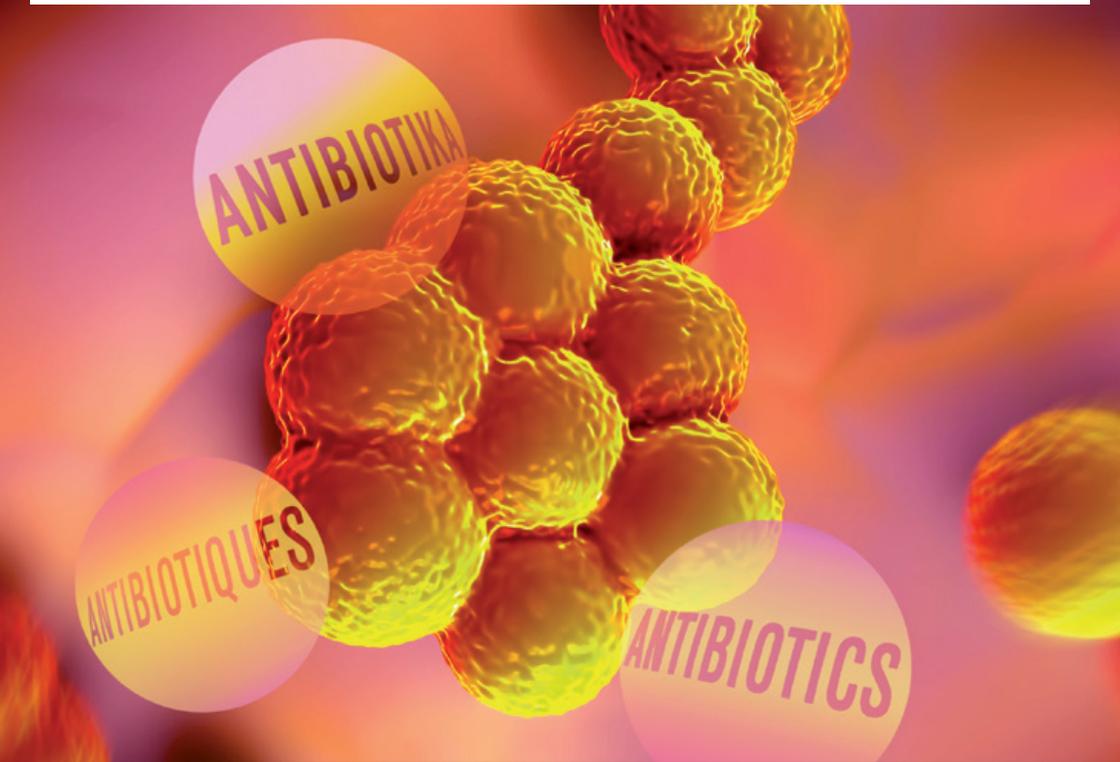




The
Federal Government



DART 2020

2nd Interim Report 2017

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Foreword



The broader significance of antibiotics extends far beyond the treatment of bacterial infections. Many therapeutic approaches in modern medicine, among them cancer treatment, complex surgery or care of premature infants, crucially depend on the availability of effective antibiotics. The global rise in antimicrobial resistance threatens the survival of various treatment options.

In 2015, the German Federal Cabinet adopted the German Antimicrobial Resistance Strategy (DART 2020) to address this problem and pool the measures required to reduce antimicrobial resistance. The strategy applies equally to human medicine, veterinary medicine and agriculture.

All stakeholders must work together and make their own contribution if the aim of reducing antimicrobial resistance is to be achieved. DART 2020, which is a joint strategy of the Federal Ministry of Health, the Federal Ministry of Food and Agriculture and the Federal Ministry of Education and Research, reflects this approach.

Since antimicrobial resistance can spread beyond borders via commercial and passenger traffic, cooperation must not be limited to the national level. The framework for joint measures at the global level is provided by the Global Action Plan on Antimicrobial Resistance developed by the World Health Organisation (WHO) in conjunction with the World Organisation for Animal Health (OIE) and the UN Food and Agriculture Organisation (FAO). Germany has been instrumental in driving the adoption of the Action Plan and is keen to see it implemented in the near future.

With antimicrobial resistance already a focal point of Germany's G7 presidency, the subject has also been placed on the agenda of Germany's G20 presidency. This underlines the importance of the problem and makes a contribution to closer international cooperation. Germany has thus adopted a pioneering role in the fight against antimicrobial resistance.

Aside from the key areas of infection prevention and the promotion of prudent antibiotic use, this also includes stepping up research in this field. The development of new antibiotics and enhanced diagnostics as well as improved understanding of the emergence and spread of resistances count among the essential contributions science can make to the fight against antimicrobial resistance. In January 2017, the G20 agricultural ministers passed a declaration and a respective action plan on the responsible use of antibiotics in animal and plant production. To achieve a sustainable decline in antimicrobial resistance, the problem must be addressed resolutely and at all levels. The continued availability of effective antibiotics to combat infections in humans and animals must be ensured.



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Introduction

In May 2015, the World Health Assembly (WHA) adopted the Global Action Plan on Antimicrobial Resistance developed by the World Health Organisation (WHO) in conjunction with the World Organisation for Animal Health (OIE) and the UN Food and Agriculture Organisation (FAO). The central element of the Global Action Plan consists of the call on member states to prepare multisectoral National Action Plans based on the One Health concept within a period of two years.

Germany is leading the way with its Antimicrobial Resistance Strategy (DART 2020) and is supporting the implementation of the Global Action Plan. DART 2020 was developed jointly by the Federal Ministry of Health (BMG), the Federal Ministry of Food and Agriculture (BMEL) and the Federal Ministry of Education and Research (BMBF) and adopted by the Federal Cabinet in May 2015¹.

Both the DART 2020 strategy and the measures contained therein are based on the One Health concept according to which the problem of resistance and the specific problems in human and veterinary medicine are approached on a holistic basis. Key elements of DART 2020 include the promotion of prudent antibiotic use and the raising of awareness among medical staff and the general population. Further focal points consist of stepping up international cooperation, improving infection prevention, enhancing monitoring and surveillance systems in the fields of antimicrobial resistance and antibiotic consumption and promoting research and development.

