higher than in the community, some bacterial clones have been more successful than others in spreading extensively, often illustrated by the rapid dissemination of epidemic clones of methicillin-resistant Staphylococcus aureus (MRSA).

A number of phenomena of modern society have enhanced the opportunities for resistant clones to spread globally, including increasing international trade, travelling and migration, ecosystem disturbances, urbanization and the increasing number of people with compromised immune systems (Figure 5).[26] It is to some extent possible to reduce the transmission rate of bacteria by infection control measures such as hygienic procedures, vaccines, the identification and isolation of patients infected with resistant bacteria, adjusted treatment for these patients and decreased density of patients in clinical wards. In addition, once patients are identified as being infected (or carriers) with resistant bacteria it is important that they are effectively treated to prevent them from transmitting these organisms further.

Figure 5. The global threat of antibiotic resistance. Worldwide spread of the penicillin-resistant *Streptococcus pneumoniae* clone 23F.[39]

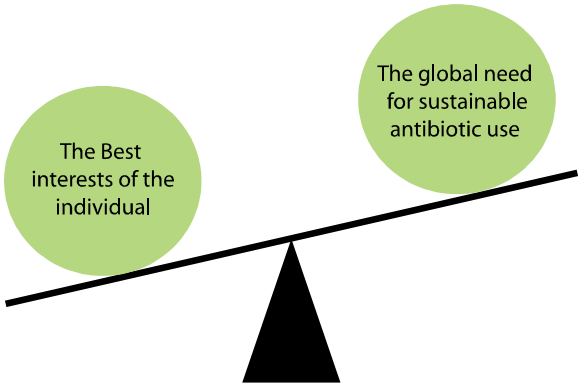
Antibiotic use

As described above, resistance development is a natural biological outcome of antibiotic use. The more we use these drugs, the more we increase the speed of emergence and selection of resistant bacteria. Globally there is an extensive overuse of antibiotic, e.g. use based on incorrect medical indications as well as misuse by using the wrong agent, administration route, dose and treatment duration. At the same time, there is a lack of antibiotics in some developing countries where the need for essential medicines is most imminent. In industrialized countries, around 80-90% of antibiotic consumption in humans takes place in the community and at least half of this is considered to be based on incorrect indications, mostly viral infections.[24,27] At the EU conference on "The Microbial Threat" (Copenhagen 1998)[28] an attempt was made to define appropriate use of antibiotics: "Treatment should be limited to bacterial infections, using antibiotics directed against the causative agent, given in optimal dosage, dosage intervals and length of treatment with steps taken to ensure maximum patient concordance with the treatment regimen, and only when

the benefit of the treatment outweighs the individual and global risks". WHO defines the appropriate use of antibiotics as "the cost-effective use of antibiotics, which maximizes clinical therapeutic effect while minimizing both drug-related toxicity and the development of antibiotic resistance".[15]

Unfortunately, no inexpensive and easily available laboratory test is able to discriminate quickly enough between viral and bacterial infections. And even if there was, the clinician would still not know which bacterial species causes the infection and its resistance pattern. Thus, improved diagnostic tools would be one of the most important steps to reduce unnecessary antibiotic use in viral infections and to limit the use of broad-spectrum antibiotics. Apart from the diagnostic dilemma, the factors influencing how antibiotics are used are many and complex. The short-term advantages of antibiotic use for patients, health care workers and drug distributors generally seem to outweigh concerns about the future consequences of resistance (Figure 6).[29]

Figure 6. Individual advantages versus future consequences. [30]

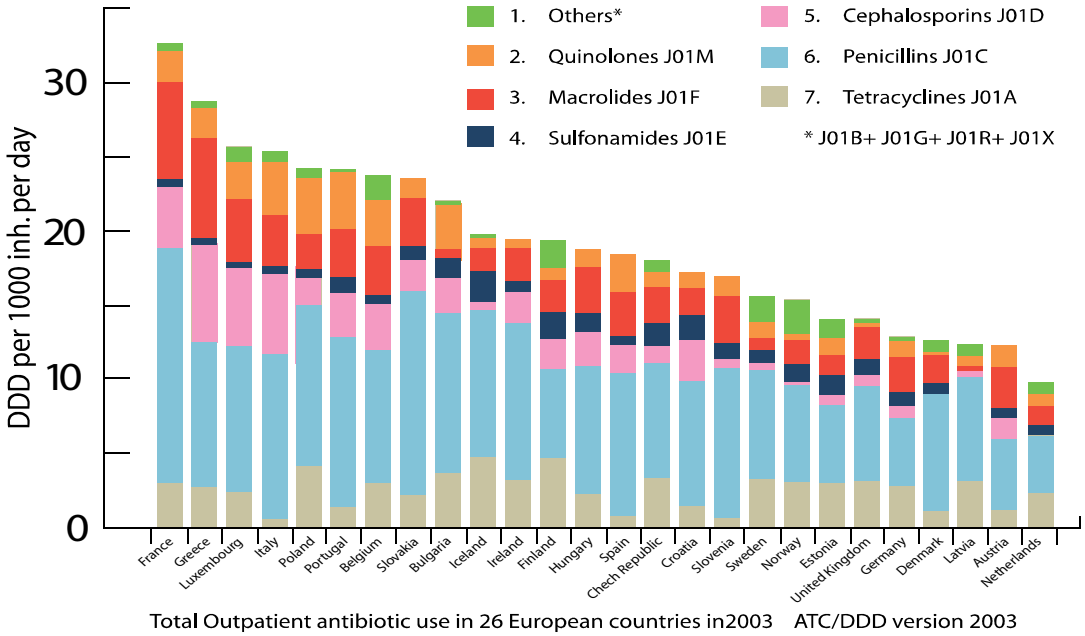


Other factors include cultural conceptions, patient demands, economic incentives, the level of training among health staff and pharmacists, and advertising to prescribers, consumers and providers from the pharmaceutical industry. Consequently the patterns of antibiotic use differ substantially between and within countries. In Europe, for example, antibiotic consumption is four times higher in France than in the Netherlands, although there is no reason to believe that the burden of disease differs between the two countries (Figure 7).

Antibiotics outside human medicine

About half of the antibiotic consumption in Europe and the USA is to treat and prevent diseases in animals, fish and plants.[32] Besides treatments, sub-therapeutic doses of antibiotics added to feed for growth promotion have been intensively used for decades in animal-rearing practices. Within the EU the use of most antibiotics in animal feed for this purpose are now prohibited, but in many countries large numbers of animals, irrespective of their health status, are exposed daily to sub-therapeutic concentrations of antibiotics. Some growth promoters belong to groups of antibiotics, such as glycopeptides, that are essential drugs in human medicine for the treatment of serious, potentially life-threatening infections. Emerging multi-resistant bacteria from farm animals are transmitted to humans mainly through the food chain or by direct contact. The parallel emergence in animals of resistant strains, especially of Salmonella and Campylobacter, is continuously bringing in new clones that cause infections in humans. This was demonstrated when fluoroquinolones were introduced in veterinary medicine since the extensive use in poultry was rapidly followed by the appearance of resistant Campylobacter.[33]

Figure 7. Total consumption of antibiotics in Europe 2001, presented in DDD per 1,000 inhabitant days. Results of the European Surveillance of Antimicrobial Consumption project retrospective data collection.[31]



Epidemiological trends

Increasing levels of resistant bacteria in Europe

The need for surveillance of antibiotic resistance is evident for several reasons. Following the changes in the prevalence of resistance is a necessary tool to guide the choice of antibiotics and to design and evaluate control measures that aim to contain antibiotic resistance. Resistance may spread easily between countries, and the situation in Europe is changing due to increased travelling, immigration, ageing populations and increased patient mobility. It is also important to be able to detect new clones that are brought into Europe from countries where resistance levels are generally higher.

In 1999, the EU Commission established a Community Network for Epidemiological Surveillance and Control of Communicable Diseases, and one area it covers is antibiotic resistance. The EU Commission supports the European Antimicrobial Resistance Surveillance System (EARSS). Other European Networks generating information on antibiotic resistance are Enter-net*, EuroTB** and Hospitals in Europe Link for Infection Control through Surveillance (HELICS)***. The most important conclusion from these programmes is that antibiotic resistance is increasing in all major pathogens in the majority of European countries.[34-37] It is anticipated that antimicrobial resistance will be one of the work areas for the European Centre for Disease Control and Prevention.

This report mainly uses data from EARSS to describe the epidemiological trends of antibiotic resistance. EARSS is a laboratory-based network of national surveillance systems that started in 1999, covering over 700 laboratories that serve 1100 hospitals in 28 European countries and contains comprehensive data concerning resistance for clinically important pathogens. Data is collected on invasive isolates from patients with blood infection and meningitis. In such infections, adequate empirical treatment is crucial because inadequate initial treatment may increase mortality and morbidity. At present, EARSS covers antibiotic resistance in *Streptococcus pneumoniae, Staphylococcus aureus, Escherichia coli, Enterococcus faecium* and *Enterococcus faecalis.*

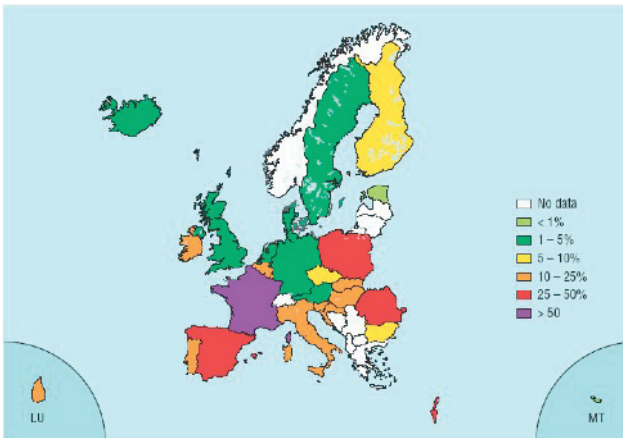
In the following sections, a model will be given for the above-mentioned pathogens. This is a far from comprehensive map of all important bacteria, but may serve as an alarming example how resistant bacteria are distributed in European countries.

Streptococcus pneumoniae

Streptococcus pneumoniae is the single most important cause of infections of the lower respiratory tract in adults and children, some of which (such as pneumonia) are potentially life threatening. It is also the main cause of otitis media in children and causes severe meningitis in children and the elderly. Penicillin and other beta-lactam antibiotics have been the drugs of choice since the 1940s. However, a steady decrease of penicillin susceptibility has been reported from many countries worldwide in the past two decades. As shown in Figure 3, there is a clear relationship between increased antibiotic consumption and increased levels of resistance in pneumococci.

In 2002, the proportion of penicillin non-susceptible *Streptococcus pneumoniae* (PNSP) was over 25% in France, Israel, Poland, Romania and Spain, the highest percentage being in France at 53% (Figure 8). Many PNSP strains were also resistant to erythromycin, which is of dual public health importance as it not only affects the clinical management of infections, but also means that the antibiotics, to which a pathogen has developed resistance, independently facilitate the success of co-resistant clones (Figure 9).

Figure 8. *Streptococcus pneumoniae*: invasive isolates non-susceptible to penicillin in 2002. [38]



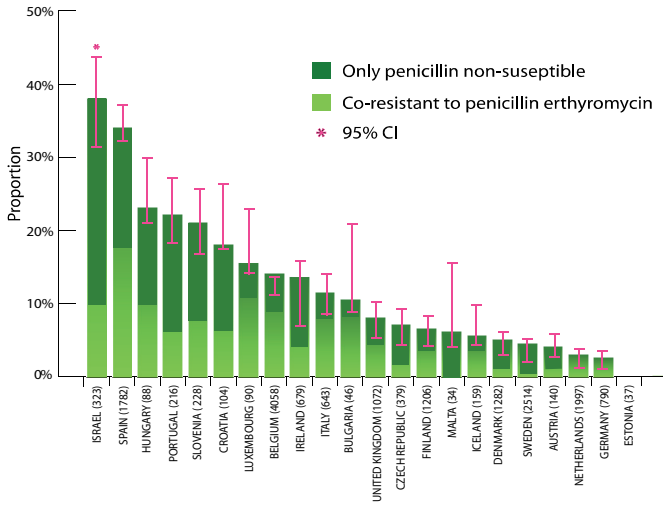
LU = Luxenbourg MT= Malta

* Enter-net is the international surveillance network for enteric infections and monitors Salmonella and verotoxin-producing Escheria coli O157 infections. It is also concerned with surveillance of antibiotic resistance in enteric pathogens.

** EURO-TB is a specific network for the surveillance of TB in Europe and provides epidemiological information for improving TB control. Since 1999, this programme has included surveillance of drug resistance as a key component.

*** HELICS 'main objectives are to produce an inventory of the number of infections and antimicrobial resistance control activities in the EU and to propose ways to harmonize these efforts, which include surveillance.

Figure 9. *Streptococcus pneumoniae*: invasive isolates non-susceptible to both penicillin, and erythromycin (co-resistant), or penicillin only, shown by country for the period 1999–2002 (Only isolates that were tested for both penicillin and erythromycin for the countries with at least 20 isolates reported in the period 1999–2002 were included). [38]

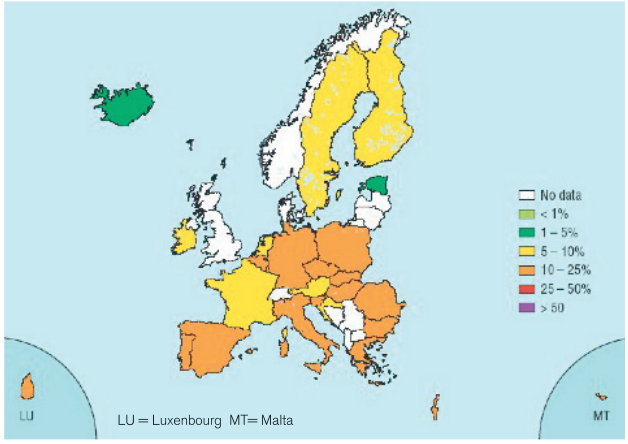


Escherichia coli

Escherichia coli is the most common Gram-negative bacterium isolated from blood cultures in clinical settings.

It is the most frequent cause of community and hospital-acquired urinary tract infections; it is associated with peritonitis; it causes synergistic wound infections; and it is one of the most important food-borne pathogens. Broad-spectrum penicillins such as amoxicillin were the treatments of choice before resistance started to emerge and to a large extent made them ineffective. In 2002, the proportion of *E. coli* isolates resistant to aminopenicillins was more than 30% for all countries in the EARSS study except for Sweden and Finland (Figure 10).

Figure 10. *Escherichia coli*: invasive isolates resistant to fluoroquinolones in 2002.[38]



In most European countries, the proportions of isolates resistant to third-generation cephalosporins remained at 6% or less in 2002. The highest levels of third-generation cephalosporin resistance were found among some of the south-eastern European countries: Bulgaria (13%), Israel (8%) and Romania (18%). In general, levels of fluoroquinolone resistance reached 10% or more in 2002 (Figure 10) and in 16 out of 21 countries the trend is increasing. The consistency of this finding reflects a worrying trend and might be a consequence of the widespread use of newer fluoroquinolones with enhanced broad-spectrum activity.

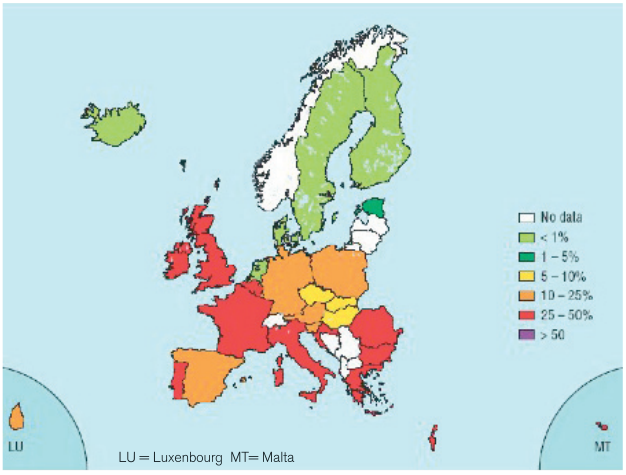
Staphylococcus aureus

Staphylococcus aureus is one of the most virulent human pathogens and is the leading cause of bone, joint and soft-tissue infections acquired in hospital and in the community. It also causes blood stream infections and endocarditis, and it is a frequent cause of food poisoning.

