

ANTIBIOTICS RESEARCH: PROBLEMS AND PERSPECTIVES

Statement

Academy of Sciences and Humanities in Hamburg

German National Academy of Sciences Leopoldina



Leopoldina
Nationale Akademie
der Wissenschaften

AKADEMIE DER
WISSENSCHAFTEN
IN HAMBURG

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The Academy of Sciences and Humanities in Hamburg was founded in 2004. Members of the Academy are scholars of all academic disciplines from northern Germany. One of its goals is to intensify interdisciplinary research and collaboration between universities and scientific institutions. The Academy promotes research on issues important for our future society as well as on fundamental scientific problems. Stimulating the dialogue between scholars and the public is of utmost importance to the Academy. The Academy of Sciences and Humanities in Hamburg is member of the Union of German Academies of Sciences and Humanities.



AKADEMIE DER
WISSENSCHAFTEN
IN HAMBURG

The German National Academy of Sciences Leopoldina brings together the expertise of some 1,500 distinguished scientists to bear on questions of social and political relevance, publishing unbiased and timely scientific opinions. The Leopoldina represents the German scientific community in international committees and pursues the advancement of science for the benefit of humankind and for a better future.



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Foreword

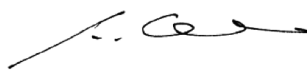
"Why do we need new antibiotics (and don't get them)?", this title of a joint symposium of the working group "Infection Research and Society" of the Academy of Sciences and Humanities in Hamburg and the German National Academy of Sciences Leopoldina held in February 2011 identifies the problem immediately. Fewer and fewer antibiotics are available for an increasing number of infections caused by antibiotic-resistant bacteria.

With the statement "Antibiotics research: problems and perspectives", the Academy of Sciences and Humanities in Hamburg and the German National Academy of Sciences Leopoldina take up this topic, which is relevant to society at large and to both human and veterinary medicine. How can future research contribute to solving the problem of resistance and the lack of new antibiotics? What regulatory and financial framework conditions are required to ensure that research results find their way into widespread application more quickly? These questions are at the core of the present statement.

The authors answer them with a series of proposals. They also encourage measures to respond effectively to the challenges of increasing antibiotic resistance. The focus is on aspects of research, but societal and legal issues are also mentioned.



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Summary

Since the introduction of penicillin in the 1940s, antibiotics have become one of the cornerstones of modern medicine. They are the foundation for the treatment of bacterial infections in humans as well as animals. However, two developments are making it more and more difficult to treat bacterial infections successfully. On the one hand, in recent years there has been an increasing number of antibiotic-resistant pathogens, both in human medicine as well as veterinary medicine. On the other hand, the number of new antibiotics developed since the 1970s has steadily decreased.

According to WHO estimates, the worldwide prevalence of antibiotic-resistances is one of the greatest dangers to human health. According to the experts, the problems related to antibiotic resistances and the lack of antibiotics can only be solved or, at least, alleviated if scientists, politicians, society as a whole and business work together nationally and internationally pursuing diverse, coordinated approaches. The search for new active agents and targets can only succeed if research continues on the causes and mechanisms of antibiotic resistances and if measures for the responsible use of antibiotics are effective.

To reduce the spread of resistances and to develop new antibiotics, firstly more research must be carried out and, secondly, framework conditions are necessary which will allow research discoveries to be implemented effectively. Some starting points are provided in this statement by the Academy of Sciences and Humanities in Hamburg and the German National Academy of Sciences Leopoldina, the basis for which was the joint workshop "Why do we need new antibiotics (and don't get them)?" held on February 25 and 26, 2011.

Amongst other things, the recommendations emphasise the importance and the potential of innovative technologies for researching antibiotic resistances and of new active agents. Clinical studies and translational approaches should be pursued more intensively and the prerequisites for their execution and financing must be improved. The path adopted by the German Antibiotic Resistance Strategy DART should continue to be pursued. In view of the urgency of the resistance problem, a rethinking of the certification conditions for new active agents is needed. Last but not least, socio-economic aspects should form an integral part of the research.

Key elements of the recommendations

1. **Increased basic research:** A broad range of basic research on the origin, spread and prevention of resistance as well as on the development of new antibiotics is indispensable.
2. **Improvement of the structural conditions for innovations:** Of particular importance is the development of a stable product pipeline. One necessary condition is the maintenance and expansion of infrastructure for the research and development of new antibiotics. In addition, it is vital to facilitate and strengthen cooperation between industry and academic research in order to more effectively link basic research resources with the diverse requirements of pharmaceutical product development. It is also essential to continue the international coordination of measures between governments and industry.
3. **Facilitation for clinical research:** Clinical studies on the duration of effective antibiotic therapies, on the use of different therapy regimes and the effect on the development of resistances should be increased and funded.
4. **Further development of regulatory framework conditions:** Due to the development of resistances, the proof of superiority of new antibiotics versus currently available substances is too high a treatment aim. Instead, multiple substances with a similar efficacy should be available. In future, a certificate of efficacy should be sufficient as the treatment aim for approval of new therapy principles and new substance classes in particular.
5. **Restriction of antibiotics use in veterinary medicine and plant protection:** Antibiotics should, if possible, only be allowed for targeted use after clinical diagnosis and based on the results of resistance tests.
6. **Consistent implementation of surveillance and antibiotics consumption records and reduction as well as promotion of education and training:** Regular surveillance of the resistance rates of important pathogens should be carried out on all levels: locally to globally and across the hospital, outpatient and animal husbandry sectors. The data should be published annually.
7. **Increased socio-economic research:** The socio-economic, legal and ethical framework conditions for the development of new antibiotics should be investigated more, hindrances should be identified and solutions found. Measures should be evaluated more on a forward-looking as well as a retrospective basis.
8. **Establishment of a round table to discuss antibiotic resistances and new antibiotics:** The academies recommend establishing a round table to discuss antibiotic resistances and new antibiotics under the umbrella of the Academies of Sciences with the participation of the German Centre for Infection Research DZIF.

In addition, the academies also propose a research agenda. Research activities should cover a wide range of topics and methods in order to approach the problems of antibiotics resistances from various sides and to allow the widest possible approach to the search for new active agents. The opinion piece also addresses in detail the various research requirements.

Areas of focus of the research agenda

- Identification of new targets through functional genome research and metagenomic approaches,
 - Development of new and more effective screening methods and the creation of efficient substance libraries,
 - Isolation and culture of microbes from environmental habitats, amongst other things, as a source of new active agents,
 - Analysis of the significance of the host-microbiome (metagenome) in the development and transmission of resistances,
 - Elucidate the clinical and molecular mechanisms of resistance in vivo.
-

1 Introduction

Since the introduction of Penicillin in the 1940s, antibiotics have become one of the cornerstones of modern medicine. They are the foundation for the treatment of bacterial infections in humans as well as animals. Without antibiotics, many of the now widely used therapies and medical procedures – such as chemotherapy, organ transplants, joint operations or the provision of care to premature babies – would not be possible.¹ In the course of the life of a human or animal, there are numerous situations in which an antibiotic treatment can be lifesaving.

However, two developments are making it more and more difficult to treat bacterial infections successfully. On the one hand, in recent years we have seen an increasing number of antibiotic-resistant pathogens, both in human medicine as well as veterinary medicine. On the other hand, the number of new antibiotics developed since the 1970s has decreased. In particular, there are not enough antibiotics for multidrug-resistant gram-negative pathogens for everyday clinical use. It is to be feared that this deficit will become more and more problematic in the years to come.

According to World Health Organization (WHO) estimates, the worldwide prevalence of antibiotic resistance is one of the greatest dangers to human health. Current estimates suggest that around 25,000 patients die of the consequences of an antibiotic-resistant bacterial infection. There is the fear that the lack of effective antibiotics seriously threatens further progress in many areas of medicine – such as in intensive care, transplant medicine, oncology and surgery.

Box 1: Antibiotic resistance and its causes

Antibiotics are substances that inhibit the growth of bacteria by blocking vital metabolic pathways or the synthesis of macromolecules. The majority of antibacterial substances affect only a few cellular functions: cell wall synthesis, protein synthesis, RNA replication, RNA synthesis or the integrity of the membrane (Figure 1). Due to genetic, structural and metabolic characteristics of individual bacterial families, there is no omnipotent antibacterial active principle.

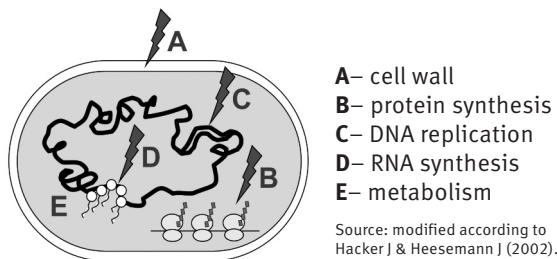


Figure 1: Targets for antibiotics

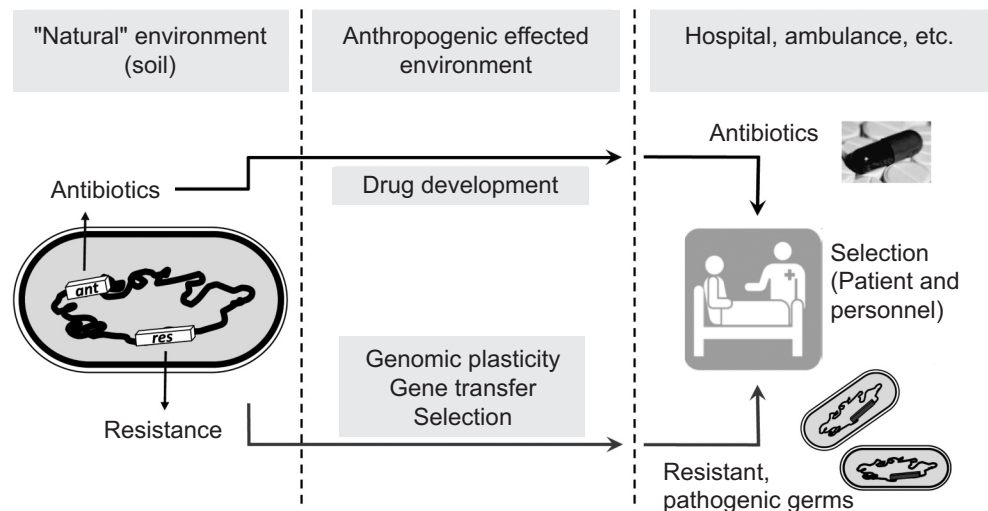
¹ White AR (2011).

Antibiotics are formed by soil microorganisms and microbes in other habitats. They play a role in the shaping of ecosystems. Many antibiotic-specific gene clusters are located in close proximity to areas of genes that encode resistance. Both the genes for antibiotic production as well as the resistance-specific genes are often transferred through horizontal gene transfer within bacterial species, but also across species boundaries.

How often and how quickly resistance is selected varies greatly between the different bacterial species. Some species that are already equipped with a so-called intrinsic resistance to many antibiotics acquire new resistance genes very easily. This is why multiple-resistant pathogens arise as described increasingly for staphylococci or pseudomonads.² These pathogens are difficult to treat. The resistance factors, which make bacteria resistant against an entire class of antibiotics or even against several classes of antibiotics (cross-resistance) are mostly located on mobile genetic elements. Several of such resistance factors can be genetically linked and are transmitted together.

Bacteria also become resistant to antibiotics through mutations. These usually alter the genes for the targets of antibiotics so that they no longer can dock on their target molecule. In addition, bacterial enzymes are capable of chemically inactivating the antibiotic. Furthermore, bacteria are capable of suppressing the transport into the cell or actively remove the antibiotic from the interior of the cell. Several of these mechanisms are used by multidrug-resistant bacteria.

The selection of antibiotic resistance and the spread of antibiotic-resistant bacteria is a dynamic process. Aside from long-term trends, acute events continue to arise because of the emergence of new resistant variants (Figure 2)



Source: modified according to Hacker J & Merkert R (unpublished).

Figure 2: Spread of antibiotic resistance

² Livermore DM (2003).

The apparent discrepancy between the rise in infections caused by multiple antibiotic-resistant bacteria and the declining development of new antibiotics results in the potential risk of a return to the pre-antibiotic era. This would be associated with dramatic implications for the treatment of infectious diseases affecting all sectors of society.

In spite of a number of strategies and activities undertaken on a national and international level aimed at curbing the spread of antibiotic-resistant bacteria, no relief of the situation is currently in sight. The situation is not only critical when it comes to bacteria, but it is paradigmatic for the control of other microbes including fungi, viruses and protozoan organisms.

The concerns of antibiotic resistance and the lack of antibiotics can only be resolved or at least alleviated if the policy makers in the fields of science, politics, society and industry decide to cooperate and act on a national and international level to pursue a variety of concerted efforts. Special emphasis should be placed on research and development. The search for new active substances and targets can only be effective if the efforts to explore the causes and mechanisms of antibiotic resistance are pursued further and if the measures aimed at a more responsible use of antibiotics as defined in previously compiled action plans start to take effect. In view of the crucial importance of this issue, the working group "Infection Research and Society" of the Academy of Sciences and Humanities in Hamburg has taken up the topic of antibiotic resistance and presented it jointly with the German National Academy of Sciences Leopoldina during a workshop entitled "Why do we need new antibiotics (and don't get them)?" on 25 and 26 February 2011.