In the context of its G7 presidency, Germany placed antimicrobial resistance on the G7 agenda for the first time in 2015. As a result, the 'Berlin Declaration on Antimicrobial Resistance'² was adopted in addition to the summit declaration whose appendix contains important agreements on the subject of antimicrobial resistance. Following the German presidency, the Japanese G7 presidency picked up the baton and established a technical task force at the level of the Chief Veterinary Officers (CVO) which is set to focus, among other subjects, on antimicrobial resistance. After China took up the issue last year

1 http://www.bundesgesundheitsministerium.de/fileadmin/Dateien/5_Publikationen/Gesundheit/Berichte/BMG_DART_2020_Bericht_en.pdf

2 https://www.bundesgesundheitsministerium.de/fileadmin/Dateien/3_Downloads/G/G7/G7_Gesundheitsminister_Erklaerung_AMR_Ebola_DE.pdf

during its G20 presidency, Germany is continuing along this path during its own G20 presidency in 2017.

The first report on the progress made under DART 2020 was published on the occasion of the WHA 2016³. This second report describes the progress achieved through measures implemented at the national and international levels and provides an outlook on the activities that have been planned for the coming years.

In September 2016, the United Nations General Assembly repeated its call for National Action Plans and issued a respective declaration, thereby committing the highest political level of the UN to combating antimicrobial resistance. Greater awareness of the problem of antimicrobial resistance and its impact among heads of state and heads of government could make a major contribution to the swift implementation of the Global Action Plan.

GOAL 1: Strengthening the One Health approach nationally and internationally

Human and animal health must be approached together. Different sectors must cooperate to contain the emergence and spread of antimicrobial resistance.

Close collaboration between all stakeholders and between the responsible federal ministries and their subordinate authorities is essential. Due to the globalised trade in animals and plants and expanding passenger traffic, close coordination with international partners, not only in the EU but worldwide, is a further prerequisite for long-term success. The implementation of the Global Action Plan, which underlines the One Health approach, is a crucial element.

3 http://www.bundesgesundheitsministerium.de/fileadmin/Dateien/3_Downloads/D/DART_2020/DART2020_Zwischenbericht_2016.pdf

Global Action Plan on Antimicrobial Resistance

The World Health Organisation (WHO) developed the Global Action Plan on Antimicrobial Resistance in conjunction with the World Organisation for Animal Health (OIE) and the UN Food and Agriculture Organisation (FAO). The Plan was adopted by the World Health Assembly in May 2015. One of its central demands is the development of multisectoral National Action Plans by all member states by May 2017. Germany has led the way with the DART 2020. The Global Action Plan aims to preserve the effectiveness of antibiotics as long as possible. This requires quality assurance and responsible use of antibiotics. At the same time, antibiotics must be accessible to anyone who needs them. This overarching objective has been broken down into five sub-goals:

1. Improve awareness and understanding of antimicrobial resistance through effective communication, education and training.
2. Strengthen the knowledge and evidence base through surveillance and research.
3. Reduce the incidence of infection through effective sanitation, hygiene and infection prevention measures.
4. Optimize the use of antimicrobial medicines in human and animal health.
5. Develop the economic case for sustainable investment that takes account of the needs of all countries and to increase investment in new medicines, diagnostic tools, vaccines and other interventions.

Progress so far

The problem of antimicrobial resistance was discussed at a high-level meeting of the United Nations in September 2016. Germany was closely involved in the preparation of the resulting political declaration. The activities were pooled within the framework of the Action Package AMR of the Global Health Security Agenda (GHSA). In conjunction with the UK, Netherlands, Sweden, Canada and Japan, Germany assumed co-leadership of this Action Package. A number of further countries are working on the same Action Package. In 2016, the Action Package AMR focused on the preparation of the Political Declaration of the UN General Assembly.

In June 2016, the Codex Alimentarius Commission (CAC) resolved to set up an AMR Task Force. Germany is an active member of this Task Force. A smaller working group was set up to revise the project documents for the Task Force and select the subject areas relevant to the call for the WHO and FAO to provide scientific expertise in consultation with the OIE. The working group, in which Germany also played an active role, has completed its tasks and the CAC 2017 will vote on the working group's documents.

United Nations General Assembly (UNGA)

The United Nations addressed the subject of antimicrobial resistance in the context of a high-level meeting on 21 September 2016. The meeting aimed to raise awareness of the problem of antimicrobial resistance among heads of state and heads of government, especially in developing countries and emerging nations, and thereby support the swift implementation of the Global Action Plan.

In a joint Political Declaration, the member states once again committed themselves to developing and implementing a national AMR strategy. The Declaration also calls for the establishment of an Interagency Coordination Group tasked with developing practical guidelines for sustainable global action to combat antimicrobial resistance and ensuring closer cooperation. The group was set up in March 2017.

Thanks to the continuous and determined commitment shown by Germany and a few other member states, FAO declared that it would earmark regular budget funds for the subject of antimicrobial resistance in its upcoming Programme of Work and Budget (PWB 2018-19).

In September 2016, Germany and the UK hosted a side event on antimicrobial resistance at a meeting of the FAO Committee on Agriculture (COAG). Under the title of 'Antimicrobial resistance: global implications', the event added to the momentum that had been launched by the recent Political Declaration of the high-level AMR meeting of the UN General Assembly.

Building on ongoing international debates and developments, Germany is working to advance the subject of antimicrobial resistance in the context of its G20 presidency in 2017. The main objective is to discuss the issues of infection prevention and the prudent use of antibiotics – based on the One Health approach in both human and veterinary medicine – as well as

incentive mechanisms designed to boost research and development of new antibiotics, alternative treatments and rapid diagnostics, and to recommend suitable action in the above-mentioned areas.

In January 2017, the G20 agricultural ministers passed a declaration and a respective action plan on the responsible use of antibiotics in animal and plant production. They agreed that antibiotics should be classed as prescription drugs for animals. In addition, they concurred that each country should submit either a national risk analysis focusing on safety or a roadmap outlining the phase-out of antibiotics as growth promoters by 2020.

After antimicrobial resistance had been the subject of the founding meeting of the G7 CVOs in Tokyo, a sub-working group met in Rome in March 2017 during the Italian G7 presidency to determine joint definitions of relevant terms. This work is to be continued by a working group relying exclusively on electronic communication.

In addition, Germany has further stepped up bilateral cooperation in the field of antimicrobial resistance. At the 5th German-Turkmen Health Forum, which took place in Ashgabat on 4/5 November 2016, attendants exchanged experiences with the national implementation of the Global Action Plan and forged closer ties. In addition, a close exchange took place with Sweden and Estonia.

