The
Federal Government

ANTIBIOTICS AVOIDING RESISTANCE

DART 2020

Third interim report 2018

Introduction

The German Antimicrobial Resistance Strategy 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, due to its fundamental significance, was approved by the Federal Cabinet in 2015. DART 2020 describes the national agenda for controlling antimicrobial resistance. In six goals it lays out how the emergence and spread of antimicrobial resistance are to be prevented in Germany. This, the third interim report, continues the series of reports documenting the implementation status, and, in particular, illustrates the progress achieved.

The central element around which DART 2020 revolves is cross-sector cooperation on combating antimicrobial resistance in human and veterinary medicine through the so-called "One Health Approach". The fundamental goal in both sectors is to use antimicrobials only in a targeted and appropriate way. This requires the population to have a better understanding of antimicrobial resistance. There is a need for information among citizens. However, in human and veterinary medicine, as well as in agricultural professions, there are still gaps in knowledge that need to be closed. Antimicrobial resistance and antimicrobial consumption monitoring systems must be developed further. Only this will allow new resistances to be detected at an early stage and important data for the development and adjustment of therapy and hygiene recommendations to be acquired. Knowledge from research into the emergence and spread of resistance can be used for this purpose.

In 2017, Germany held the G20 presidency. For the first time during a G20 presidency, health-related topics were addressed. Antimicrobial resistance was the subject of consultation, along with global health crisis management and the strengthening of healthcare systems. In implementation of the DART 2020 goals, the German presidency placed an emphasis on strengthening

the One Health approach, which requires close cooperation of all affected areas, such as human and veterinary medicine, agriculture, research and the environmental sector.

GOAL 1: Strengthening the One Health approach nationally and internationally

Human and animal health must be considered as one. Controlling the emergence and spread of antimicrobial resistances can only be done with a cross-sector approach.

This requires close cooperation between all stakeholders involved and between the responsible federal ministries and their higher federal authorities. Due to globalised trade in animals and plants and increased travel, close cooperation between international partners, not just in the EU, but worldwide, is a condition for sustainable success. The implementation of the WHO Global Action Plan, which emphasises the One Health approach, is the prerequisite for this.

What was achieved

Under the German G20 presidency, agriculture and health ministers, as well as heads of state and government at the Hamburg summit, discussed antimicrobial resistance. The contents of the G20 Agriculture Ministers' Declaration under the German presidency were already presented in the 2nd DART 2020 interim report. The "Berlin Declaration" of G20 health ministers anticipated a strengthening of antimicrobial resistance and antimicrobial consumption surveillance, among other things. The ministers also considered it necessary to enhance awareness of the problem among the population and medical staff. Infection prevention assumes a critical role in the Berlin Declaration. Measures to strengthen hygiene and vaccination should therefore be taken. The application of relevant diagnostics should support the prudent use of antimicrobials. The G20 countries will also fund programmes related to the prudent

use of antimicrobials (Antibiotic Stewardship Programme). The G20 ministers also agreed that antimicrobials should be issued only on prescription. At the same time, everyone who needs antimicrobials must have access to them. The One Health approach should be promoted and the research and development of new antimicrobials, alternative therapies, vaccines and rapid diagnostics intensified. The financial support for product development partnerships and financing initiatives should be built up further.

In implementation of the G20 declarations, the first meeting of representatives of Public Health and Veterinary Public Health Institutes of the G20 took place on 13th and 14th September in Berlin with the aim of strengthening the One Health approach. At this meeting, the focus was on the networking of the experts working there. The aim was to lay the basis for new partnerships and intensive exchange by allowing the persons involved to get to know one another. Representatives of international organisations such as the World Health Organization (WHO) and the World Organisation for Animal Health (OIE) also participated.

In three parallel workshops, experts from the fields of human and veterinary medicine discussed “Infection prevention”, “Rational Antibiotic Use” and “Surveillance Systems”. The discussion was based on a study on handling of antimicrobials and antimicrobial resistance, which the Institute for Veterinary Epidemiology and Biostatistics at the Free University of Berlin carried out in the countries of the G20 and guest countries.