In this statement, the academies emphasise the urgency of actively addressing the issue of rising antibiotic resistance while the number of available effective antibiotics at the same time continues to decline. The academies suggest proposals for the research agenda and provide the legislator with recommendations for the implementation of effective action strategies. An additional goal is to educate the public about the concern of antibiotic resistance.

The present statement is based on recommendations from national and international bodies and organisations – such as the European Academies Science Advisory Council (EASAC)³, the German Antibiotic Resistance Strategy (DART)⁴ and the European Centre for Disease Prevention and Control (ECDC)⁵.

³ EASAC (2005, 2006, 2007).

⁴ <http://www.bmg.bund.de/praevention/krankenhausinfektionen/antibiotikaresistenzstrategie.html> (accessed on: 13 April 2012).

⁵ ECDC/EMEA (2009).

2 Antibiotic resistance and development – status quo

2.1 Multidrug-resistant bacteria – underlying data

A growing insensitivity to multiple antibiotics or classes of antibiotics (see Annex 11.1) was documented in a variety of reports in Germany and throughout Europe for many of the prevalent pathogens (see Table 1) during the past decade.⁶ For instance, an increase in infections induced by multidrug-resistant gram-negative bacteria (mainly third-generation Cephalosporin-resistant *Escherichia coli* and *Klebsiella pneumoniae* as well as Carbapenem-resistant *Pseudomonas aeruginosa*) has been documented since 2007. However, the resistance incidence rates in Europe vary considerably, depending on the type of bacteria, the antimicrobial substance and the geographic region.

Bacteria	Resistance
Gram-positive bacteria	
<i>Staphylococcus aureus</i>	MRSA = Methicillin-resistant <i>Staphylococcus aureus</i>
<i>Staphylococcus epidermidis</i>	MRSE = Methicillin-resistant <i>Staphylococcus epidermidis</i>
	GISE = Glycopeptide-intermediate <i>Staphylococcus epidermidis</i>
<i>Enterococcus faecium</i> and <i>Enterococcus faecalis</i>	VRE = Vancomycin-resistant <i>Enterococcus</i>
<i>Streptococcus pneumoniae</i>	PNSP = Penicillin-resistant <i>Streptococcus pneumoniae</i>
<i>Mycobacterium tuberculosis</i>	MDR-TB = multidrug-resistant <i>Mycobacterium tuberculosis</i>
	XDR-TB = extensively drug-resistant <i>Mycobacterium tuberculosis</i>
Gram-negative bacteria	
<i>Escherichia coli</i>	ESBL = strains that produce Extended Spectrum Beta-Lactamases, resistance to 3rd generation Cephalosporins and Carbapenems
<i>Klebsiella spp.</i>	ESBL-producing strains, resistance to 3rd generation Cephalosporins and Carbapenems
<i>Pseudomonas aeruginosa</i>	ESBL-producing strains, Carbapenemresistance
<i>Enterobacter spp.</i>	ESBL-producing strains
<i>Acinetobacter spp.</i>	ESBL-producing strains (Carbapenemases)

Table 1: The most common multidrug-resistant bacteria

Although the concern about the global spread of antibiotic-resistant bacteria has been known for many years, the analyses of the scope and the realisation of the consequences for a number of fields are fairly rudimentary. A growing public awareness has emerged in recent years, mainly in connection with clusters of cases in hospitals.

⁶ BVL et al (2011); ECDC (2011) und EARS-Net <http://www.ecdc.europa.eu/en/activities/surveillance/EARS-Net> (accessed on: 27 April 2012).

Data relating to resistance are available both for Germany⁷ as well as on the EU level.⁸ The data are essentially based on blood culture isolates, which are considered an indicator of general antibiotic resistance of a pathogen. In the process, individual resistances are used as marker for the multidrug-resistance of a disease-inducing (pathogenic) bacterium. However, the available data do not appear to adequately reflect the actual problem, not least because not all institutions publish their data.^{9, 10} What is more, experts currently believe that the scientific foundation should be improved.

The so-called ESKAPE pathogens – *Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa* and the Enterobacter species along with *Escherichia coli* and *Staphylococcus epidermidis* – are considered the key culprits in hospitals. *Mycobacterium tuberculosis* is one of the main causes of illness and death around the world.

2.2 Development of resistance amongst select multidrug-resistant pathogens

Methicillin-resistant *Staphylococcus aureus* (MRSA)

MRSA is currently considered the leading cause of antibiotic-resistant infections worldwide. In the European Union, *Staphylococcus aureus* was the most prevalent multidrug-resistant bacterium (MRSA) in 2011. Because of emerging complications, MRSA-induced infections result in prolonged hospital stays, thus incurring considerable costs.

Between 1990 and 2005, the incidence of MRSA as percentage of *Staphylococcus aureus* (*S. aureus*) rose continuously in Germany, peaking at 22 per cent in 2005.¹¹ Since then, the MRSA rate has been declining slightly and now accounts for approximately 20 per cent of analysed blood cultures.

MRSA rates vary considerably amongst EU member states.¹² For example, the MRSA incidence of *S. aureus* was 1 per cent in Denmark and Holland in 2010, while it was higher than 53 per cent in countries like Portugal. In other EU member states, the MRSA incidence is also at a high level (France: 22 per cent, Great Britain: 22 per cent, Spain: 25 per cent).¹³

The MRSA incidence can be effectively reduced with specific hygiene-based long-term control and prevention programmes. For instance, the MRSA incidence in France was reduced from 39 to 21 per cent between 1993 and 2007.¹⁴

Vancomycin-intermediate and Vancomycin-resistant *Staphylococcus aureus* (VISA/VRSA)

The incidence of *S. aureus* with intermediate resistance to Vancomycin is generally very low in Europe, accounting for less than 0.1 per cent of all *S. aureus* iso-

⁷ BVL et al (2011).

⁸ <http://www.ecdc.europa.eu/en/activities/surveillance/EARS-Net> (accessed on: 20. November 2011) und ECDC (2011).

⁹ Fears R et al (2011).

¹⁰ The monitoring of resistance is discussed separately in Chapter 2.6.3.

¹¹ In Germany it is mandatory to report MRSA since 1 July 2009.

¹² Köck et al (2010).

¹³ ECDC (2011).

¹⁴ Jarlier V et al (2010).

lates.¹⁵ No *S. aureus* bacteria that are completely resistant to Vancomycin have yet been found in vivo and the virulence of the pathogens is often reduced. In spite of the currently low incidence, the concern is that the resistance to Vancomycin will rise and that virulent strains will develop as well.

Methicillin-resistant *Staphylococcus epidermidis* (MRSE)

Staphylococcus epidermidis (*S. epidermidis*) is the most common causative agent of foreign body-associated and bloodstream infections. In 2007, the ratio of Methicillin-resistant and multidrug-resistant isolates in relation to all *S. epidermidis* isolates in Germany was close to 73.8 per cent.¹⁶ Because of its biofilm formation, *S. epidermidis* is considered extremely difficult to treat, even though its intrinsic virulence potential is low. A rise is expected because of the growing number of implanted exogenous materials (e.g. artificial joints or indwelling catheters).

Vancomycin-resistant enterococci (VRE)

Enterococci are part of the intestinal flora and have the potential of causing infections with different degrees of severity. *Enterococcus faecalis* and *Enterococcus faecium* have the greatest clinical significance. For *Enterococcus faecium*, the resistance to Vancomycin is considerably less common in Europe with an average of 7.4 per cent¹⁷ compared to the USA, where it by far exceeds 50 per cent.¹⁸ However, the picture is extremely heterogeneous in Europe: while the rate of resistance in Germany is close to 8 per cent, it is under 1 per cent in many other EU member states. Yet, the rates for example in Ireland, Greece and Portugal are greater than 20 per cent. The number of infections and colonisations induced by *Enterococcus faecium* has risen sharply in Germany in recent years.

Penicillin-resistant *Streptococcus pneumoniae* (PNSP)

Streptococcus pneumoniae is a common cause of disease, especially in children, the elderly and patients with impaired immune systems. Based on WHO estimates worldwide, nearly 1.6 million people died as a result of pneumococci-induced infections in 2005, including between 700,000 and 1 million children younger than five years of age.¹⁹ High rates of resistance to Penicillin are reported in France (27.6 per cent), Spain (29.8 per cent), Poland (24 per cent), Finland (14.2 per cent), Romania (30.8 per cent), Bulgaria (18.2 per cent), Ireland (18.1 per cent) and Cyprus (41.7 per cent).²⁰ Between 0.3 and 9 per cent of *S. pneumoniae* isolates are resistant to Penicillin in Germany depending on the disease pattern.²¹ The resistance rates to Macrolides exceed 10 per cent in many countries (close to 9.2 per cent in Germany).

¹⁵ ECDC/EMA (2009).

¹⁶ BVL et al (2011).

¹⁷ ECDC (2011).

¹⁸ Arias CA et al (2012).

¹⁹ <http://www.who.int/ith/diseases/pneumococcal/en/> (accessed on: 7 June 2012).

²⁰ ECDC (2011).

²¹ BVL et al (2011).

Third-generation Cephalosporin-resistant *Escherichia coli*

A steady rise in the incidence of *Escherichia coli* (*E. coli*) resistant to third-generation Cephalosporins²² is observed in most countries. The resistance rates in ten of 28 examined European countries exceeded 10 per cent in 2010 (close to 8.4 per cent in Germany).²³ A considerable rise was determined in half of the examined countries between 2007 and 2010. *E. coli* that are resistant to third-generation Cephalosporins are often and increasingly also resistant to substances of other classes of antibiotics.

Third-generation Cephalosporin-resistant and Carbapenem-resistant *Klebsiella pneumoniae*

The average incidence of *Klebsiella pneumoniae* (*K. pneumoniae*) resistant to third-generation Cephalosporins was close to 27.5 per cent in the EU in 2010.²⁴ The frequency was between 25 and 50 per cent in five countries (Italy, Poland, Czech Republic, Hungary, Cyprus) and even higher than 50 per cent in five more countries (Greece, Bulgaria, Lithuania, Latvia, Romania). The average resistance to Carbapenems in the 28 reporting countries was close to 8 per cent, with a particularly high incidence of resistant isolates reported in Greece (49.1 per cent), Cyprus (16.4 per cent) and Italy (15.2 per cent). However, it was lower than 1 per cent in 23 countries. The alarmingly high value in Greece is due to the epidemic spread of a Carbapenemase-producing clone. It was likely triggered by high environmental pressure resulting from excessive Carbapenem use. The worldwide development of multidrug-resistant *K. pneumoniae* strains is worrisome, since more than 10 per cent of all isolates are already multidrug-resistant.²⁵

ESBL and New Delhi type

Gram-negative pathogens determined to be therapy-resistant have recently gained increasing notoriety. They include multidrug-resistant *E. coli*, *Acinetobacter* as well as *Pseudomonas* strains. Many of these pathogens carry an ESBL gene cluster (extended spectrum beta-lactamase) acquired through horizontal gene transfer. The ratio of ESBL-forming strains in all *E. coli* isolates rose from 1 to 9.9 per cent between 1995 and 2007. During the same period, the resistance to Cefotaxim increased from less than 1 to 10.3 per cent. In addition, gram-negative pathogens that formed a certain type of Carbapenemase were frequently described. This mechanism of resistance, also known as "New Delhi type", is observed in several countries. The "New Delhi type" is characterised by the fact that also Carbapenems are no longer effective against corresponding pathogens.

²² Cephalosporins are broad-spectrum antibiotics. Third-generation cephalosporins have a high stability against beta-lactamase, an enzyme used by some bacteria to protect themselves against such antibiotics.

²³ ECDC (2011).

²⁴ ECDC (2011).

²⁵ Ho J et al (2010).

Multidrug-resistant *Pseudomonas aeruginosa*

Multidrug-resistance to the beta-lactam, Aminoglycoside and Fluoroquinolone classes of antibiotics was determined in 15 per cent of strains examined in Europe in 2010.²⁶ At between 25 and 50 per cent, the frequency was particularly high in four countries (Czech Republic, Greece, Malta, Romania). In 2010, the Europe-wide average of the pseudomonas Carbapenem resistance was close to 17.9 per cent of isolates.

***Acinetobacter* spp.**

Infections with *Acinetobacter baumannii*, a main pathogen of the *Acinetobacter* species, are difficult to treat due to high intrinsic resistance and a growing incidence of acquired resistance. In particular, the incidence of Imipenem-resistant strains has increased substantially from 3.8 per cent in 2001 to 7.7 per cent in 2007; they are capable of splitting Carbapenems.²⁷ The resistance rates have risen sharply in many countries.²⁸

***Enterobacter* spp.**

Resistance to Cefotaxim and other third-generation Cephalosporins is common in Enterobacter strains. The incidence of *Enterobacter cloacae* strains resistant to Piperacillin/Tazobactam increased from 8 to 20 per cent between 1995 and 2004. The resistance to Cefotaxim simultaneously rose from 27 to 34 per cent. The Carbapenem (Meropenem) sensitivity was higher than 99 per cent in Germany.