Since May 2016, projects combating AMR primarily in Africa and South-East Asia have been funded via the Global Health Programme set up by the German Federal Ministry of Health. Supported by the Robert Koch Institute (RKI) and the Federal Institute for Drugs and Medical Devices (BfArM), the projects aim to build global capacities to combat antimicrobial resistance and assist the implementation of the Global Action Plan. In specific, the projects focus on building capacities in the fields of laboratory diagnostics and surveillance, the impact and antimicrobial resistance profiles of infections in out-patient and in-patient care, promoting the prudent use of antibiotics and expanding the capacities of drug control laboratories.

On top of this, Germany also funds projects set up by the WHO Regional Office for Europe to help non-EU countries in Europe develop and implement national action plans.

Furthermore, funds are provided in support of OIE projects aiming to combat zoonoses/antimicrobial resistance or ensure food security via animal health

measures particularly in southern Africa. These measures also contribute towards strengthening global capacities.

Outlook

The fight against diseases that can be transmitted from humans to animals and vice versa (zoonoses) represents a major challenge. At the national level, the BMG's planned 'zoonoses' funding priority will further promote cooperation between the different areas. A respective announcement will be made in May 2017. In this context, the problem of resistant bacterial pathogens will also be addressed.

Strengthening international capacities to combat antimicrobial resistance requires a long-term approach. Germany will continue, and step up, its cooperation with partner countries and its involvement in committee work at international organisations in the coming years.

Under the new 2017 EU Action Plan on Antimicrobial Resistance, Europe is set to turn into a best practice region with respect to the implementation of the Global Action Plan. Germany will be closely involved in the preparation of the action plan. This is to ensure the consideration of national distinctions as well as close coordination with current activities (e.g. activities ensuing from the G20 presidency).

In autumn 2017, a meeting of the G20 public health and veterinary public health institutes is planned in Berlin during the German G20 presidency. The practical implementation of measures will take priority. The meeting will serve to establish networks between public health and veterinary public health institutes at the G20 level. Subjects that equally concern both areas, such as surveillance, prudent use of antibiotics and infection prevention, will be discussed on the basis of real-life examples.

In 2017, the European Commission (EC) launched an initiative to improve co-ordination between member states' research and development activities in the field of 'One Health/zoonoses' and to develop a respective joint programme. In the context of the 2017 work schedule of its Horizon 2020 programme, the Commission has called for tenders for its Societal Challenge no. 2 'Food security, sustainable agriculture, marine and maritime research, and the bioeconomy' (SC2), which is to be funded through the new European Joint Programme Cofund (EJP COFUND). The funding volume amounts to € 45 million.

GOAL 2: Recognising changes in resistance at an early stage

Representative data on the emergence of new and established pathogens and resistances are required to facilitate the adjustment of treatment and hygiene recommendations to the latest developments and assist the development of specific prevention strategies. Such data will also contribute towards adapting the prescription behaviour among doctors. The development of resistance rates over time indicates the effectiveness of the measures taken.

Progress so far

The number of laboratories participating in RKI's antimicrobial resistance surveillance (ARS) has risen continuously. Since 2010, the number of hospitals in the programme has tripled, while the number of surgeries rose by approx. 50 % in the last year. This expansion has also improved the database at the European and international levels.

The WHO's Global Antimicrobial Resistance Surveillance System (GLASS) was set up to facilitate standardised antimicrobial resistance surveillance as part of the implementation of the Global Action Plan. Validated, comparable data on antimicrobial resistance are collected and evaluated in support of specific measures. At the same time, GLASS helps verify progress in the implementation of the national surveillance systems. Germany is involved in the early introductory phase of GLASS and will thus contribute towards the identification of areas in need of adjustment.

Resistance monitoring of animal pathogenic bacteria at the Federal Office of Consumer Protection and Food Safety (BVL) is continuing similar to resistance monitoring of zoonotic pathogens and commensals by the state authorities and Federal Institute for Risk Assessment (BfR). Commensals are organisms, for instance bacteria, which feed on the leftovers of their host organisms without damaging the latter.

September 2016 saw the publication of GERMAP 2015, the fourth report on trends in antibiotic consumption and the spread of antimicrobial resistance in human and veterinary medicine in Germany. The report was published by the BVL and the Paul Ehrlich Society for Chemotherapy (PEG). It summarises the trends observed in the last years, thereby providing a basis for the

development of guidelines and recommendations for the antibiotic treatment of infectious diseases among humans and animals.

The inclusion of the selective substantiation of ESBL/AmpC-producing and carbapenemase-producing Enterobacteriaceae completed the adaptation of resistance monitoring of zoonotic pathogens and commensals to new EU legislation. In this context, the BfR established various methods for studying *Escherichia coli* and *Salmonella* and substantiated the existence of the first carbapenem resistance genes in animal isolates. In addition, studies are being conducted to establish how these resistance genes, or pathogens with the resistance genes, enter animal populations and their environment. In the European Union, the use of antibiotics in the carbapenem class is not permitted in animal treatment.

Outlook

In the context of infection events in Germany, the national reference centres (NRZ) and consultant laboratories (KL) serve as early warning and reaction systems. They focus primarily on the development or improvement of diagnostic procedures for their assigned pathogens and their specific diagnostics as well as their resistance and virulence aspects. Furthermore, the NRZ provide consultancy services to public health authorities and the medical community. Due to the high relevance of *Clostridium difficile* to public health, not least in connection with antibiotics prescriptions, a dedicated *C. difficile* NRZ will replace the previous KL by the end of 2017.

It is essential that data on infection events are transmitted swiftly from the local level to the respective state and federal authorities. This requires a uniform data collection and processing system. The creation of a respective electronic reporting procedure (German Electronic Reporting System for Infection Prevention/DEMIS) and its mandatory use are currently being written into German law.

The BfR will carry on its in-depth research into the factors that lead, or may contribute, to the detection of carbapenem resistant genes in animal bacteria.

GOAL 3: Retaining and improving therapy options

The prudent use of antibiotics is essential if the effectiveness of antibiotics is to be preserved in the long run. In Germany, antibiotic use varies from region to region and from animal species to animal species. The reasons can be manifold. To get a better understanding of the matter, data of antibiotic sales and consumption volumes are required. These data also form the basis for specific intervention measures and help assess their effectiveness.

Progress so far

The antibiotic consumption surveillance (AVS) established at the RKI in 2014 has expanded continuously. Last year, the number of laboratories in the programme increased by approx. 30%. At present, 282 hospitals are part of AVS.

