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Bacterial resistance: A sensitive issue
Complexity of the challenge and containment strategy in Europe

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Abstract

The development of antimicrobial agents has been a key achievement of modern medicine. However, their overuse has led to an increasing incidence of infections due to antibiotic-resistant microorganisms. Quantitative figures on the current economic and health impact of antimicrobial resistance are scant, but it is clearly a growing challenge that requires timely action. That action should be at the educational, ethical, economic and political level. An important first step would be to increase public awareness and willingness to take the necessary measures to curb resistance. Hence, studies are needed that would provide solid, quantitative data on the societal impact of antibiotic resistance. This review discusses the complexity of resistance, identifies its main drivers and proposes measures to contain it on a European scale.

Keywords: Antibiotics; Resistance; European; Impact

1. Introduction

Antibiotic resistance is increasingly recognized as a public health concern and is generally considered to be a consequence of the wide use – and misuse – of antibiotics. Currently, no coherent action is taken to address the problem. In 2002, the University Medical Center, Utrecht, founded the Strategic Council on Antibiotic resistance in Europe (SCORE) to ascertain the current situation and provide a roadmap to curb antibiotic resistance in Europe. To achieve those goals, SCORE organized several symposia attended by European experts on antibiotic resistance, including microbiologists, infectious disease specialists, and pharmaceutical industry scientists. These meetings, a questionnaire on antibiotic resistance, a continuous flow of comments and suggestions via e-mail, publicly available reports and literature have been summarized in a widely supported and consensus-based report (Verhoef et al., 2004). This review is based on the SCORE report, recent information from literature and data from major European surveillance networks. In contrast to reports on antibiotic resistance which generally cover a single topic in the field, this review aims to demonstrate the complexity of resistance; identify the main factors involved; propose adequate measures to contain resistance on a European scale.

2. Current situation

In the 1960s and 1970s, life-threatening infections were regarded as diseases from the past, given the availability and success of antibiotics and vaccines. This has been a miscalculation. Today, infectious diseases are back in the spotlight and antimicrobial resistance increasingly hampers successful therapy. In the case of bacterial infections, problems are being encountered with methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant enterococci (VRE), multiresistant *Streptococcus pneumoniae*, multiresistant *Mycobacterium tuberculosis*, intrinsically multiresistant *Pseudomonas aeruginosa* and *Acinetobacter baumanii*, and multiresistant Enterobacteriaceae, including extended-spectrum β-lactamase-positive strains (ESBL). In spite of a great geographical variation in resistance levels, antibiotic

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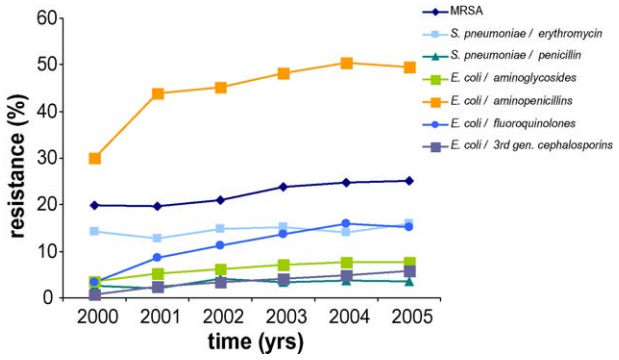

Fig. 1. Annual European resistance data for three major human pathogens. Data are adapted from The European Antimicrobial Resistance Surveillance System (EARSS). The graph only shows species for which broad surveillance data between 2000 and 2005 are available in the EARSS database. There is a slow increase in antibiotic resistance for most pathogen/antibiotic regimen combinations.

resistance is clearly rising in major human pathogens (Fig. 1). A resistance level of 10% against an empirically used antibiotic has been proposed as a guide to switch therapy (Gemmell et al., 2006; Noone, 1978). Therefore, extrapolation of the antibiotic resistance trends in Fig. 1 predicts that empirical therapy against these pathogens becomes problematic in the near future.

Another important observation is that every currently marketed antibiotic already faces bacteria that have acquired resistance against it. For newly introduced antibiotics it is therefore not a matter of if, but when resistance arises. Unfortunately, during the last decades only a few new antibiotic classes have been discovered and experts are pessimistic about the introduction of new classes in the near future. Therefore, efforts are urgently needed to slow down resistance development to *existing* antibiotics.

3. Antibiotic resistance in major human pathogens

3.1. Gram-positive bacteria

3.1.1. Staphylococcus aureus

S. aureus is a common human pathogen by virtue of being part of the normal skin flora. One of the greatest concerns with regard to antibiotic resistance is MRSA. The first MRSA emerged shortly after the introduction of β-lactamase-stable penicillins, such as methicillin, in the early 1960s. However, it was in the late 1970s that series of epidemic MRSA strains evolved and have since spread throughout hospitals in the world. In the 1990s, community-associated (CA) MRSA emerged, which has now rapidly spread both in the hospitals and the community as documented by molecular epidemiological studies involving pulsed field gel electrophoresis (PFGE) (Kollef and Micek, 2006; Zetola et al., 2005). PFGE is a suitable tool to investigate MRSA outbreaks because of its high discriminatory power (Robinson and Enright, 2004). CA MRSA strains are a threat to healthy individuals too as they typically carry the Panton-Valentine leukocidine toxin, which is associated with necrotising pneumonia (Genestier et al., 2005). The complete genome sequence of an epidemic CA MRSA clone, USA300, which is a major source of community-acquired infections in the USA, Canada, and Europe, revealed the presence of an additional virulence element, named arginine catabolic mobile element that encodes an arginine deiminase pathway and an oligopeptide permease system that could contribute to the fitness of that clone (Diep et al., 2006).