Since the emergence of the first strains with resistance to anti-staphylococcal penicillins, methicillin-resistant *Staphylococcus aureus* (MRSA) has spread throughout the world. MRSA has become a symbol of antibiotic-resistant bacteria and is without doubt one of the best-studied pathogens. Since the 1980s the frequency of isolates of MRSA among *Staphylococcus aureus* has increased from close to zero to nearly 70% in Japan and the Republic of Korea and around 40% in the USA.[40] An increasing number of MRSA strains are susceptible only to vancomycin and other glycopeptides, but decreased vancomycin susceptibility has now emerged within all pandemic MRSA lineages.[41]

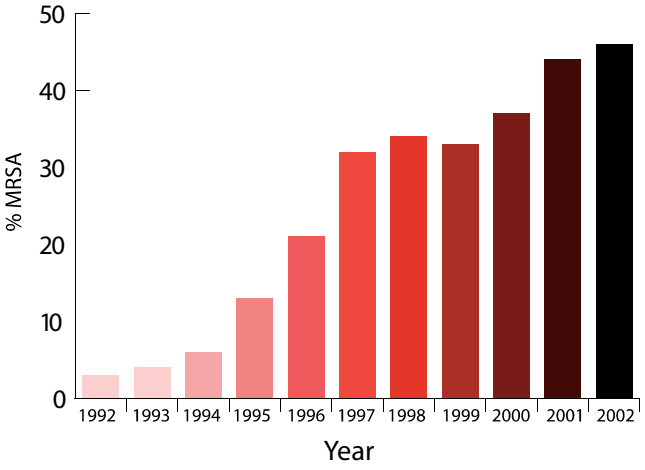
A steadily increasing trend is seen within European countries with MRSA levels around 40% in the UK, Ireland, Greece, Italy, Malta and Portugal (Figure 11). Over the last four years the most rapid expansion has been seen in Germany and Austria: from 8 to 19% and from 5 to 11%, respectively.

Figure 11. *Staphylococcus aureus*: invasive isolates resistant to methicillin (MRSA) in 2002. [38]



MRSA has been more successful than other bacteria in spreading extensively in the hospital setting, where epidemic clones quickly exploit ecological opportunities. One striking example of the rapid dissemination of such clones is the MRSA epidemic in England and Wales where the frequency of MRSA among Staphylococcus aureus in blood cultures increased from less than 5% in 1993 to present levels of just below 50% (Figure 12).

Figure 12. The frequency of MRSA among blood cultures with *Staphylococcus aureus* in England and Wales 1992-2002. [42]



The problem of MRSA is greater in intensive care units (ICUs) than in other hospital wards or in the community. A multicentre study in 17 European countries revealed that rates in ICUs were approximately 80% in Italy and France, 77% in Greece, 67% in Portugal and Belgium, 54% in Spain, 53% in Austria and 37% in Germany.[43] Another study investigating blood isolates from 25 European centres in 1997 showed a mean MRSA prevalence at ICUs of 39%, although levels varied widely between and within countries.[44]

Recently, considerable epidemiological research has been directed at the spread of MRSA strains in the community setting. These MRSA strains seem to arise independently of local nosocomial strains and tend to be more virulent than hospital clones. They often infect healthy young people who do not have the typical risk factors, such as recent hospitalization, chronic disease, immunosuppression, or recent antibiotic therapy.[45] Strains producing a special cytotoxin (Panton-Valentine leukocidin cytotoxin) are particularly associated with severe skin infections and necrotizing pneumonia.[46]

Precise data on the growing threat of community-acquired MRSA (CA-MRSA) are clearly lacking. A recent meta-analysis including studies from Portugal and the United Kingdom estimated the prevalence to be between 0.2 and 1.3%.[47] The number of people carrying these bacteria, as well as how many of them eventually develop a clinical infection is largely unknown.

Enterococci

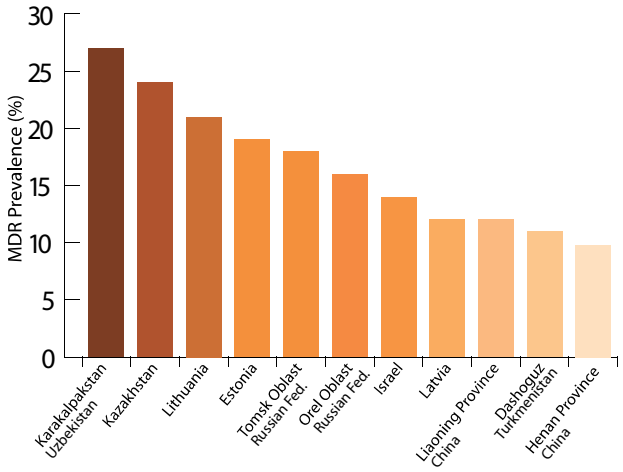
Although not as virulent as the other pathogens recorded by the EARSS, enterococci are common causes of urinary tract infections and are frequently involved in intra-abdominal infections. They cause endocarditis, and are opportunistic pathogens in immuno-compromised patients, where they cause septicaemia, meningitis and bone infections. With their outstanding ability to collect genetic elements coding for resistance mechanisms, enterococci were the first significant human pathogens to develop full resistance against third-line glycopeptide antibiotics (vancomycin and teicoplanin). Vancomycin-resistant enterococci (VRE) are one of the most prominent examples of pathogens approaching the post-antibiotic era.[48] The spread of this mechanism to other pathogens, such as MRSA, would be serious.

The proportion of vancomycin-resistant *E. faecium* among all enterococcal isolates was reported to be above 10% in Ireland, Italy, Greece, Croatia and Romania in 2002, and it was between 5% and 10% in Germany, Austria, the Czech Republic and Israel. However, the European picture is incomplete since EARSS does not yet receive data from all countries.

Mycobacterium tuberculosis

In TB the problems with multi-drug resistant (MDR) strains are dramatic. A total of 300 000 cases of MDR strains is seen globally, out of which around 80% are resistant to three or four first-line drugs.[49] Figure 13 illustrates the situation in countries with MDR-TB prevalence above 10% of total TB cases. In Central and Western Europe the prevalence of MDR-TB is generally low, with a median prevalence below 1%. However, trends are increasing trends in Germany, Poland and Spain. In Eastern Europe and the former Soviet Union, patients infected with TB are 10 times more likely to have a multi-resistant strain. In Estonia it appears that the increase in MDR-TB strains during the 1990s has been contained, whereas in Latvia and Lithuania there are steady increases in the prevalence of MDR-TB.

Figure 13. Countries/settings with combined MDR prevalence higher than 10%, 1999-2002. [49]



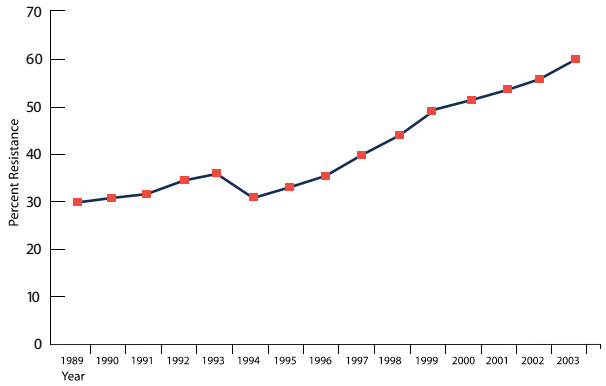
Antibiotic resistance in other regions

USA

The continuing increase in antibiotic resistance in US hospitals remains a concern. In intensive care units, the proportion of MRSA isolates continues to rise and has now reached more than 55% in ICUs (Figure 14).[50] In addition, the level of resistant enterococci (VRE) is increasing and now represents 27.5% of all enterococcal infections in critical care.

MRSA in the community is an increasing problem in the USA with several alarming outbreaks in the last years. In a paediatric hospital in Chicago, the prevalence of MRSA during 1988-1990 was compared with the prevalence during 1993-1995. In children community-acquired infections had risen from 10 cases per 100 000 admissions to 259 per 100 000, a 25-fold increase.[51] Additionally, deaths in children have been reported in cases where they were admitted to hospitals with community-acquired MRSA infections that were treated empirically with cephalosporin antibiotics, ineffective in such cases.[52] This leads to a further shift in empiric therapy for community-acquired infections towards antibiotics normally restricted to critical care.

Figure 14. Proportion of *S. aureus*, nosocomial infections resistant to oxacillin (MRSA) among intensive care unit patients in the USA, 1989-2003.[50]

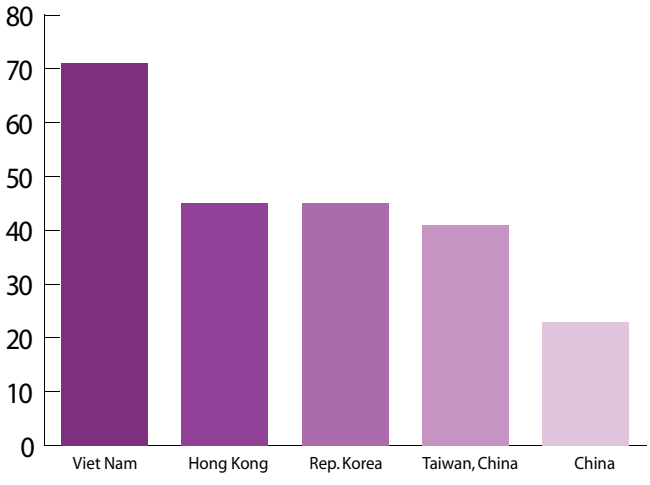


Asia

Asia is one of the regions where the resistance problem is most prominent. In particular, the rates of resistant pneumococci in Asian countries have been alarming. The Asian Network for Surveillance of Resistant Pathogens, ANSORP, was initiated in 1996 and recently reported the results of the third project of surveillance for pneumococcal resistance among clinical *S. pneumoniae* isolates collected from 14 centres in 11 countries in Asia and the Middle East between 2000 and 2001 (Figure 15).[53]

Isolates from Viet Nam showed the highest prevalence of penicillin resistance (71%), followed by those from the Republic of Korea (55%), China, Hong Kong Special Administrative Region (43%), and Taiwan, China (39%). The prevalence of erythromycin resistance was also very high in Viet Nam (92%), Taiwan, China (86%), the Republic of Korea (81%), Hong Kong SAR (77%), and the People's Republic of China (excluding the Province of Taiwan and Hong Kong SAR) (74%). Isolates from Hong Kong SAR showed the highest rate of ciprofloxacin resistance (12%), followed by isolates from Sri Lanka (9.5%), the Philippines (9.1%), and the Republic of Korea (6.5%). Escalating levels have been seen for multiresistant Salmonella and Shigella, which cause severe infections that are difficult to treat, especially in children. In a recent report from Japan where travellers had acquired infections with Shigella in Indonesia, Thailand and India, 80-90% of the strains were resistant to two or more antibiotics.[54]

Figure 15. Multi-drug resistance in Asia: Pneumococcal resistance.[53]



The disease burden of antibiotic resistance

Infectious diseases are the second leading cause of mortality in the world, resulting in more than 11 million deaths annually.[1] The burden of bacterial infections continues to rise, with changing patterns of microbial aetiology, an increase in the number of hosts with impaired immunity, ageing Western populations, and the spread of disease through globalization and urbanization. With the exception of multi-drug resistant TB, for which the evidence is compelling, published data concerning the impact of antibiotic resistance are increasing, but remain incomplete.

Estimating disease burden and mortality caused by resistant bacteria is a difficult and challenging task, because it involves diverse pathogens, transmitted in unique ways, which cause a wide range of diseases. The consequences for the patient such as a prolonged disease or increased mortality, that could be attributable to antibiotic resistance, are hidden within a variety of clinical syndromes and are difficult to measure. Since antibiotic resistance is not by itself a disease entity, invisibility characterizes the issue, making it unknown and faceless for many people outside the medical field.

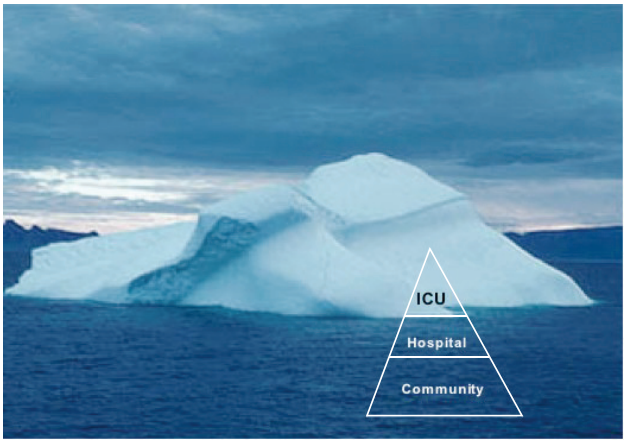
At present there is no systematic prospective collection of data on deaths resulting from infections caused by resistant bacteria. Despite the high mortality rate in infections, death certificates are generally not designed to register whether the causative pathogen was resistant to the antibiotic therapy given or not. This is very unfortunate, as resistance to therapy is a significant cause of fatality in many cases.[55-58] As long as there is no system to report this, e.g. a diagnosis code, resistance will not appear as a significant cause of mortality on a larger scale.

The previously continuous development of new antibiotics made it possible, in countries where new drugs are affordable, to change the therapy to new antibiotics when resistance levels to older ones became 'uncomfortably' high. This has not been possible in developing countries where many of the second- and third-line therapies for drug-resistant infections are unavailable due to cost, making the potential harm of resistance to first-line antibiotics considerably greater. The limited numbers of antibiotics in these countries are becoming increasingly inadequate for treating infections, and antibiotics necessary to deal with infections caused by resistant pathogens are absent from many essential medicines lists.[59] The situation is also changing in industrialized countries. Because of the scarcity of new drugs in the pipeline, clinicians are now facing a situation where the likelihood of success from empiric antibiotic treatment is reduced.

Public health impact

Through the selection pressure caused by antibiotic use, a large pool of resistance genes has been created. Slowly, as the health impact is emerging, we are starting to see the "tip of the iceberg". The consequences are most evident in severe infections in hospital settings, especially at ICUs where the antibiotic pressure is highest and the selection of resistant bacteria is greatest (Figure 16).

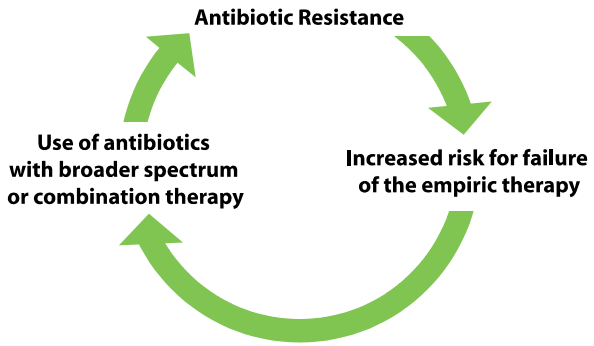
Figure 16. The increasing health impact of resistance is most visible in the critical care area.



At present, this is most evident in Staphylococcus aureus where the mortality from bloodstream infections without effective antibiotic treatment is high. In the case of MRSA, studies repeatedly show the mortality to be double that in infections with non-resistant strains, after considering differences in severity of illness and underlying disease of affected patients.[57, 58] Failure of the initial antibiotic regimen due to resistant bacteria increases the risk of secondary complications and fatal outcome, underscoring the clinical dilemma of empirical therapy and the prevailing lack of rapid diagnostic tests.

Consequently, in many situations there is a clear justification for initial broad-spectrum therapy in severe infections. This moves us into a vicious circle where increasing levels of resistance necessitate the use of broader, more potent antibiotics to secure patient survival, but where using these reserve antibiotics exacerbates the problem as resistance develops and creates a situation where effective antibiotics are lacking (Figure 17).

Figure 17. The clinician's dilemma of empiric therapy.