Mycobacterium tuberculosis

Tuberculosis is the most common bacterial infectious disease in the world, accounting for an estimated 8.8 million new diagnoses in 2010 and nearly 1.45 million deaths.²⁹ In 2011, Germany registered 4,330 tuberculosis cases, including 136 deaths.³⁰

Five antibiotics are used in the first-line therapy of tuberculosis: Isoniazid (H), Rifampicin (R), Pyrazinamide (Z), Ethambutol (E) and Streptomycin (S). In 2010, the incidence of pathogens resistant to at least one of these five first-line drugs was close to 12.6 per cent.³¹ Multidrug-resistance (MDR-TB) to at least Isoniazid and Rifampicin was determined in 1.7 per cent of cases.³² At the present time, it is impossible to make any conclusions about the incidence of the so-called extensively drug-resistant tuberculosis (XDR-TB) in Germany. Based on WHO estimates, the ratio varies significantly worldwide, including within the EU.

²⁶ ECDC (2011).

²⁷ BVL et al (2011).

²⁸ Higgins PG et al (2010).

²⁹ WHO (2011).

³⁰ Robert Koch Institute (2012).

³¹ Robert Koch Institute (2012).

³² Robert Koch Institute (2012).

The disease and resistance rates in Germany are relatively low by international comparison, largely because of consistent diagnostic procedures and therapy outcome measures governed by law, highly suitable conditions for dealing with the growing risk of bacterial spread and resistance. At the same time, no new targeted antituberculosis agents have been developed in the past 40 years. Consequently, the therapy of resistant tuberculosis cases will have to rely on less effective second- and third-line drugs in the foreseeable future. They are associated with a considerably greater incidence of adverse reactions and require longer treatment times.

2.3 Antibiotic use and development of resistance

Although resistance is a natural biological phenomenon, it is associated with the use of antibiotics as illustrated in Figure 3 based on the example of Penicillin-nonsusceptible *S. pneumoniae* bacteria. In fact, the high antibiotic prescribing rate is one of the leading causes for the development and spread of antibiotic-resistant pathogens. The speed of the resistance development varies depending on the pathogen and the antibiotic.³³

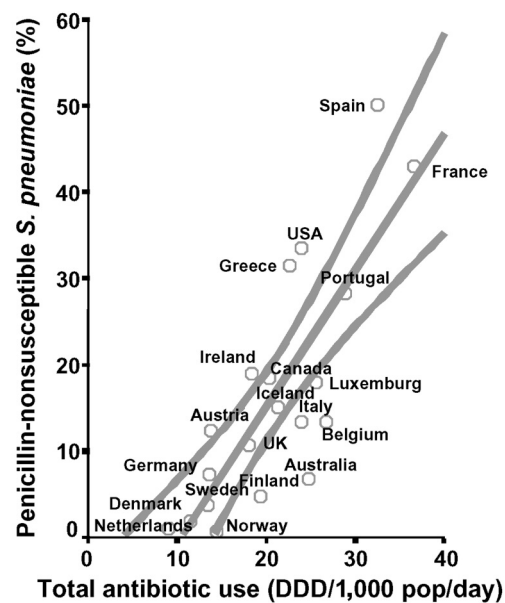


Figure 3: Total antibiotic use measured in daily defined doses (DDD) (horizontal axis) versus Penicillin-nonsusceptible *S. pneumoniae* (vertical axis) in 20 industrialised nations (regression line with a 95 per cent confidence interval, $r = 0.75$; $p < 0.001$).

Source: Albrich WC et al (2004), <http://wwwnc.cdc.gov/eid/article/10/3/03-0252-f1.htm>.

The overall outpatient antibiotic use has risen slightly in the European Union since 1997, with an average increase in daily defined doses (DDD) of 0.05 per 1,000 inhabitants per day in a quarter.³⁴ However, the use fluctuates considerably between the individual EU member states: a reduction in some countries is off-

³³ Högberg LD et al (2010).

³⁴ Adriaenssens N et al (2011).

set by an increase in other countries. For example, an average of 38.6 daily defined doses per 1,000 residents per day were prescribed in the outpatient setting in 2009 in Greece versus only 10.2 in Romania.³⁵ Beta-lactam antibiotics account for the highest prescribing rate.

In the European comparison, Germany's prescribing intensity is in the lower third. The report on antibiotic resistance and use (GERMAP 2010) for the outpatient setting in Germany is based on a prescribing intensity of 14.9 daily defined doses per 1,000 insured subjects and day.³⁶ This corresponds to nearly 41 million prescriptions accounting for sales in excess of 753 million Euros.³⁷ The outpatient prescribing volume in daily defined doses and the sales rose slightly by nearly 5 per cent between 2003 and 2008.

Concerted efforts were initiated in several European countries aimed at curbing antibiotic use, combined with the call for a rationally justified antibiotic therapy (European Surveillance of Antimicrobial Consumption – ESAC).³⁸ However, it is not expected that the incidence of antibiotic resistance will decline within the short timeframe of this programme.

2.4 Ramifications of antibiotic resistance

2.4.1 ... for society

Antibiotic resistance represents an additional burden to society, because it is associated with higher treatment costs, additional sick days, longer hospitalisations and a greater number of deaths. The European Centre for Disease Prevention and Control (ECDC) estimates that approximately 25,000 patients die in Europe each year as a result of a multidrug-resistant bacteria-induced infection, with gram-negative bacteria accounting for approximately two thirds of the total. In Germany, the estimated number of hospital-acquired infections is 400,000 to 600,000 with 7,500 to 15,000 deaths per year, predominantly caused by antibiotic-resistant bacteria. Throughout Europe, antibiotic-resistant bacteria are responsible for approximately 2.5 million additional hospitalisation days each year. All of these figures are associated with a high degree of uncertainty and should be regarded with caution.

The ECDC estimates the total costs incurred as a result of infections with antibiotic-resistant bacteria to be nearly 1.5 billion Euros each year; more than 600 million Euros of this amount are associated with missed work.³⁹ In a recent study, the costs for additional hospitalisations due to bacterial infections of the blood induced by MRSA- and Cephalosporin-resistant *E. coli* bacteria are assessed at nearly 62 million Euros.⁴⁰ These infections only account for a small fraction of

35 Adriaenssens N et al (2011).

36 BVL et al (2011).

37 BVL et al (2011).

38 Mölsted S et al (2008); Sabuncu E et al (2009); Bruce J et al (2009); van de Sande-Bruinsma N (2008).

39 ECDC/EMEA (2009).

40 The study by de Kraker et al (2011) is based on data from 31 countries participating in the European Resistance Surveillance System (EARSS). If the current trends continue, the number of blood infections caused by the gram-negative pathogens (G3CREC) will significantly increase and exceed the number of MRSA blood infections.

all bacterial infections, but their outcome is extremely severe. In reality, the actual amounts are likely much higher.

2.4.2 ... for healthcare

Infections induced by resistant bacteria are associated with the risk of therapy failure. This normally requires a longer treatment period, incurs higher costs and in the worst case results in the patient's death.⁴¹ A distinction has to be made between the administration of antibiotics in the outpatient and the inpatient setting. The rate of antibiotic prescribing in human medicine is considerably higher in the outpatient than in the inpatient setting.⁴² However, more antibiotics are used per patient in hospitals and therefore, resistant bacteria are more likely to be selected. They are not only colonising patients, but also hospital staff and family members and can be transmitted to other patients via this pathway. The required isolation of patients diagnosed with resistant bacteria increases the hospital costs.

The rise in multidrug-resistant bacteria observed in the past 20 years is also a direct consequence of the fact that antibiotics are broadly used, both for the prevention as well as for the therapy of infections. As a result, pathogenic bacteria already exist, which can no longer be kept at bay with traditional antibiotics or are only sensitive to less active substances or drugs associated with greater toxicity.⁴³ Broad-spectrum antibiotics as well as several concomitantly administered antibiotics are increasingly being used to combat the growing rate of resistance. This in turn promotes the development of additional resistance, increases the costs and the risk of adverse drug reactions.

Multidrug-resistant bacteria have a negative impact on the treatment outcome in all areas of medicine. However, certain groups of people are particularly susceptible to infections, including organ transplant recipients, patients undergoing dialysis and cancer patients. Diseases induced by resistant bacteria make treatment management considerably more difficult. The treating physicians are often forced to switch from oral treatment to intravenous therapy, which in turn is associated with the risk of a catheter-related infection.

Even though the problems are pervasive, only a very small number of studies examining the specific consequences of infections caused by resistant pathogens on the different levels of society have been conducted across the EU. Only a limited amount of data on morbidity, mortality and the economic consequences for the healthcare systems and society is available to date. Yet, these types of analyses are the prerequisite for a more effective problem management.⁴⁴ It should also be appreciated that antibiotic resistance is a global concern. Multidrug-resistant bacteria easily cross geographic borders and the increasing mobility of people results in a rapid spread of new variants.⁴⁵

⁴¹ Zilberberg MD & Shorr AF (2010).

⁴² Latest figures from several European countries assume a proportion of 85 to 90 per cent of the total consumption of antibiotics for the outpatient setting. Current figures for Germany are currently not available (BVL et al (2011)).

⁴³ Kumarasamy KK et al (2010).

⁴⁴ Wilke MH (2010).

⁴⁵ MacPherson DW et al (2009).

2.5 Approval and development of new antibiotics

So far, the response to the introduction of any new antibiotic has been the development of resistant bacterial variants. Therefore, there is a constant need for new developments aimed at making alternative drugs available. During the "golden era" of antibiotic development between 1940 and 1970, new substances with new mechanisms of action were continuously developed, which made it possible to manage the issue of emerging resistant strains.⁴⁶

2.5.1 Approvals in Europe and in the USA

Since 2000, the European Medicines Agency (EMA) and the American Food and Drug Administration (FDA) were in charge of making approval decisions for new antibiotics (Table 2). Only four of the substances approved by October 2012 – namely Oxazolidinones (Linezolid), Lipopeptides (Daptomycin), Mutilins (Retapamulin) and Lipiarmycins (Fidaxomicin) – are based on new classes of antibiotics, which are however only effective against gram-positive bacteria. The other substances are modifications of previously used compounds.

With the exception of Carbapenems, which were launched in 1985, all other antibiotics approved for clinical applications between the early 1960s and 2000 were synthetic derivatives of existing compounds developed as early as between the mid-1930s to the early 1960s.⁴⁷ Just four substance classes - Cephalosporines, Penicillins, Quinolones and Macrolides – were used as structural scaffold for 73 per cent of antibiotics approved between 1981 and 2005.

Substance	Class of antibiotic	Rejected by the FDA	Approved by the FDA	Approved by the EMA
<i>Linezolid</i>	<i>Oxazolidinones</i>		2000	
Ertapenem	Carbapenems		2001	2002
Cefditoren	Cephalosporines		2001	
Gemifloxacin	Fluoroquinolones		2003	
<i>Daptomycin</i>	<i>Lipopeptides</i>		2003	2006
Telithromycin	Macrolides		2004	2001
Tigecycline	Glycylcyclines		2005	2006
Faropenem	Penems	2006		
<i>Retapamulin</i>	<i>Pleuromutilins</i>		2007	2007
Dalbavancin	Glycopeptides	2007		
Doripenem	Carbapenems		2007	2008
Oritavancin	Glycopeptides	2008		
Cethromycin	Macrolides	2009		

⁴⁶ Fischbach MA & Walsh CT (2009).

⁴⁷ Fischbach MA & Walsh CT (2009).

Cethromycin	Macrolides	2009	
Iclaprim	Trimethoprim	2009	
Besifloxacin	Fluoroquinolones		2009
Telavancin	Glycopeptides	2009	2011
Ceftobiprole	Cephalosporines	2009	
Ceftaroline	Cephalosporines		2010 2012
<i>Fidaxomicin</i>	<i>Lipiarmycins</i>		2011 2011
Colistimethate sodiums	Colistin		2012

Table 2: Status of active ingredients approved by the FDA and the EMA between 2000 and 2011 (new classes of antibiotics are italicised)

Source: Silver LL (2011b) updated; EMA: <http://www.ema.europa.eu> (Last updated: October 2012)

Between 1987 and 2011 there have been no successful discoveries of novel classes of antibiotics.⁴⁸ In 2010, only two substances in this field were in clinical testing, however, neither of them are in late clinical trials.⁴⁹

2.5.2 State of the development of new antibiotics

The majority of new antibiotics are in the early development phase. In 2009, approximately 150 antibiotic substances were in preclinical development.⁵⁰ For 2009, the European Centre for Disease Control and Prevention (ECDC) reported only 15 systemically applicable substances with a new mechanism of action; for the most part, they were in the early phase I development.⁵¹ In early 2011, 12 substances were tested in phase I studies, 22 substances in phase II studies and six in phase III studies.^{52, 53} The substances are predominantly derivatives of previously known classes of antibiotics.

To reiterate, a major and continuing discrepancy has been in existence for more than 20 years between the need for new antibiotics and the availability of new substances. During this time, the pharmaceutical industry has largely withdrawn from researching antibiotics.⁵⁴ Many companies have stopped their antibiotic research and development activities for economic reasons. The return on investment into the development of antibiotics is low or non-existent due to high costs – the average development costs for a drug are estimated to be 1 billion US dollars –, uncertain economic prospects and regulatory hurdles.⁵⁵ The approvals of Fidaxomicin and Ceftaroline in 2012 are welcome developments, as is the potentially impending approval of Ceftobiprole. Yet, these specific developments do not change anything in terms of the general outlook. Considerably higher profits

⁴⁸ Silver LL (2011).

⁴⁹ Hamad B (2010).