Multi-locus sequence typing (MLST) has shown that hospital-acquired (HA) MRSA strains cluster in five dominant lineages, whereas CA MRSA genotypes are more dispersed (Robinson and Enright, 2004). β-Lactam resistance in MRSA is conferred by the *mecA* gene on the staphylococcal chromosome cassette mec (SCC*mec*). Five types of SCC*mec* have been described. SCC*mec* I, II and III are associated with HA MRSA, whereas SCC*mec* type IV and V are mainly found in CA MRSA. Since SCC*mec* IV and V do not contain any resistance genes except for *mec*A, CA MRSA are less multi-resistant than HA MRSA (Hanssen and Ericson Sollid, 2006). Remarkably, in the US strains USA 400 (Sequence Type 1) and USA 300 (Sequence Type 8) are the most predominant CA MRSA, whereas in Australia and Europe mainly Sequence Type 30 and Type 80 are found, respectively (Chambers, 2005; Vandenesch et al., 2003).

Successful treatment of MRSA with vancomycin is hampered by the emergence of glycopeptide intermediate-resistant *S. aureus* strains (Appelbaum, 2006; Cui et al., 2006) and the first reports of vancomycin-resistant MRSA strains in Europe, Japan, USA and France (Tenover and McDonald, 2005). New antibiotics such as linezolid, quinupristin–dalfopristin and daptomycin are effective against MRSA, although the latter two antibiotics are not recommended for pulmonary infections for pharmacokinetic reasons (Schmidt-Ioanas et al., 2005). Significantly, resistance to linezolid and daptomycin has recently been reported for *S. aureus* (Gales et al., 2006; Marty et al., 2006; Skiest, 2006).

3.1.2. Streptococcus pneumoniae

S. pneumoniae is the most important cause of community-acquired pneumonia, and the second most common cause of bacterial meningitis. In the past, *S. pneumoniae* was exquisitely susceptible to penicillin. Penicillin and erythromycin resistance now impede successful treatment of pneumococcal infections (Tleyjeh et al., 2006). In addition, rapid increases in quinolone resistance rates have been reported, which may hamper the use of that antibacterial class in the eradication of penicillin-resistant pneumococci (Deshpande et al., 2006). Given the documented treatment failures with penicillin (although rare), macrolides and quinolones, cephalosporins such as cefotaxime and ceftriaxone are recommended for the treatment of pneumococcal pneumonia (Peterson, 2006). Cephalosporin-resistant pneumococcal infections may be effectively treated with a combi-

nation of ceftriaxone or rifampicin with vancomycin (Ribes et al., 2005).

3.1.3. Enterococci

Enterococci are considered a resistance reservoir. These pathogens, although hardly virulent, are an increasing health concern given their intrinsic resistance to many antibiotics, including cephalosporins, and their ability to acquire resistance against the remaining antibiotics. Enterococci have readily gained resistance to a wide range of antibiotics, including fluoroquinolones, ampicillin, tetracyclins, macrolides, chloramphenicol, trimethoprim, quinopristin/dalfopristin and vancomycin, leaving very few treatment options (Bonten et al., 2001). Recently, resistance against daptomycin was reported (Long et al., 2005). Increasing numbers of severely ill patients in combination with increased use of these agents may fuel the clinical importance of multi-resistant enterococci. *Enterococcus faecium* is considered less pathogenic and is less frequently isolated than *Enterococcus faecalis*, but is nevertheless a growing clinical problem because of its potential to develop resistance against multiple antibiotics including linezolid (Bonora et al., 2006). Daptomycin in combination with rifampicin may be a new effective therapy against multi-resistant enterococci (Pankey et al., 2005).

3.2. Gram-negative bacteria

Many Gram-negative rods are opportunistic nosocomial pathogens. Resistance rates vary among different species and antibiotics. *Escherichia coli* and *Proteus mirabilis* are among the least resistant, whereas *Enterobacter* spp., *Klebsiella* spp., and *P. aeruginosa* show greater innate and acquired resistance. *Acinetobacter* and *Stenotrophomonas* are of low virulence, but tend to be multi-drug resistant (Fournier et al., 2006; Looney, 2005). The new glycylcycline antibiotic tigecycline holds promise for efficacy against these multiresistant species, but decreased susceptibility is common among *Proteus* spp. and *P. aeruginosa*, whereas isolates with decreased susceptibility have been found in *Klebsiella* and *Enterobacter* spp. (Sader et al., 2005a, 2005b; Zhanel et al., 2006).