In today's society, a growing number of people need effective antibiotic treatment. We see an ageing population with an increased need of health care and effective drugs. With high-risk patients – such as those having cytostatic therapy for cancer, transplantation surgery, or implantation of prostheses - treatment to prevent infections and to deal with complications is essential. Other susceptible groups who depend on effective antibiotics are premature babies with undeveloped immune defence and immunocompromised patients, such as those with HIV/AIDS. The emergence of antibiotic resistance is thus threatening our chances of successfully treating these particularly vulnerable groups.

In conclusion, knowledge of the full magnitude of the consequences for society is still in its infancy, but awaiting more data before taking further action to contain the development of resistant bacteria is unjustifiable. At the individual level, patients infected with resistant bacteria are less likely than those infected with sensitive bacteria to recover from infections. They may require additional investigations and additional treatments, which often includes an increased risk for toxic adverse effects. As shown in many studies, delayed effective therapy will lead to longer hospital stay and longer periods of time away from work. The most serious effect of resistant bacteria for the individual is the increased likelihood of remaining sequelae and of premature death.[55-58, 60, 61]

The economic costs of antibiotic resistance

Besides the medical consequences, antibiotic resistance is associated with large costs to society. The most concrete example and the easiest to measure is the cost of drugs, as new empirical treatments are needed to combat resistant pathogens. Antibiotics make up 20-30 % of a hospital drug budget.[62] The increasing prevalence of MRSA described in previous sections inevitably drives changes to empirical and prophylactic regimens in favour of much greater use of glycopeptides.[63] Calculations made in a hospital suggest that this shift in therapy would increase the total antibiotic budget by 100%. The second cost of increasing use of glycopeptides is a microbiological one, in the form of a rising prevalence of vancomycin-resistant enterococci.[64]

Among other factors that influence the cost are increased length of hospitalization, increased risks of complications and mortality, costs associated with isolation of patients and the need to temporarily dismiss carriers of resistant bacteria within the staff.

In 1995, estimates of the annual health care costs associated with the treatment of resistant infections in the USA reached over US$ 4 billion.[65] In a single district general hospital in the United Kingdom, the cost of containing an MRSA outbreak in 1995 was more than £400,000 (approximately US$ 753 000).[66] The figures produced so far probably underestimate the total current costs of resistance, as they are limited to health care costs, the majority of these being incurred by the health care system. Furthermore, none of these calculations include any estimate of costs to be incurred by future generations, which almost certainly will be larger than those being experienced currently.

The economic and health costs of resistance, serious enough in the industrialized world, are often made more severe in developing countries.[67] The economic and health systems and infrastructures of these countries, resulting in irregular supply and availability of drugs and often a dependence on unofficial sources, have led to extensive and inappropriate use of antibiotics. This has led to infections from strains far more resistant than those currently encountered in high-income countries.

From an economic perspective, antibiotic resistance is considered as a negative externality, i.e. the cost imposed on others/society is not taken into account during the decision to manufacture or consume antibiotics. Time preference, i.e. the level of willingness to trade current advantages against future costs and benefits, is an economic concept that may be useful to deal with negative externality. In one attempt, where this economic model was used, the financial burden on society for the USA was estimated between 75 million and 35 billion dollars annually. This broad range is largely attributable to the uncertain contribution of mortality and a debatable value of life. In the calculation a 'per dose annual loss' was used to express the societal cost associated with each single antibiotic prescription and was multiplied by the number of prescriptions. Estimates which are mainly intended to give an impression of the order of magnitude of the resistance problem in Europe indicates that the excess mortality of MRSA cases is approximately 1,300 deaths annually.[68] The cost of MRSA bloodstream infections, which is only one of many bacteria with antibiotic resistance, is estimated at 117 million Euro a year. The annual costs of MRSA bloodstream infections alone already exceed the EU budget for antimicrobial resistance research for 1999-2002.

What are the current control strategies?

Over the years a number of national and international programmes have developed, particularly in Western Europe and North America.[69] Many of the key components in these programmes are common, e.g. surveillance of resistance patterns and antibiotic consumption, the encouragement of appropriate use, and promotion of infection control. Yet, there remains a pressing need for the implementation of effective actions to address these issues. Furthermore, research is necessary to fill the substantial gaps in our knowledge as little is known about the effectiveness of the many types of interventions aimed at controlling resistance.[70]

European Union

In 1998, The Economic and Social Committee of the EU (ECOSOC) published its own-initiative opinion "Resistance to antibiotics as a threat to public health". The same year, the meeting, "The Microbial Threat" was arranged in Copenhagen and, in 1999 the Council of the EU adopted a resolution, entitled 'A Strategy Against the Microbial Threat'.[71] This resolution urged Member States to promote national programmes for the prevention and control of infectious diseases in humans. The Council stressed the need for a multidisciplinary and cross-sectoral approach, for an overall strategy, and for coordinated action. The resolution was soon widened to include the principle of restricted antibiotic use in veterinary medicine, in animal feed and plant production. In 2001, a communication from the Commission, 'Community Strategy Against Anti-microbial Resistance', was launched. This proposes four key areas for action:

- **Surveillance:** monitoring the evolution and the effects of interventions through the establishment/strengthening of accurate surveillance systems on antimicrobial resistance in the human and veterinary sector and the consumption of antimicrobial agents.
- **Prevention:** prevention of communicable diseases and infection control to reduce the needs for antimicrobial agents.
- **Research and product development:** new modalities for prevention and treatment of infection and continued support for research into new drugs and alternatives.
- **International cooperation:** an effective strategy requires close cooperation and consultation between the Commission, the EU Member States and other involved parties, especially at international level.

In 2001, the Council issued a "Recommendation on the Prudent Use of Antimicrobial Agents in Human Medicine", which is the most powerful document so far within the EU concerning antibiotic resistance.[72] Apart from the recommendation to ensure that specific strategies targeted towards prudent antibiotic use and containment of resistance exist and are implemented, the document recommends Member States to have an intersectoral mechanism in place to coordinate the implementation of strategies. Member States should report to the Commission within two years on the implementation of the recommendation.

The European Parliament, on the basis of the precautionary principle, later agreed legislation to address the fact that antimicrobial agents also enter humans through the food chain via their use in veterinary medicine, animal rearing and crop cultivation. Furthermore, the European Parliament recommended that the effectiveness, and hence necessity, of routine preventive use of antimicrobial agents should be evaluated, as should the effectiveness of vaccines.

In summary, the Council Recommendations and the European Commission Communication represent important steps at the European level for a multifaceted approach to containing the problem of antibiotic resistance. It is foreseen that antibiotic resistance will be one important task of the new European Centre for Disease Control and Prevention.

National programmes

In Europe, national programmes exist in several countries, and the main target is usually to contain resistance in the community outpatient setting, where the majority of antibiotic use occurs. The community setting represents a 'macro' system with a large number of relatively isolated prescribers who are difficult to reach. Prescriptions for antibiotics in the community are, in the vast majority of cases, purely empiric and issued without previous cultures or other microbiological diagnostic tests. Also, community physicians are

subject to various pressures to prescribe antibiotics, even in situations that do not require them (e.g. from patients, health systems, physician's own concerns regarding infective complications, and potentially from inappropriate pharmaceutical industry marketing). Comprehensive, nationwide programmes are needed to overcome the development and spread of resistance in the community. Common methods for existing national control strategies are focusing on:[69]

- Surveillance of antibiotic use and resistance rates
- Optimizing antibiotic use with treatment guidelines and diagnostic testing
- Education of professionals and the public
- Prevention with infection control measures and immunization
- Industry involvement and drug development
- Regulatory issues with central prescribing restrictions and advertising restrictions
- Audit with evaluation of interventions, audit of compliance and physician feedback
- International cooperation

In contrast, hospitals represent a 'micro' ecological system in which microbiologic surveillance of resistance, control of antibiotic prescribing, and the provision of feedback to prescribers regarding the impact of interventions to control resistance are relatively easy. The effectiveness of interventions combining transmission control (hygiene) and antibiotic usage control in hospitals has been demonstrated in several hospitals.[69] These have been successful in numerous very specific conditions, as measured by decreased antibiotic use and reduction in resistance rates. For instance, limiting third-generation cephalosporin and glycopeptide use has been shown to reduce the prevalence of extended spectrum beta-lactamase-producing Klebsiella pneumoniae and vancomycin-resistant enterococci.[73]

USA

In the USA, the Centers for Disease Control and Prevention (CDC) have collaborated with nine other federal agencies, including the Food and Drug Administration and the National Institutes of Health, to form the Interagency Task Force on Antimicrobial Resistance.[74] In 2001, this group published Part 1 of its 'Public Health Action Plan to Combat Antimicrobial Resistance', focusing on domestic actions. In common with many other published recommendations, the Interagency Task Force takes a broad-based approach to controlling resistance to all antimicrobials (i.e. those active against bacteria, viruses, fungi, etc.). It defines a series of goals and national actions focusing on surveillance, prevention and control, research, and product development. For each action, the coordinating and collaborating organizations involved are named and broad timelines for initiation (stretching over 5 years) are given. Implementation of the plan will be incremental, contingent upon resources, and hence 13 'Top Priority Action Items' are highlighted.

World Health Organization

WHO published the comprehensive "Global Strategy for the Containment of Antimicrobial Resistance" in 2001.[15] This document was developed after wide-ranging international consultation with all the sectors involved, including infectious disease practitioners, professional and scientific societies, national governments, industry representatives, consumer groups, and veterinary groups. It focuses particularly, though not exclusively, on resistance to antibacterial drugs with the stated aim being "to provide . . . a framework of interventions to stimulate the prevention of infection, to slow the emergence of resistance and to reduce the spread of resistant micro-organisms, to reduce the impact of resistance on health and health-care costs, while improving access to existing agents and encouraging the development of new agents".

The numerous interventions recommended are grouped under the following six key areas:

- reducing the disease burden and spread of resistance
- improving access to appropriate antibiotic therapy
- improving antibiotic use
- strengthening health-care systems and their surveillance capacities
- enforcing regulations and legislation
- encouraging the development of appropriate new antibiotics and vaccines.

Antimicrobial use in animals is integrated but not emphasized as most of the interventions in the Global Strategy concern human medicine. The document stresses the importance of concerted international actions, it also offers some guidance on the implementation of the specific interventions at national level.

Why does the problem persist?

Global level

International collective action is essential to tackle the global resistance problem. Yet, as responsibility for health remains predominantly national, there is a potentially significant disparity between the problems and potential solutions associated with antibiotic resistance and the institutions and mechanisms available to deal with them.

The comprehensive WHO Global Strategy includes all the well-known measures for containment of resistance. However, it is not user-friendly for the Organization's Member States, as there is little guidance on prioritizing the 67 recommendations made. The need for selecting the right interventions in different contexts is crucial and this is one reason why the Strategy has to some extent become more a knowledge bank and reference manual than an instrument for implementing concrete, achievable measures in different contexts. The responsibility for implementation falls on individual countries, and where the need is most evident, e.g. in developing countries, other health issues are at present overshadowing the threat of antibiotic resistance.

The EU has very limited powers to influence its Member States on health care issues. At present, there are no effective tools to ensure implementation of recommendations in any health matter, including containment of antibiotic resistance. In practice, the strong recommendations from the Council to develop national strategies within a year and a planned evaluation report after two years may well be disregarded. This is unfortunate as the EU has been successful in other global matters such as environmental issues, prohibiting use of certain chemical compounds and improved practices in dealing with animals. The difficulties in finding a way to enforce recommendations at global level are evident. At present, the links between the proposed strategies at the level of global society and their acceptance by national policy-makers are weak. Identifying these barriers and overcoming them are still major challenges.

National level

For many years, medical professionals in the academic setting have defined antibiotic resistance as a major public health problem. The issue has also received increased attention from several international bodies and is now more generally recognized as a threat to global health. Still, the consequences have not been sufficiently convincing to place this issue high on the political agenda in individual countries. There may be several reasons for this.
Firstly, public funding for research on antibiotic resistance has been low. In most industrialized countries the problem has been considered an annoying but inevitable side-effect of antibiotic use, and the epidemiological and societal aspects of antibiotic resistance have been neglected while the research agenda has been decided by the pharmaceutical industry. This way of looking at the problem has been detrimental and has caused a situation where today we face many fundamental knowledge gaps, including the health and economic consequences of antibiotic resistance, especially in the community.

Secondly, to find the right tools to describe the disease burden and economic consequences has been difficult, as antibiotic resistance is not of itself a disease entity but is hidden within all infections, which makes the issue less concrete to deal with than other major health threats, such as HIV, TB and malaria. This invisibility along with the complexity of the issue has prevented a clear and consistent message from reaching politicians and making them act.

Thirdly, because of the previously continuous development of new antibacterial agents it has been possible, in countries where new medicines are affordable, to change the therapy to new antibiotics when resistance levels to older ones have become too high. This has not been possible in poor countries where many of the second and third-line therapies for drug-resistant infections are unavailable, making the danger of resistance to first-line antibiotics considerably greater. The limited numbers of antibiotics in these countries are becoming increasingly inadequate for treating infections, and the necessary antibiotics to deal with infections caused by resistant pathogens are absent from many essential medicines lists.[59] The situation is now changing in industrialized countries, too. Because of the virtually empty pipeline of new drugs, clinicians are facing a situation where the likelihood of success from empiric antibiotic treatment is reduced and where patients are sometimes infected with bacteria resistant to all available antibiotics.

Consumers and providers

To change behaviour and reduce unnecessary antibiotic use, health care providers and patients must be convinced that the benefit to the global community offered by appropriate antibiotic use does not translate into increased risks for individual patients. This is an intricate task in a society that is becoming increasingly individualistic. In general, the clinicians' perspective is focused primarily on individual patients and, to a lesser degree on public health concerns. Uncertainty in diagnostics, together with limited possibilities to follow up

patients' progress, creates further concern over the outcome. This uncertainty leads to 'overkill' in treatment, as the fear of not covering the bacteria causing the infection favours the choice of an antibiotic with a broader spectrum or combinations of several agents.

Prescribing of antibiotics is influenced by numerous factors indicating that incentives and barriers may be as important as knowledge in the use of antibiotics. Along with actual and perceived patient demands to receive an antibiotic prescription there are often economic reasons to prescribe. In several countries, the financial incentives for physicians to prescribe new and expensive broad-spectrum antibiotic agents are obvious, since there is often no separation of prescribing and dispensing. In industrial countries physicians might fear legal consequences if they fail to secure adequate treatment in every situation, leading to over-prescribing to relieve the doctor of anxiety. The possibility for individuals to turn directly to drug dispensaries without first consulting health personnel is widespread globally. In all Member States of the EU antibiotics are 'prescription-only' drugs, but still over-the-counter sale is common in some countries, reflecting the prevailing lack of enforcement of existing regulations.

Although 'prudent' antibiotic use, a term often interpreted as 'restricted' use, has been advocated to counteract the threat of resistance, its practicability has not been explored. It is obvious that 'prudent' antibiotic use excludes inappropriate use, e.g. for the management of viral infections, or for extended periods in the case of routine surgical prophylaxis. However, whenever there is uncertainty in the clinical diagnosis and/or in the aetiology of the infection, 'prudent' antibiotic use turns out to be an ill-defined 'grey area', and a matter of personal experience rather than a clear-cut concept. For some infections, e.g. otitis media, the early use of antibiotics is still controversial, and different countries have different medical practices.[75] Studies are needed to evaluate the outcomes of these infections according to the therapeutic strategy employed, including the withholding of antibiotics.

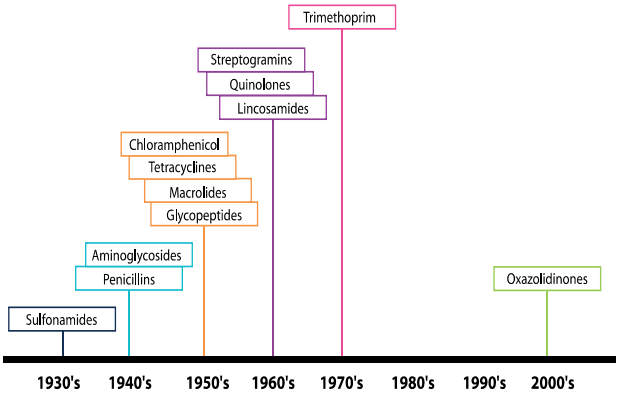
Research into past and present pharmaceutical interventions: what can be learnt?