⁵⁰ Hamad B (2010).

⁵¹ ECDC/EMA (2009).

⁵² Butler MS & Cooper MA (2011).

⁵³ The substance Fidaxomicin was approved in the summer/autumn of 2011 by the American FDA and EMA.

⁵⁴ Katz ML et al (2006).

⁵⁵ White AR (2011).

can be generated with the development of symptom-relieving drugs prescribed for chronic illnesses than with short-term curative antibiotics due to the long-term administration of the former and the growing need in an ageing population.

In aggregate, the prescribing volume (in daily defined doses) and the sales of antibiotics are lower than for other groups of medicinal products such as cardiovascular drugs, antidiabetic drugs and psychotropics.⁵⁶ In the past five years, the global market for antibiotics rose by an average of 4 per cent each year. In contrast, the growth rates for antiviral drugs and vaccines were 16.7 or 16.4 per cent,⁵⁷ respectively. Moreover, new antibiotics often have to compete with more economical generic drugs.

From a commercial point of view, it is necessary to sell a successfully developed antibiotic on a large market and preferably to develop broad-spectrum antibiotics. However, from a healthcare perspective and in view of the prevention of the spread of antibiotic resistance, it is preferable to develop pathogen-specific antibiotics and to confine prescribing new antibiotics as a last resort whenever possible. Efforts aimed at regulating the administration of antibiotics as well as well-founded recommendations issued by professional associations regarding a more cautious use of antibiotics also discourage profit expectations.⁵⁸ Thus, diverse factors affect the search for new antibiotics and the associated spread of antibiotic resistance.

Hopes for identifying new compounds using the high throughput screening methods have been high since the 1990s. The dismal success rate of this search – even genomic approaches have not yet been successful – induced some companies to abandon their antibiotics research or return to the traditional search for active ingredients or switch to researching natural materials.⁵⁹

Nevertheless, examples show that it is possible for new antibiotics to establish themselves on the market. The sale of Linezolid and Daptomycin, two representatives of new classes of antibiotics, generated profits in the amount of 1,283 billion US dollars (Linezolid)⁶⁰ and 735.5 million US dollars (Daptomycin)⁶¹ in 2011.

2.6 Strategies and initiatives for a rational handling of antibiotic resistance

The issue of antibiotic resistance has been known for years. A number of strategies and initiatives have been launched on an international (UN, WHO, EU) and national level. The purpose of these initiatives is to reduce, curb or prevent the development of new antibiotic resistance and its spread. In so doing, the proper use of antibiotics and the observation of hygiene measures aimed at preventing infections are of particular short-term significance. Because antibiotic resistance is a global phenomenon, the cooperation of academic research, the

⁵⁶ Schwabe U & Paffrath D (2011).

⁵⁷ Hamad B (2010).

⁵⁸ So AD et al (2011).

⁵⁹ Payne DJ et al (2007).

⁶⁰ Pfizer Financial Report 2011 Appendix A; <http://www.pfizer.com/files/annualreport/2011/financial/financial2011.pdf> (accessed on: 8 June 2012).

⁶¹ Boston Business Journal (2012).

pharmaceutical and diagnostic industry, policy makers, authorities, professional associations and patients' organisations among others is required worldwide.

In addition to the consistent implementation and compliance with measures aimed at averting and preventing infections, the existing national and international strategies and initiatives urgently demand the development of new antibiotics in an effort to combat multidrug-resistant bacteria. Research and development of antibiotic substances continues to be the path that promises the greatest success for the effective treatment of future bacterial infections.

2.6.1 Strategies at the international level

Initiatives on an international level include:

- The **World Health Organisation (WHO)** considers the rise in antibiotic resistance one of the most significant health-related problems and declared antibiotic resistance to be the topic of the World Health Day 2011.⁶²
- On 17 November 2011, the **European Commission** published a 5-year action plan to prevent the growing risk of antibiotic resistance. According to the EU initiative "One health" (in which human and animal health must be considered as one), the action plan pursues a holistic approach, which includes "public health", food safety, consumer safety, environment, animal health and animal welfare as well as the non-therapeutic utilisation of antibiotics.⁶³
- The global network **Action on Antibiotic resistance (ReAct)**, sponsored by the Swedish International Development Cooperation Agency (SIDA) is committed to contributing to a global change in awareness concerning the handling of antibiotics and resistance amongst all social stakeholders.
- **The goal of the Transatlantic Taskforce on Antibiotic resistance (TATFAR)**^{64, 65} between the European Union and the USA is to strengthen the transatlantic dialogue and the mutual exchange of information about antibiotic resistance.
- The **Infectious Diseases Society of America (IDSA)** recommended the establishment of a global alliance for the development of ten new antibiotics by 2020.

2.6.2 German Antibiotic Resistance Strategy: a first step aimed at reducing the development of antibiotic resistance

The German Antibiotic Resistance Strategy (DART) was initiated in Germany in 2008 under the aegis of the Federal Ministry of Health (BMG) in collaboration with the Federal Ministry of Food, Agriculture and Consumer Protection (BMELV) and the Federal Ministry of Education and Research (BMBF).⁶⁶ The

⁶² <http://www.who.int/world-health-day/2011/en/index.html>; (accessed on: 13 April 2012).

⁶³ EU-KOM (2011).

⁶⁴ <http://ecdc.europa.eu/en/activities/diseaseprogrammes/TATFAR/Pages/index.aspx> (accessed on: 13 April 2012).

⁶⁵ Involved were institutions of the EU Commission (EFSA, EMA, ECDC, Directorate-General for Research and Innovation, Directorate-General for Health and Consumers), the United States (OGHA, CDC, FDA, NIH, NIAD) and the Council of the European Union.

⁶⁶ <http://www.bmg.bund.de/praevention/krankenhausinfektionen/antibiotikaresistenzstrategie.html> (accessed on: 13 April 2012).

purpose of DART is to combat the development and spread of antibiotic resistance.⁶⁷ Ten measures aimed at reaching this goal were defined, including amongst others:

- the establishment of surveillance systems on antibiotic resistance and antibiotic use,
- the creation of a commission for "Anti-infective agents, Resistance and Therapy" (ART) at the Robert Koch Institute,
- the improvement of the education, continuing education and training of healthcare professionals in hospitals for infectious diseases, in particular on antibiotic stewardship in hospitals (ABS) in cooperation with the professional associations German Society for Hygiene and Microbiology (DGHM) and German Society for Infectious Diseases (DGI),
- the support of regional networks aimed at the epidemiological documentation of bacteria, at improving the communication within the referral structures of the healthcare system and at better implementing guidelines,
- mandatory reporting of MRSA,
- the analysis of the attitude toward antibiotic use amongst doctors and patients.

Essentially, DART was created to document antibiotic resistance and the consumption of antibiotics as well as to improve the infectious diseases-related training of doctors. Measures aimed at improving the quality of the evaluation of antibiotic resistance, including the effect of medicinal substances on the organism (pharmacodynamics) and the specific growth conditions of bacteria at the site of the infection, are not taken into consideration.⁶⁸ The methods for determining the assessment of antibiotic resistance are not uniform and hence difficult to compare with each other.⁶⁹ This dilemma has led to a consensus definition of resistance on a European level (EUCAST).⁷⁰ Moreover, there is a need for research aimed at developing better antibiotic resistance test systems that takes into account the *in vivo* situation of the pathogen (including the host's reaction to the antibiotic). In addition, animal models using model bacteria have to be established for experiments with antibiotic therapies.

2.6.3 Surveillance

Antibiotic resistance surveillance in Germany

The "Antibiotic Resistance Surveillance in Germany" (ARS) is a key component of the German Antibiotic Resistance Strategy.⁷¹ The nationwide monitoring of antibiotic resistance has been developed by the network of national reference centres (NRZ) co-ordinated by the Robert Koch Institute. The Federal Office for Consumer Protection and Food Safety is in charge of the national resistance monitoring of veterinary pathogens in Germany. Since 2008, the bi-annually published GERMAP report contains a summary of data on antibiotic consumption and resistance.

⁶⁷ Gastmeier P et al (2009); Robert Koch Institute (2011).

⁶⁸ Dalhoff A et al (2009); Rybak MJ (2006).

⁶⁹ Turnidge J & Paterson DL (2007).

⁷⁰ A national committee supervises the application and implementation of the EUCAST limits in Germany.

⁷¹ <https://ars.rki.de> (accessed on: 19 June 2012).

The central co-ordinating body for the documentation of data on antibiotic resistance on a European level is the European Centre for Disease Prevention and Control (ECDC).⁷² Several European networks including the European Antibiotic resistance Surveillance Network (EARS-Net)⁷³ and the European Surveillance of Antimicrobial Consumption (ESAC)⁷⁴ are involved in the surveillance of antibiotic resistance and the consumption of antibiotics in Europe. However, these networks are not always representative, because a different number of institutions are taking part in it from different countries. In the long term, it is important to achieve a greater degree of representativeness and the continuous support of these networks is required. Uniform methodological standards such as created with the EUCAST project are the basic requirement for these networks.⁷⁵

Reliable resistance monitoring is a prerequisite for the establishment of regional networks whose goal it is to interrupt the dissemination pathways of multidrug-resistant bacterial infectious agents, between inpatient healthcare institutions, within the population and into hospitals. The cross-border EUREGIO project MRSA-net established at the border between Germany and The Netherlands in Münsterland/Twente is one example.⁷⁶ In this project, MRSA rates are documented on the German side of the border with the objective to lower them to match the Dutch levels. The MRSA rate in The Netherlands is below three per cent and has been stable at a low rate for years. This success is dependent on a strategy whereby patients are consistently tested upon admission to the hospital and isolated and treated in case of a positive MRSA test.⁷⁷ The purpose of MRSA-net is to establish and implement cross-border quality standards aimed at improving the medical care on the German side of the border by means of a sustainable reduction of the MRSA rate. If successful, the established quality standards and experience could be transferred to other regions and other, in particular gram-negative, pathogens.

Molecular epidemiology of antibiotic resistance

The objective of molecular epidemiology of antibiotic resistance is to uncover the rationale of resistance development trends derived from surveillance systems and newly emerging antibiotic resistance. As demonstrated with the example of Methicillin-resistant *Staphylococcus aureus* (MRSA), it is possible to identify the evolution of multidrug-resistant epidemic strains by means of genome-based analyses and to track their regional and worldwide spread.⁷⁸ For early warning systems, it is additionally essential to track the emergence and spread of resistance genes. Current examples include the *cfi*-gene-coded resistance to Linezolid in staphylococci as well as the resistance gene bla_{NDM-1} ("New Delhi metallo-beta-lactamase"), which induces resistance to Carbapenems, one of the most important groups of antibiotics for the treatment of gram-negative bacteria.⁷⁹

⁷² <http://www.ecdc.europa.eu> (accessed on: 13 April 2012).

⁷³ <http://www.ecdc.europa.eu/en/activities/surveillance/EARS-Net/Pages/index.aspx> (accessed on: 13 April 2012).

⁷⁴ <http://www.ecdc.europa.eu/en/activities/surveillance/ESAC-Net/Pages/index.aspx> (accessed on: 13. April 2012).

⁷⁵ <http://www.eucast.org> (accessed on: 19 June 2012).

⁷⁶ <http://www.mrsa-net.org/indexEuregioDE.html> (accessed on: 19 June 2012).

⁷⁷ In the course of a rehabilitation therapy, the MRSA bacteria are removed from the skin and the mucous membranes of the carrier.

⁷⁸ Nübel U et al (2010); Harris SR et al (2010).

⁷⁹ Witte W & Cuny C (2011); Nordmann P et al (2011).

3 Antibiotic resistance in livestock and plant protection

3.1 Livestock

The transfer of antibiotic resistance from animals to humans contributes to the current resistance problems.⁸⁰ Gram-negative ESBL-forming bacteria (see also Chapter 2.2) are particularly problematic. Resistant bacteria can be transferred to humans via food or direct contact with animals. The transfer of MRSA isolates of the sequence type ST398 predominantly from pigs to humans has been demonstrated on several occasions.⁸¹ The horizontal gene transfer between animal and human pathogens also plays a potential role in the spread of resistance.

As a basic principle, antibiotics should only be used if strictly indicated. As already defined in the 2010 guidelines of the Federal Veterinary Association, antibiotics should generally only be used for therapeutic purposes in animals – aside from a few justified exceptions – rather than for prophylactic purposes.^{82, 83} The use of substances with antimicrobial action with the purpose of increasing the production outcome for livestock farming was banned in the EU in 2006.

Antibiotic resistance emerging in connection with animal husbandry can impair the efficacy of important antibiotics in human medicine. Certain classes of antibiotics should be reserved for use in human medicine.⁸⁴ Additionally, the use of newly developed substances in veterinary medicine should be restricted to an absolute minimum. Furthermore, it is imperative to monitor animal pathogenic bacteria and zoonotic parasites and to continue documenting resistance data such as has been done in Germany since 2001 within the scope of the national resistance monitoring programme GermVet conducted by the Federal Office for Consumer Protection and Food Safety.

The awareness of antibiotic resistance and the mechanisms of their development and spread must also be heightened amongst employees in the agricultural and food industries with regular measures for continuing education.