An important resistance mechanism to β-lactam antibiotics, which is increasingly found in Enterobacteriaceae, is the extended-spectrum β-lactamases (ESBL) (Paterson and Bonomo, 2005). ESBLs were discovered in Europe in the early 1980s after the widespread use of β-lactamase-resistant, extended spectrum cephalosporins. Typically, ESBLs are derivatives of class A β-lactamases, are sensitive to clavulanic acid and sulbactam, are located on plasmids transferable within and between different bacterial species, and confer resistance to extended-spectrum cephalosporins (Paterson and Bonomo, 2005).

In addition, plasmid-mediated ampC β-lactamases have emerged, which have a resistance profiles similar to ESBLs (Pfaller and Segreti, 2006). Currently, carbapenems are recommended for therapy for infections with ESBL-producing bacteria. However, the use of carbapemens has been associated with the emergence of carbapenem-resistant *Stenotrophomonas* spp., *Pseudomonas* spp. and Enterobacteriaceae (Paterson and Bonomo, 2005; Rupp and Fey, 2003). Genes encoding ESBLs are frequently found as part of integron-like structures, together with other resistance genes (Bradford, 2001). ESBL producing strains are frequently associated with quinolone resistance (Poirel et al., 2005).

Resistance to fluoroquinolones arises as a result of mutations in the target enzymes DNA gyrase and topoisomerase IV, of changes in drug entry and efflux, and by plasmids that produce the Qnr protein, which protects the quinolone targets from inhibition (Jacoby, 2005).

3.2.1. Neisseria gonorrhoea

An increasing prevalence of quinolone-resistant *Neisseria gonorrhoea* is observed in the Western world. Whereas these resistant pathogens used to be associated with travel to Asia, nowadays quinolone-resistant *N. gonorrhoea* may spread endemic in certain risk groups (Macomber et al., 2005; Martin et al., 2005). These resistance patterns have necessitated replacement of inexpensive, oral ciprofloxacin with more expensive, injectable ceftriaxone in the treatment of gonorrhea (Roy et al., 2005).

3.3. Mycobacterium tuberculosis

Tuberculosis (TB) remains the most common bacterial cause of death from any single infectious agent in adults worldwide. An estimated 2 million deaths are reported annually, whereas millions of new infections occur each year, mostly in the developing world. The HIV pandemic has reversed the steady decline in TB cases in the developed world. *M. tuberculosis* requires treatment with combinations of three or four agents for at least 6 months. Monotherapy rapidly leads to resistance, due to selection of spontaneous mutants (Ginsburg et al., 2003; Kaufmann and McMichael, 2005). Low quality antibiotics in the developing world and lack of patient compliance also contribute to the problem.

4. Public health impact of bacterial resistance

During the past 5 years, global microbial health threats – bioterrorism, severe acute respiratory syndrome (SARS) and avian influenza – have received far more political and public attention than antimicrobial resistance (Smith and Coast, 2002). The acute, visible danger posed by bioterrorism and SARS has led to an array of international measures and has accelerated the creation of a European Centre for Disease Prevention and Control (ECDC) (Gouvras, 2004). Although antimicrobial resistance may be perceived as less acute, little is known of its impact on mortality and the economic cost incurred by society. Many studies have been performed on attributable mortality and economic cost, but these studies are difficult to interpret due to many confounders and/or lack

Table 1
Analogies between antimicrobial resistance and the greenhouse effect

Analogy	Need
Global	Global approach
Multifactorial	Integrated approach
Intergenerational	Long-term vision
Current impact unclear, controversial	Impact studies
Anticipated problem, effects may be irreversible	Precautionary measures

of appropriate controls (i.e. infections with susceptible bacteria). These data are needed for a public and political debate on this issue and are required to determine the cost-effectiveness of measures to contain antimicrobial resistance (Coast et al., 1996; Coast et al., 2002; McConnell, 2004; Schoch, 2003).

Antimicrobial resistance shares some properties with the greenhouse effect (Table 1). Both are complex, global and intergenerational problems. Currently, the societal burdens of both problems are largely unknown and may be relatively mild. However, extrapolation of the current trends predicts the possibility of disastrous consequences if continued unchecked. Moreover, the extent to which future problems are reversible is uncertain.

These properties summarize the paradox of antimicrobial resistance: timely action is needed to prevent a possible doom scenario, but at the same time, concrete figures on the current impact of antimicrobial resistance are lacking.

4.1. Impact of resistance: the MRSA example

Surprisingly little is known on the actual clinical and economical impact of antibiotic resistance. In this paragraph, a simple model for MRSA bacteremia is presented that can be used to estimate the excess economical and clinical cost of these infections as compared to MSSA bacteremia. Studies on the European public health impact of antimicrobial resistance have not been performed before. Recently, data on the attributable risk of mortality due to methicillin-resistant MRSA bacteremia (Cosgrove et al., 2003) and data from The European Antimicrobial Resistance Surveillance System (EARSS) have become available (European Antimicrobial Resistance Surveillance System, 2004), which can be combined to provide a 'guestimate' on the impact of MRSA bacteremia on a European scale.