The joint discussion improved mutual understanding of the approach in human and veterinary medicine and in the individual countries and laid the basis for future cooperation.

In parallel, the directors of the Public Health and Veterinary Public Health Institutes considered future cooperation. Their view was that joint activities to counter antimicrobial resistance should be intensified. Cooperation should not be limited to this, however. Other topics

should be covered, too, in keeping with the One Health approach. Germany is committed to ensuring that the meetings include other sectors too, such as the environmental sector.

In June 2017, the European Commission published a new EU action plan to tackle antimicrobial resistance. With this, the Commission aims to make the EU a "Best Practice Region" in combating antimicrobial resistance and in implementing national action plans. A Joint Action on Antimicrobial Resistances and nosocomial Infections (JAMRAI) is intended to support this. For Germany the Robert Koch Institute (RKI) is participating. The Joint Action breaks down into several work packages. The German focus is on the work packages "Implementation of One Health national strategies and national Action Plans for AMR" and "Appropriate use of antimicrobials in humans and animals".

Following on from the G20 Leaders' Declaration, the Global AMR R&D Hub was set up by the BMBF under Germany's leadership. The Global AMR R&D Hub is an overarching initiative for state and non-state funders of research and development in the field of antimicrobial resistance. It follows the One Health approach but is expected initially to concentrate on the research and development of antimicrobials, alternative therapies and diagnostics in the field of human medicine.

Within the framework of the BMG-initiated Global Health Protection Program[1] the RKI has been supporting, since 2016, several countries in Africa and Asia in, among other things, establishing microbiological diagnostics for the detection and resistance-testing of bacterial pathogens. The availability of diagnostic methods is an essential prerequisite both for proper patient care and for the surveillance of antimicrobial resistance. In 2017, a one-week workshop on microbiological diagnosis was held in the Ivory Coast with participants from the Ivory Coast and Burkina Faso. The required labora-

1 https://www.rki.de/DE/Content/Institut/Internationales/Global_health/Global_health_node.html

tory diagnostic methods have already been established in a participating centre in the Ivory Coast. The aim of a further sub-project in Bangladesh, Cambodia and Vietnam is to study the causes, the disease burden and the antimicrobial resistance profile of bacterial infections acquired in hospitals or in outpatient care. A surveillance system was developed, with several centres participating. Samples acquired there are studied via DNA sequencing. Among other things, the results give indications of trends in pathogen resistance.

Within the BMBF-funded research network for health innovations in Sub-Saharan Africa, the "African Network for improved Diagnostics, Epidemiology and Management of Common Infectious Agents" (ANDEMIA)[2] also studies the emergence and development mechanisms of antimicrobial resistance in various regions and local settings under the One Health aspect.

Germany is also participating in the AMR Action Package of the Global Health Security Agenda (GHSA) and is thus supporting implementation of the global action plans of the WHO, FAO and OIE. In addition, the Action Package serves as a communication platform for the participating countries.

With the "German One Health Initiative" (GOHI)[3], the Federal Institute for Risk Assessment (BfR), the Friedrich Loeffler Institute (FLI), the Paul Ehrlich Institute (PEI) and the RKI founded, in 2017, a platform for networking of the four sectoral research institutions. In the first round, funding was provided for several PhD theses dealing with data on antimicrobial resistance in humans and animals and with the appearance of resistance in specific pathogens.

In addition, the subordinate authorities of the BMG and BMEL are working together in other projects. The goal of the "European Joint Programme One Health" is the development of suitable strategies

2 http://www.andemia.org/

3 https://www.gohi.online/GOHI/EN/Home/Homepage_node.html

for fighting zoonoses. Several projects deal with antimicrobial resistance. The BfR and the RKI are participating in the Project ARDig (Antimicrobial Resistance Dynamics: the influence of geographic origin and management systems on resistance gene flows within humans, animals and the environment), which deals with the emergence and spread of antimicrobial resistance in humans, animals, food and the environment.