The effects of antibiotic use in animals on the development of resistance and the identification of the transmission pathways are already being discussed by a number of research networks. For instance, the RESET⁸⁵ network is examining the development of resistance using enterobacteria (*Escherichia coli* and *Salmonella enterica*) as an example, while the MedVet-Staph network is investigating *Staphylococcus aureus* (MRSA).⁸⁶ Nevertheless, research efforts aimed at examining the

80 Bywater RJ & Casewell MW (2000) estimate that veterinary medicine / animal production contributes less than 4 per cent to the resistance problem.

81 Voss A et al (2005); Wulf M & Voss A (2008); van Loo I et al (2007); Cuny C et al (2010).

82 Federal Veterinary Association (2010).

83 An exception is, for example, the perioperative administration of antibiotics if the bowel is opened to surgically remove foreign bodies in dogs.

84 Currently, there are no veterinary approvals for Oxazolidinone (Linezolid), cyclic Lipopeptides (Daptomycin), Glycopeptides (Vancomycin, Teicoplanin), Glycylcycline (Tigecycline), Streptogramins (Synercid - Quinu/Dalfopristin), Mupirocin. However, in a therapeutic emergency (e.g. pan-resistant *Staphylococcus* in dogs), all these substances can be used for animals that are not used for food production (dog/cat).

85 <http://www.reset-verbund.de/> (accessed on: 13 April 2012).

86 <http://www.medvetstaph.net/index.html> (accessed on: 13 April 2012).

influence of antibiotic administration in animals on the development of resistance and the transfer of resistance factors to human pathogenic bacteria or the transmission of pathogenic bacteria from farm animals to humans should be intensified.

3.2 Plant protection

Some antibiotics such as Streptomycin and Oxytetracycline are used for fruit and vegetable growing to combat plant pathogenic bacteria. Streptomycin is used in many EU member states and outside of Europe to prevent fire blight, which is caused by the bacterium *Erwinia amylovora*. This indeed effectively prevents the breakout of the disease, but the development of antibiotic resistance is promoted. Streptomycin resistance genes were found on mobile genetic elements that code for a phosphotransferase enzyme (StrA, StrB). The same genes have demonstrably been identified in 17 species of environmental bacteria and pathogenic organisms.⁸⁷ Although the quantity of used antibiotics is far lower in fruit growing than in human and veterinary medicine, any extensive application of antibiotics should nevertheless be avoided and replaced with other measures aimed at preventing infection.

⁸⁷ McGhee GC et al (2011).

4 Research structures

Diverse research efforts on a national and European level are addressing the issue of the rise in antibiotic resistance and the simultaneous decline in the development of new antibiotics.

In Germany, the research activities are predominantly sponsored by the Federal government (Federal Ministry of Education and Research – BMBF, Federal Ministry of Health – BMG) and the German Research Foundation (DFG). The DFG finances two Collaborative Research Centres (SFB) and a Research Unit involved in the search for new active ingredients to combat infection-causing bacteria and bacterial structures and possible points of action of new antibiotics.^{88, 89, 90} The field of functional genome research has enjoyed major growth in recent years and it is expected to continue to play a key role in antibiotics research in the future.

Aside from these research organisations, networks on local, regional and national levels were established in recent years, funded by the BMG, aimed at working on model projects. The emphasis is for example on antibiotic consumption and its different effects, the prevention of MRSA infections and the improvement of the treatment of patients with MRSA infections.⁹¹ The establishment of healthcare regions (example: HICARE healthcare region Baltic Sea Shore – action alliance to combat multidrug-resistant bacteria) pursues a similar concept. The purpose is to create management models with the inclusion of all components, ranging from basic research and clinical interventions to healthcare-related economic evaluations. The Integrated Research and Treatment Centre (IFB) for Sepsis and Consequences of Sepsis was set up in Jena.⁹² Here, the focus is on early effective diagnosis and treatment of severe systemic infections.

Research on new antibiotics is a topic not only dealt with in existing research projects and networks, but also addressed by the German Centre for Infection Research (DZIF), which is tasked with bringing together and co-ordinating leading establishments involved in the research of infectious diseases in Germany.⁹³ Aspects of translation and translational structures aimed, among other objectives, at the search for new active ingredients also play a role in the conceptual design of the DZIF.

On a European level, the Innovative Medicines Initiative (IMI) as a public-private network – with the involvement of the European Commission and the European Umbrella Organisation of the Pharmaceutical Industry – supports the search for new active ingredients and antimicrobial substances.⁹⁴ Some projects

88 <http://www.sfb630.uni-wuerzburg.de> (accessed on: 13 April 2012).

89 <http://www.uni-tuebingen.de/forschung/forschungsschwerpunkte/sonderforschungsbereiche/sfb-766/home.html> (accessed on: 28 August 2012).

90 <http://www3.uni-bonn.de/forschung/forschungsprofil/forschergruppen/for-854> (accessed on: 28 August 2012).

91 http://www.rki.de/DE/Content/Infekt/Krankenhaushygiene/Netzwerke/Netzwerke_node.html (accessed on: 9 August 2012).

92 <http://www.cscck.uk-j.de/CSCC.html> (accessed on: 13 April 2012).

93 <http://www.dzif.de> (accessed on: 12 June 2013).

94 <http://www.imi.europa.eu/> (accessed on: 9 August 2012).

within the scope of the 6th EU research framework programme were dedicated to the issue of antibiotic resistance.⁹⁵ The research alliance ERA-NET PathoGenoMics, a consortium of nine countries, which was active until August 2012, examined molecular mechanisms of the pathogenicity of microorganisms, developed new diagnostic tools and analysed epidemiologic correlations involved in the spread of pathogenic microorganisms. Leading European research institutions have pooled their expertise in the Network of Excellence (NoE) EuroPathoGenomics.⁹⁶ Fifteen states participated in the Joint Programming Initiative "The Microbial Challenge – An Emerging Threat to Human Health". Within the scope of this initiative, researchers examined the biology and dynamics of resistance, devised strategies for the prevention of resistance development and evaluated innovative treatment options.⁹⁷ Networks within the 7th EU research framework programme are working on a wide array of scientific problems with respect to the development and spread of antibiotic resistance, in the search for new antibiotics and targets for antibiotic therapy as well as for faster and more powerful diagnostic methods. The scope of the 2013 work plan of the 7th EU research framework programme is aligned with the resolution of the EU Commission on antibiotic resistance published in 2011.

Some small and medium-sized enterprises (SMEs) are also actively and successfully participating in the development of antibiotics research sponsored by the EU and BMBF.

Despite these currently existing research structures, greater support is required in view of the needs for urgent development of new antibiotics, involving the longer-term establishment of research structures beyond national borders. In addition, the success of projects conducted in recent years should be evaluated and favourable approaches pursued further.

⁹⁵ http://cordis.europa.eu/projects/home_en.html (accessed on: 30 August 2012).

⁹⁶ <http://www.noe-epg.uni-wuerzburg.de/> (accessed on: 9 August 2012).

⁹⁷ http://cordis.europa.eu/fp7/home_en.html (accessed on: 27 April 2012).

5 Research agenda

In order to reduce the spread of resistance and to develop new antibiotics, greater research efforts are necessary and should be accompanied by improved framework conditions that allow the effective implementation of scientific knowledge into practice. From the academies' point of view, research activities should cover a broad portfolio of topics and methods in order to combat the problem of antibiotic resistance from different angles. Research is required in particular to support developing assays for the identification, validation and modification of targets, the development of relevant animal models, the implementation of knowledge gained from structural biology, analyses on the structure-activity relationship and for medicinal chemistry.

5.1 Genome research

For over 15 years it has been possible to decode and analyse whole genomes of microorganisms. This new methodological approach has revolutionised biomedical sciences and is also important for the research in the field of antibiotic resistance. In recent years, new technologies have been developed (such as Next Generation Sequencing – NGS) and been made available for research on resistance. To facilitate these advances, it is also necessary to establish powerful bioinformatics capacity. What matters most is the ability to analyse large sequence packages and address those functions playing an essential role in the analysis of changes in the genome of pathogenic microorganisms, in particular the analysis of point mutations. In this context, genome research offers direct access to the exploration of virulence and resistance with respect to functional genome analysis.

Gene expression under *in vivo* and *in vitro* conditions is another crucial factor. Deep sequencing plays a role by means of which it is also possible to analyse the expression of small RNA molecules. This approach should be utilised for resistance research and for analysing the expression of resistance-relevant genes.⁹⁸

Meanwhile, genome research has also revolutionised the field of epidemiology (genome-wide association analysis of epidemiology). This approach should be used more broadly to explore the spread of resistant pathogens. In this context, it also makes sense to use the methods of metagenome analysis. With respect to resistance research, it is necessary to track the expression of genes that are relevant for the metabolism (metabolomics) in order to evaluate new resistance mechanisms. Such methods can be used as basis for the development of new test systems that allow a faster and safer analysis of antibiotic resistance.

No new antibiotics have yet been developed based on genome research findings. This is attributed in part to poorly designed test systems and the use of low diversity substance libraries.⁹⁹ The available potential of genome-related information should, therefore, be used more widely by means of smart screening systems.¹⁰⁰ A systematic and broadly designed analysis of the available potential targets may be the key to future success.

⁹⁸ Wenzel SC & Müller R (2009).

⁹⁹ Payne DJ et al (2007).

¹⁰⁰ Payne DJ et al (2007).¹⁰¹ Molinski TF et al (2009).

New genome research methods such as genome mining along with advances involving DNA sequencing methods allow an increasingly detailed genomic analysis of symbiotic communities in complex ecological niches and can contribute to the identification of new potentially active ingredients. For example, more than 25 gene clusters for the production of secondary metabolites were discovered with the genomic analysis of actinomycetes and myxobacteria.

In this context, the possibility of analysing the genomes of host cells should equally be considered. Metabolic functions of the host cells could potentially represent new points of action for active ingredients.

5.2 Synthetic biology

The research field of synthetic biology has enjoyed a dynamic development in recent years. Its purpose is to replicate living processes in the laboratory and to establish (micro-) organisms with new properties. In so doing, there are significant possibilities of synthesising major DNA regions in the laboratory and the new methods developed in the process should be made available to antibiotics research. The synthesis of major metabolic determinants in the laboratory should be improved to help optimise the production of antibiotics. Examples involving the therapy of malaria (artemisinic acid) give rise to optimism with respect to the use of these methods. Moreover, the synthesis of major DNA regions is also used to optimise DNA immunisation and DNA therapy. In the long term, it might be possible to study molecules with new properties in the laboratory, representing major potential for the development of new antibiotics.

5.3 Identification and further development of active ingredients and targets

5.3.1 Natural materials research

More than two thirds of all antibiotics are developed using natural materials or are themselves natural materials.¹⁰¹ Consequently, it is expected that other potential active ingredients occur in nature. The development of new substance libraries with a greater structural variety than many traditional libraries is one of the key conditions for the identification of these potential candidates. Interesting compounds were, for instance, isolated from actinomycetes in ocean sediments.

Other encouraging sources include terrestrial and marine symbiotic communities as well as microbial genera that have yet to be explored. New research projects are aimed at the investigation of bacterial symbionts of marine sponges, insects and fungi. However, natural materials derived from tropical plants also supply promising candidates.¹⁰² Some less thoroughly researched groups including myxobacteria yield a number of natural antibiotic substances, such as e.g. Myxopyronins, which possess a broad antibacterial therapeutic spectrum by specifically inhibiting the RNA polymerase of bacteria using a novel mechanism.¹⁰³

¹⁰¹ Molinski TF et al (2009).

¹⁰² Li JWH & Vederas JC (2009).

¹⁰³ Mukhopadhyay J et al (2008).

5.3.2 Screening methods

The enormous possibilities of synthetic chemistry regularly produced new modifications that ensured the continuous replenishment of the antibiotics pipeline.¹⁰⁴ However, the dramatic reduction of new approvals of antibiotics since the mid-1990s is also due to the fact that the possibilities of chemically modifying established structures are largely exhausted. The systematic search for producers of potential antibiotic lead structures is therefore an alternative promising approach in the future to enable the continued battle against antibiotic-resistant bacteria. The diversity of various ecological habitats also justifies the conduct of such a search. In order to increase the potential of natural materials and to find suitable candidates in natural material libraries, the development of new and more effective screening methods is essential. Traditional methods of microbiology play a significant role in the process.

Other active ingredients against antibiotic-resistant bacteria can potentially be found amongst pre-existing compounds. The recently introduced classes of antibiotics – Oxazolidinones, Lipopeptides and Mutilines – were discovered as early as two decades ago, but not developed further because of the many available antibiotics that were still effective at the time.

Improved screening systems as well as molecular biological production optimisation of natural materials can both contribute to improving the yield of the search for new active ingredients. For example, the use of indicator strains carrying several resistance determinants minimises the risk of the selection of known compounds and those that have already been deemed ineffective because of cross-resistance. Another worthwhile approach consists in the screening of different substance libraries for antibacterial activity in whole-cell assays rather than in a target-directed preparation.

The failure of many target-based programs made it doubtful whether novel compounds can be found at all with these types of search programs. However, the success rate might rise with the development of new test systems. In addition, antibiotic targets exist which have yet to be examined more closely and which affect metabolic pathways, such as the fatty acid synthesis or bacterial cell division.¹⁰⁵

Other opportunities involve the elimination of metabolic functions of intracellular bacteria whose own metabolism is often restricted by their limited genetic conditions and which therefore strongly rely on the metabolism of the host cells (e.g. *Rickettsia*, *Chlamydia*, *Listeria*). Here, the metabolism of the affected host cells could also provide attractive points of action for antibacterial active ingredients aimed at preventing the propagation and possibly the persistence of these bacteria. The exploration of these targets would be particularly relevant to the objective of developing antimicrobial active ingredients with a narrow pathogenic spectrum, which could likely prevent multiple antibiotic resistance.