The public health impact of MRSA bacteremia is directly related to the absolute number of bloodstream infections with MRSA (NI). The proportion of mortality (PM) represents the fraction of patients that die from MRSA bacteremia. The excess mortality attributed to methicillin resistance (and not to infection per se) within this group of patients, depends on the attributable risk of resistance (AR). AR is a function of the relative risk (RR) and is defined as $AR = (RR - 1)/RR$. Excess mortality (M) due to MRSA bacteremia can thus be formulated as: $M = NI \times PM \times AR$ (Formula 1). The total number of MRSA bacteremias (NI) in the European Union in 2002 was estimated to be about 16,000 cases, derived from EARSS data (European Antimicrobial Resistance Surveillance System, 2004; Fluit et al., 2001) and EU population size data obtained from the CIA World Factbook 2003 (Central Intelligence Agency USA, 2005). The mean reported mortality rate for MRSA bacteremias is 36.4% (Cosgrove et al., 2003). A meta-analysis estimated the pooled relative risk (RR) of death from MRSA bacteremias at 1.42 (95% CI, 1.25–1.63) (Cosgrove et al., 2003). Using Formula 1, total attributable mortality due to MRSA bacteremia in the European Union was estimated to be approximately 1700 deaths in 2002.

Likewise, the economic impact of MRSA bacteremia (EC) is the product of the absolute number of MRSA bloodstream infections (NI) and the attributable cost per infection (AC): $EC = NI \times AC$ (Formula 2). Several studies estimated the average attributable cost of a case of hospital acquired MRSA bacteremia to be around €10,000 (Abramson and Sexton, 1999; Cosgrove et al., 2005; McHugh and Riley, 2004). This excess cost of MRSA infection mainly originates from increased duration of hospital or intensive care unit stay. Using Formula 2, the estimated number of 16,000 MRSA bacteremias in Europe in 2002 may thus have caused an attributable cost of around €160 million.

The lack of detailed data and possible confounding factors means that the figures given above should be regarded as a first example on how resistance costs can be estimated. Obviously, more research is needed on the attributable cost (mortality and economics) for MRSA bacteremia to improve the accuracy of these figures. Similarly, these figures can be extended to other major resistant pathogens when data become available. However, based on the estimates presented above, the annual cost of MRSA bacteraemia alone would already exceed the total European Union budget for antimicrobial resistance research from 1999 to 2002 (European Commission, 2003). Even worse, extrapolation of current, rising trends in antimicrobial resistance suggests that the real problems are still ahead of us. The worst case scenario, i.e. the emergence of fully antimicrobial-resistant microorganisms leading to a situation similar to the pre-antimicrobial era, would have an enormous impact on human suffering and large financial consequences, even if it concerns only a fraction of the common microorganisms within the hospitals or the community. A broad public and political awareness is critical to set the priorities required to contain antimicrobial resistance in the near future (Smith and Coast, 2002).

5. Curbing antibiotic resistance: strategy components

5.1. Surveillance

Surveillance of antibiotic resistance is needed to determine resistance levels and trends in a certain geographical area. This information can be used to ensure appropriate antibiotic prescriptions, to detect timely new mechanisms of

resistance and to monitor interventions. Reports on pathogens with new resistance phenotypes, such as VRSA in Japan and the US (Appelbaum, 2006), underscore the importance of a European surveillance network to obtain timely information on emerging resistant pathogens. Despite many difficulties, much can be gained by combining efforts to institute broad surveillance networks. However, initiating new surveillance programs is costly. An alternative is to start with a central analysis of quality-assured, local surveillance data that are obtained anyway to guide antimicrobial therapy of individual patients. The pharmaceutical industry may also contribute to such a surveillance program in return for including newer antibiotics.

EARSS may be a useful starting point. The objective of EARSS is to collect comparable and reliable European antimicrobial resistance data to benefit public health across Europe. EARSS is, however, limited by the number of microorganisms and participating hospitals. Additional hospitals and microorganisms, such as *M. tuberculosis*, need to be included. Since standardized methodology for antibiotic susceptibility determinations is not achievable across Europe, quality control is of extreme importance. EARSS data can be combined with antibiotic consumption data obtained from European Surveillance on Antibiotic Consumption (ESAC; http://www.esac.ua.ac.be/main.aspx?c=*ESAC2) to gain further insight in the link between antibiotic consumption and resistance (Bronzwaer et al., 2002).

Despite a large number of surveillance programs, little is known about resistance reservoirs outside the hospitals, including nursing homes, kindergartens, food, the veterinary sector, the environment, and pets. The DANMAP (Danish Integrated Antimicrobial Resistance Monitoring and Research Programme; http://www.keepantibioticsworking.com/new/resources_library.cfm?refID=36925) addresses the problem of antibiotic-resistant isolates in animals, food, and humans (Bager, 2000). Antibiotic consumption data for food animals are collected according to the VETSTAT programme (http://www.dbmc.co.uk/tech_info/tech_reports/vetstat_report.asp) and are recorded for each herd (Stege et al., 2003). Ideally, the veterinary sector should follow the DANMAP/VETSTAT approach. The environment may also function as a resistance reservoir. Costa et al. describe the presence of an "antibiotic resistome" among Actinomycetes (D'Costa et al., 2006). These soil-dwelling bacteria are naturally resistant against a wide range of antibiotic in clinical use, by producing enzymes that inactivate at least 6 antibiotics, including rifampicin, synercid and daptomycin. The genes encoding these resistance elements may be horizontally transmitted to human pathogens. Such an event may have occurred for the vancomycin resistance determinants in VRE.