Within the framework of the EU project "COMPARE" [4] the RKI and the FLI are working together with academics from university and non-university institutions. Among other things, the project deals with the use of whole genome data for early detection of multispecies outbreaks, i.e. outbreaks in which various pathogen species, with the same resistance characteristics however, are involved.

In 2016, WHO designated the RKI as the WHO Collaborating Centre for Emerging Infections and Biological Threats. WHO collaborating centres are designated worldwide by WHO to deal with different issues. These are national institutions that support WHO in the implementation of its programmes and responsibilities through their specialist knowledge and staff. The WHO Collaborating Centre at the RKI also offers support for, among other things, the "WHO AMR Surveillance and Quality Assessment Collaborating Centre Network" work plan, primarily through surveillance and laboratory activities.

In October 2017, the chief veterinary officers (CVO) agreed on relevant definitions for the use of antimicrobials in animals, thus supporting a joint understanding in respect of implementing G7 agreements in this field.

At the end of November, the 5th session of the Task Force AMR (TFAMR) of the Codex Alimentarius took place in Korea, the first under the new mandate. During this session, the German representatives supported the European Commission on site while engaging in the consultations for an ambitious implementation

4 http://www.compare-europe.eu/

of the TFAMR mandate issued in July 2017 against resistance from other parts of the world.

In January 2018, agriculture ministers from around the world met for the 10th time at the BMEL-hosted Global Forum for Food and Agriculture (GFFA) in Berlin. The GFFA was held under the motto "The future of livestock production – sustainable, responsible, efficient". In their unanimously agreed final statement, the agriculture ministers from 69 states have committed, among other things, to take measures to reduce the risks of disease, to avoid the unnecessary use of antimicrobials and to cease use of antimicrobial agents for growth promotion purposes in the absence of a risk analysis conducted in line with codex CAC / RCP 61-2005 of Codex Alimentarius. In addition, the ministers declared that they wished to contain the emergence and spread of antimicrobial resistance in accordance with the One Health approach and limit the use of antimicrobials in veterinary medicine exclusively for therapeutic purposes.

Outlook

Zoonoses are caused by pathogens that are mutually transferable between animals and humans. Research into zoonoses serves the purposes of protecting both human and animal health. The BMG funding priority "Zoonoses" should ensure that cooperation between the various sectors is promoted further. The announcement of this funding priority was published in January 2018. Antimicrobial resistance is taken up in topic area 1 "Integrated genome-based surveillance of zoonotic pathogens and pathogens with special antimicrobial resistance". The projects are expected to begin in early 2019 after the expert review process ends.

The cross-sector coordination, evaluation and adjustment of the national antimicrobial resistance strategy are done through an inter-ministerial Antimicrobial Resistance Working Group (IMAG AMR). Information about current projects at the national and international level is also exchanged in regular meetings. In future, the environmental sector should be more strongly integrated into

DART 2020 and the IMAG AMR in order to be able to react to the latest findings about drug-resistant pathogens in the environment, including in bathing waters.

This year the BMBF is co-organiser of the Grand Challenges Meeting (GC) of the Bill and Melinda Gates Foundation, to be held on 16–18th October 2018 in Berlin. The event will bring together around 1000 international experts to deal with the topic of global health in the broadest possible sense. Together with the Wellcome Trust and the BMG, with the involvement of the BMEL and the BMU, the BMBF will organise the part of the event dealing with antimicrobial resistance.

The work of the TFAMR of the Codex Alimentarius will be continued in the form of electronic working groups in which Germany will participate as actively as in the next session of the TFAMR in December 2018.

Germany is keen to see the topic of antimicrobial resistance taken up again in the G20 negotiations under the Argentinean presidency. Among the group of agriculture ministers, the BMEL has taken on the responsibility of delivering an assessment of the implementation of the decisions of the G20 agriculture ministers' declaration and the Action Plan of 22 January 2017 on the subject of containing antimicrobial resistance. The first related report is due in 2019.