Structure-based modelling approaches require the identification of specific inhibitors of validated targets. In the approach, we have to keep in mind that target-based approaches fail to address the problem of crossing cell membranes as the first step. Based on experience, natural materials again have an advantage in this respect, because of their evolutionary optimisation of properties that are beneficial for the application.

¹⁰⁴ A "pipeline" is the set of drug candidates that a pharmaceutical company has under discovery or development at any given point in time (source: Wikipedia, keyword "drug pipeline" http://en.wikipedia.org/wiki/Drug_pipeline (accessed on: 25 October 2012)).

¹⁰⁵ Fabbretti A et al (2011).

Once new lead structures have been identified, the pharmaceutical properties of the active ingredients generally have to be optimised for use in the clinical setting. For this purpose, the field of medicinal chemistry has developed a variety of methods in recent decades, aimed at answering the questions about absorption, distribution within the body, metabolism, elimination and possible toxicities (ADME). It is crucial to view these activities as part of the development of new anti-infectious agents, because they contribute considerably to the transition from the early identification of lead structures to the clinical application.

A greater number of test systems should be developed which take into account the aspects of virulence, host-pathogen interaction and *in vivo* function. For instance, the availability of certain fatty acids or trace elements such as iron for the survival of infectious agents is different *in vivo* than in the commonly used standard *in vitro* test systems.¹⁰⁶ In the past, metabolic factors have not been adequately examined, although they might supply attractive targets. However, pathogen-specific metabolic pathways usually do not allow the development of broad-spectrum antibiotics.

Similarly, the expected advances associated with pathogen-specific diagnostics should boost the development of antibiotics with a narrow therapeutic spectrum in the future.

5.3.3 Chemical synthesis and structural biology

The improvement of existing active ingredients continues to be a critical strategy for the further development of antibiotics. This approach has gained new significance because medicinal products can be analysed with respect to their structure (including by means of X-ray structure analysis) and because it is possible to model receptor-ligand interactions. Further research is warranted on the determination of structures. The field of medicinal chemistry has enjoyed a partial renaissance in recent years and provides new methods of chemical synthesis and imaging procedures allow the optical tracking of the dynamic processes of antibiotic action.

With the exception of Carbapenems, all antibiotics approved between the 1960s and 2000 were synthetic derivatives of existing compounds (see Chapter 2.5.1). A new substance class, namely the Oxazolidinones, was only introduced to clinical practice in 2000 with Linezolid, used mainly for the treatment of MRSA. During derivatisation, the basic antibiotic scaffold remains intact and is altered by different chemical groups outside of this nuclear matrix. This often results in differences in the efficacy to different groups of pathogens, in the resistance properties as well as in the pharmacological behaviour.

5.4 Other antibiotic agents

Antimicrobial peptides (defensins) or aptamers supply additional starting points for the development of new antibiotics and should be explored further. In nature, antibiotic peptides are widely used to combat bacterial infections. 1,399 antimi-

106 Brinster S et al (2009).

crobial peptides had been described in August 2011 (see *The Antimicrobial Peptide Database*).¹⁰⁷ Many possess high antimicrobial activity against different pathogens.¹⁰⁸ One substance, PMX-30063, is used in clinical phase II studies.¹⁰⁹ Aptamers, e.g. against beta-lactamases, might help restore the efficacy of beta-lactam antibiotics.¹¹⁰ When using peptides and aptamers, the priority in the future will be to solve problems relating to the systemic distribution, the stability and access to the target.

5.5 Molecular environmental biology

As noted previously, with a few exceptions, antibiotics represent natural substances, produced by microorganisms, predominantly by bacteria and fungi. The producers are commonly isolates from environmental habitats, mainly soil microorganisms such as actinomycetes or bacilli. More recently, natural materials have increasingly been isolated from habitats of sponges or corals. Knowledge about the role antibiotics play in the natural environment is inadequate. It is notable that the genes for the synthesis of antibiotics often occur in combination with resistance-specific gene clusters. Gene clusters which code for production, but also for resistance, are often localised on mobile genetic elements such as plasmids, genomic islands or transposons. The role antibiotics play with respect to the gene transfer processes is only partly understood. It is clear that the horizontal gene transfer between soil microorganisms and strains with medical relevance plays a major role in the spread of antibiotic resistance genes. To the extent that these processes occur in natural environmental habitats, they are for the most part poorly understood.

In addition to the analysis of individual microbial strains that determine the production of, and the resistance to, antibiotics, the comprehensive study of environmental consortia, for example by means of metagenomic analysis, represents another challenge for research on antibiotics. Such research would help to improve understanding of the relevance of antibiotics in environmental habitats. The analysis of the biological action of subinhibitory antibiotic concentrations on the gene transfer and also on the metabolism and the interaction of microbes in the habitats is equally important. The comprehensive molecular analysis of environmental consortia would make it possible to learn more about the natural significance of antibiotics, to better understand the spread of resistance genes and hence to be better able to influence it.

5.6 Ecological aspects of the development of antibiotic resistance and the host flora

In the future, the goal is to examine the effects associated with the administration of antibiotics on the host more intensively. Not only does the overuse of antibiotics promote resistance, but it also causes alterations of the body's entire

¹⁰⁷ <http://aps.unmc.edu/AP/main.php> (accessed on: 13. April 2012).

¹⁰⁸ Hancock RE & Patrzykat A (2002).

¹⁰⁹ Butler MS & Cooper MA (2011).

¹¹⁰ Kim SK et al (2009).

intrinsic microbial flora. In the long term, this might also promote diseases such as diabetes, adiposity, allergies or chronic inflammatory bowel diseases.¹¹¹ The use of probiotics plays a relevant role as well. These types of microbes are capable of influencing disease processes as apathogenic strains and of contributing to the physiological balance predominantly of the intestinal flora.

Researchers have used metagenomic methods to analyse the natural physiological flora in humans and mice with respect to the composition of cultivatable and non-cultivatable bacteria. This allowed the determination of the totality of genomes (microbiome) and genera (microbiota). Chronological fluctuations, dependence on diet and the effect of antibiotics on the microbial flora were determined.¹¹² Furthermore, it was possible for the first time to define more accurately the protective microflora (protection against *Salmonella* or *Clostridium difficile*).¹¹³ In addition, it was demonstrated that the colonic milieu has a particularly beneficial effect on horizontal gene transfer between bacteria through plasmids and phages.¹¹⁴

Based on this knowledge, it is now possible to identify the totality of the resistance genes (the resistome of the microbiota) as well as the totality of the facultative pathogenic bacteria of the intestinal flora of hospitalised patients in advance. In particular, Vancomycin-resistant enterococci and extra-intestinal pathogenic *E. coli* (pathotype ExPEC) should be determined. Analogous to the successful differentiation of *E. coli* into more than ten different pathotypes, it is now possible to differentiate the remaining genera of the enterobacteria species present in the intestine by pathotypes and to predict their hospital-acquired pathogenicity potential. In terms of managing infectious diseases, this would allow the predetermination of the risk of hospitalised patients for endogenous infections, including antibiotic resistance.¹¹⁵

The horizontal gene transfer mechanisms such as transposition, transformation, transduction and conjugation have been known for years. Important questions raised in this regard concern the mechanisms of the selection pressure, the inducers of gene spread and persistence as well as the possibilities to control or suppress these mechanisms.

Meanwhile, experiments have demonstrated that subinhibitory antibiotic concentrations such as occur in the waste water of industrial facilities and sewage treatment plants contribute to the selection of antibiotic-resistant bacteria.¹¹⁶ In addition, subinhibitory concentrations of antibiotics can increase the mutation rate by forming oxygen radicals, thus expanding e.g. the substrate spectrum of beta-lactamase or even triggering the horizontal resistance gene transfer.¹¹⁷

According to latest insights, conjugative plasmid transfer in the inflammatory bowel (e.g. in salmonellosis) is particularly efficient.¹¹⁸ These observations give reason to review the traditional therapy recommendations for antibiotics established as monotherapy and frequently administered as insufficient doses.

111 Blaser M (2011).

112 Costello EK et al (2009); Buffie CG et al (2012); Jernberg C et al (2007); Jakobsson HE et al (2010); Blaser M (2011).

113 Blaser M (2011); Stecher B & Hardt WD (2011).

114 Stecher B (2012).

115 Littmann DR & Pamer EG (2011).

116 Aminov RI (2009); Davies J et al (2006); Gullberg E et al (2011).

117 Kohanski MA et al (2010).

118 Stecher B et al (2012).

Therefore, microbiologists are defining the need for substances aimed at controlling the spread of antibiotic resistance (penetration, promiscuity, persistence and plasticity)¹¹⁹ in addition to antibiotics for the direct elimination of bacteria. Substances to combat these four "Ps" are known as *eco-evo* drugs. Their purpose is to limit the modification, new development and spread of antibiotic resistance in the environment. Inhibitors of plasmid conjugation, bacteriocins and phages have already been used in vitro to this end.¹²⁰ This approach is promising and might be able to bring the patients' microbiota of the gastrointestinal tract – the main hub of antibiotic resistance – under control.

5.7 In vitro sensitivity versus in vivo efficacy

Bacterial patient isolates are tested for antibiotic resistance by means of standardised in vitro methods (nutrient agar or solution) under aerobic conditions and with exponential growth. These conventional test methods only rarely coincide with the growth conditions of bacteria in vivo. This is not only a pharmacokinetic problem; it is also about taking into account the different growth conditions and states of bacterial infectious agents in the patient.¹²¹

The propagation of bacteria can be intracellular or extracellular, they can grow as planktonic/dispersal or biofilm-like microcolonies in the tissue. The oxygen tension at the site of infection (aerobic, microaerophilic, anaerobic) as well as the available nutrients determine the metabolism and the structure of the outer envelope of bacteria and hence also the receptiveness for antibiotics. These parameters are not considered in the conventional test for antibiotic resistance. The predictive value of in vitro antibiograms is impaired as a result, which helps explain the failure of therapies.¹²²

To improve the antibiotic therapy of *Pseudomonas* infections in mucoviscidosis/cystic fibrosis (CF), researchers have already laid impressive groundwork: they matched antibiotic resistance test media to the mucus secretion in CF bronchi, created anaerobic conditions and took into account the biofilm formation.¹²³ Preliminary data about alterations in the metabolism and life cycle in the extra-intestinal milieu are also available for endogenous *E. coli* infections (from the intestinal commensal bacterium to the pathogenic agent of urinary tract infection or sepsis).¹²⁴

Chronic and recurrent (relapsing) infections often develop in spite of antibiotic therapy. Bacterial persisters are the likely culprit; their metabolism is severely reduced, allowing them to elude antibiotic therapy. Preliminary metabolic analyses demonstrated that the effect of *aminoglycosides* rises sharply when *Escherichia coli* persisters are fed with glucose or pyruvate.¹²⁵

These novel approaches in which the pathogen's metabolism and way of life when exposed to infection are considered (e.g. mouse model of infection) are

119 Baquero F et al (2011).

120 Baquero F et al (2011); Lujan SA et al (2007).

121 Brown SA et al (2008).

122 Brook I & Gilmore JD (1993).

123 Sriramulu DD et al (2005); Hill D et al (2005); Dubreuil L & Odou MF (2010).

124 Alteri CJ & Mobley HL (2012).

125 Allison KR et al (2011).

promising with respect to new therapeutic strategies and test procedures for antibiotic resistance.¹²⁶

In addition, it is necessary to improve clinical analyses of therapy failures, e.g. in intensive care units or in connection with the treatment of implant-induced infections; this requires interdisciplinary cooperation between infectious disease specialists, microbiologists and pharmacists.

Based on positive experience involving the delay of future resistance development following the introduction of new classes of antibiotic substances for the therapy of tuberculosis and HIV, there is high demand for research relating to the preferential use of new antibiotics as combination substances when added to existing therapy regimens. The repercussions of this strategy on the development of resistance even in connection with short-term treatments of infections remain for the most part unexplored.

5.8 Antibiotic-induced adverse reactions: effect on the immune system and bacterial virulence

Antibiotic-induced pharmacotoxic adverse reactions as listed in the summary of product characteristics (e.g. nephrotoxicity and ototoxicity of aminoglycosides) are generally taken into account. However, the anti-inflammatory or immunosuppressive effects of antibiotics which can mimic a successful therapy of the infection are not as well known.