For these and other reservoirs, dedicated surveillance programs are required. Linking surveillance networks and integrating data such as conducted by EARSS and ESAC is a first step. Ultimately, surveillance may be centralized and performed as part of the European Center of Disease Prevention and Control.

5.2. Antibiotic consumption

Interest in antibiotic consumption has been raised by the evolutionary concept that antibiotics provide the selective pressure needed for the emergence and spread of bacterial resistance. Consequently, the modification of antibiotic consumption may be an important way to influence the incidence and prevalence of resistant bacteria. Since the emergence of resistance is intrinsically linked to the use of antibiotics, complete prevention of resistance is impossible. As defined by the Interagency Task Force on Antimicrobial Resistance, 'prudent use of antibiotics encourages maximal therapeutic impact while minimizing toxicity and the development of resistance' (2001). Prudent use, therefore, does not simply imply reduction in antibiotic consumption, but prevention of misuse and overuse. In this way, the life span of a single antibiotic can be extended, allowing more time for the development of new antibiotics and the implementation of other approaches to combat antimicrobial resistance. Prudent use of antibiotics may be especially important when resistance levels are still low, as the decline in resistance after treatment cessation is much slower than its emergence. The persistence of resistance may depend on the fitness cost of resistance and on the linkage of multiple resistance genes on mobile elements (Andersson, 2003).

The collection of consumption data on a European scale has been conducted by ESAC (2006). There is a huge variation in local, national and European antibiotic prescription practises. The percentage of patients given antibiotics may vary from 10% to 50%. In general, above-average consumption of antibiotics occurs in Mediterranean countries such as Italy and Spain, whereas consumption is below average for Northern Europe. Besides volume differences, there is also a different trend in the choice of therapy: Mediterranean countries tend to prescribe more broad-spectrum antibiotics (Coenen et al., 2001). Finally, considerable self-medication may occur in Southern Europe (Vaananen et al., 2005).

How can prudent use of antibiotics be achieved? Education is the main tool to improve antibiotic prescription. The general public and farmers, who are often large-scale users of antimicrobial agents, politicians and healthcare workers, often have limited knowledge about the extent of the antibiotic-resistance problem and are generally not fully aware of the problems associated with antibiotic use. Medical microbiologists and infectious disease specialists play a central role in this education. However, even though the Union of European Medical Specialists has drawn up a Training Record & Training Program for candidates to be trained in medical microbiology and the European Society for Clinical Microbiology and Infectious Diseases (ESCMID) organizes courses for trainees from all over Europe, the training of these specialists is not harmonized within the EU (Grundmann and Goossens, 2005). This lack of harmonization has led to dif-

ferent opinions about the problem of antibiotic resistance. Harmonization can be achieved by providing scientific evidence. Therefore, monitoring of antibiotic consumption in combination with surveillance is necessary to acquire more insight into the complex interaction between antibiotic use and resistance. The data obtained should also be used for feedback to the prescribers to influence behaviour and to increase public awareness. Computer-assisted decision support programs for antimicrobial prescription may aid the physician in accurate antibiotic prescription. In combination with local surveillance data on antimicrobial susceptibility, programs can be tailor made to advice on empiric drug use on a local level. Promising results have been reported on stabilizing or reducing antibiotic resistance with such decision support programs (Burke and Pestotnik, 1999; Sintchenko et al., 2005).

Prudent use of antibiotics is greatly aided by the development of rapid diagnostic tests. Broad-spectrum empirical therapy then can be quickly adjusted to narrow-spectrum therapy. In addition, rapid and accurate diagnosis may limit the spread of infections, which diminishes the use of antibiotics and thereby the risk of emerging resistant bacteria. Molecular biological techniques based on (real-time) PCR, microarrays, and 'nano-particle' technology have the potential of providing rapid, accurate diagnosis of bacterial infections. Rapid tests are particularly useful when they provide information on the most appropriate antibacterial therapy (Peterson and Dalhoff, 2004).

Cycling of antibiotics has been proposed as a strategy to limit the selective pressure of specific antibiotic classes, by periodically changing standard antibiotic regimens in patient populations. However, the efficacy of this strategy is still highly debatable (van Loon et al., 2005).

From an economic perspective, antimicrobial resistance is considered a negative externality. This means that the societal cost is not a criterion in the manufacturing and consumption of antibiotics (Coast et al., 1998). The level of willingness to balance current, individual benefits – perceived or real – against future, societal costs is crucial in attempts to curb antimicrobial resistance. An economic concept that deals with future societal costs of antibiotic use, is the "per dose annual loss". This loss can be regarded as a virtual price tag, expressing the future societal costs for each single antibiotic prescription. The cost for society is due to increased antimicrobial resistance, which may lead to the use of more expensive antibiotics, increased hospitalisation, morbidity and mortality. This virtual price tag depends on the relation between antibiotic use and resistance, and the annual impact of resistance (Phelps, 1989). An antibiotic price tag may provide an indication for the magnitude of the resistance problem in relation to antibiotic use, and provides a handle to measure the cost-effectiveness of measures to promote prudent use of antibiotics.