Among other objectives, the national antimicrobial resistance (ARS) and consumption (AVS) surveillance systems aim to help hospitals implementing the local antibiotic stewardship measures. A feasibility study funded by the BMG is currently developing a model for the combined evaluation and provision of resistance and consumption data. The pooling of data, their processing and structured feedback is to support and advance the introduction and operation of local antibiotic management.

In day-to-day hospital operations, infectiological guidelines are not always implemented. The Commission on Anti-Infectives, Resistance and Therapy (ART) has published a current policy document entitled ‘Prerequisites and strategies for the successful implementation of infectiological guidelines’. In this paper, the Commission proposes the introduction of infectiological guidelines based on best practice examples and evidence-based intervention strategies in in-patient and out-patient care⁴.

4 http://www.rki.de/DE/Content/Kommissionen/ART/Positionspapier/Positionspapier_Leitlinien_Implementierung.html

Commission on Anti-Infectives, Resistance and Therapy

The Commission on Anti-Infectives, Resistance and Therapy (ART) is an independent body of experts established in 2013 on the basis of the Infection Prevention Act. It is the Commission's task to issue recommendations on standards relating to the diagnosis and treatment of infectious diseases according to the current state of the art of medical science. On this basis, the Commission performs a medical-epidemiological risk-benefit assessment weighing the individual's interest in effective treatment against the public interest in the preservation of effective anti-infectives.

In addition, it examines existing recommendations and guidelines and assesses the need for current guidelines in the fields of diagnostics and therapy of infectious diseases. With respect to expert associations, other scientific institutions and self-managing bodies, the Commission works to promote compliance of recommendations and guidelines with the above standards and the development or updating of respective guidelines. To achieve this aim, the Commission analyses and evaluates data relating to changes in the pathogen spectrum according to type and prevalence, medical use of antimicrobial drugs and desired as well as undesired effects including changing effects.

In the period 2011 to 2015, the total volume of antibiotics sold by pharmaceutical companies and wholesalers to veterinarians in Germany declined by more than half from 1,706 tonnes to 805 tonnes (down 53 percent). In the period 2014 to 2015, the total volume of antibiotics sold declined by 433 tonnes (down 35 percent). Sales volumes of antibiotics which are of particular relevance to humans also recorded a slight decline.

The Veterinary Consumption of Antibiotics (VetCAB) project

This project aims to describe the consumption of antibiotics in farm animals in Germany as well as providing a database for scientific analysis. Consumption is measured by the average number of times a farm animal is treated with antibiotics in Germany. On top of this, the project collects data on types of active substances, their volumes and the frequency of their application. In the long term, the data will be used to form an assessment of the impact of antibiotic consumption on bacterial resistance to antibiotics and provide a basis for recommendations of respective countermeasures to prevent the development of further resistances.

The Institute of Biometrics, Epidemiology and Information Processing of the University of Veterinary Medicine Foundation in Hanover is implementing the VetCAB project on behalf of the BfR; in the first few years, the Institute of Pharmacology, Pharmacy and Toxicology at the Faculty of Veterinary Medicine of the University of Leipzig was also involved.

A study was conducted in 2007 and 2008 to assess the feasibility of a comprehensive record of antibiotic consumption in Germany, which data could be used as a basis and how such data can be collected. As a next step, a pilot study was conducted in the period 2011 to 2013 which collected scientifically representative data on nationwide antibiotic consumption for the first time. Since 2013, the project has been carried on by the VetCAB-Sentinel study which investigates the question whether the volume and frequency of the documented antibiotics remain constant over an extended period or change over time.

Antibiotic minimisation concept

The 16th amendment of the German Medicinal Products Act established a benchmarking system as a tool to minimise the use of antibiotics in farm animals. The system centres on comparative analysis of individual treatment frequencies in farms compared to average nationwide figures. The analysis is broken down into different farm animal species and age brackets.

Where treatment frequencies of farms exceed the reference figure 1 or the reference figure 2, livestock owners are required to consult a veterinarian to establish the cause. Analysis of the cause may result in mandatory measures to reduce the consumption of antibiotics in the enterprise. The reduction of individual treatment frequencies lowers the nationwide figures calculated on the basis of the individual figures, making this a dynamic antibiotic minimisation system. The aim is to continuously reduce the nationwide use of these substances to the necessary minimum and hence curtail the development of antimicrobial resistance.

The Federal Office of Consumer Protection and Food Safety (BVL) calculates the nationwide figures twice a year, in March and September, and publishes them in the Federal Gazette.

Based on the white paper on further regulations relating to the use of antibiotics in animals, a draft regulation amending the Veterinary House Dispensary Ordinance was drawn up and discussed in detail with state governments and associations.

Outlook

Among other purposes, the budget of the Innovation Fund (total annual volume: € 300 million) is used to finance the innovative supply projects entitled 'Resistance prevention through adequate use of antibiotics in respiratory tract infections' (RESIST) and 'Sustainable prevention of antimicrobial resistance formation' (ARENA). The 'Converting Habits of Antibiotics Use for Respiratory Tract Infections in German Primary Care' (CHANGE-3) project is financed in the context of the Federal Ministry of Health's 'Antimicrobial resistance and hospital-acquired infections' funding priority (cf. Goal 5). In the period until 2020, these research projects are charged with identifying suitable measures to achieve prudent use of antibiotics in out-patient care. The target group includes patients as well as medical staff. This includes research into the impact of various measures on antibiotic use.

Work on the regulation amending the Veterinary House Dispensary Ordinance continues with the aim of reducing the use of antibiotics in animals, especially antibiotics which are of special relevance to humans, via strict regulations.

A report on the effectiveness of the antibiotic minimisation concept will be submitted to the German Federal Parliament in April 2019.

GOAL 4: Breaking chains of infection early and avoiding infections

Prevention of infections is the most effective instrument for reducing the use of antibiotics. Compliance with hygiene measures by qualified hospital staff and livestock owners is crucial. On top of this, up-to-date diagnostics are essential if antibiotics are to be employed in a focused manner and the spread of resistant pathogens is to be prevented. Regional networks promoting the prevention and control of resistant infectious pathogens can make

an important contribution towards the identification and removal of local application barriers and implementation problems.

Progress so far

Diagnostics assist the focused use of antibiotics. The German government's 'pharma dialogue' has furnished important stipulations that have now been written into law. The amendment of regulations on refunds for diagnostic procedures is creating the right conditions for enhanced use of diagnostics promoting swift and quality-assured antibiotic treatment in SHI care. In addition, the resistance situation will be given more weight in the pharmaceuticals price formation system.