For instance, Doxycycline acts as inhibitor of metalloproteases, as scavenger for oxygen radicals and as neuroprotective agent by inhibiting programmed cell death. Macrolide antibiotics have a similar anti-inflammatory action.¹²⁷ In contrast, the immunomodulatory effects of fluoroquinolones are more complex and poorly understood.¹²⁸ They can increase the formation of blood cells (haematopoiesis), inhibit one form of programmed cell death (apoptosis) and the distribution of the TNF (tumour necrosis factor) signalling mechanism as well as bring about the synthesis of the interleukin 2 messenger.¹²⁹

The effect of antibiotics on bacteria can be bactericidal or bacteriostatic. Antibiotics with a bactericidal effect induce bacteriolysis and the release of substances, so-called microbial/pathogen associated molecular patterns (MAMP/PAMP) triggering e.g. cytokines and chemokines with a pro-inflammatory or anti-inflammatory effect through toll-like receptors (TLRs), which determine the symptoms of the infection and the extent of organ damage.¹³⁰ In the past, the analyses were limited to cell culture models and artificial mouse models of infection. Comparisons with defined knockout mice (e.g. TLR4^{-/-}, Myd88^{-/-}) were only conducted in a few cases.¹³¹ Since knockout mice models are now available for all known PAMP receptors and signal transduction components, the effects of a therapy with antibiotics on the innate immune response to infections in mice should be systematically analysed with adjusted model pathogens. These kinds

126 Lee HH & Collins JJ (2012).

127 Griffin MO et al (2011).

128 Amsden GW (2005).

129 Dalhoff A & Shalit I (2003).

130 Ginsburg I (2002); Vianna RC et al (2004).

131 Trautmann M et al (2010); Weighardt H & Holzmann B (2007).

of analyses could also serve as basis for a personalised therapy of infectious diseases, e.g. for known TLR signalling defects.

Another aspect of the exploration of the effect of antibiotics deals with the regulative effect of subinhibitory concentrations on the expression of virulence. The classical example in this respect are Shiga toxin (STx)-producing enterohemorrhagic *Escherichia coli* (STEC, EHEC, HUSEC) induced by the administration of antibiotics.¹³² A stress response (including SOS response), which leads to the activation of prophage genes (including stx genes), is induced in particular by subinhibitory antibiotics with bactericidal effect. In addition, microarrays for transcriptome analyses of bacterial pathogens following subinhibitory antibiotic treatment indicate a complex gene regulation which affects the pathogenicity and development of antibiotic resistance.¹³³

5.9 Inhibition of virulence factors

An alternative strategy to the traditional approach of killing bacteria with antibiotics is aimed at inhibiting virulence factors. It is worthwhile to continue exploring this strategy, because the specific inhibition of toxins or adhesins of a pathogen potentially prevents or reduces an infection without harming beneficial bacteria. This strategy boosts natural defence mechanisms and would induce fewer adverse reactions.¹³⁴

This kind of approach could be especially successful for pathogens in which a single virulence factor is essential for inducing the disease. Aside from the patients' disposition, a variety of virulence factors are involved in the emergence of the infection with many hospital-acquired pathogens, and removing a single factor would therefore not appear to be very promising. Fast and reliable diagnostics which not only unmistakably identify the pathogen but also the corresponding virulence factors are the prerequisite for this type of therapy approach. This could be achieved with state-of-the-art chip-based diagnostic systems, which are however not yet available.

5.10 Socio-economic research

The socio-economic, legal and ethical framework conditions for the development of new antibiotics should be investigated more thoroughly, hindrances should be identified and solutions found. Measures should be evaluated more with regard to their impacts in the past and in the future. In addition, socio-economic research can help to develop measures for faster and more efficient development and use of antibiotics. Furthermore, focus should be placed on the design of appropriate incentive mechanisms and the study of their effects, as well as a better understanding of the decision-making behaviour of users and producers. The rapid implementation of scientific findings into clinical practice in clinical and health services research is of the greatest importance.

¹³² McGannon CM et al (2010); Mellmann A et al (2011).

¹³³ Davies J et al (2006); Fajardo A & Martínez JL (2008).

¹³⁴ Cegelski L et al (2008).

6 Conditions for the development and use of new antibiotics

6.1 Incentives for the research and development of antibiotics

Experience gathered over the past 20 years suggests that the market alone is unable to solve the problem associated with the lack in research and development of antibiotics. A number of incentive models were therefore discussed aimed at encouraging the industry to resume antibiotics research and development.¹³⁵

A nationally guaranteed product procurement strategy could be considered, e.g. for vaccines or bioterrorism-relevant active ingredients. In addition, the government could promote not-for-profit research initiatives and private investments to a greater degree. Some foundations, such as e.g. the Bill and Melinda Gates Foundation donate considerable amounts in particular for the development of vaccines against AIDS, malaria and tuberculosis. The goal is to get other public-private partnerships and antibiotic research foundations involved. Tax incentives might be an option to encourage the pharmaceutical industry to invest in their own antibiotic research activities.

Moreover, well-balanced and extensive public and private funding of both basic as well as applied research is essential. Co-operations between the industry and academic research institutions should be supported to a greater extent. These models are not mutually exclusive, but in fact offer the possibility of combining components, including on an international level.¹³⁶

The European Academies Science Advisory Council (EASAC) proposes a number of procedures for activities which legislative bodies, regulatory agencies as well as funding organisations could act upon in order to promote innovations in the development of antibiotics (see Annex 11.2).¹³⁷

Restructuring within companies arising from the neglect of the research and development of antibiotics resulted in the loss of expertise which is extremely difficult to reverse. Long-term partnerships between academic groups and users have been abandoned as well. For this reason, the existing and established structures of antibiotics research and development should be preserved and expanded.

6.2 Clinical research

Facilitation of clinical research is a prerequisite for the faster introduction of antibiotics. Corresponding initiatives were launched in recent years in Germany and the EU and the situation has improved considerably. For instance, with its groups of clinical researchers (translationale), the DFG is supporting clinical research units and the permanent establishment of working groups in clinical institutions.¹³⁸ These days, clinical studies are being conducted in a co-ordinated

135 This section is based on EASAC (2007) as well as IDSA (2004) and Nathan C & Goldberg FM (2005).

136 The Innovative Medicines Initiative's (IMI) pre-competitive consortia are an example for such an effort.

137 EASAC (2007).

138 http://www.dfg.de/foerderung/programme/koordinierte_programme/klinische_forschergruppen/index.html (accessed on: 10 August 2012).

format at virtually every faculty of medicine. Between 1999 and 2012, BMBF funds were used to establish coordination centres for clinical studies aimed at permanently supporting all sequences of clinical trials and at improving the quality of clinical research at universities.¹³⁹ However, the coordination centres are not in the possession of their own funds for financing studies initiated by independent researchers at academic or non-academic institutions (Investigator Initiated Trials – IITs). Public funds, e.g. from the Federal Ministry of Education and Research (BMBF) should be allocated to this purpose. What is more, the studies should be approved in a less bureaucratic and more efficient fashion.

Issues related to the funding of all study phases indicate that new financing approaches should be pursued. Clinical phase II and III studies can only be financed in cooperation with the industry. However, the financial risks associated with time-consuming and costly clinical phase III studies should not have to be borne exclusively by companies, but jointly by the industry and the public authorities. Another option is the further development of public-private partnership models, in which the costs for clinical studies are covered with public funds which are reimbursed on a pro-rata basis if the product is used commercially.

Public funding programmes should also cover the insurance costs for clinical studies. Centres for clinical research ensure the proper training of professionals, supply the required infrastructure and provide some funding for preliminary clinical studies. The allocation of funds to these kinds of clinical research centres should be evaluated, according to the quality and innovative outcome of the clinical research organised at these centres.

The majority of smaller enterprises lack the expertise across the entire value chain of drug development. Many venture capital companies consider the risk associated with investing in antibiotics development as being too high. Therefore, alternative investment options at EU or at the national level as well as incentives through tax relief represent possible approaches to finance antibiotics research projects. Public authorities should accept part of the liability risks to limit possible liability risks for the manufacturers of new antibiotics.

6.3 Approval processes

In the past, the approval process for antibiotics was fast compared to other drugs. However, the regulatory requirements have gradually become more stringent, especially when it comes to clinical studies.

For new drug developments, the FDA now requires proof of superiority of the new active ingredient compared to the currently used comparator substances.¹⁴⁰ For companies, this means that a considerably greater number of patients have to be enrolled in clinical phase III studies, which in turn significantly drives up the costs of the studies and their duration. Many pharmaceutical companies are unwilling or unable to keep up with these expenses.

Based on the development of resistance described above, the proof of superiority of new antibiotics compared to currently available substances is an excessively high therapeutic goal. Instead, several substances with comparable action should be available in this clinical situation. We should keep in mind that

¹³⁹ <http://www.bmbf.de/de/1173.php> (accessed on: 10 August 2012).

¹⁴⁰ Marra A (2011).

the future resistance development is unpredictable and that less common individual risks might occur (allergies, drug interactions, etc.). In future, a certificate of efficacy should be sufficient as the treatment aim for approval of new therapy principles and new substance classes in particular.

The approval of new antibiotics, initially exclusively within the scope of combination regimens, might prevent or at least delay the development of resistance. This type of therapy, which is commonly used for the treatment of tuberculosis and HIV does not promise the generation of high profits in the short term. Yet, the profit expectations would rise if it were able to prevent or delay the development of resistance over the medium or long term.

7 Recommendations

In view of the situation described above, the Academy of Sciences and Humanities in Hamburg took up the topic "Antibiotic resistance" and, together with the German Academy of Sciences Leopoldina, organised a workshop on the topic "Why do we need new antibiotics (and don't get them)?" on 25 and 26 February 2011. Following the workshop, the working group "Infection Research and Society" of the Academy of Sciences and Humanities in Hamburg and experts of the German Academy of Sciences Leopoldina presented the results of the workshop in the present statement. The academies give the following recommendations.

Recommendation 1: Strengthen basic research

A broad range of basic research on the origin, spread and prevention of resistance as well as on the development of new antibiotics is indispensable. The research fields discussed in this statement should be given priority. In this respect the methodologies of classical microbiology play an important role. Particularly important points are:

- identification of new targets through functional genome research and metagenomic approaches,
- development of new and more effective screening methods and the creation of efficient substance libraries,
- isolation and culture of microbes from environmental habitats as a source of new active agents,
- analysis of the significance of the host-microbiome (metagenome) in the development and transmission of resistances,
- elucidation of the clinical and molecular mechanisms of resistance in vivo.

Recommendation 2: Improvement of the structural conditions for innovation

Preferably, antibiotics should be developed that attack new target structures or inhibit previously not involved metabolic pathways. Of particular importance is the development of a stable product pipeline. One necessary condition is the maintenance and expansion of infrastructure for the research and development of new antibiotics. In addition, it is vital to facilitate and strengthen cooperation between industry and academic research in order to more effectively link basic research resources with the diverse requirements of pharmaceutical product development.

Also essential is the continued international coordination of measures between governments and industry. Public incentive schemes should be established that promote a return of the industry to the research into and development of antibiotics. To encourage the industry to maintain enough reserve antibiotics, so-called "reserve bonuses" should be introduced. The financial risks for the elaborate and expensive phase III clinical trials should be shared by industry and public sector.

In spite of the already existing networks, greater support with regard to the development of new antibiotics is required so that research infrastructure across national borders can be established in the long term. In particular, projects conducted in recent years should be evaluated and favourable approaches pursued further.

Recommendation 3: Facilitation of clinical research

Clinical studies on the duration of effective antibiotic therapies, on the use of different therapy regimes and the effect on the development of resistance should be increased and funded. Translational research approaches play a central role in the introduction of new active agents in clinical use and should also receive more funding.

Trials initiated by independent scientists at universities or non-university institutions (Investigator Initiated Trials – IIT) should be examined faster and in a less complicated manner and possibly approved and supported by public funding.

Centres for clinical trials should ensure the training of skilled personnel and provide the necessary infrastructure and also the funding for the initial clinical trials. The allocation of funding to such centres of clinical research should be evaluated depending on the quality and innovative outcome of the clinical research organised at these centres. Private-Public Partnership models in which the costs of clinical trials are paid by public funds, but are refunded proportionately in the case of commercial use and in which the funding bodies receive an appropriate share of the proceeds, should be further developed.

Recommendation 4: Further development of regulatory framework conditions

Because of the development of resistance, the requirement for proof of superiority of new antibiotics versus currently available substances is too high a treatment aim. Instead, multiple substances with a similar efficacy should be available. It should be taken into account that the future development of resistance is not predictable and that individually rare risks could arise (for example, allergies, drug interactions). In future, a certificate of efficacy should be sufficient as the treatment aim for approval of new therapy principles and new substance classes in particular.

This problem of the development of antibiotic resistance should be considered in the regulatory requirements. The approval of new antibiotics, initially only within the scope of combination regimes, should be made possible as this could help avoid or at least delay the development of resistance. Regulatory requirements for the development and approval of new antibiotics should be formulated clearly. What would also be very welcome are simplified regulatory standards and a faster approval procedure, in particular for new developments against especially critical pathogens.

Recommendation 5: Restriction of antibiotic use in veterinary medicine and plant protection

Antibiotics should, if possible, only be allowed for targeted use after clinical diagnosis and based on the results of resistance tests. It must be ensured that the pathogen to be controlled is of bacterial nature. Antibiotics should be used only if prescribed by a veterinary professional. Animal pathogenic bacteria and zoonotic agents should be monitored continuously. The continuous collection of resistance data, as is already common practice in Germany, should be expanded. The measures suggested by the Federal Government in September 2012 to reduce the use of antibiotics in animal husbandry are therefore to be welcomed. In particular the collection of data on the frequency in a central database gives the authorities a tool that, for the first time ever, allows the use of different antibiotic groups used to fight infections in different animal species to be captured throughout Germany.