For many years, society's medical needs for antibacterial drugs were met by the pharmaceutical industry. An apparent symbiosis between the interests of the community and those of the industry prevailed. In the 1970s, innovative research to develop new antibiotics gradually waned, and the focus of R&D shifted to modification of existing antibiotic classes. Although such developments have been important to improve the drugs' antibacterial spectrum, pharmacokinetics and pharmacodynamics, these modified antibiotics are basically using the same mechanism to attack bacteria as the preceding ones, making it easy for bacteria to develop resistance to the drugs. The insecure durability of antibiotics, as a result of emerging resistance, is one of the reasons why the development of new products is decelerating. The industry is increasingly weighing up its responsibilities towards shareholders on the one hand, and public trust and accountability to the community at large on the other. The split between public and private interests has grown wider with the development of national and international medicines policies aimed at containing resistance and restricting and rationalizing the use of antibiotics. Heightened demands from regulatory bodies have increased the development cost of new medicines, and prioritizing measures to secure optimal returns on investment have driven the industry into other pharmaceutical areas with bigger and safer markets. At present, the industry's ventures are shifting from therapy for acute conditions towards long-term treatment of chronic diseases. Prospective investments in antibiotics are more than ever competing with drugs for musculoskeletal and neurological diseases with 10 or 15 times greater 'Net Present Value', a measure used by industry to predict the potential success of products. However, the need for antibiotics is anticipated to remain consistently high. From a broad societal perspective, the industry might be expected to supply communities with effective drugs, which correlate with the medical needs. Today, in the field of antibiotics, this is not the case and new ways must be sought to stimulate R&D to curtail the increasing disease burden caused by resistance to antibiotics.

Antibiotic development

Following the development of penicillin as a commercial antibacterial during World War II, most other major classes of antibacterial drugs, such as cephalosporins, tetracyclines, macrolides and quinolones, were discovered between the end of the 1940s and the early 1960s (Figure 18). This was done mostly by screening cultures of various microorganisms for antibiotic activity. Following the discovery of a new class, R&D then focused on extending the antibacterial spectrum of existing compounds by means of semi-synthetic optimization. One early example in the 1950s was the development of penicillinase-resistant penicillins to treat infections caused by penicillin-resistant staphylococci that had emerged following the therapeutic use of penicillin.

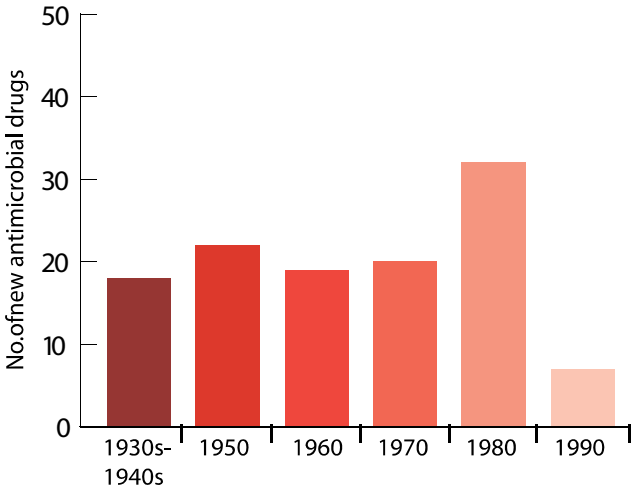
Figure 18. Discovery of new classes of antibacterial drugs.[76]



During the 1960s and 1970s, the antibacterial drug industry emerged globally with high return of investments and by the early 1970s, more than 270 antibiotics had been produced.[77] One example is the third and fourth generation cephalosporins, for which the market in 1980 was increasing at the rate of nearly 30% a year.[78] Already then, there were so many antibiotics on the market that the projected profits from the development of new drugs were seriously reduced.[79] As the antibiotic field became increasingly saturated, other markets grew rapidly. Pharmaceutical companies started to invest in R&D of new drugs for chronic

illnesses, where long-term daily treatment meant higher profits. This development is considered one of the major reasons for the scarcity of new antibiotics in the 1990s (Figure 19).[79]

Figure 19. Discovery of new antibacterial drugs.[80]



In 1991, approximately 50% of large pharmaceutical companies had ended, or seriously decreased, their funding of antibiotic research programmes because of the unfavourable financial prospects.[81] However, the increased frequency of multi-resistant bacteria especially in hospital settings, created a niche market for drugs that potentially could overcome this development. This market opportunity may have been a driving force behind the development and commercialization of the antibiotics from the mid-1990s onwards (Table 1). Among these oxazolidinone is the only truly new class of antibiotics.

Table 1. Recently approved antibiotics. [4, 82-86]

COMPOUND	CLASS
Quinupristin-dalfopristin	Synergistin (close to macrolide)
Linezolid	**Oxazolidinone (new class)**
Moxifloxacin	Quinolone
Gatifloxacin	Quinolone
Gemifloxacin	Quinolone
Cefditoren	Cephalosporin
Ertapenem	Carbapenem
Telithromycin	Ketolide (close to macrolide)
Daptomycin	Cyclic lipopeptide
Telithromycin	Ketolide (close to macrolide)
Rifaximin	Rifamycin
Panipenem/betamipron[a]	Carbapenem
Tosufloxacin[a]	Quinolone
Pazufloxacin[a]	Quinolone
Prulifoxacin[a]	Quinolone

[a]Only in Japan.

Are incentives insufficient for the pharmaceutical industry?

Although potential new targets for antibacterial drugs are still being discovered, the question is whether these will be developed into drugs and marketed. The financial incentives for the pharmaceutical industry to bring a new antibiotic compound through the stages of drug development do not seem convincing enough. Consequently, we are facing a paradoxical situation with increased levels of resistant bacteria along with a downward trend in antibiotic development.

In 2002 the total worldwide revenue for the antibiotic market was US$ 26,9 billion and the market is estimated to grow to over US$ 30 billion within the next five years.[87] Despite that, 10 out of the top 15 pharmaceutical companies active in 2000 have since seriously curtailed or ceased research on antibiotics.[88-90] The number of scientists involved in antibiotic drug discovery, both in large pharmaceutical companies and in pharmaceutical biotech companies, has fallen dramatically, which means that a whole generation of scientists specializing in antibacterial drugs may be forced to change research area.[89] Whether through discovery of new agents, development of existing agents or in-licensing of potential agents, the efforts of those companies still interested in antibiotic development are now directed at finding compounds with commercial potential with expected annual sales of US$1 billion or more, so called 'blockbusters'. This will certainly result in a reduction in the number of future antibiotics[88] since very few reach the status of 'blockbuster'. In 2000, amoxicillin-clavulanate, with sales of US$ 1.3 billion, was the only antibiotic in the list of the top 20 prescription drugs [91] and ranked 16th despite intensive marketing.[92] Its sales were about one third those of anti-ulcerant Prilosec® and cholesterol-lowering Lipitor® listed as number 1 and 2 respectively.[91]

In the present environment, the pharmaceutical industry argues that the risks of marketing an antibiotic are considered higher than for other drugs. Among the reasons given are:

- Developing an antibiotic is potentially more difficult because it involves different bacterial species and infections at different body sites.

- New antibiotics must be as effective as existing ones against susceptible strains, but must also be effective against bacterial strains that have acquired resistance to existing drugs.

- Increasing concern about overuse and misuse among physicians and the general public has led to implementation of drug policies which are emphasizing rational use of antibiotics and a general decrease in antibiotic use in several European countries and in the USA.

- There is increasing pressure from health care and insurance systems to use fewer and cheaper antibiotics, and despite renewed alerts about emerging resistance, most infections, especially within the community, are still treatable with existing antibacterial drugs.[89]

- Some new agents specifically launched to target resistance have not captured their projected market.[89,93]

- Resistance to a new agent will eventually develop after a period of use of any new antibiotic, as shown by the recent reports of linezolid resistance in methicillin-resistant Staphylococcus aureus[94] and vancomycin-resistant Enterococcus faecium.[95]

In the pharmaceutical industry, various projects must be prioritized and a key parameter in this is the Net Present Value (NPV), which is the determination of the value of a given project after projecting expenses and revenues in the future and discounting for the potential investment value of the money that will be spent on the project.[89] The NPV is usually risk-adjusted, most risk being associated with the earlier stages of the project. Antibacterial drugs are not especially attractive when NPV is considered. One NPV estimation of an injectable antibiotic targeting Gram-positive bacteria was less than one tenth of that of a particular musculo-skeletal drug.[89] Oral antibiotics, which can be marketed in the community, are more attractive to the industry.

According to a 2001 estimate from the Tufts University Center for the Study of Drug Development, the average cost of bringing a pharmaceutical compound through screening, chemistry, pre-clinical development and clinical testing is US$ 800 million.[77] Although this figure has been cited by many, it has also been challenged. The Public Citizen/Congress Watch, for example, came up with the value of US$ 71 million, using another method of calculation, adjusting for tax deductibility of R&D expenses.[77] The truth probably lies somewhere in between. However, antibiotics have the first or second shortest mean and median clinical development time in every 4-year period since 1982, mostly because of the short duration of treatment and well-known endpoints for clinical trials, as well as the highest approval rate by the FDA since 1964, both of which should translate into fewer R&D expenses than for other drugs.[96] Obviously other factors, such as the NPV of a potential product, are of greater importance when deciding to invest in new antibacterial drugs.

Large pharmaceutical companies need annual sales of US$ 500-800 million to recoup R&D costs.[97] For a small biotech company annual sales of US$ 100-200 million, for example from an injectable antibiotic used in hospitals, may represent a substantial opportunity to recoup the investment.[97] However, the biotech companies that have prospered over the past eight years did not discover new antibiotics but were licensed to sell antibiotics discovered by others. Even more than large pharmaceutical companies, biotech companies depend on investors, who have been very cautious because expensive investments in genomics, combinatorial chemistry and high throughput screening failed to deliver new useful compounds.

Difficulties in attracting venture capital and a more stringent economic climate have forced many biotech companies to close, or at least to restructure. This often means a reduction in drug discovery efforts.[88] Due to limited financial stability, biotech companies are unlikely to make investments in the drug discovery phase, and if they do, they will not be able to finance development, which is significantly more costly.

Public resources for basic and applied research

Antibiotic resistance does not rank high on the lists of priorities for funding.[24] Nevertheless, Europe has recently started to prepare the ground for research in this area, and some funding for basic and applied research for the development of new antibacterial drugs and diagnostic tests is available. In the USA, funding priorities have partly shifted from a focus on emerging infectious diseases, including fighting antibiotic resistance, to the prevention of bioterrorism. The best example is Project Bioshield, which is a comprehensive effort on the part of the USA to develop and make available modern, effective drugs and vaccines to protect citizens against potential attack by biological and chemical weapons or dangerous pathogens. In July 2004 the Infectious Diseases Society of America, IDSA, launched the report 'Bad bugs, no drugs', which urges policy-makers in the USA to place the issue on the political agenda. [98]

Between 1999 and 2002, as part of its 5th Framework Programme for Research and Technological Development, the Directorate General for Research of the European Commission devoted around €40 million to research on

the development of new antibiotics and diagnostic tests, and more than €15 million to projects aimed at improving knowledge of antibiotic resistance epidemiology including interventions (See Annex 1).[99] Most of the R&D projects are conducted as partnerships between academia and small/medium-sized companies. Realizing that research in the EU was fragmented, the European Commission launched its 6th Framework Programme for Research and Technological Development under the name 'Integrating and strengthening the European Research Area'.[100] Since 2002, several areas of this Framework Programme have addressed or are presently addressing antibacterial-drug discovery and diagnostic tests (Table 2). Although it is too early to know how much will be assigned to each project, it could be expected that, e.g. for 2004, approximately €10-20 million, out of a total of more than €500 million, will be assigned to projects aiming to 'combat resistance to antibiotics' in the areas addressed by the call (Table 2).

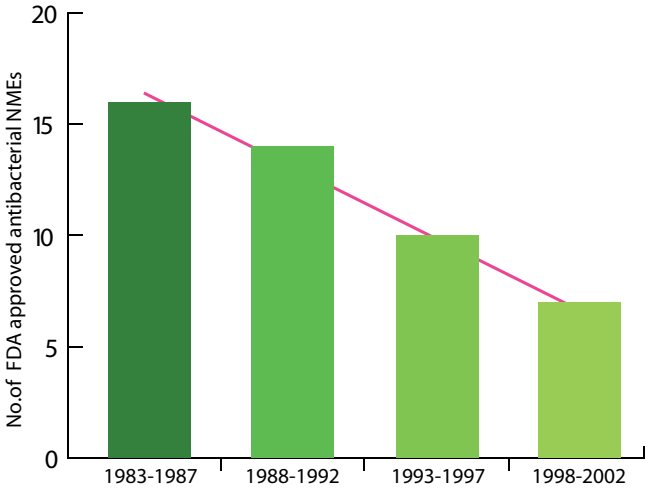
Table 2. Antibacterial drug research areas addressed in calls for the 6th EU Framework Programme for Research and Technological Development 'Integrating and Strengthening the European Research Area', 2002-2004.[100]

Year	Area addressed
2002	Broadening the knowledge base on the molecular mechanisms behind resistance
2003	Functional genomics of antibiotic-producing organisms New molecular targets for the development of drugs against pathogens causing severe resistance problems Novel approaches to address antimicrobial resistance through non-antimicrobial based therapies
2004	The role of mobile genetic elements in the generation of antimicrobial resistance Improved understanding of ecological factors with impact on the genetic and molecular determinants of fitness and virulence of resistant bacterial pathogens Management of lower respiratory tract infections

What is in the current antibiotic pipeline?

Globally, the number of new active substances launched is falling. To modify existing compounds means a shorter development time, reduced costs and safer return on investment, but such so called 'me-too' drugs will have little or no advantage over current antibiotics in overcoming resistance.
Recent research has focused on the DNA sequences of micro-organisms and on potential new targets. High-throughput screening of large numbers of compounds for action on DNA and biochemical targets was found more complicated, time-consuming and expensive than expected. Even more frustrating is that the new technique has not delivered the compounds it promised.[101,102] This is probably one of the reasons why the number of approved antibacterial drugs gradually decreased from 1983 to 2002 (Figure 20).

Figure 20. Antibacterial new molecular entities (NMEs), excluding topical drugs, approved for use in the United States by the U.S. Food and Drug Administration (FDA), 1983-2002.[86]
Linear regression, R2=0.99, p=0.007



The list of antibiotics currently in the development pipeline is as depressing[4,82,103-112] (See Annex 2). Although there are several antibacterial drugs in the pipeline most of them do not represent true innovation, but are additions to existing classes of antibiotics. Additionally, as confirmed by a recent PhRMA report,[103-112] another trend is to use R&D resources to modify the formulation of an existing drug, e.g. amoxicillin-clavulanate, ciprofloxacin or clindamycin, to change its pharmacokinetic properties, thus allowing extended patent protection of the drug in its new formulation. In this case, the registered new formulation may have very limited, if any, advantages over the old formulation when it comes to combating resistance.

The oxazolidinones represent the first new antibiotic class in 25 years (Figure 18) – its first member, linezolid, having been licensed in 2000.[113] Even the ketolides, the glycylcyclines and the aminomethylcyclines, which are presented by companies as new classes, originate from known classes. Although at present they overcome existing resistance, the risk is that resistance to these new agents will probably emerge faster than for a drug with a truly new mechanism of action. There are already fears that resistance to the recently approved ketolide telithromycin, which has a chemical structure close to that of macrolides, will quickly emerge in pneumococci.[114] There are some potential new antibiotic classes with new mechanisms of action, but most of these are still in their first stages of development.

How should antibiotics be marketed?