Since January 2017, data reflecting the quality of out-patient and in-patient services in post-surgery wound infection prevention have been collected, subjected to comparative analysis and evaluated in compliance with the guideline issued by the Federal Joint Committee (G-BA) on 'cross-institutional and cross-sector quality assurance: prevention of hospital-acquired infections (post-surgery wound infections)'. Principally, these data are to help determine and evaluate institution-specific wound infection rates after certain surgical interventions.

In December 2016, the 5th meeting of facilitators of the regional networks for multi-resistant pathogens took place at the RKI in Wernigerode. Responsible use of antibiotics was one of the key subjects of the meeting. The regional networks bring together various stakeholders, among them hospitals and registered doctors as well as retirement and care homes coordinated by the German Public Health Service (ÖGD). The aim is to adopt a joint approach and implement coordinated measures to prevent the emergence and spread of multi-resistant pathogens. A further objective is improved communication between the stakeholders. Regular meetings are used as opportunities to exchange experiences. In addition, information material drawn up by individual networks can be shared via a protected website.

The hygiene promotion programme, which was launched in 2013, has been extended until 2019 with the aim of helping hospitals meet the specialised hygiene staff requirements. Infectiology was added as a further subject. The programme offers financial support in the areas of recruitment, advanced training and consultancy services. A total of € 460 million have been earmarked for the programme over its full term.

Committee for Hospital Hygiene and Infection Prevention (KRINKO)

The legal basis of the Committee for Hospital Hygiene and Infection Prevention (KRINKO) is the Infection Prevention Act (IfSG). The Committee provides evidence-based recommendations on the prevention of hospital-acquired infections and the managerial/organisational and construction/functional aspects of hygiene measures in hospitals and other medical institutions. Published by the Robert Koch Institute, the recommendations are continuously refined on the basis of current infection epidemiological evaluations.

Pursuant to the Infection Prevention Act, managers of medical institutions are required to implement the measures necessary to fight hospital-acquired infections according to the current state of the art of medical science. In this field, compliance with the KRINKO recommendations is assumed to satisfy the current state of the art of medical science.

At the beginning of each three-year term, KRINKO draws up a work schedule which systematically addresses known problem areas. The schedule also takes current epidemiological requirements into consideration.

Standing Vaccination Committee (STIKO)

The German Standing Vaccination Committee (STIKO), an independent body of experts established by the Infection Prevention Act, develops national vaccination recommendations. STIKO considers the benefits of vaccinations both at the individual level and in terms of public health. Recommendations are given according to the criteria of evidence-based medicine. While effectiveness (mostly in comparison to placebos), safety and pharmaceutical quality are decisive for the approval of vaccinations, STIKO also uses these data as a basis to study individual risk-benefit ratios, the epidemiology at the public health level and the effects of a nationwide vaccination strategy for Germany. Furthermore, STIKO develops criteria to distinguish between common vaccine reactions and health damage that goes beyond the usual extent. STIKO recommendations are considered medical standards.

Infection prevention was a priority subject at the second international Patient Safety Summit which took place in Germany in March 2017. The UK and

Germany joined forces to set up this international conference of ministers which will now take place on a regular basis. At the second summit, infection prevention was primarily discussed in the context of hospital-acquired infections and sepsis and with reference to curtailing the general need for antibiotics as a means of preventing resistances. Core messages were drawn up at an expert workshop and refined within the framework of a meeting of ministers. It emerged that hospital-acquired infections and sepsis have a significant impact. Both can be reduced through infection prevention and control programmes. The WHO has developed respective recommendations. Further essential factors are standardised monitoring and feedback on infection prevention measures. All of these measures should be patient-centred and cost-effective.

In autumn 2016, the German Veterinary Society (DVG) completed the development of standardised protocols used to verify resistance for seven key pathogens in farm animal husbandry. The project was funded by the BMEL. Its results were used to adapt the layout of microwell plates used to examine the susceptibility of animal pathogens with the broth microdilution method. These DVG recommendations are to help encourage the sale of microwell plates in larger batches and thus promote their cost-effective use in routine diagnostics.

Funded by the BMEL Innovation Promotion programme, a project was launched to develop an innovative broiler husbandry system (fitavis) to raise hygiene in coops and reduce infection and recontamination risks during the fattening period. This approach improves animal health and helps curtail the use of antibiotics during the fattening period.

A further research project (Reduced use of antibiotics in pig production through integration of epidemiological information from clinical, hygienic, microbiological and pharmacological veterinary consulting, VASIB in short) investigates various options of optimising veterinary consulting services using the example of respiratory tract diseases in pigs. The project aims to establish whether specific diagnostic measures and in-depth, comprehensive management consulting can lead to improved treatment strategies and the minimisation of antibiotic use. Furthermore, the development and validation of software suitable for veterinary surgeries is to pool epidemiological data from preventative veterinary medicine with agricultural operations data. Based on this data pool, ongoing consulting services will be provided to agricultural enterprises and the development of resistances in bacterial pathogens of respiratory tract infections in correlation to the use of antibiotics will be

traced along the entire production chain. The results will serve as the basis for applied agricultural training and teaching concepts.

Outlook

In 2016, the German Charité Institute for Hygiene and Environmental Medicine participated in the second Point Prevalence Survey of Healthcare-Associated Infections and Antimicrobial Use conducted by the European Centre for Disease Prevention and Control (ECDC). In autumn 2016, Germany also took part in a Point Prevalence Survey in the context of the ‘Healthcare-Associated Infections in European Long-Term Care Facilities (HALT-3)’ project. The evaluated survey results will yield data that can be used to assess the effectiveness of current regulations and recommendations.

In 2018, the third Patient Safety Summit will take place in Japan. Germany will attend the summit and contribute to an agreement on further concrete measures.

Research projects on interrupting infection chains between animal populations and along the food chain, which have been launched in the veterinary field, will be continued.

GOAL 5: Raising awareness and strengthening skills

The prudent use of antibiotics and treatment of multi-resistant pathogens requires specific knowledge. A significant need for information and substantial gaps in knowledge are prevalent not only among the population but also among medical and veterinary professionals and livestock owners. This situation must be remedied.

Progress so far

In the past, extensive information material on the prudent use of antibiotics and on antimicrobial resistance and its consequences was developed and distributed by various institutions, among them the Federal Centre for Health Education (BZgA).