Workers in agriculture and the food industry should be educated as part of training programmes about how antibiotic resistance arises and what measures counteract its development. More research should also focus on what impact the use of antibiotics in animal husbandry and plant protection has on the emergence and spread of antibiotic-resistant bacteria and what the effects of the transmission of pathogenic bacteria from animals to humans are.

Recommendation 6: Consistent implementation of surveillance and antibiotic consumption records and reduction as well as promotion of education and training

Regular surveillance of the resistance rates of important pathogens should be carried out on all levels: from locally to globally and across the hospital, outpatient and animal husbandry sectors. The data should be published annually. On the one hand, this kind of data acquisition requires the cooperation of the parties involved on all levels. On the other hand, standardised and uniform test systems and limits for diagnostic laboratories should be defined and introduced. In addition to pathogens, commensal bacteria should be monitored continuously. Treatment recommendations for the clinical and outpatient areas should continue to be issued and made widely available on the basis of the collected resistance information by the competent bodies, in particular the Commission for Anti-infective, Resistance and Therapy (ART) at the Robert Koch Institute.

The academies welcome the approach of the German Antibiotic Resistance Strategy (DART). With the change of the German Infectious Diseases Protection Act in the summer of 2011, necessary measures were taken to use antibiotics more rationally and prevent infectious diseases. These measures should be continued to contribute to the reduction of nosocomial infections and prevention of infections. Their development and implementation should therefore be promoted consistently. The effects of measures should be documented and checked more intensely through monitoring activities. Epidemiological studies and investigations into the transfer of resistance genes should accompany the monitoring activities.

In particular, the consumption of antibiotics for clinical and outpatient use should be determined and analysed more comprehensively. Prophylactic antibiotics should be reduced; instead, initial adequate antibiotic therapies should be used more frequently. The coordination and publication of data on the consumption of antibiotics and resistance at national and EU level by the Robert Koch Institute or by the ECDC should be continued and expanded. The representativeness of the underlying data should be improved.

The prerequisite for improved use of antibiotics and the prevention or delay of resistance requires an awareness of all stakeholders in health care of the issue of antimicrobial resistance. For this reason, regular training courses and specific teams at clinics should be introduced. In addition, courses should be introduced that educate health care personnel on rational antibiotic therapies, provide them with a better understanding of resistance mechanisms and inform them on the current resistance situation.

Recommendation 7: Increased socio-economic research

The socio-economic, legal and ethical framework conditions for the development of new antibiotics should be investigated thoroughly, hindrances should be identified and solutions found. Measures should be evaluated more on a forward-looking as well as a retrospective basis. In addition, socio-economic research can help to develop measures for faster and more efficient development and use of antibiotics. Furthermore, focus should be placed on the design of appropriate incentive mechanisms and the study of their effects, as well as a better understanding of the decision-making behaviour of users and producers. Clinical and health services research are of great importance to the rapid implementation of scientific findings into clinical practice.

Recommendation 8: Establishment of a round table to discuss antibiotic resistance and new antibiotics

The academies recommend establishing a round table to discuss antibiotics resistance and new antibiotics under the umbrella of the Academies of Sciences with the participation of the German Centre for Infection Research DZIF. Together with the relevant stakeholders from science, politics and independent institutions, the Academies of Sciences provide a framework to inform authorities about problems and suggest solutions. The task of the round table could be to identify topics, to identify the need for action and adapt the research agenda for current developments.

8 List of abbreviations

BMBF	Bundesministerium für Bildung und Forschung (Federal Ministry of Education and Research)
caMRSA	community-acquired MRSA
CDC	U.S. Centers for Disease Control and Prevention
DDD	Defined Daily Dose
DART	Deutsche Antibiotika-Resistenzstrategie (German Antimicrobial Resistance Strategy)
DFG	Deutsche Forschungsgemeinschaft (German Research Foundation)
DZIF	Deutsche Zentrum für Infektionsforschung (German Centre for Infection Research)
EARS	European Antimicrobial Resistance Surveillance
EASAC	European Academies Science Advisory Council
ECDC	European Centre for Disease Prevention and Control
EHEC	Enterohaemorrhagic <i>Escherichia coli</i>
EFSA	European Food Safety Authority
EMA	European Medicines Agency
ESAC	European Surveillance of Antimicrobial Consumption
ESBL	Extended Spectrum b-Lactamase
FDA	U.S. Food and Drug Administration
R&D	Research and Development
HUSEC	Hemolytic Uremic Syndrome–associated <i>Enterohemorrhagic E. Coli</i>
IDSA	Infectious Diseases Society of America
SME	Small and Medium-sized Enterprises
MDR-TB	Multi Drug-Resistant Tuberculosis
MRSA	Methicillin-Resistant <i>Staphylococcus Aureus</i>
MRSE	Methicillin-Resistant <i>Staphylococcus Epidermidis</i>
NIH	U.S. National Institutes of Health
OGHA	U.S. Office of Global Health Affairs
PNSP	Penicillin-Resistant <i>Streptococcus Pneumoniae</i>
RKI	Robert Koch Institute
SIDA	Swedish International Development Cooperation Agency
CRC	Collaborative Research Centre
STEC	Shiga Toxin-Producing <i>E. Coli</i>
VRE	Vancomycin-Resistant Enterococci
WHO	World Health Organization
XDR-TB	Extremely Drug-Resistant Tuberculosis

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10 Methods

10.1 Participants in the working group

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Participants in the working group

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- Prof. Dr. Werner Solbach, Member of the Academy of Sciences and Humanities in Hamburg, Institute for Medical Microbiology and Hygiene, University Medical Center Schleswig-Holstein, Lübeck
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- Prof. Dr. Peter Zabel, Member of the Academy of Sciences and Humanities in Hamburg, Medical Director of the Research Centre Borstel

Scientific secretariat

- Dr. Kathrin Happe, German National Academy of Sciences Leopoldina
- PD. Dr. Knut Ohlsen, University of Würzburg
- Dr. Robin Fears (Editing)

Translation

SciTech – Übersetzungsbüro, Heidelberg

10.2 Peer reviewers

This statement has been reviewed by five independent scientists. The following persons have reviewed the text:

Prof. Dr. Werner Goebel, Member of Leopoldina, Senior Professor, Max von Pettenkofer Institute of Hygiene and Medical Microbiology, Ludwig Maximilian University of Munich

Prof. Dr. Martin Mielke, Department of Infectious Diseases, Robert Koch Institute, Berlin

Prof. Dr. Ernst Th. Rietschel, Member of Leopoldina, former President of the Leibniz Association

Prof. Dr. Jos van der Meer, Head of the Department of General Internal Medicine at the Radboud University Nijmegen Medical Centre, Vice President of EASAC

Prof. Dr. Rainer Weber, Clinic for Infectious Diseases and Hospital Epidemiology, University Hospital Zurich

The academies would like to thank the peer reviewers for their many suggestions for improvements, which were discussed and incorporated as far as possible by the working group. Thanks also goes to the participants of the workshop "Why do we need new antibiotics (and don't get them)?" who, with their comments and tips, assisted in an advisory capacity and provided material.

10.3 Proceedings

On 25 and 26 February 2011, a workshop was held at the University of Lübeck on the topic "Why do we need new antibiotics (and don't get them)?" The working group "Infection Research and Society" of the Academy of Sciences and Humanities in Hamburg and experts of the German National Academy of Sciences Leopoldina subsequently combined the results of the workshop in this statement. On 29 June 2012, the Executive Board of the Academy of Sciences and Humanities in Hamburg together with Leopoldina commissioned five independent scientists with the peer review of the text. The amended version of the statement was adopted on 17.08.2012 by the working group "Infection Research and Society", on 24.09.2012 by the Board of Directors of the Academy of Sciences and Humanities in Hamburg and on 12.09.2012 by the Presidium of Leopoldina.

11 Annex

11.1 Classes of antibiotics and their most important representatives

Class	Subgroup	Main approved antibiotics
Beta-lactam antibiotics	Penicillins	Penicillin G, Flucloxacillin, Ampicillin, Amoxicillin
	Cephalosporines	Cefazolin, Cefalexin, Cefotiam, Cefuroxin, Cefotaxime, Ceftriaxone, Ceftazidime, Cefepim, Cefpodxin, Ceftiofur (V)
	Carbapenems	Imipenem, Meropenem, Ertapenem
	Monobactame	Aztreonam
	Beta-lactamase inhibitors	Clavulanic acid, Sulbactam, Tazobactam
Gyrase inhibitors	Quinolones	Nalidixic acid
	Fluoroquinolones	Ciprofloxacin, Ofloxacin, Levofloxacin, Moxifloxacin
Aminoglycosides		Streptomycin, Kanamycin, Gentamicin, Netilmicin, Amikacin
Tetracycline		Oxytetracyclin, Minocycline, Doxycycline
Phenicol		Chloramphenicol, Florphenicol (V)
Macrolides		Erythromycin, Azithromycin, Clarithromycin, Tylosin (V), Fidaxomicin
Lincosamides		Clindamycin
Streptogramins		Quinupristin and Dalfopristin as a combination
Pleuromutilins		Retapamulin, Tiamulin (V)
Glykopeptides		Vancomycin, Teicoplanin
Oxazolidinones		Linezolid
Lipopeptides		Daptomycin
Cyclic peptides		Colistin
Glycylcyclines		Tigecyclin
Sulfonamides		Sulfamethoxazole
Diaminopyrimidine (folic acid antagonists)		Trimethoprim, only in combination with sulfamethoxazole
Nitroimidazoles		Metronidazole
Nitrofurans		Nitrofurantoin

Note: V = approved in veterinary medicine

11.2 Options for the stimulation of innovation recommended by EASAC

Proposals for legislative action (European Commission and Member States)

- Supplemental intellectual property protections (for example ‘wild-card’ patent extension; extended market exclusivity).
- Tax incentives for R&D.
- Guaranteed market.
- Liability protections.
- SME-specific support.
- Establish and empower independent body to prioritise discovery research objectives, to target incentives.

Proposals for regulatory authority action (EMA)

- Update guidelines for clinical trials and encourage innovative trial design (for example surrogate markers; alternative statistical analysis).
- Greater harmonisation and simplification of regulatory requirements.
- Encourage use of novel animal models and in vitro technologies to reduce clinical efficacy studies required for additional indications.
- Accelerated priority review status: mechanisms for conditional approval when high medical need (based on Phase II data plus commitment to post-marketing studies).
- Introducing culture of company-regulatory agency partnership for development.

Proposals for funding agency action (European Commission and Member States)

- Stimulate research on basic studies in model microbes for exploitation in access to targets and better understanding of pathogen biology.
 - Promote translational research and clinical trials (bench to bedside).
 - Significantly increase funding in key areas of resistance R&D and diagnosis.
 - Progress new funding models for collaboration with industry for technology and tools, drug discovery and early stage development.
 - Support research to quantify economic and public health burden of resistance as evidence for setting priorities for drug discovery.
-

Source: EASAC (2007)

11.3 Workshop topic "Why do we need new antibiotics (and don't get them)?"

Place: Institute for the History of Medicine and Science Studies at the University of Lübeck
Date: 25 and 26 February 2011

25 February 2011

- 3:00pm Prof. Dr. Witte (Robert Koch Institute)
Development of resistance in Germany and abroad: figures, trends and mortality
- 3:30pm Prof. Dr. Hacker (Leopoldina)
Biological and evolutionary reasons for further development of resistance
- 4:00pm Prof. Dr. Linder (Techniker Krankenkasse health insurance company)
Cost of antibiotic-resistant infections
- 4:30pm Break
- 5:00pm Prof. Dr. Rübsamen-Schaeff (AiCuris)
Economic considerations I: Is the development of antibiotics too expensive?
- 5:30pm Prof. Dr. Hamann (Sanofi-Aventis)
Economic considerations II: Why have most pharmaceutical companies stopped developing antibiotics / do not have them in their portfolio?
- 6:00pm Prof. Dr. Löwer (BfArM)
Obstacles and possible solutions in the authorisation procedure
- 6:30pm Dr. Kopp (Project Management Health Research of the Federal Ministry of Education and Research) Previous strategies and possible approaches of the BMBF to support antibiotic therapy
- 7:00pm Prof. Dr. Dr. Heesemann (Max von Pettenkofer Institute) "Yersinia beta-lactamases: countless tigers in beta-lactam antibiotic therapy"

26 February 2011

- 9:00am Prof. Dr. Müller (HZI)
Active agents: lead development
- 9:30am Prof. Dr. Hecker (University of Greifswald) / Prof. Dr. Sahl (University of Bonn)
Where could new approaches to antibiotic therapy and substances come from?
- 10:00am Break
- 10.30am Joint discussion
Debaters: all speakers and Dr. Greve, Prof. Dr. Dr. Hilgenfeld, A. Meusch
- 1:00pm Conclusion
-

With the statement "Antibiotic research: problems and perspectives", the Academy of Sciences and Humanities in Hamburg and the German National Academy of Sciences Leopoldina take up a topic, which is relevant to society at large and to both human and veterinary medicine. How can future research contribute to solving the problem of resistance and the lack of new antibiotics? What regulatory and financial framework conditions are required to ensure that research results find their way into widespread application more quickly? These questions are at the core of the present statement.

The authors answer them with a series of proposals. They also encourage measures to respond effectively to the challenges of increasing antibiotic resistance. The focus is on aspects of research, but societal and legal issues are also mentioned.