Increased marketing of antibiotics leads to increased use and resistance. Resistance to one drug will also affect related compounds within the same class (cross-resistance). For example the widespread use of older fluoroquinolones, such as ciprofloxacin, has promoted emergence of resistance to the newest compounds in this antibiotic class. Many large pharmaceutical companies have a fluoroquinolone in their portfolio and compete with each other for the same indications and market, which results in increasing levels of resistance. In the case of carbapenems, the drugs imipenem-cilastatin and meropenem have for a long time been the only ones in this class. With the expected introduction of several new carbapenems on the market this situation will certainly change. The pattern is the same, and increasing competition for market share is likely to result in increasing use and therefore carbapenem resistance, thus impairing the usefulness of the whole carbapenem class of antibacterial drugs. This may also happen with resistance to glycopeptides after the introduction of new compounds with a chemical structure close to that of vancomycin.

Any unnecessary use of antibiotics is a waste of resources, both for the individual and for society as a whole. As the relationship between antibiotic use and resistance is so well established, it seems rational to consider if antibiotics should be marketed in any other way than to maximize the return of investment for pharmaceutical companies. Globally, campaigns targeting prescribers and dispensers, as well as consumers, represent one major intervention through which the overuse and misuse of antibiotics could be decreased. There is also the question of how new products should be launched to best prolong their capability to treat infections caused by resistant bacteria.

Other approaches to meet the threat of resistant bacteria

Vaccines

There is no vaccine that specifically targets antibiotic-resistant bacteria. However, immunization is an effective control measure to reduce spread of certain microorganisms between individuals and reduce the number of carriers of these pathogens. Vaccines that prevent common bacterial infections where resistance has emerged, may contribute to reducing the burden of antibiotic resistance. In addition, reduced burden of bacterial infections may result in a lower antibiotic use, thus reducing the likelihood of resistance emerging. One example is the introduction of the multi-valent pneumococcal conjugate vaccine to prevent invasive pneumococcal infections in young children. There is now evidence that the vaccine not only reduces the incidence of invasive pneumococcal infections, but also to some extent reduces infections caused by resistant strains in the vaccinated children. In addition, it reduces the transmission of resistant strains to their siblings and to adults.[115-117] The *Haemophilus influenzae* type b conjugate vaccine is used to prevent invasive infection, e.g. meningitis and epiglottitis, but also reduces carriage in vaccinated children. Another example is the influenza vaccine. Here the effect is more indirect in that the number of patients receiving unnecessary antibiotic treatment for a viral infection is reduced, and the potential bacterial complications of an influenza episode are prevented.

New vaccines for the prevention of bacterial infections, as well as antibodies, are in the pipelines of several companies (See Annex 3).[90,118-127] One advance in this field that potentially could limit the spread of resistant bacteria is a bivalent polysaccharide vaccine against *Staphylococcus aureus* infections. This vaccine, which is presently in Phase III, can confer partial immunity to prevent *S. aureus* bacteraemia in haemodialysis patients.[118,119] Another market for this vaccine could be patients scheduled for surgery. Considering the high prevalence of MRSA in some European hospitals, this vaccine could be seen as an aid to prevent MRSA infections in surgical patients.

The genomic technique has promoted development of vaccines for bacterial infections. Many new antigens with properties that could overcome the limits of previous vaccine candidates have been identified through "reverse vaccinology". This genome-based approach is being applied to streptococci, *Chlamydiae,* staphylococci and *Yersinia pestis.*[120] As shown in Annex 3, vaccines against the bacteria the most frequently associated with infections, e.g. *S. aureus, E. coli* from urinary tract infections, *P. aeruginosa* and enterococci, are already in the pipeline. These vaccines are likely to be expensive and indicated to prevent infections in selected high-risk patients. Their contribution to the control of antibiotic resistance must be evaluated. Companies will certainly try to extend indications of these vaccines to the prevention of infections in larger populations, e.g. systematic vaccination against *S. aureus* infections before surgical intervention. The cost-effectiveness of such large-scale vaccination programs must be evaluated. If these vaccines help control resistance, new processes to develop cheaper antibacterial vaccines should be encouraged.

Diagnostics

A test that would distinguish between viral and bacterial infection could potentially reduce antibiotic consumption by 50%. At present this type of point-of-care rapid diagnostic test only exists in tonsillitis where group A streptococci can be differentiated from viral infections. Evidence from several countries shows that the introduction of this test has contributed to a reduction of unnecessary antibiotic use in respiratory tract infections.[128,129] Rapid detection of bacteria and their antibiotic resistance in clinical samples could allow antibiotic therapy to be tailored to the responsible microorganism. This is obviously one of the keys to a more rational use of antibiotics. Access to such affordable rapid point-of-care diagnostic tests designed to assist the clinician in the process of selecting the most appropriate drug might seem distant, but recent technological advances suggest that this will be possible. To allow large-scale access and use and therefore make a public health impact, companies should be encouraged to develop affordable tests, to be sold in large quantities, rather than expensive tests reserved for industrialized countries. Wide use, and possibly differential pricing between industrialized and developing countries should make this possible.

Detection of antibiotic-resistant bacteria in screening samples is important to identify and isolate carriers of resistant bacteria, such as MRSA. PCR-based tests remain the reference to identify antibiotic-resistant bacteria, but must generally be performed on DNA extracted from pure cultures of the bacteria. At present this necessitates a culture, which takes approximately one day before the PCR can be performed. Also the so-called commercial "rapid" tests only allow identification of MRSA once it has been isolated from the sample, i.e. approximately one day after the sample was taken.[130] Some of these tests are as specific as PCR-based methods and easy to perform, but still require preliminary culture.[131] Recently publications have reported on two PCR-based tests[132,133] and one non-PCR test[134] that rapidly detect the presence of MRSA directly from nasal swabs. If consistently applied to high-risk patients admitted to hospital, such tests could contribute to MRSA control by allowing immediate isolation of MRSA carriers.

Other rapid diagnostic products in development that are specifically designed to detect resistance include a test for rapid detection and identification of vancomycin-resistant enterococci and a test for the rapid detection and identification of antibiotic resistance.[135] Additionally, tests are in development for the rapid detection of the presence of bacteria in samples from sterile body sites and for the rapid detection and identification of bacteria from positive cultures. The development stage of these products is not yet specified.[135]

In summary, major concerns about the discrepancy between the growth of the resistance problem and the pace at which new drugs, vaccines and diagnostic tests are being developed are justified. Adequate mechanisms need to be put in place urgently to further boost R&D of tools to help control and manage drug resistance.

What are the gaps between current research and potential research issues which could make a difference?

As extensively discussed above, we are increasingly facing a situation of shortage of effective drugs against a number of serious infections. The current rising trends in antibiotic resistance suggest that the real problems are still ahead of us. If nothing is done now, this trend is likely to accelerate into a public health catastrophe of unforeseeable consequences. On the other hand, even if massive resources were mobilized today in order to break this trend now, we would still suffer on account of the backlog of the current crisis, with an increase in antibiotic resistance problems for at least another 10 years, as a result of a dry and long drug development pipeline.

A number of legislative and financial measures will be needed to increase industrial incentives to re-enter the antibacterial drug development field. More effective public health measures aiming at rational antibiotic use need to be installed. Perhaps the most important will be to draw up a research agenda for Europe specifically designed to address antibacterial drug resistance. This research agenda will have to take into account new scientific opportunities and technological developments together with European strengths and resources, and channel these towards the most urgent needs. New comprehensive approaches to antibiotic development will have to be accompanied by basic research on resistance mechanisms, the dynamics of resistance development, improved surveillance and methods to improve prescribing and use patterns.

The prevailing market system has often led to heavy sales promotion of a drug after market authorization, to obtain a fast return of investment. In the case of antibiotics, this is increasing the risk of a rapid development of resistance. When new drugs are developed, systems must be in place to secure their appropriate use to reduce emergence of resistance. In this field there is a need for a comprehensive approach involving health, education, finance and industrial policy. Containment of antibiotic resistance will depend on coordinated interventions that will minimize unnecessary antibiotic consumption. To target the behaviour of prescribers, dispensers and patients and to change important features of the environment in which they interact are essential, as are managerial and policy issues.

The EU's Fifth Framework Programme served to launch a number of individual research projects in Europe, particularly on finding new molecular targets for antibacterial drug development and for alternative therapeutic approaches. Many of these are still running and the results start to emerge (See Annex 1). The current Sixth Framework Programme places emphasis on structuring and integrating research activities and to reach specific objectives within a limited number of prioritized areas (Table 2).

The development of new antibiotics

Identifying the most urgent needs for new antibiotics

The need for antibiotics will remain high and is anticipated to increase with an ageing population, increased global infection rates, increasing numbers of immuno-compromised patients (mainly HIV), who often require longer courses of antibiotic treatment, increasing bacterial resistance and increased specialized surgery, such as organ transplantation. Until now, the research agenda has been decided by the pharmaceutical industry and mechanisms for governments and society to direct the development of antibiotics towards the areas with the greatest needs have been very limited. An inventory detailing the antibiotics needed within each setting would serve as a tool both for the industry and governments

to contain the development of antibiotic resistance. Approximately 90% of antibiotics are used in the community, and for the pharmaceutical industry this large market has been more attractive than hospitals. Consequently, the focus for companies has been to develop antibiotics that can be used in the community, preferably for more than one diagnosis. In the community, resistance to clinically important pathogens, such as pneumococci, streptococci and MRSA are rising. Thus, there is a need for oral antibiotics targeting resistant pathogens that could be used in the community, Although only approximately 10% of antibiotics is used in hospitals, the higher antibiotic selection pressure in hospitals creates greater opportunities for resistance to emerge and for multi-resistant bacteria to develop. At present, the need for new antibiotics to combat resistance is greatest in these settings. As stated previously, intensive care units in Europe and the USA are facing MRSA levels in up to 50-80% of total staphylococcal infections. Emerging vancomycin-resistant enterococci endanger the few therapy alternatives left as their genetic elements coding for resistance continue to spread to other bacteria. In this much smaller market, the opportunity lies in developing high-value, niche products for specific, targeted indications. To invest in these antibiotics with limited indications (e.g. only to be used in hospital settings for patients with severe infections) is not a very tempting option. This may be one reason why antibiotics that could be reserved for critically ill patients in hospitals are promoted for broader indications and for use in outpatient settings, to ensure a maximum return on investment.

Because some hospital microorganisms are already resistant to several existing classes of antibiotics, the difficulty resides in identifying compounds with new mechanisms of action to be developed and marketed for this indication. Additionally, compounds that are less prone to see rapid emergence of resistance should be sought.

Incentives for drug development

Incentives for the development of antibacterial drugs with new mechanisms of action are essential since increased demand currently contrasts with the diminished accountability of the pharmaceutical industry. To get out of this impasse the industry must be sufficiently attracted to return to investing in new antibiotics. This requires concrete measures, including reducing the costs of R&D as well as securing the longer use of products. There may be a need for a special regulatory regime for antibiotics in situations of great public health need, such as to treat infections due to multidrug-resistant microorganisms where little or no alternative treatment is available. Increasing the returns on investment is the obvious key factor in promoting drug development within the present framework. However, alternative options could be found outside the existing structures. Using a public health approach to fill preventive and curative gaps in respect of diseases where the industry has lost interest would be an attractive path to explore.
With a few exceptions, the incentives listed below have not been used specifically for antibacterial drugs and a combination of several incentives is probably needed; however, financial incentives should not be applied indiscriminately to any antibiotic coming out of R&D and only to truly new compounds with a new mechanism of action. Companies should also be encouraged to make the decision to limit indications of a new antibiotic to the most severely ill patients or to treat infections due to multidrug-resistant microorganisms.

- **Speeding up the regulatory review or restoration of patent time lost during the review.** This could be a helpful method, especially for small companies, but probably insufficient to encourage more R&D if used alone.[136] The FDA has reduced delays and costs for product approval by avoiding multiple review cycles and improving the review process through a quality systems approach to medical product review.[137] The European Agency for the Evaluation of Medicinal Products (EMEA) and the FDA both have an accelerated or fast-track procedure for evaluating products indicated for life-threatening diseases.[87,138,139] The procedure could be used for antibacterial drugs. As regulatory review time for new antibiotic applications varies extensively, the patent time lost during the review may be restored.

- **Clinical trials.** Clinical trials for needed antibiotics could be made easier, shorter, and therefore less costly, by using surrogate endpoints, well-defined inclusion criteria and possibly with no comparator in Phase III.[89,140-142] Another mechanism would be an approval for limited indications after Phase II trials and conditional release for restricted use in hospitals. Phase III studies would be conducted after this limited approval and depending on results from these trials, decisions could be made on extending the limited permission. Phase IV studies would serve to document broadened indications, confirm safety and efficacy, and for surveillance of emergence of resistance. Such selective-approval mechanism has been proposed for targeted cancer or AIDS drugs and could be use as a model for antibacterial drugs.[143]

- **Patent extension for essential antibiotics.** Extension of patent term could be applied for new classes of antibiotics to ensure return on investment, as generic copies of the drug may not be approved or marketed during

this time. This may be useful, particularly when the development time has been prolonged, leaving only a few years of patent protection. In the EU, a possibility exists for extension of patent term due to a long R&D period. Although rules were differently applied between countries, this 'supplementary protection certificate' can now be granted by individual countries according to a common EU rule designed to provide up to a maximum of 15 years monopoly on marketed drugs.[144] A similar mechanism could be designed specifically for antibiotics and the length of exclusivity could be calculated from the point in time when the drug is approved for broad use. Elements from existing orphan drug and paediatric drug legislation, including extended patent times, could be applied to design a regulatory regime specific to new classes of antibacterial drugs with limited indications. Extended patent in exchange for restricted marketing has also been proposed, and that length of patent protection should be based on sales.[145]

- **Transferable patent extension.** Market exclusivity on antibiotics with limited returns might not be attractive enough, because of the rapid and high returns expected by the pharmaceutical industry.[89] Another controversial proposal is to extend patent term or market exclusivity on an alternative product, also known as 'transferable patent extension' or 'wild card exclusivity'.[136] For antibiotics, this would mean that, for a new class of antibiotic with specific targeted indications, the company would be able to pick any drug in its portfolio and add, for example, between six months and one year of market exclusivity.[89] This solution primarily refers to products in markets in industrialized countries. It is potentially very attractive to established companies, but is politically challenging because the economic burden would be placed on patients or payers for different medicines, possibly in other countries.[136]

- **Tax incentives.** Tax credit on sales could spread the burden on the whole tax base but might encourage indiscriminate use if applied to antibiotics; other possibilities are subsidization of price increases to offset reduced sales volumes; and advance purchase deals to secure an incentive for investment.[40]

- **Responsibility of governments.** The strength of academic research is in basic science, which should be encouraged. At present governments are less involved in the later stages of drug development, but exceptions exist. The ways in which the public sector can constructively intervene in the industrial value chain of antibacterial drug R&D should be thoroughly explored, as the pharmaceutical industry continues to show little interest. Such interventions may range from taxation and strict regulation, via the provision of incentives, to full public financing and development. Public money can be invested alone or in conjunction with private industry. Various models of public-private partnership, academic research consortia, and licensing of a publicly funded R&D product to generic drug companies deserve consideration. Interventions may draw on experience of the development of the first antibiotics, e.g. penicillin, when governments played a decisive role, but also from other relevant areas including current discussions on global public goods for health. With greater public investment, new antibacterial drugs should better reflect public health priorities and be more affordable upon market entry. Different pricing models may be considered for niche antibiotics with limited indications, such as infections caused by resistant pathogens.

Scientific opportunities for antibiotic development

One important reason for the sharp decline in new antibacterial drug development after the 1960s is that many of the obvious targets had already been identified and exploited (Figure 18). From the traditional approach of random screening of natural products and modification of known antibacterial agents, the genomic revolution has dramatically changed the approaches to drug development. Over 100 bacterial genomes are now available and this number continues to grow exponentially. However, the initial euphoria with its expectations of immediate therapeutic development has been dampened as these new opportunities turned out to be more complicated than expected. It remains a fact though, that the steadily growing collection of sequenced microbial genomes offers significant opportunities to rapidly identify conserved and unique sequences that could serve as potential drug targets.