GOAL 2: Recognising changes in resistance at an early stage

Representative data about the appearance of new pathogens and resistances is required to be able to adapt therapy and hygiene recommendations to the current situation on an ongoing basis and to be able to develop targeted prevention strategies. This data can also contribute to changing individual prescription behaviour, among other things. The development of resistance rates over time gives an indication of the effectiveness of countermeasures.

What was achieved

The RKI has continuously developed further the laboratory-based Antimicrobial Resistance Surveillance (ARS)[5]. The participation of additional laboratories also increased the share of care institutions covered by the surveillance system; in 2016 it was at around 23 per cent of general hospitals and 17 doctor's practices / 100,000 inhabitants. In the last three years, in particular, it has been possible to significantly improve coverage of the federal Laender that were previously somewhat under-represented. This significantly strengthens the basis for a regional analysis of antimicrobial resistance data in Germany.

In 2017, for the first time Germany provided ARS data for 2016 to WHO's Global Antimicrobial Resistance Surveillance System (GLASS), besides the annual data transfer to the EARS-Net network coordinated by the European Centre for Disease Prevention and Control (ECDC).

Within the framework of the Northern Dimension Partnership in Public Health and Social Wellbeing, the RKI participated in the NorthernGLASS project, whose focus was on the early implementation of GLASS. The objective of the project, which received funding

5 https://ars.rki.de/

from Sweden, was to identify opportunities and obstacles during the implementation, as well as the need for adaptation. The project was conducted in close cooperation with the WHO and the ECDC.

In 2017, the National Reference Centre for *Clostridium difficile* was appointed to take account of the significance of the pathogen particularly also in connection with the use of antimicrobials. By adjusting the reporting obligation for *Clostridium difficile* with serious clinical progression and introducing the reporting criterion "inpatient admission due to community-acquired Clostridium-difficile infection" *C. difficile* infections acquired from outpatient care will be recorded for the first time. Initial analyses show that there is a greater need for research on the occurrence and spread of *C. difficile*, particularly for the outpatient sector.

To improve laboratory diagnosis and the data situation on gonococcal resistance in Germany, the BMG is providing funding until 2019 for a cooperative project (GORENET, Gonococci Resistance Network)[6] between RKI and the Consultant Laboratory (KL) for Gonococci. The data is required to be able to adapt evidence-based therapy recommendations and develop targeted preventive measures. Within the laboratory network, gonococcal isolates are sent from across Germany to the Consultant Laboratory (KL) for Gonococci. Resistance tests continuously give a current picture of the resistance situation of gonococci. In addition, more in-depth molecular genetic analyses are done on the spread dynamics and on genotypes with unusual resistance profiles. The resistance data acquired are sent annually to the EURO-GASP network based at the ECDC. To provide quality assurance of the diagnosis of resistance in gonococci, laboratory trainings and round robin tests will be carried out by RKI and the KL for gonococci.

6 https://www.rki.de/DE/Content/InfAZ/G/Gonorrhoe/GORENET/GORENET_inhalt.html

Antimicrobial resistance monitoring in zoonotic pathogens and commensal germs in the food chain[7] was continued and adapted by the BfR to new requirements, e.g. in respect of the study methods to be employed. It was also extended by the study of enterococci and *Clostridium difficile* and from 2018 by the obligatory selective detection of Carbapenemase-forming *E. coli*. The special studies into the appearance of colistin resistance genes were continued with the methods being continuously adapted in line with the latest knowledge.

The results of the resistance monitoring of veterinary pathogens[8] from the years 2014 and 2015 were published by the Federal Office of Consumer Protection and Food Safety (BVL). This data makes it possible to take coordinating measures and give the treating veterinarian decision-making assistance on empiric therapy. Additional studies on resistance in animal pathogens were carried out at the FLI. The collected data are used to estimate the resistance situation among notifiable epizootic diseases and reportable animal diseases.