Reduction of antimicrobial use may also require ethical decisions: should we put societal interests before individual interests? As a consequence, some patients will not receive optimal treatment in order to curb resistance. In this respect, resistance is similar to the social dilemma "the tragedy of the commons". This dilemma refers to pastures shared by herdsman. Individual benefits of introducing a new cow are for the owner, but all herders (society) pay the prize of overgrazing (Foster and Grundmann, 2006).

In conclusion, to define and implement prudent use of antibiotics, many ethical, political, economical, and research questions remain to be answered. Ideally, antibiotics should be classified and accordingly used, as first-choice antibiotics, restricted choice antibiotics (to treat resistant microorganisms), and reserve antibiotics to combat life-threatening infections. Framework guidelines for prudent use of antibiotics need to be adapted to the local situation and approved by local prescribers. Implementation of such guidelines will be a strenuous ongoing process, addressing all relevant parties on a regularly basis with predefined outcome indicators to monitor efficacy (Grol and Grimshaw, 2003).

5.3. *Infection prevention*

Infection control is a very important component in curbing antibiotic resistance. Whereas the prudent use of antibiotics reduces the emergence and spread of antibiotic-resistant bacteria, infection prevention measures mainly control the spread of (antibiotic-resistant) bacteria. It has been estimated that adherence to proper infection control measures may reduce nosocomial infections by 30% (Haley et al., 1985). Infection prevention policies should in particular focus on a number of specific nosocomial infections, such as surgical site infections, infections related to intravascular devices, nosocomial pneumonia and urinary tract infections (Verhoef et al., 2004).

In 2003, the Society for Healthcare Epidemiology of America (SHEA) formulated guidelines to prevent the spread of MRSA and VRE. In addition to contact precautions for patients colonized or infected with these multiresistant organisms, active surveillance is necessary to identify the source and to control further transmissions (Muto et al., 2003). Facing a worldwide increase of multiresistant bacteria, additional guidelines are needed for other resistant pathogens as well, including penicillin-resistant *S. pneumoniae* and ESBL producing Enterobacteriaceae (Kluytmans-Vandenbergh et al., 2005). In 2004, the Dutch Working Party on Infection Prevention issued a guideline for the prevention of nosocomial transmission of highly resistant pathogens. The guideline provides a specific definition for highly resistant microorganisms, which are human pathogens that have the potential to spread in the hospital and have acquired antimicrobial resistance hampering (empirical) therapy. Depending on the class of highly resistant microorganism, specific isolation measures, active surveillance and contact tracing is conducted (Kluytmans-Vandenbergh et al., 2005). The eventual success of the national implementation and obtained results need to be evaluated in the coming years and may serve as a blueprint for formulating guidelines on a broader, European scale.

One of the most profound infection prevention policies is the "search\-and-destroy policy" for MRSA. This policy

includes identification and treatment of carriers, isolation or cohorting of MRSA-positive patients, strict hygiene policies, screening contact persons, and closure of wards. Countries that use this policy, The Netherlands and Scandinavia, have a low MRSA prevalence, which is an indication for the success of this approach (Wertheim et al., 2004). But this policy is costly and there is little evidence about the necessity and efficacy of its individual components. Mathematical models suggest that a subset of measures may suffice to control MRSA prevalence in low-endemic settings. The models indicate that in a high-endemic setting appropriate measures can reduce MRSA levels (Bootsma et al., 2006; Pan et al., 2005). A serious threat to the feasibility of this policy is the emergence of MRSA in the community, as this may have huge consequences for the capacity of a hospital to screen and isolate patients in order to maintain the search and destroy strategy. Nevertheless, a search-and-destroy strategy should be considered for new pathogen-resistance combinations, such as VRSA.

Infection prevention measurements also include vaccination programs in the community. An example of a vaccination program that may have contributed to a reduction in resistance is the application of a pneumococcal conjugate vaccine in children (Whitney and Klugman, 2004).

One of the main obstacles in infection prevention is the lack of evidence-based measures and consequently the lack of consensus on infection prevention policies. As mentioned, solid evidence on the efficacy of search and destroy is lacking. Another example is the ongoing discussion on the benefits of closed versus open suction systems to prevent catheter related infections. Clearly, studies on evidence-based interventions are needed that can then be used to formulate guidelines. In order to properly address the effect of infection-prevention measures, studies should be performed according to the 'Effective Practise and Organization of Care (EPOC)' methodology. Mathematical modeling may aid in predicting the success and cost-effectiveness of infection prevention policies (Smith et al., 2005). The design, presence, and implementation of infection-control and prevention protocols should become mandatory for hospitals in the near future (Verhoef et al., 2004).