The development of new drugs and treatment and the current inadequacy of technology to translate new antibiotic targets into new drugs is frustrating. Although the number of potential molecular targets for antibacterial drug action is not unlimited it is also most likely that the old target sites have not been fully explored. Thus, we could find new classes of antibiotics directed at the old targets, such as cell wall biosynthesis, DNA replication, RNA synthesis and protein synthesis. This is illustrated by the fact that the oxazolidinones, the only new class of antibiotics to have been introduced during the last 30 years, are directed at the protein synthesis machinery, raising the important question

of whether our focus should be on finding new potential targets or if in fact we could successfully use the 'old' targets to find the new antibiotics. The latter approach would certainly save us time.

Combinatorial chemistry is one important recent advance in medical chemistry. Modern industrial pharmacology relies on high-throughput screening of biological libraries for inhibitors of new drug targets. However, not only new classes of antibiotics with potentially greater ability to withstand resistance should be developed. Other approaches should be considered as well where the primary goal is not to kill the bacteria but to reduce their virulence and reproduction and thereby limit their possibilities to harm the affected host. Knowledge about pathogenesis and bacterial/host interactions opens up the possibility for drug targets related to the pathogenic process such as bacterial virulence factors rather than an integral function of the microorganism itself.

Other alternative therapeutic approaches to classical antibacterial drugs include bacteriophages, which have been shown to selectively kill pathogenic streptococci, including antibiotic-resistant strains, without affecting the normal flora.[146,147] Present efforts to develop phage into reliable therapeutic agents might lead to a new way of combating antibacterial drug resistance,[148] even though it should be noted that resistance against bacteriophages is likely to develop if phage treatment were to be used on a large scale. Synthetic antibiotic fusion products represent a promising new approach and are currently being developed for hybrid molecules, which combine an antibacterial activity with an effector molecule of the innate immune system. Other therapies such as immunomodulators, resistance inhibitors and gene therapy with anti-sense inhibitors have also been proposed as alternatives to antibacterial drugs. This broad research field offers many opportunities and urgently needs a massive boost of activity in order to be able to exploit the genomics field more effectively.

By exploiting the phenomenon of bacterial colonization, new therapies have been developed based on prebiotic, probiotic and synbiotic approaches. As an example, vaginal capsules with lactobacilli have been used to prevent recurrent urinary tract infections with a similar rate of re-infection as found in studies using daily antibiotics for one year.[149] Such probiotics could be used to prevent infections and reduce the ecological pressure due to antibiotics.

Academic research institutions should remain in the lead of the basic research initiatives, such as microbial physiology, mechanisms of pathogenesis, target identification and validation. Industrial partners should take over screening of potential drug targets and the downstream drug development stages of any promising candidates, such as screening for modes of activity and toxicity testing.

Evolution and dynamics of antibiotic resistance

Microbial population biology

To correctly identify the factors relevant to the progression of resistance development in a population is essential if we want to implement rational strategies to control resistance. This will require analysis of how rapidly and by which mechanisms resistance develops as well as the stability and transmissibility of the resistance within the bacterial population. Many of the basic mechanisms of resistance are already known, but less is known about the dynamics of how these resistance genes are moving around within and between different bacterial species. Other central questions in this area are how resistance affects bacterial fitness, virulence and transmission. For instance, the vast geographical expansion of epidemic clones of multidrug resistant beta-lactam resistant *Streptococcus pneumoniae* and MRSA are prominent examples of how resistance may interplay with fitness in a highly successful combination. In addition, experimental analysis of these problems in relevant systems (animals and human volunteers) has to be complemented with mathematical approaches to attempt to create predictive models. Without this type of experimental knowledge and strict quantitative analysis, our attempts to control resistance will be based more on belief than on rational decisions.

Impact of antibiotics on human ecology

Antibiotic treatment of bacterial infections not only exerts a selective pressure against the pathogen to which it is directed, but it also affects the normal bacterial flora. Consequently, regardless of the indications for their use, antibiotics will both affect the composition of the normal flora and select for resistance in it. The consequences of this need to be further elucidated. Thus, what are the short- and long-term consequences of ecological imbalances in the flora on human health with regard to susceptibility to

secondary infections, immunological status, susceptibility to cancer and other diseases? Secondly, the bacterial flora of the body constitute a reservoir of resistance genes that can be transferred to other bacteria, and we need to determine how important this is for resistance development in pathogens and whether we can devise strategies to prevent transfer between different species.

Impact on the global environment

Antibiotic resistance is a global and intergenerational issue. The ecological consequences are basically still unknown. Use of antibacterial drugs during the last 60 years has upset the balance in which microorganisms coexisted for millions of years. Antibiotic compounds can currently be detected in liquid waste at animal feedlots and fish-breeding locations, in lakes and ground-water supplies. Ecological niches outside the health care sector are changing, as bacteria formerly susceptible to antibiotics develop resistance to them. Resistant bacteria are spreading via the food chain between animals and humans. What are the long-term health consequences and potential environmental effects of reduced microbial diversity in the global microbial flora through antibiotic use? Similarities with other environmental problems can be seen, such as global warming and the reduction of the ozone layer, where the approaching impact is difficult to predict.

Quantification of the resistance problem

Surveillance of antibiotic resistance

Surveillance is a key element in the strategy to contain antibiotic resistance. The lack of standardization of methods and definitions in resistance monitoring is still a problem, making national and international comparisons difficult. Progress has been made in Europe to improve and coordinate laboratory surveillance of resistance. Nevertheless, further improvements are essential. Most surveillance studies are still based on laboratory-derived aggregated data. There is a great need for surveillance focused upon specific settings using a defined population as a denominator. It is also important to develop better methods of surveillance both of antibiotics resistance and use in the community. It will be necessary to identify national and local data sources, including hitherto inaccessible data from the private domain. Cross-sectoral coordination should be developed to support corresponding improvements in related sectors, such as veterinary practice and agriculture. The establishment of the European Centre for Disease Control and Prevention offers a great opportunity for an EU-wide surveillance system that would link antibiotic surveillance with monitoring of drug consumption, and prescribing practices with the evaluation of interventions to prevent the emergence of resistance.

Burden of disease

Multi-resistant bacteria are accumulating all over the world. Today there is evidence that resistant bacteria, such as MRSA, are affecting the severity of infections and resulting in longer hospital stays and higher mortality. The problem is not limited to hospital wards, where the antibiotic pressure is higher, as evidence also shows that bacterial strains are increasingly emerging in the community. However, information in Europe and globally on the magnitude of the consequences for society is still scarce. The burden of antibiotic resistance including mortality, morbidity, prolongation of hospital stay and the economic impact on individuals and health care systems needs to be studied in a systematic way. Such studies require a multinational and multidisciplinary approach. There has been recent discussion on whether it would be worthwhile to conduct a longitudinal epidemiological study on antibiotic usage and health outcomes, such as those performed for cardiovascular disease.

A clear quantification of the risks of resistance would provide a firmer basis for policies and would aid compliance among patients, physicians and other stakeholders. It is essential to develop validated, internationally accepted outcome measurements that assess the clinical and economic impact of antibiotic-resistant infections and, in turn, provide a means of assessing the impact of a particular intervention.

Rational use of antibiotics

Surveillance of antibiotic use

There is a need for data on both antibiotic use and determinants of use from all regions in the world. In too many countries there is no adequate surveillance of prescribing, of drug quality, or of the resistance problem.[150] This needs to be developed if governments are to be alerted to problems that exist within their own borders. Through the ESAC project, significant improvements in the surveillance of antibiotic use in Europe have been achieved. However, a global approach is needed where comparable data are generated.

Optimization of antibiotic dosing regimens

Despite the many years of clinical use of antibiotics, little is known about how these drugs should be used optimally in the clinic. Studies are needed to document the optimal dose, dosage interval and length of therapy. A central and still largely unanswered question is how antibiotics should be administered clinically to minimize resistance development without compromising safety and efficacy. Studies of pharmacokinetic/pharmacodynamic parameters need to be performed under laboratory conditions and in relevant experimental hosts in order to define which types of treatment regimes cause the slowest rate of resistance development. This type of knowledge, and its implementation in clinical settings, could potentially result in slowed resistance development. Equally important are the studies of antibiotics to determine which drugs may correlate to an increased tendency to select for resistance than others. Clinical trial protocols thus need to be designed so that the role of resistance in determining clinical and microbiological outcome can be assessed.

Combination treatment has been used in the treatment of TB and some other bacteria e.g. Pseudomonas spp. for which rapid resistance development is well known. Treatment with two or more antibiotics has shown effective in reducing the emergence of resistance in these pathogens with high ability to obtain resistance. To apply the same general strategy in the treatment of bacterial infections is much more uncertain as many variables are different. Each pathogen is unique in the way resistance emerges within the species, and the rate and extent to which resistance develops are strongly dependent on the particular combination of bacterial species and type of drug. However, to use fixed-dose combinations in certain patient groups could be a strategy to reduce the probability for resistance to emerge towards new classes of antibiotics. The use of two or more antibiotics is already practiced in the hospital setting were resistance is more likely to emerge, e.g. high-risk patients in intensive care units. It needs to be explored if this strategy could be more widely employed in these settings to prevent the emergence of resistance.

Improving clinical use of antibiotics

Little is known about the effectiveness of various interventions aimed at controlling antibiotic resistance. There is therefore a great need for ongoing research, including prospective, well-controlled studies comparing single and combined interventions and the associated costs. Research is needed to define which is the best policy to promote prudent antibiotic use taking into account differences in cultural and socio-economic backgrounds. Quality indicators for optimal use that could be implemented in different context should be developed. The most productive approach is to combine quantitative studies on the patterns of antibiotic use with the rich variety of qualitative methods to investigate why people seek treatment, achieving a greater understanding of risk perceptions on antibiotics amongst prescribers and users. Implementing programmes to change antibiotic practices in the absence of adequate information about the motivations and constraints of different stakeholders can easily lead to a waste of efforts and resources. Even if knowledge is adequate amongst prescribers, practices may still be inappropriate, and studies need to look in more depth at the reasons for this.

References

1. The world health report 2003 – shaping the future. Geneva: World Health Organization; 2003. Available from: URL: http://www.who.int/whr/2003/en/
2. Davison HC, Low JC, Woolhouse ME. What is antibiotic resistance and how can we measure it? Trends Microbiol 2000;8:554-9.
3. Andersson DI. Persistence of antibiotic resistant bacteria. Curr Opin Microbiol 2003;6:452-6.
4. Livermore D. Can better prescribing turn the tide of resistance? Nat Rev Microbiol 2004;2:73-8.
5. Livermore DM. Bacterial resistance: origins, epidemiology, and impact. Clin Infect Dis 2003;36(Suppl 1):S11-23.
6. Neu H. The crisis in antibiotic resistance. Science 1992;257:1064-73.
7. Andersson D. The ways in which bacteria resist antibiotics (background document) Seminar on the Global Threat of Antibiotic Resistance – Exploring Roads Towards Concerted Action, Uppsala, Sweden, 5-7 May 2004. Available from: URL: http://www.reactgroup.org
8. Baquero F, Negri C. Strategies to minimize the development of antibiotic resistance. Journal of Chemotherapy 1997;9(Suppl 3):29-37.
9. Lipsitch M, Levin BR. The population dynamics of antimicrobial chemotherapy. Antimicrob Agents Chemother 1997;41:363-73.
10. Austin DJ, Kristinsson KG, Anderson RM. The relationship between the volume of antimicrobial consumption in human communities and the frequency of resistance. Proc Natl Acad Sci U S A. 1999;96:1152-6.
11. Colgan R, Powers JH. Appropriate antimicrobial prescribing: approaches that limit antibiotic resistance. Am Fam Physician 2001;64:999-1004.
12. Hanberger H, Diekema D, Fluit A, Jones R, Struelens M, Spencer R, Wolff M. Surveillance of antibiotic resistance in European ICUs. J Hosp Infect 2001;48:161-76.
13. Albrich WC, Monnet DL, Harbarth S. Antibiotic selection pressure and resistance in Streptococcus pneumoniae and Streptococcus pyogenes. Emerg Infect Dis 2004;10:514-7.
14. Sullivan A, Edlund C, Nord CE. Effect of antimicrobial agents on the ecological balance of human microflora. Lancet Infect Dis 2001;1:101-14.
15. World Health Organization. WHO Global Strategy for Containment of Antimicrobial Resistance. Geneva: WHO, 2001. Available from: URL: http://www.who.int/entity/csr/resources/publications/drugresist/en/EGlobal_Strat.pdf
16. Odenholt I, Gustafsson I, Löwdin E, Cars O. Suboptimal antibiotic dosage as a risk factor for selection of penicillin-resistant Streptococcus pneumoniae: In vitro kinetic model. Antimicrob Agents Chemother 2003;47(2):518-23.
17. Levin BR, Lipsitch M, Perrot V, et al. The population genetics of antibiotic resistance. Clin Infect Dis 1997;24(suppl 1):S9-16.
18. Austin DJ, Anderson RM. Studies of antibiotic resistance within the patient, hospitals and the community using simple mathematical models. Philos Trans R Soc Lond B Biol Sci 1999;354:721-38.
19. Seppälä H, Klaukka T, Vuopio-Varkila J, Muotiala A, Helenius H, Lager K, Huovinen P, Finnish Study Group for Antimicrobial Resistance. The effect of changes in the consumption of macrolide antibiotics on erythromycin resistance in group A streptococci in Finland. N Engl J Med 1997;337:441-6.
20. Andersson DI, Levin BR. The biological cost of antibiotic resistance. Curr Opin Microbiol 1999;2:489-93.
21. Levin BR. Minimizing potential resistance: a population dynamics view. Clin Infect Dis. 2001;33(Suppl 3):S161-9.
22. McCormick AW, Whitney CG, Farley MM, et al. Geographic diversity and temporal trends of antimicrobial resistance in Streptococcus pneumoniae in the United States. Nature Medicine 2003;9:424-30.
23. Lipsitch M, Bergstrom CT, Levin BR. The epidemiology of antibiotic resistance in hospitals: paradoxes and prescriptions. Proc Natl Acad Sci U S A 2000;97:1938-43.
24. Cornaglia G, Lönnroth A, Struelens M, Participants in the Conference. Report from the European Conference on the Role of Research in Combating Antibiotic Resistance, 2003. Clin Microbiol Infect 2004;10:473-97.
25. Melander E, Mölstad S, Persson K, et al. Previous antibiotic consumption and other risk factors for carriage of penicillin-resistant Streptococcus pneumoniae in children. Eur J Clin Microbiol Infect Dis 1998;17:834-8.
26. Smith R, Beaglehole R, Woodward D, Drager. Global public goods for health. Oxford: Oxford University Press; 2003.
27. Wise R, Hart T, Cars O, Struelens M, Helmuth R, Huovinen P, Sprenger M. Resistance is a major threat to public health. BMJ 1998;317:609-10.
28. The Copenhagen Recommendations. Report from the Invitational EU Conference on the Microbial Threat, Copenhagen, Denmark, 9-10 September 1998. Available from: URL: http://www.im.dk/publikationer/micro98/index.htm
29. Radyowijati A, Haak, H. Determinants of antimicrobial use in the developing world. Child Health Research Project Special Report. 2002;4(1). Available from: URL: http://www.childhealthresearch.org/doc/AMR_vol4.pdf
30. Cars O, Nordberg P. Antibiotic resistance –The faceless threat [background document], Seminar on the Global Threat of Antibiotic Resistance – Exploring Roads Towards Concerted Action, Uppsala, Sweden, 5-7 May 2004. Available from: URL: http://www.reactgroup.org
31. European Surveillance of Antimicrobial Consumption (ESAC). http://www.ua.ac.be/esac/
32. World Health Organization. Fact sheet No. 194. Antimicrobial resistance. Available from: URL: http://www.who.int/mediacentre/factsheets/fs194/en/print.html
33. Endtz HP, Ruijs GJ, van Klingeren B, Jansen WH, van der Reyden T, Mouton RP. Quinolone resistance in campylobacter isolated from man and poultry following the introduction of fluoroquinolones in veterinary medicine. J Antimicrob Chemother 1991;27:199-208.
34. European Antimicrobial Resistance Surveillance System (EARSS). http://www.earss.rivm.nl
35. International surveillance network for the enteric infections Salmonella and VTEC O157 (Enter-Net). http://www.hpa.org.uk/hpa/inter/enter-net_menu.htm
36. Hospitals in Europe Link for Infection Control through Surveillance (HELICS). http://helics.univ-lyon1.fr/
37. Surveillance of Tuberculosis in Europe (EuroTB). http://www.eurotb.org/
38. EARSS Annual Report 2002. Available from: URL: http://www.earss.rivm.nl/PAGINA/DOC/rep2002/annual-report-2002.pdf
39. Song J-H, Thamlikitkul V. ANSORP – Asian Network for Surveillance of Resistant Pathogens. 2nd International Conference on Improving the Use of Medicines (ICIUM), Chiang Mai (Thailand), March 30-April 2, 2004. Available from: URL: http://mednet3.who.int/icium/icium2004/resources/ppt/O_AM048.ppt#2
40. Smith RD, Coast J. Antimicrobial resistance: a global response. Bull World Health Organ 2002;80:126-33.
41. Howe RA, Monk A, Wootton M, Walsh TR, Enright MC. Vancomycin susceptibility within methicillin-resistant Staphylococcus aureus lineages. Emerg Infect Dis 2004;10:855-7.
42. Health Protection Agency. Staphylococcus aureus bacteraemia laboratory reports and methicillin susceptibility (voluntary reporting scheme): England and Wales, 1990 – 2003. Available from: URL: http://www.hpa.org.uk/infections/topics_az/staphylo/lab_data_staphyl.htm
43. Vincent JL, Bihari DJ, Suter PM, Bruining HA, White J, Nicolas-Chanoine MH, Wolff M, Spencer RC, Hemmer M, EPIC International Advisory Committee. The prevalence of nosocomial infection in intensive care units in Europe. Results of the European Prevalence of Infection in Intensive Care (EPIC) Study. JAMA 1995;274:639-44.
44. Fluit AC, Verhoef J, Schmitz FJ; European SENTRY Participants. Frequency of isolation and antimicrobial resistance of gram-negative and gram-positive bacteria from patients in intensive care units of 25 European university hospitals participating in the European arm of the SENTRY Antimicrobial Surveillance Program 1997-1998. Eur J Clin Microbiol Infect Dis 2001;20:617-25.
45. Vandenesch F, Naimi T, Enright MC, Lina G, Nimmo GR, Heffernan H, Liassine N, Bes M, Greenland T, Reverdy ME, Etienne J. Community-acquired methicillin-resistant Staphylococcus aureus carrying Panton-Valentine leukocidin genes: worldwide emergence. Emerg Infect Dis 2003;9:978-84.
46. Lina G, Piemont Y, Godail-Gamot F, Bes M, Peter MO, Gauduchon V, Vandenesch F, Etienne J. Involvement of Panton-Valentine leukocidin-producing Staphylococcus aureus in primary skin infections and pneumonia. Clin Infect Dis 1999;29:1128-32.
47. Salgado CD, Farr BM, Calfee DP. Community-acquired methicillin-resistant Staphylococcus aureus: a meta-analysis of prevalence and risk factors. Clin Infect Dis 2003;36:131-9.
48. Cohen ML. Epidemiology of drug resistance: implications for a post-antimicrobial era. Science 1992;257:1050-5.
49. Global Tuberculosis Control: Surveillance, Planning Financing. Geneva: World Health Organization; 2004. Available from: URL: http://www.who.int/tb/publications/global_report/2004/en/full.pdf
50. National Nosocomial Infections Surveillance (NNIS) System report, data summary from January 1992 through June 2003, issued August 2003. Am J Infect Control 2003; 31:481-98