Outlook

Knowledge gained from the genome-based typing of infectious agents (molecular surveillance) represents an important basis for identifying related cases and possible causative agents of an infectious disease. It can help contribute to clarifying outbreak incidents more quickly and introducing specific monitoring measures at an earlier stage. Within the framework of the funding priorities described under Goal 1 some of the projects funded are intended to deal with the integrated genome-based surveillance of zoonotic pathogens or bacterial infectious agents with special antimicrobial resistance in day-to-day care (outbreak clarification, source attribution and identification of outbreak vehicles).

7 https://www.bvl.bund.de/DE/01_Lebensmittel/01_Aufgaben/02_AmtlicheLebensmittelueberwachung/06_ZoonosenMonitoring/lm_zoonosen_monitoring_node.html

8 https://www.bvl.bund.de/DE/09_Untersuchungen/01_Aufgaben/03_Nationales%20Resistenz-Monitoring/untersuchungen_NatResistenzmonitoring_node.html

The BfR is participating in a working group of the European Food Safety Authority which should work on the scientific bases for the further development of resistance monitoring in zoonotic pathogens and commensal germs.

With GERMAP 2018, the BVL is preparing the 5th report on the development of antimicrobial consumption and the development of resistance in human and veterinary medicine in Germany. BVL publishes this report together with the Paul Ehrlich Society. It summarises the trends of recent years and forms a basis for developing guidelines and recommendations for antimicrobial therapy of infectious diseases in humans and animals.

The FLI is working on the validation of an alternative procedure for rapid antimicrobial resistance testing (Raman spectroscopy). The EMERGE project, coordinated by the RKI and co-financed by the EU Health Programme, is seeking, among other things, to establish the limit values and technical aspects of in vitro phenotypic susceptibility testing for EUCAST / ECDC. From Germany, the RKI, FLI and Microbiology Institute of the Federal Armed Forces are participating in this.

GOAL 3: Retaining and improving therapy options

To be able to maintain the long-term effectiveness of antimicrobials, prudent use of antimicrobials is required. In Germany, there is significant regional variation in the use of antimicrobials; there can be many causes for this. To improve the understanding of this variation, data about the amount of antimicrobials supplied or used is needed. This data also forms the basis for targeted intervention measures and offers support for an assessment of their effectiveness.

What was achieved

In cooperation with the Charité University Hospital, the RKI has built up a higher-level Antimicrobial Consumption Surveillance (AVS)[9] system for hospitals. This should help hospitals in carrying out the Antimicrobials Consumption Surveillance in accordance with legal requirements and local Antibiotic Stewardship (ABS) activities. The electronic, web-based surveillance system makes it possible to upload data at any time and call up timely consumption reports via an interactive database with password-protected access. Various feedback report formats are available to support the different assessment approaches. The quality of the data is monitored by regular systematic validations. 331 hospitals and rehabilitation institutions have registered since the start of the project in 2014. Since November 2017, the consumption data has been made publicly available in an interactive database on the AVS homepage.

Via the BMG-funded ARVIA project (Antimicrobial Resistance and Consumption – integrated Analysis) a model will be developed to bring together data from both surveillance systems, ARS (see Goal 2) and AVS, and to analyse them with reference to one another. The analyses should support hospitals in their ABS activities.[10] The first institutions have been recruited for the pilot phase.

The Commission on Anti-infectives, Resistance and Therapy (ART), in cooperation with scientific medical societies, has published opinions on therapy alternatives when Piperacillin/Tazobactam is unavailable.

The second regulation to change the Veterinary House Dispensary Ordinance entered into force on 1 March 2018. It contains additional regulations on the use of antimicrobials in animals, which should also, in particular, address antimicrobials with special significance for humans.

9 https://avs.rki.de/

10 https://ars.rki.de/Content/ARVIA/Main.aspx

The recording of the amount of antimicrobials supplied by pharmaceutical companies and wholesalers to veterinarians, which began in 2011, has been continued. By 2016 this amount had fallen by 56.6 % to 742 t.