Over the next three years, the ‘Converting Habits of Antibiotics Use for Respiratory Tract Infections in German Primary Care’ (CHANGE-3) project launched by the BMG under its ‘Antimicrobial resistance and hospital-acquired infections’ funding priority will, inter alia, investigate the effectiveness of a comprehensive public information campaign, which is to raise awareness of antimicrobial resistance and prudent antibiotic use among the population (insured individuals, patients, relatives). The project is considering various media as potential information carriers. It is the aim of the campaign to provide all individuals with sufficient competence to involve themselves in the decision for or against antibiotic treatment and thereby, ultimately, reduce the consumption of antibiotics.

In the course of the amendment of the German Regulation Pertaining to the Licensing of Veterinarians (TAppV), resistance development risks were included in the pharmacology and toxicology examination subject. Thus, the impact of the prescription of antimicrobial drugs is already highlighted at the veterinary training stage and responsible use of antibiotics is promoted.

VetMAB – joint project promoting the development and introduction of an Internet-based training and data management tool to minimise the use of antibiotics in farm animal husbandry

VetMAB is an e-learning course funded by the BMEL and recognised by the Academy of Advanced Veterinary Training that gives veterinarians access to advanced training in the fields of resistance emergence and spreading as well as current test procedures. The course consists of one basic module and a number of species-specific advanced modules. All modules offer exercises based on model agricultural enterprises and provide opportunities for the interactive discussion of problems. On top of this, a chat room has been set up for the participants.

A further key element is the resistance monitoring tool – a database system including interfaces with surgery management programs. The tool can be used to archive resistance test results and record individual resistance situations of the bacteria found in the agricultural enterprises under the care of the participating veterinarians. It also offers interpretation aids. The registering veterinarians determine who can view and use these data. Veterinarians participate via a website that also provides current information as well as legal regulations and reports on the subject of antimicrobial resistance. In addition, participating veterinarians can seek advice on specific issues.

Outlook

The enhancement of basic and advanced training in the field of antimicrobial resistance will remain a central element of the implementation of DART 2020. For this purpose, the BMG maintains close links with expert societies and the German Medical Association. Expert talks are planned for the year 2018.

Every two years, the Robert Koch Foundation presents a hospital hygiene award. The award is conferred for outstanding scientific work and practical measures in the field of hospital hygiene and infection prevention. The Federal Ministry of Health, which funds the Robert Koch Foundation, is involved in the selection of the award winners. In September 2017, the award will be presented for the third time. In the area of practical hospital procedures, this provides an incentive to make improved workflows available to the public as best practice examples.

VetMAB II⁵ will continue to promote the Internet-based training and data management tool to minimise the use of antibiotics in farm animal husbandry. New objectives consist of the introduction of a basic module for farmers and a module for practising veterinarians and farmers outlining the objectives pursued by action plans to reduce antibiotic use pursuant to the requirements of the Medicinal Products Act, including their structure, as well as a module for veterinarians in the public sector outlining specialised knowledge in the field of appraising and evaluating measures. In addition, exchanges between the three groups will be encouraged.

GOAL 6: Supporting research and development

Research makes an essential contribution towards gaining the knowledge necessary to develop enhanced diagnostics and identify new anti-infective agents. DART 2020 therefore endeavours to strengthen all respective research areas in both human and veterinary medicine, from fundamental research, clinical research and public health issues to research in conjunction with the health, agriculture and food industries. Aside from the need for a better understanding of the emergence and spread of resistances, there is also an urgent need

⁵ <https://www.vetmab.de/>

for new drug candidates. Nationally and internationally coordinated initiatives are encouraging research and development in the field of anti-infectives.

Progress so far

In October 2016, a meeting of the global expert network, which had been set up in 2015 during the German G7 presidency, took place in Berlin. Over 130 international experts in the fields of science, pharmaceutical industry, human and veterinary medicine, regulation authorities, the European Union and international organisations, including the WHO and the OIE, met on the occasion. Based on the One Health approach, workshops discussed strategies for the improvement of innovations in antibiotic research and development, antibiotic use at the interface between human and veterinary medicine and the preparation of a list of resistant pathogens by the WHO. The list, which has meanwhile been published by the WHO, specifies the pathogens that currently pose the greatest threat to human health. It is to act as a guidepost for research and development. At the fourth workshop, the 'Global Antibiotic Research and Development Partnership (GARDP)' presented initial projects relating to the 'Drug Combination Platform & Antibiotic Memory Recovery initiative (AMRi)' as well as to gonorrhoea and sepsis in new born infants. Germany made a financial contribution during the GARDP founding phase and continues to support the partnership in 2017.

Global Antibiotic Research and Development Partnership (GARDP)

The Global Antibiotic Research and Development Partnership (GARDP) is a non-profit research and development organisation set up by the WHO and the 'Drugs for Neglected Disease Initiative (DNDi)' in 2016. Its objectives consist of research and development of new antibiotics and simultaneous promotion of prudent antibiotic use. This also includes the issue of access to antibiotics.

Three of the programmes focus on specific issues, namely sepsis in newborn infants, sexually transmitted diseases and antibiotics in paediatric medicine. The fourth programme concentrates on overarching aspects, among them the introduction of a platform to safeguard research results which can be used for future approaches.

Supporting GARDP also advances the implementation of the Global Action Plan on Antimicrobial Resistance which calls for new public-private partnerships to promote research and development of new antibiotics and diagnostics.

In 2015, the G7 health ministers also agreed to support the continuous recording, evaluation and joint definition of the most dangerous global pathogens. In response to a request by the BMG, the WHO has prepared a global list of multi-resistant bacterial pathogens which was published at the end of February 2017. The list is to serve as a guide for new antibiotic research and development, alternative treatment options and diagnostics.

‘Breaking through the Wall – A Call for Concerted Action on Antibiotics Research and Development’ – a follow-up appraisal drawn up by order of the Federal Ministry of Health – was submitted at the beginning of 2017⁶. The first appraisal had been prepared in 2015 under the German G7 presidency. The follow-up appraisal contains suggestions for the practical implementation of incentive mechanisms to advance research and development in the fields of new antibiotics, alternative treatments and diagnostics.