51. Herold BC, Immergluck LC, Maranan MC, Lauderdale DS, Gaskin RE, Boyle-Vavra S, Leitch CD, Daum RS. Community-acquired methicillin-resistant Staphylococcus aureus in children with no identified predisposing risk. JAMA 1998;279:593-8.

52. Centers for Disease Control and Prevention. Four pediatric deaths from community-acquired methicillin-resistant Staphylococcus aureus--Minnesota and North Dakota, 1997-1999. MMWR 1999;48:707-10.

53. Song J-H, Jung S-I, Ko KS, Kim NY, Son JS, Chang H-H, et al. High prevalence of antimicrobial resistance among clinical Streptococcus pneumoniae isolates in Asia (an ANSORP study). Antimicrob Agents Chemother 2004;48:2101-7.

54. Okumura J, Osaka K, Okabe N. Widespread multi-antimicrobial–resistant Shigella in Asia: What does it mean? [abstract AM 011]. 2nd International Conference on Improving Use of Medicines, Chiang Mai, Thailand, 430 March-2 April 2004.

55. Kollef MH, Sherman G, Ward S, Fraser VJ. Inadequate antimicrobial treatment of infections: a risk factor for hospital mortality among critically ill patients. Chest 1999;115:462-74.

56. Turnidge J. Impact of antibiotic resistance on the treatment of sepsis. Scand J Infect Dis 2003;35:677-82.

57. Melander E, Whitby M, McLaws ML, Berry G. Risk of death from methicillin-resistant Staphylococcus aureus bacteremia meta-analysis. Med J Austr 2002;175:264-7.

58. Cosgrove SE, Sakoulas G, Perencevich EN, Schwaber MJ, Karchmer AW, Carmeli Y. Comparison of mortality associated with methicillin-resistant and methicillin-susceptible Staphylococcus aureus bacteremia: a meta-analysis. Clin Infect Dis 2003;36:53-9.

59. Fasehun F. The antibacterial paradox: essential drugs, effectiveness, and cost. Bull World Health Organ 1999;77:211-6.

60. Harbarth S, Garbino J, Pugin J, Romand JA, Lew D, Pittet D. Inappropriate initial antimicrobial therapy and its effect on survival in a clinical trial of immunomodulating therapy for severe sepsis. Am J Med 2003;115:529-35.

61. Smith RD, Coast J, Millar MR. Over-the-counter antimicrobials: the hidden costs of resistance. J Antimicrob Chemother 1996;37:1031-2.

62. Emmerson AM, Enstone JE, Griffin M, Kelsey MC, Smyth ET. The Second National Prevalence Survey of infection in hospitals--overview of the results. J Hosp Infect 1996;32:175-90.

63. Bowler IC. Is control of methicillin-resistant Staphylococcus aureus justified? Q J Med 1997;90:243-6.

64. Chadwick PR. Controlling glycopeptide-resistant enterococci. Clin Microbiol Infect 1995;3:7-11.

65. American Society for Microbiology. Report of the ASM taskforce on antibiotic resistance. Antimicrob Agents Chemother 1995; (Suppl): 1-23.

66. Cox RA, Conquest C, Mallaghan C, Marples RR. A major outbreak of methicillin-resistant Staphylococcus aureus caused by a new phage-type (EMRSA-16). J Hosp Infect. 1995 Feb;29:87-106.

67. Okeke IN, Lamikanra A, Edelman R. Socioeconomic and behavioral factors leading to acquired bacterial resistance to antibiotics in developing countries. Emerg Infect Dis 1999;5:18-27.

68. Resistance: a sensitive issue. Report from the Strategic Council on Resistance in Europe (SCORE). EU grant QLK2-2002-30599. van der Bruggen JT, Jansen WTM, Fluit AC, Verhoef J (eds.). University Medical Center Utrecht; (2005, in press).

69. Carbon C, Cars O, Christiansen K. Moving from recommendation to implementation and audit: part 1. Current recommendations and programs: a critical commentary. Clin Microbiol Infect 2002;8(Suppl 2):92-106.

70. Christiansen K, Carbon C, Cars O. Moving from recommendation to implementation and audit: part 2. Review of interventions and audit. Clin Microbiol Infect 2002;8(Suppl 2):107-28.

71. Council of the European Union. Council Resolution of 8 June 1999 on antibiotic resistance. A strategy against the microbial threat. Official J Europ Communities 1999; 41(C195): 1–3.

72. Council of the European Union. EU-issued Recommendations on the Prudent Use of Antimicrobial Agents in Human Medicine. Proposal for a Council Recommendation, Comm. 2001, 333, Vol. II. Brussels: Council of the European Union, 2001.

73. Patterson JE. Antibiotic utilization: is there an effect on antimicrobial resistance? Chest 2001;119(2 Suppl):426S-30S.

74. Interagency Task Force on Antimicrobial Resistance. Public Health Action Plan to Combat Antimicrobial Resistance. Atlanta: Centers for Disease Control and Prevention, 2001.

75. Hendley JO. Clinical practice. Otitis media. N Engl J Med 2002;347:1169-74.

76. Singh MP, Greenstein M. Antibacterial leads from microbial natural products discovery. Curr Opin Drug Discov Dev 2000;3:167-76.

77. Goozner M. The $800 million pill. The truth behind the cost of new drugs. Berkeley (CA): California University Press, 2004.

78. Bax R. How to evaluate and predict the ecologic impact of antibiotics: the pharmaceutical industry view from research and development. Clin Microbiol Infect 2001;7(Suppl 5):46-8.

79. Reed SD, Laxminarayan R, Black DJ, Sullivan SD. Economic issues and antibiotic resistance in the community. Ann Pharmacother 2002;36:148-54.

80. Greenwood D. Historical introduction. In: .Finch RG, Greenwood D & Norrby RS (eds.). Antibiotic and chemotherapy. Anti-infective agents and their use in therapy. 8th ed. London: Churchill Livingstone; 2003;3-10.

81. Shlaes DM, Levy S, Archer G. Antimicrobial resistance: new directions. Am Soc Microbiol News 1991;57:455-8.

82. Drugs of tomorrow: antibacterials – Beyond the fluoroquinolones. Datamonitor, 2002.

83. Kohno S. Clinical assessment of tosufloxacin tosilate. J Infect Chemother 2002;8:19-27.

84. Larkin M. Daptomycin approved for skin and skin-structure infections. Lancet Infect Dis 2003;3:677.

85. Shibuya Y, Kitamura S, Tani G, Fukushima Y, Yatagai S, Nakamoto T, Motojima S. Evaluation of panipenem/betamipron (PAPM/BP) in pneumonia in elderly patients. J Infect Chemother 2002;8:151-4.

86. U.S. Food and Drug Administration, Center for Drug Evaluation and Research. New molecular entities (NMEs) reports. Available from: URL: http://www.fda.gov/cder/rdmt/ (Accessed 28 July 2004).

87. The world antibiotics market 2002-2009. United Kingdom: Visiongain, 2004.

88. White AJ. The pharmaceutical company approach to antibiotic policies. In: Gould IM & van der Meer JWM (eds.). Antibiotic Policies: Theory & Practice. New York: Kluwer Academic/Plenum, 2005;673-99.

89. Projan SJ. Why is big Pharma getting out of antibacterial drug discovery? Curr Opin Microbiol 2003;6:427-30.

90. Shlaes DM. The abandonment of antibacterials: why and wherefore? Curr Opin Pharmacol 2003;3:470-3.

91. Kreling DH, Mott DA, Wiederholt JB, Lundy J, Levitt L. Prescription drug trends. A chartbook update. Menlo Park (CA): The Henry J. Kaiser Family Foundation; 2001.

92. IMS Health. Product sampling continues to spike in U.S. Available from: URL: http://www.imshealth.com/public/structure/dispcontent/1,2779,1203-143626,00.html (Accessed 7 April 2002).

93. Stakeholder insight: the hospital antibacterial market – specialist products drive market growth. Datamonitor, 2003.

94. Tsiodras S, Gold HS, Sakoulas G, Eliopoulos GM, Wennersten C, Venkataraman L, Moellering RC, Ferraro MJ. Linezolid resistance in a clinical isolate of Staphylococcus aureus. Lancet 2001;358:207-8.

95. Herrero IA, Issa NC, Patel R. Nosocomial spread of linezolid-resistant, vancomycin-resistant Enterococcus faecium. N Engl J Med 2002;346:867-9.

96. Powers JH. Development of drugs for antimicrobial-resistant pathogens. Curr Opin Infect Dis 2003;16:547-51.

97. White RJ. Are the rules different for biotech companies? [abstract 1126]. In: Abstracts of the 43rd Annual Interscience Conference on Antimicrobial Agents and Chemotherapy, Chicago (IL), September 14-17, 2003. Washington (DC): American Society for Microbiology, 2003, 519.

98. Infectious Diseases Society of America. Bad bugs, no drugs. As antibiotic discovery stagnates… a public health crisis brews. White paper, July 2004. Available from: URL: http://www.idsociety.org/pa/IDSA_Paper4_final_web.pdf

99. European Commission, Directorate General for Research (Lönnroth A, editor). Antimicrobial Resistance Research in the Quality Of Life Programme. Luxembourg: Office for Official Publications of the European Communities; 2003. Available from: URL: http://europa.eu.int/comm/research/quality-of-life/pdf/qol_antimicrobialfinal.pdf (Accessed 31 July 2004).

100. European Commission. Sixth EU Framework Programme for Research and Technological Development. Latest information on LifeSciHealth calls. Available from: URL: http://fp6.cordis.lu/lifescihealth/calls.cfm (Accessed 29 July 2004).

101. Courvalin P, Davies J. Antimicrobials: time to act! Curr Opin Microbiol 2003;6:425-6.

102. Projan SJ, Youngman PJ. Antimicrobials: new solutions badly needed. Curr Opin Microbiol 2002;5:463-5.

103. Medicines in Development for Infectious Diseases 2004. Washington (DC): Pharmaceutical Research and Manufacturers of America (PhRMA), 2004. Available from: URL: http://www.phrma.org/newmedicines/resources/2004-04-22.130.pdf (Accessed 16 August 2004).

104. Abbanat D, Macielag M, Bush K. Novel antibacterial agents for the treatment of serious Gram-positive infections. Expert Opin Investig Drugs 2003;12:379-99.

105. Abstracts of the 43rd Annual Interscience Conference on Antimicrobial Agents and Chemotherapy, Chicago (IL), September 14-17, 2003. Washington (DC): American Society for Microbiology; 2003.

106. Artsimovitch I, Chu C, Lynch AS, Landick R. A new class of bacterial RNA polymerase inhibitor affects nucleotide addition. Science 2003;302:650-4.

107. Dandliker PJ, Pratt SD, Nilius AM, Black-Schaefer C, Ruan X, Towne DL, et al. Novel antibacterial class. Antimicrob Agents Chemother 2003;47:3831-9.

108. Drugwatch. Antibacterial and antifungal agents. Formulary 2002;37:322.

109. Ida T, Tsushima M, Ishii T, Atsumi K, Tamura A. CP6679, a new injectable cephalosporin with broad spectrum and potent activities against methicillin-resistant Staphylococcus aureus and Pseudomonas aeruginosa. J Infect Chemother 2002;8:138-44.

110. Phillips OA. Antibacterial agents: patent highlights January to June 2003. Curr Opin Investig Drugs 2003;4:926-36.

111. Spellberg B, Powers JH, Brass EP, Miller LG, Edwards JE Jr. Trends in antimicrobial drug development: implications for the future. Clin Infect Dis 2004;38:1279-86.

112. Yilmaz Coban A, Ekinci B, Durupinar B. A multidrug efflux pump inhibitor reduces fluoroquinolone resistance in Pseudomonas aeruginosa isolates. Chemotherapy 2004;50:22-6.

113. Diekema DI, Jones RN. Oxazolidinones: a review. Drugs 2000;59:7-16.

114. Gootz TD. The current state of antibacterial research. Future Drugs 2003;1:1-3.

115. Dagan R, Givon-Lavi N, Zamir O, Fraser D. Effect of a nonavalent conjugate vaccine on carriage of antibiotic-resistant Streptococcus pneumoniae in day-care centers. Pediatr Infect Dis J 2003;22:532-40.

116. Klugman KP, Madhi SA, Huebner RE, Kohberger R, Mbelle N, Pierce N, for the Vaccine Trialists Group. A trial of a 9-valent pneumococcal conjugate vaccine in children with and those without HIV infection. N Engl J Med 2003;349:1341-8.