Joint experiments of the Thünen Institute (TI) and Max Rubner Institute (MRI) on the drying off of milk cows have shown that through selective antimicrobial treatment of only the infected udder quarters the quantity of antimicrobials used can be significantly reduced, without impairing the rates of cure.

Outlook

For the outpatient sector, there is currently no higher-level surveillance system for antimicrobial consumption comparable to AVS, containing a structured feedback mechanism. But there, too, a system of this type is helpful in improving the prudent use of antimicrobials. From 2018, a feasibility study is planned to examine how such a system could be developed for the outpatient sector.

In accordance with §58g of the Medicinal Products Act (AMG), the BMEL must submit a report evaluating the effectiveness of the antimicrobial minimisation concept introduced by the 16th AMG amendment to the German Bundestag in April 2019. Evaluation of the data by the BfR and BVL has now begun for this purpose. In addition, a tender was published which, first of all, related to technical advice for the creation of the evaluation report, and secondly carrying out a poll of livestock breeders and veterinarians, whose results would form part of the report. States were also asked for a contribution from the perspective of monitoring.

A further joint study by TI and MRI on drying off examines the question of whether the use of internal teat sealers instead of long-term antimicrobials can protect the healthy udder quarters against new infections during the drying period.

The FLI is working on the validation of possible alternatives to antimicrobial treatment, specifically phage therapy for Enterobacteria and *Staphylococcus aureus*.

GOAL 4: Breaking chains of infection early and avoiding infections

Avoiding infections is the most important measure to reduce antimicrobial consumption. Compliance with hygiene measures in hospitals by qualified medical staff and professional livestock owners is a crucial part of this. But timely diagnosis is also important, to be able to use antimicrobials in a more targeted way and prevent the spread of resistant pathogens. Regional networks for the prevention and monitoring of multi-drug-resistant infective agents can help identify and overcome application obstacles and implementation problems.

What was achieved

For Germany, the Commission for hospital hygiene and infection prevention (KRINKO)[11] is creating evidence-based recommendations for the prevention of nosocomial infections and operational / organisational and structural / functional hygiene measures in hospitals and other medical institutions. The goal is to identify, prevent and counter nosocomial infections. The recommendations are constantly developed further and updated by taking current infection-epidemiological assessments into account, in order to adapt them to the latest state of medical knowledge. In 2017, KRINKO's recommendation on the "Prevention of infections arising from vessel catheters" was updated and supplemented with appendices on the topic of blood culture diagnostics and implementation of the recommendation. The recommendation on the "Prevention of post-operative wound infections" has also been revised and updated; it will be published in Spring 2018.

11 https://www.rki.de/DE/Content/Kommissionen/KRINKO/krinko_node.html)

In 2016, Germany participated with the Institute for Hygiene and Environmental Medicine of the Charité University Hospital in the second point prevalence survey on nosocomial infections and on antimicrobials application. The prevalence of nosocomial infections (share of those sick with a nosocomial infection on a sample day) has fallen slightly in comparison to the first survey in 2011. The prevalence of antimicrobial application remained substantially the same. Currently, further evaluations are being done that will be used to adapt recommendations for action.

Vaccines can effectively prevent infections and so lead to a reduction in the consumption of antimicrobials. They therefore represent one of the pillars of the fight against antimicrobial resistance in the global action plan. The increase in the use of already available vaccines (e.g. against pneumococci or against virus infections such as influenza) is a declared goal. But the development and introduction of new and more effective vaccines, especially for vaccination against pathogens that present drug-resistance problems, is an important component of the global action plan.

In Germany, the Standing Committee on Vaccination based at the RKI[12] develops vaccine recommendations for the population. This includes recommendations on occupational vaccinations for staff in health care institutions, both to protect the employees and to avoid nosocomial infections (third-party protection). In 2016, among others, the recommendation for vaccination against pneumococci for at-risk patients and seniors (as a standard vaccination from the age of 60) was reassessed and updated.