Taking over an assignment from the Chinese G20 presidency⁷, the German government used its own G20 presidency to commission the OECD, in conjunction with the WHO, FAO and OIE, to draw up a report entitled ‘Tackling Antimicrobial Resistance, Ensuring Sustainable R&D’ which contains recommendations for action the G20 can take to combat antimicrobial resistance and proposes strategies to boost the development of new antibiotics. The OECD report is to be submitted at the G20 Summit in Hamburg at the beginning of July.

The BMG-funded project ‘Evaluation of wastewater treatment techniques promoting the reduction of clinically relevant infectious pathogens and determinants of antimicrobial resistances (REDU-Antiresist)’ studied the impact of wastewater treatment techniques on the spread of antimicrobial resistance through wastewater from hospitals. The results may provide an important impetus to the development of recommendations regarding wastewater treatment methods, especially in the area of hospital wastewater.

Scientists at non-university research institutes run by the Max Planck Society, the Helmholtz Association, the Leibniz Association, the Fraunhofer Society and the German Health Research Centres are also studying antimicrobial resistance. These institutes include the Helmholtz Centre for Infection

6 http://www.bundesgesundheitsministerium.de/fileadmin/Dateien/5_Publikationen/Gesundheit/Berichte/GUARD_Follow_Up_Report_Full_Report_final.pdf

7 http://www.fmprc.gov.cn/mfa_eng/zxxx_662805/t1395000.shtml

Research (HZI) and the Helmholtz Institute for Pharmaceutical Research (HIPS) in Saarbrücken, the German Center for Infection Research (DZIF), the Max Planck Institute for Infection Biology (MPI-IB) and the Leibniz Institute for Natural Product Research and Infection Biology – Hans Knöll Institute (HKI).

Over the last few years, the HZI has systematically expanded its research activities in the field of new antibiotics. The institute is researching antibiotics with new, resistance-breaking modes of action. Primarily, it investigates active agents that occur in nature, optimises such agents and prepares them for future use as pharmaceuticals. Following their development of a pipeline to identify new antibiotic active agents, the HZI researchers discovered a number of novel antibiotic candidates, among them cystobactamides and amidochelecardins, which are effective against particularly resistant gram-negative pathogens. In conjunction with partners in the pharmaceutical industry, the researchers recently analysed and explained the mode of action of griselimycin, an agent active against multi-resistant tuberculosis pathogens.

To step up the HZI's efforts in the field of antibiotic research, the new building of the Helmholtz Institute for Pharmaceutical Research Saarland (HIPS) in Saarbrücken was put into service in 2016. The institute also applies medical chemistry methods to address the problem of antimicrobial resistance based on promising target structures. A new HZI active agent and functional genome research centre, whose key research areas will include translational antibiotic research and larger-scale production of natural agents, is currently under construction.

The DZIF is conducting an antibiotic treatment optimisation study (ATHOS) which focuses on the implementation of an antibiotic stewardship (ABS) programme in doctors' surgeries and hospitals based on existing guidelines. The aim is to optimise antibiotic use and assess the impact of the ABS programme on the spread of multi-resistant pathogens at the participating clinics. The study primarily concentrates on third-generation cephalosporin-resistant enterobacteriaceae (3GCREB) and vancomycin-resistant enterococci.

The DZIF is conducting several studies which monitor the spread of multi-resistant pathogens in hospitals. Key results: In a nationwide study on 3GCREB, researchers found that patients were responsible for introducing

just under ten percent of the multi-resistant pathogens found in hospitals. *Escherichia coli* bacteria, which produce beta lactamases – so-called ESBL Enterobacteriaceae –, were exceptionally frequent. A Europe-wide study also showed that particularly dangerous multi-resistant intestinal bacteria, such as *Escherichia coli* or *Klebsiella pneumoniae*, are increasingly resistant against carbapenem, an antibiotic of last resort. The DZIF employs state-of-the-art genome sequencing methods to help monitor the global spread of multi-resistant and extremely resistant tuberculosis bacteria.

Scientists at the non-university research institutions are also successfully involved in projects in the BMBF's temporary funding programme. One example is InfectControl2020 – a consortium of academic and industry partners that develops new anti-infective strategies. The project also provides impetus for further economic development in the new federal states. Its coordination is in the hands of the Leibniz Institute for Natural Product Research and Infection Biology – the Hans Knöll Institute in Jena.

The BMBF is funding a collaborative research project entitled 'Biological and hygiene-medical relevance and control of antibiotic-resistant pathogens in clinical, agricultural and communal wastewater and their impact on untreated water (HyReKA)' whose participants include scientists from various research institutions as well as water suppliers and wastewater disposal companies, industrial partners and authorities. The project is headed by the Institute for Hygiene and Public Health at Bonn's University Hospital. It researches the spread of resistant pathogens through wastewater from hospitals, communal areas, animal fattening and slaughter businesses and airports, and analyses suitable counter-strategies.

The joint HyReKA project is part of the BMBF funding initiative entitled 'Risk management of new toxins and pathogens in the water cycle (RiSKWa)' under the 'Sustainable Water Management (NaWaM)' funding priority.

The newly established Center for Sepsis Control and Care, CSCC, has outstanding expertise in the field. Antimicrobial resistance is a particularly obstructive factor in the treatment of sepsis. Increasing susceptibility to resistant pathogens is jeopardising the swift antibiotic action required by sepsis patients.

The 'Clinical studies with high relevance to patient care' funding priority finances multi-centric, prospective and controlled clinical studies researching evidence of treatment effectiveness. This research is to close evidence gaps

and pave the way for the integration of research results into patient care. The respective invitations for tenders are open to a wide range of subject areas. Furthermore, funding is also provided to several antibiotic treatment studies due to their high relevance to patient care. For instance, it has been shown that the use of antibiotics in the treatment of uncomplicated urinary tract infections can be substantially reduced through symptomatic treatment with Ibuprofen.

In the context of the ‘Zoonotic infectious diseases’ funding priority, the BMBF has financed research into the transmission of resistant bacteria between humans and animals conducted by two consortia (RESET and MedVetStaph). In April 2017, on conclusion of the funding period, the two consortia organised a joint symposium at the BfR in Berlin.