5.4. New antibiotics

Most of the 'new' antibiotics that have been marketed during the last decades are variations on common themes. Resistance against these antibiotics develops relatively easily because of their homology with older antibiotics from the same class. Only a few new classes of antibiotics, such as the oxazolidinones, have been added to the arsenal in the past 20 years (Wilcox, 2005). The dearth of new antibiotics will form an important health threat in Europe in the next 20 years. Large pharmaceutical companies are moving away from the field of antibiotic development (Shlaes, 2003). There are several reasons for this worrisome phenomenon. The development of a new antibiotic costs about €500 million, takes 10–15 years and yields a product that is used for brief periods against targets that are prone to develop resistance. In addition, new drugs face restricting policies towards their use. How can incentives be improved for companies to reinvest in antibiotic development? Several measures can be considered, such as a faster registration process for new "last-resort antibiotics" (Abraham, 2002), patent extension, joined non-profit research platforms (Nathan, 2004), subsidies and tax-incentives (Nathan and Goldberg, 2005). These actions should be considered to stimulate the development of new antibiotics.

Although large pharmaceutical companies ceased antibiotic development, a positive trend is that the gap is at least partially filled with small biotech companies. These smaller companies, however, need a partner to perform clinical trials. Companies use a variety of strategies to develop new antibiotics, from genomics-based approaches to screening natural product libraries (Fig. 2).

Traditionally, new antibiotics have been identified from sources such as Actinomycetes and fungi from soil samples, sponges and large collections of individual compounds. Phage lytic enzymes have regained some interest as highly specific antibacterial molecules (Brown, 2004). However, narrow host ranges, emergence of bacterial resistance and failure to achieve high phage (polypeptide) concentrations at the site of infection are important limitations.

Genomic approaches have revealed a range of new, potentially bacteria-specific targets. These targets may comprise

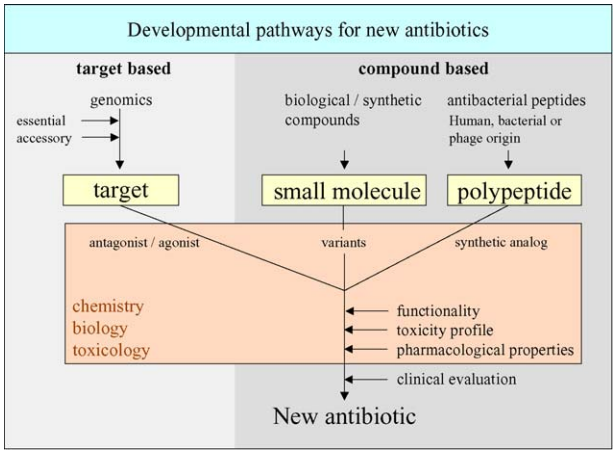

Fig. 2. Simplified scheme of different routes to develop new classes of antibiotics. The 'target-based' approach implies the development of new antibacterials starting from a unique bacterial target. This target may comprise essential or accessory (e.g. virulence) genes. Only a very limited number of (broad-spectrum) targets may exist. A 'compound-based' approach aims at identifying new lead compounds by means of screening compound libraries or human, bacterial or phage peptides with functional in vitro assays. In principle, small molecules are better drug candidates than, for example peptides. Thus, the resulting targets, small molecules and peptides have to be translated into (non-protein) lead compounds. This involves complex technology like structural biology, computer-assisted drug design and (combinatorial) chemistry. During the next cycles, lead compounds are optimised for functionality, minimal side effects and undesirable pharmacokinetic and dynamic properties.

essential genes, for which loss of function is lethal for the bacterium, and accessory genes, such as virulence genes. Using structural biology and combinatorial chemistry, libraries of lead compounds can be generated and examined on their interaction with the bacterial target. In theory, this genomics-based approach allows the rational design of antibiotics against novel, broad-spectrum targets to reduce the probability of emerging resistance (Chalker and Lunsford, 2002). In practice, however, translating lead compounds into novel drugs has had limited success so far. The technology is still at its infancy and to date not a single marketed antibacterial agent has been discovered by this approach. Major bottlenecks are generating sufficient variants of a lead compound and predicting and improving efficacy and toxicity (Hughes, 2003). Another limitation of the genomics-based approach is that it yields protein targets only, whereas some of the most important classes of antibiotics such as glycopeptides act on non-protein targets.

In summary, the economic incentives for the pharmaceutical industry are poor, but also the success rate of finding new antibiotics has generally been disappointing. This may reflect an insufficient technology base to translate targets and natural compounds into new antibiotics (Schmid, 2006).

6. Concluding remarks

6.1. Formulating the future approach to resistance

Antimicrobial resistance is a cross-border issue and, although several networks have arisen that address issues related to antibiotic resistance, the EU has only recently started to develop a joint European policy. In 1999, the Council of the European Union issued a statement that antimicrobial resistance requires a cohesive approach at a European level (Bronzwaer et al., 2004). Since Europe shares the consequences of antimicrobial resistance, it should also share the efforts to contain the problem. Given the global dimensions and the complexity of the problem, a concerted approach is needed. Hence the subsidiarity principle, which states that action is required only when the European approach is proven superior to the national approach, warrants implementation of a strong European policy against antibiotic resistance.

