Recommendation 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. 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 is of great importance to the rapid implementation of scientific findings into clinical practice.

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

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

The Academy of Sciences and Humanities in Hamburg

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.

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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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IN HAMBURG

Briefing paper

Akademie der Wissenschaften in Hamburg
Deutsche Akademie der Naturforscher Leopoldina — Nationale Akademie der Wissenschaften

January 2013

Summary and recommendations

Antibiotic Research

Problems and Perspectives

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 resistance 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 resistance 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 25th and 26th 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 Antimicrobial 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.

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 antibiotic 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.

The academies give the following recommendations:

Recommendation 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. The research fields discussed in the 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, 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

Recommendation 2: Improvement of the structural conditions for innovations

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 the 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 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 structures across national borders can be established in the long term. In particular, projects of recent years should be evaluated and promising approaches pursued.

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Recommendation 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. 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 innovativeness of the clinical research organised by 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

Due to the development of the described resistances, the proof of the 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 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. It must be ensured that the pathogen to be controlled is of bacterial nature. Antibiotics should be used only if prescribed by a veterinary. Animal pathogenic bacteria and zoonotic agents should be monitored continuously. The continuous collection of resistance data, as it 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 therapy frequency in a central database gives the authorities a tool that, for the first time ever,

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allows the use of different antibiotic groups used to fight infections in different animal species to be captured nationwide.

Workers in agriculture and the food industry should be educated as part of training programmes about how antibiotic resistances arise and what measures counteract their 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 livestock to humans are.

Recommendation 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. On the one side, this kind of data acquisition requires the cooperation of the parties involved on all levels. On the other side, 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 area should be continued 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-Infectives, Resistance and Therapy (ART) at the Robert Koch Institute.

The academies welcome the approach of the German Antimicrobial 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 and 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. Administration of prophylactic antibiotics should be reduced; instead, initial adequate antibiotics 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 European Centre for Disease Prevention and Control (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 the health care sector 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.