Successful collaboration between project and institutional funding (RESET and DZIF)

As an interdisciplinary research consortium, RESET primarily focuses on specific resistance mechanisms occurring in Enterobacteriaceae *Escherichia coli* and *Salmonella enterica*. In collaboration with the DZIF (in particular the Institute of Medical Microbiology at the DZIF’s Gießen site), the project partners compiled an extensive collection of microbial strains in the context of various studies researching the spread of such pathogens in animals, food and humans. Information regarding the origin of the samples and the results of the respective laboratory tests were collated in a joint database. For in-depth study, the Institute of Medical Microbiology in Gießen sequenced the genome of a selection of the microbial strains. The sequencing data allowed the scientists to substantiate the existence of the newly discovered resistance gene *mcr-1* against colistin (widely used for animal treatment) in three pig isolates which had been collected since 2011, as well as in one human multi-resistant isolate from the year 2014. The scientists also discovered other resistance genes in all four *mcr-1*-carrying isolates, which further restricts antibiotic treatment options.

Hence, the research consortium and the DZIF were the first to provide evidence that the resistance gene *mcr-1* occurs in *Escherichia coli* in farm animals as well as in humans in Germany, suggesting the possibility of transmission between animals and humans.

In January 2016, the Joint Programming Initiative on Antimicrobial Resistance (JPIAMR) announced a funding programme for transnational research projects within ERA-NET COFUND on antimicrobial resistance (JPI-EC-AMR). This announcement focused predominantly on the transmission of antimicrobial resistance. 19 projects, among them 10 involving German scientists, were selected and received a total of € 28.4 million.

In January 2017, a further announcement was made on prevention, control and intervention strategies against the development and transmission of, and infection with, antibiotic-resistant pathogens. The selection process is set to be completed in October 2017. All in all, around € 13 million are available for funding.

Outlook

After the launch of the Federal Ministry of Health's 'Antimicrobial resistance and hospital-acquired infections' funding priority in February 2017, a further funding priority ('Zoonoses') is planned for 2018. The preparations for this priority will be progressing throughout 2017. Moreover, as part of the implementation of the 'Pharma dialogue' agreement, a study is to be commissioned in the second half of 2017. The study will research the cause of prescription divergences with respect to regional distribution and within age groups. On this basis, measures are to be developed to promote the prudent use of antibiotics.

The 'Antibiotics' sub-working group of the 'Pharma dialogue' programme will continue its work in the form of the 'Antibiotic research, development and supply' competence team which aims to set the course for enhanced antibiotic research and development. In conjunction with the BMG, BMBF and BMWi government departments, experts in the fields of science, the licensing authorities, the RKI, pharmaceutical and biotechnology associations as well as industry will address the following subjects:

- Antibiotic research and development, rapid diagnostics and alternative treatment approaches in the global context
- Incentive models in the fields of antibiotic research and development, rapid diagnostics and alternative treatment approaches that have been discussed and must be implemented at the international level
- Cooperation models and collaboration
- Antibiotic production and supply

Expert talks planned in 2017 are to determine further research needs, especially in regard of measures required in the out-patient area.

On 1 July 2017, the BMBF-funded national research network on zoonotic infectious diseases will commence work with the aim of expanding the One Health approach and setting up closer links between research and the health-care system to speed up the practical implementation of research results. The public health service in the fields of human and veterinary medicine is thus directly involved in several research projects. One research consortium is concentrating its efforts on the transmission of antimicrobial resistance from animals to humans. The consortium is researching the zoonotic distribution and transmission channels of multi-resistant microorganisms and aims to interrupt these channels via suitable intervention strategies. On the one hand, the consortium is investigating measures affecting direct transmission paths, for instance changes in animal husbandry. On the other hand, it develops feasible prevention measures in the clinical field on the basis of the antibiotic stewardship concept (ABS). The consortium is set to continue the work of the previously funded RESET and MedVetStaph research consortia and will keep a close eye on application-relevant issues.

The German government is planning to set up a 'National active agent initiative' to boost pharmaceutical research and development and combat infectious diseases. The initiative will have the aim of encouraging active pharmaceutical agent research especially in the field of infectious diseases and promoting the development of new pharmaceutical products. To safeguard and improve medical care in the field of infectious diseases both in Germany and worldwide, research must come up with new candidate antibiotics which can be turned into effective new drugs. In pursuit of this aim, fundamental research in natural product medicine and medical chemistry is receiving a boost and the establishment of interdisciplinary networks involving universities, research institutes and enterprises is being encouraged at the national and the international level.

In the run-up to the drug development initiative, the BMBF published its funding guidelines – 'Diagnostics and innovative treatment of bacterial infections' and 'Target validation of active pharmaceutical agent development' – in September 2016 and March 2017 respectively. Further publication of funding guidelines relating to later added value phases in the pharmaceutical sector will follow.

Established by the BMBF in 2015, the Health Research Forum and its ‘Value-added chain’ working group also focus on this issue and are currently developing strategies to overcome barriers in the health research value-added chain.

Concluding remarks

With a view to the German G20 presidency, among other priority areas, activities continue to centre on international cooperation and the strengthening of global capacities in the fight against antimicrobial resistance. There are still a number of countries which have so far failed to develop the required cross-sectoral national action plans to combat antimicrobial resistance. However, the swift implementation of submitted action plans is also of great importance. Germany is making use of several fora and formats to provide support in this area. In respect of the implementation of measures, international exchanges allow Germany to learn from other countries’ experiences and adapt its own activities where appropriate.

Progress in the fight against antimicrobial resistance at the national and international levels crucially depends on a smooth process involving comprehensive hygiene, application of diagnostics and prudent antibiotic use. This process must be complemented by the development of new antibiotics, which requires a multidisciplinary pooling of expertise at the international level. Among other fields, further DART implementation measures until 2020 will concentrate on out-patient care. This is where around 85 % of all antibiotics are being prescribed. Hence, out-patient care plays a particularly important role for the long-term improvement of the prudent antibiotic use. The results of the current research projects on measures suitable for reducing antibiotic prescriptions in out-patient care are therefore of great significance. They can serve as a measure of the effectiveness of current mechanisms and statutory regulations.

The results gained from this and other research projects will contribute to the further, specific development of the DART 2020 measures.

In the field of veterinary medicine, the focus will be on raising awareness among all stakeholders and along the entire food chain of the risks associated with inappropriate use of antibiotics. Greater emphasis must be placed on hygienic measures in farms and in food production and processing. Contributions to this objective will be made not only via information campaigns and the

inclusion of the subject in basic and advanced training of veterinary staff and livestock owners but also via the evaluation of the monitoring and surveillance data. Specific use of vaccines, including stable-specific vaccines, is being evaluated as part of the work conducted by the Standing Vaccination Committee Vet (StiKo Vet) at the Friedrich-Loeffler Institute and should gain significance in future strategies to minimise antibiotic use.

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