117. Whitney CG, Klugman KP. Vaccines as tools against resistance: the example of pneumococcal conjugate vaccine. Semin Pediatr Infect Dis 2004;15:86-93.

118. Fattom AI, Horwith G, Fuller S, Propst M, Naso R. Development of StaphVAX®, a polysaccharide conjugate vaccine against S. aureus infection: from the lab bench to phase III clinical trials. Vaccine 2004;22:880-7.

119. Shinefield H, Black S, Fattom A, Horwith G, Rasgon S, Ordonez J, Yeoh H, Law D, Robbins JB, Schneerson R, Muenz L, Fuller S, Johnson J, Fireman B, Alcorn H, Naso R. Use of a Staphylococcus aureus conjugate vaccine in patients receiving hemodialysis. N Engl J Med 2002;346:491-6.

120. Rappuoli R, Covacci A. Reverse vaccinology and genomics. Science 2003;302:602.

121. Berna Biotech AG. Pipeline. Available from: URL: http://www.bernabiotech.com/rd/pipeline/index.html (Accessed 31 July 2004).

122. Habeck M. Staphylococcal vaccine one step closer to reality. Lancet Infect Dis 2002;2:201.

123. Koch S, Hufnagel M, Theilacker C, Huebner J. Enterococcal infections: host response, therapeutic, and prophylactic possibilities. Vaccine. 2004;22:822-30.

124. Langermann S, Ballou WR. Development of a recombinant FimCH vaccine for urinary tract infections. Adv Exp Med Biol 2003;539(Pt B):635-48.

125. Li X, Lockatell CV, Johnson DE, Lane MC, Warren JW, Mobley HL. Development of an intranasal vaccine to prevent urinary tract infection by Proteus mirabilis. Infect Immun. 2004;72:66-75.

126. Roberts JA, Kaack MB, Baskin G, Chapman MR, Hunstad DA, Pinkner JS, Hultgren SJ. Antibody responses and protection from pyelonephritis following vaccination with purified Escherichia coli PapDG protein. J Urol 2004;171:1682-5.

127. Uehling DT, Hopkins WJ, Elkahwaji JE, Schmidt DM, Leverson GE. Phase 2 clinical trial of a vaginal mucosal vaccine for urinary tract infections. J Urol 2003;170:867-9.

128. Contessotto Spadetto C, Camara Simon M, Aviles Ingles MJ, Ojeda Escuriet JM, Cascales Barcelo I, Rodriguez Sanchez F. [Rational use of antibiotics in pediatrics: impact of a rapid test for detection of beta-haemolytic group A streptococci in acute pharyngotonsillitis]. An Esp Pediatr 2000;52:212-9.

129. Damsgaard JJ, Schaefer K, Michelsen JW, Frimodt-Møller N, Munck AP, Vach K, Kragstrup J. [Antibiotic treatment of infections in general practice. Effect of audit assessed by prescriptions data from health insurance registry and physicians' own registration]. Ugeskr Læger 2001;163:165-8.

130. Arbique J, Forward K, Haldane D, Davidson R. Comparison of the Velogene Rapid MRSA Identification Assay, Denka MRSA-Screen Assay, and BBL Crystal MRSA ID System for rapid identification of methicillin-resistant Staphylococcus aureus. Diagn Microbiol Infect Dis 2001;40:5-10.

131. Levi K, Towner KJ. Detection of methicillin-resistant Staphylococcus aureus (MRSA) in blood with the EVIGENE MRSA detection kit. J Clin Microbiol 2003;41:3890-2.

132. Francois P, Pittet D, Bento M, Pepey B, Vaudaux P, Lew D, Schrenzel J. Rapid detection of methicillin-resistant Staphylococcus aureus directly from sterile and nonsterile clinical samples by a new molecular assay. J Clin Microbiol 2003;41:254-60.

133. Huletsky A, Giroux R, Rossbach V, Gagnon M, Vaillancourt M, Bernier M, Gagnon F, Truchon K, Bastien M, Picard FJ, van Belkum A, Ouellette M, Roy PH, Bergeron MG. New real-time PCR assay for rapid detection of methicillin-resistant Staphylococcus aureus directly from specimens containing a mixture of staphylococci. J Clin Microbiol 2004;42:1875-84.

134. Nelson L. Defence work sheds light on hospital bacteria. Nature 2004;428:457.

135. Infectio Diagnostic. Products in development. Available from: URL: http://www.infectio.com/en/produits/produits.html (Accessed 27 July 2004).

136. Webber D, Kremer M. Perspectives on stimulating industrial research and development for neglected infectious diseases. Bull World Health Organ 2001;79:735-41.

137. U.S. Food and Drug Administration (FDA). Improving innovation in medical technology: beyond 2002. Rockville, MD: FDA; 2003. Available from: URL: http://www.fda.gov/bbs/topics/news/2003/beyond2002/report.html (Accessed 16 August 2004).

138. European Agency for the Evaluation of Medicinal Products (EMEA). Accelerated evaluation of products indicated for serious diseases (life threatening or heavily disabling diseases). London: EMEA; 2001. Available from: URL: http://www.emea.eu.int/pdfs/human/regaffair/049596en.pdf (Accessed 16 August 2004).

139. U.S. Food and Drug Administration (FDA). Guidance for industry. Fast track drug development programs – Designation, development and application review. Rockville, MD: FDA; 2004. Available from: URL: http://www.fda.gov/cber/gdlns/fsttrk.pdf (Accessed 16 August 2004).

140. Baquero F, Bax R, Phillips I. Antibiotic clinical trials revisited. J Antimicrob Chemother 2000;46:651-2.

141. Bax R, Gabbay F, Phillips I, the Witley Park Study Group. Antibiotic clinical trials – the Witley Park Symposium. Clin Microbiol Infect 1999;5:774-88.

142. Shlaes DM, Moellering RC Jr. The United States Food and Drug Administration and the end of antibiotics. Clin Infect Dis. 2002;34:420-2.

143. Roberts TG, Chabner BA. Beyond fast track for drug approvals. New Engl J Med 2004;351:501-5.

144. IMS Health. What is a supplementary protection certificate? Available from: URL: http://www.ims-global.com/insight/news_story/news_story_000417b.htm (Accessed 16 August 2004).

145. Mardikar HM, Deshpande NV, Ghadyalpatil NS, Mardikar M. Patent protection: a need for value-based patents. Lancet 2003;361:613.

146. Loeffler JM, Nelson D, Fischetti VA. Rapid killing of Streptococcus pneumoniae with a bacteriophage cell wall hydrolase. Science 2001;294:2170-2.

147. Nelson D, Loomis L, Fischetti VA. Prevention and elimination of upper respiratory colonization of mice by group A streptococci by using a bacteriophage lytic enzyme. Proc Natl Acad Sci U S A 2001;98:4107-12.

148. Merril CR, Scholl D, Adhya SL. The prospect for bacteriophage therapy in Western medicine. Nat Rev Drug Discov 2003;2:489-97.

149. Reid G, Bruce AW. Urogenital infections in women: can probiotics help? Postgrad Med J 2003;79:428-32.

150. Byarugaba DK. A view on antimicrobial resistance in developing countries and responsible risk factors. Int J Antimicrob Agents 2004;24:105-10.

Annex 1. Antibacterial-drug projects funded by the EU 5th Framework Programme for Research and Technological Development, 1999-2002.[99]

Year of start	Project acronym	Project name	EU Contribution (million)
2000	NAACAP	Development and evaluation of nucleic acid amplification methods for the detection of respiratory pathogens in community acquired pneumonia	1.2
	TB prevention cluster	New strategies for treatment and prevention of mycobacterial diseases	2.0
	DISSARM	Development of integratable sensors for screening of antibiotic resistance in *Mycobacterium*	0.9
	PANAD	Development of antimicrobial peptides as novel anti-infective drugs	1.8
	TCS-Targets	Bacterial two-component system as targets for the development of novel antibacterials and anti-infectives	1.3
	DNA replication inhibitors	Replication initiation proteins as new targets for bacterial growth inhibition	2.0
	MOL-MECH-MAC	Molecular mechanism of macrolide antibiotic action and resistance: application in drug development	0.7
	EBP	Comparative analysis of proteome modulation in human pathogenic bacteria for the identification of new vaccines, diagnostics and antibacterial drug targets	0.7
	GENOVA	Glycosylation engineering for novel antibiotics	1.8
	Mega-Top	Metabolic engineering of glycopeptide antibiotics: technology, optimisation and production	1.2
	EURIS	European resistance intervention study reducing resistance in respiratory tract pathogens in children	1.7
	PNC-EURO	Pneumococcal disease in Europe	1.5
	Strep-EURO	Severe *Streptococcus pyogenes* disease in Europe	1.2
	Mol. Epidemiology TB	New generation genetic markers and techniques for the epidemiology and control of tuberculosis	0.9
	TREAT	TREAT – a system for balancing antibiotic treatment against development of drug resistance	1.4
	Gene	Network for automated bacterial strain fingerprinting in Europe	0.4
2001	Pseudomonas virulence	Microbiological and structural strategies for the diagnostics and epidemiology of *Pseudomonas aeruginosa* infections	1.2
	X-TB	Structural and functional genomics of *Mycobacterium tuberculosis*	2.3
	Persistent TB	Novel drug targets specific to persistent (latent) tuberculosis infection: crystallisation, structure determination and functional studies	0.8
	TFSS	Type IV secretion systems as targets for anti-infectious therapies	1.6
	TNA	Towards new antibiotics	1.4

Year of start	Project acronym	Project name	EU Contribution (million)
	BAS anti-microbials	Development of novel anti-bacterials and anti-infectives that target programmed bacterial cell death	2.0
	ACTAPHARM	Novel sources of actinomycete diversity for detection of antimicrobial agents with pharmaceutical applications	2.1
	Cyanomyces	Combinatorial biosynthesis: generation of novel therapeutic substances by combining genes from *Actinomyces* and cyanobacteria	1.7
	COINS	Discovery of a new class of bioactive compounds: bacterial conjugation inhibitors	0.5
	ADRI	Novel inhibitors of adhesin/receptor interactions involved in microbial infection at mucosal surfaces	1.9
	DYNAMICRO	Development of photodynamic treatment to eradicate and control the current spread of infectious antibiotic resistant microorganisms in man	0.7
	SANITAS	Screening assays for new bacterial inhibitors based on targets active in septation	1.5
	PROSAFE	Biosafety evaluation of probiotic lactic acid bacteria used for human consumption	1.3
	DEAR	Dynamics of the evolution of antimicrobial drug resistance	1.3
	EU-MENNET	Impact of meningococcal epidemiology and population biology on public health in Europe	1.9
	SALM-GENE	Strengthening international *Salmonella* surveillance through strain typing and differentiation	1.2
	Genus Clostridium	Pathology and ecology of the genus *Clostridium* in humans, animals, and foodstuffs: identification, epidemiology and prophylaxis	0.4
2002	New antimycobacterials	Inhibitors of the non-mevalonate pathway of isoprenoid biosynthesis as drugs against tuberculosis	1.5
	Upgrade Diagno MDR-TB	Improved diagnosis, drug resistance detection, and control of tuberculosis in Latin America	1.0
	Ribosome inhibitors	New antimicrobials targeting translation in bacteria and fungi	2.2
	ANTISTAPH	Novel non-antibiotic treatment of staphylococcal diseases	2.3
	POLYCARB	Treatment and prevention of bacterial infections by anti-adhesion compounds	1.8
	RASTUD	Rapid antibiotic susceptibility testing using dielectrophoresis	0.8
	PulmInfect	Differential diagnosis of infectious lung diseases	0.9
	LONG-DRUG	Characterisation of *Mycobacterium tuberculosis* populations during infection: a longitudinal study on drug resistance development	1.1
	Upgrade Diagno MDR-TB	Improved diagnosis, drug resistance detection and control of tuberculosis in Latin America	1.0
	ARPAC	Development of strategies for control and prevention of antibiotic resistance in European hospitals	0.7
	ANTRES	Towards controlling antimicrobial use and resistance in low-income countries – an intervention study in Latin America	1.1
	ARMed	Antibiotic resistance surveillance and control in the Mediterranean region	0.7
	ARTRADI	Antimicrobial resistance transfer from and between gram-positive bacteria of the digestive tract and consequences for virulence	1.5
	ARBAO-II	Antibiotic resistance in bacteria of animal origin - II	0.4
	ROR (SCORE)	Resist on resistance: mobilising the research efforts for combating multi-resistance against antibiotics	0.3

Annex 2. Antibacterial drugs in the development pipeline [4,79,109,112-121]

Development phase	Compound	Class
Phase III	Garenoxacin	Quinolone
	Tigecycline	Glycylcycline (close to tetracycline)
	Doripenem	Carbapenem
	Faropenem daloxate	Carbapenem
	Ramoplanin	Glycolipopeptide
	Cethromycin	Ketolide (close to macrolide)
	Oritavancin	Glycopeptide
	Dalvabancin	Glycopeptide
Phase II	Iclaprim (AR-100)	Dihydrofolate reductase inhibitor (new class)
	BAL-5788 (pro-drug of BAL-9141)	Cephalosporin
	CS-023 (R-115685)	Carbapenem
	Telavancin (TD-6424)	Glycopeptide
	XRP-2868	Streptogramin (close to macrolide)
	AVE-6971	Topoisomerase IV inhibitor (same mechanism as quinolone)
	ABT-492	Quinolone
	Cefmatilen (S-1090)	Cephalosporin
	Rifalazil	Rifamycin (against *Chlamydia*)
Phase I	Not disclosed	Deformylase inhibitor (new class)
	R-1558	Beta-lactam
	Tebipenem (L-084, pro-drug of LJC-11036/L-036)	Carbapenem
	CAB-175	Cephalosporin
	MC-02479 (RWJ-54428)	Cephalosporin
	TAK-599	Cephalosporin
	Sitafloxacin	Quinolone
	Olamufloxacin (HSR-903)	Quinolone
	DX-619	Quinolone
Pre-clinical or not disclosed[b]	BAY 73-7388 (PTK-0796)	Aminomethylcycline (close to tetracycline)
	A-72310 & A-692345	Ribosome inhibitor (new class)
	CBR-703	RNA polymerase inhibitor (new class)
	MC-207110	Efflux pump inhibitor (new class)
	E-1010	Carbapenem
	DZ-2640	Carbapenem
	CP-5609	Carbapenem
	BK-218	Cephalosporin
	KP-736	Cephalosporin
	CP-6679	Cephalosporin
	Fandofloxacin (DW-116)	Quinolone
	ECO-00501	Unknown or not disclosed
	LMB-415	Unknown or not disclosed

[a]Excluding antibacterials for topical use.

[b]This list may not be exhaustive.

Annex 3. Vaccines that could be used to prevent bacterial infections and may contribute to combating bacterial resistance: development pipeline [87,122-131]

Development phase	Vaccine	Indication
Phase III	Bivalent *Staphylococcus aureus* glycoconjugate vaccine	Prevention of *S. aureus* bacteremia in high-risk patients
	Pseudomonas aeruginosa vaccine	Prevention of *P. aeruginosa* infection in cystic fibrosis patients
Phase II	Vaginal mucosal vaccine (mixture of 10 heat-killed bacteria) for urinary tract infections	Prevention of recurrent urinary tract infections in women
	Multivalent group A streptococcal vaccine	Prevention of diseases caused by group A *Streptococcus*
Pre-clinical	*Enterococcus faecium*/*E. faecalis* conjugate vaccine	Prevention and/or treatment of systemic enterococcal infections
	Recombinant FimCH vaccine for urinary tract infections due to *Escherichia coli*	Prevention of recurrent urinary tract infections in at-risk patients
	Escherichia coli PapG P fimbriae adhesion vaccine for urinary tract infections	Prevention of recurrent urinary tract infections in at-risk patients
	Intranasal vaccine for urinary tract infections due to *Proteus mirabilis*	Prevention of urinary tract infections due to *P. mirabilis* in patients with indwelling catheters
	Trivalent *Staphylococcus aureus* glycoconjugate vaccine	Prevention of *S. aureus* infections in high-risk patients