In 2001, the European Commission proposed a ‘Community Strategy against Antimicrobial Resistance’ consisting of four key components: surveillance, prevention, research and product development and international co-operation. Surveillance actions are to strengthen surveillance networks at the European level for both antimicrobial resistance and antibiotic consumption data. Prevention actions include educational campaigns, infection prevention programs (in particular vaccination) and reduction of antibiotic self-medication. The research actions should encourage the development of new antimicrobial agents, alternative treatments (vaccines) and rapid and reliable diagnostic tests. Finally, the EU seeks international co-operation, especially with the WHO, to promote rational use of antibiotics (Bronzwaer et al., 2004). Another important step towards a unified approach against antimicrobial resistance is the recent foundation of the ECDC, which also has powers in the field of antimicrobial resistance.

6.2. The European research agenda

Clearly, the EU and health care specialists recognize the threat of antimicrobial resistance. However, the public awareness remains low, as is the European budget to address this complex issue. The ‘guestimates’ on the surplus economic costs of MRSA bacteremia suggest that these annual costs alone already exceed the total European Union budget for antimicrobial resistance research for 1999–2002 (European Commission, 2003). Sufficient political resolve to implement effective counter-measures is crucial to tackle the resistance problem. An important prerequisite is to increase the public awareness of the resistance problem and to put it higher on European and national political agendas. This is hampered by the lack of quantitative data on the impact of resistance on public health. Hence, the first priority is to obtain these data (Fig. 3). Although new classes of antibiotics are definitely needed, economic and scientific obstacles may hamper their development for the next 15 years. Thus, the focus should be on measures that prolong the life of current (and new) antibi-

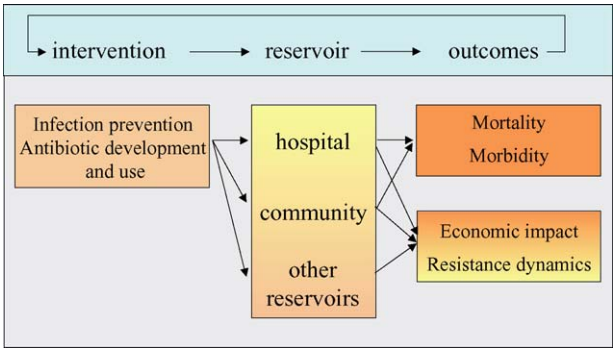

Fig. 3. Intervention measures, their effect on resistance levels, and the most important relations with relevant outcome parameters. The colour scale from yellow to red indicates the need for low- to high-priority research, respectively. Infection prevention measures include hygiene-control and isolation policies in hospitals and vaccination programs in the community and veterinary sector. Antibiotic development implies the need for better technologies in order to develop new antibiotics and alternative strategies. Antibiotic use refers to prudent use in the hospitals, restricted use in the community (i.e. better compliance with the prohibition of over-the-counter sales of antibiotics), and therapeutic use only in the veterinary sector. Standardized evidence-based guidelines and education programs for healthcare professionals and the public are needed to implement intervention measures. Well-designed standardized surveillance programs are needed to study the cost-effectiveness of intervention measures in the hospital, the community, and other resistance reservoirs such as the veterinary sector. Resistance levels, in turn, should be linked to relevant outcome parameters like mortality, morbidity, economic costs of resistance, and cost-effectiveness of intervention measures. Finally, resistance dynamics should be analysed in relation to intervention measures using mathematical modelling, and the spread and mechanisms of resistance should be addressed by coupling resistance data to the genetic background of the strains.

otics. For these intervention strategies, research is needed that can be translated into evidence-based guidelines to be implemented by the EU. Finally, much more fundamental knowledge is required to understand the spread and fitness of resistant bacteria at a genetic level. Based on these arguments, the essential areas of research can be prioritized as follows:

(a) Determine the burden of resistance in terms of mortality and economic impact.
(b) Determine the most effective infection-prevention and antibiotic-use measures to curb resistance.
(c) Develop improved technologies and/or alternative strategies to acquire new classes of antibiotics, and alternatives like immune-enhancing compounds.
(d) Examine fitness (resistance and virulence genes) and spread (clonal, horizontal transfer) of resistant microbes among different resistance reservoirs including hospitals, the community, and the veterinary sector.

The above four research areas are obviously interdependent and the suggested priority simply reflects a certain focus for future research in the area.

6.3. Summing up: the challenge and the hope

Antimicrobial resistance is a complex, global, and intergenerational problem that requires timely action given the potentially enormous impact on human health. Many study groups have been set up to investigate the resistance problem; national programs have been adopted to cope with the problem, and the EU is involved. These efforts, however, have been usually limited in scope, time, and funding. Whereas medical experts seem willing to tackle the problem (Verhoef et al., 2004), political willingness to provide the incentives and necessary legislation is crucial to curb resistance. A more thorough understanding on the societal impact of antibiotic resistance, both in clinical and economic terms, is essential to set the priorities. Although local and single measures can be taken, a coherent approach along multiple lines should be followed if the battle against antimicrobial resistance is to be successful.

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