The RKI is also involved in the nationwide information campaign of the Federal Centre for Health Information (BZgA) “We’ll beat the flu” and is included as a consortium partner in the BMBF-funded project “impfen60+”. The project aims at increasing influenza and pneumococcal vaccination rates among seniors as well as knowledge of

12 STIKO; https://www.rki.de/DE/Content/Kommissionen/STIKO/stiko_node.html

sepsis or sepsis prevention through vaccination.[13] In addition, the RKI initiated a federal monitoring of vaccination rates among medical staff in clinics (Okapii)[14], in which more than 50 clinics had already participated in 2017 and which should be extended further.

In the context of work on modelling process chains in the food sector, the BfR looked at, inter alia, the spread of Extended Spectrum-ß-Lactamase (ESBL)-forming *E. coli* across the food chain. Studies on the carryover of MRSA and ESBLs into kitchens are currently still being evaluated. On the basis of the models developed, intervention measures such as the introduction of process hygiene criteria can be tested for their predicted effectiveness.

At the FLI, studies are carried out on an ongoing basis at the genetic level on a wide range of bacterial pathogens originating in animals. In a long-term study, a classification system for ESBL burden will be developed in conventional and organic pig fattening farms, including intervention measures to reduce the ESBL load.

Outlook

A central goal of the KRINKO recommendations is to reduce the spread of pathogens with special resistance in hospitals and other medical and care institutions. In this respect, a recommendation on the prevention of infections through enterococci with special antimicrobial resistance (e. g. Vancomycin-resistant enterococci, VRE) and another on the prevention of Clostridium difficile infections are currently being drawn up.

In the context of a point prevalence survey on nosocomial infections and the use of antimicrobials in long-term care institutions, Germany participated in the ECDC-initiated study "Healthcare-associated Infections in European Long-term Care Facilities" ("HALT-3"). The results are currently being evaluated and prepared for publication.

13 https://www.rki.de/DE/Content/Infekt/Impfen/Forschungsprojekte/Impfen60plus/impfen60plus_node.html

14 https://www.rki.de/DE/Content/Infekt/EpidBull/Archiv/2016/Ausgaben/47_16.pdf?__blob=publicationFile

In May 2017, the World Health Assembly passed a resolution on sepsis initiated by Germany. This imposes a series of requirements on the member states, including better information about the early symptoms of sepsis, an increase in vaccination rates, an increase in infection prevention, funding of research and development of vaccines, preventive measures, diagnostics and therapeutics as well as boosting measures to counter antimicrobial resistance. Various measures are to be started for their implementation. In addition, the RKI is working with the WHO on a systematic review of the burden of disease caused by nosocomial sepsis.

Beside projects on the professional use of antimicrobials, described in more detail in the second interim report, the resources of the innovation fund will be used for sepsis projects, currently the project "STAU-free – pre-ward detection and remediation for the avoidance of STaphylococcus AUreus complications in elective patients" is being funded. The aim of the project is to avoid the transmission of MRSA or MSSA (Methicillin-sensitive *Staphylococcus aureus*) at the transition between the outpatient and ward sector. This involves performing a screening for the pathogens mentioned prior to planned hospital stays and – if they are detected – performing remediation.

The project group "Govern effectively" at the Federal Chancellery has been carrying out a Germany-wide project "Together for infection prevention" since 2016. The National Reference Centre for Surveillance of Nosocomial Infections at the Charité Hospital in Berlin (NRZ) is a partner in this. The aim of the project is to increase hand hygiene quality, to build up greater hygiene competence at care units and to reduce the number of nosocomial infections. The final report will be available in the third quarter of 2018. The extent to which it would be sensible and feasible to transfer the approach to other institutions will then be studied.

In the field of basic research, the FLI is working on the identification of bacterial structures that could be the attack points for newly developed vaccines against various bacterial pathogens.

GOAL 5: Raising awareness and strengthening skills

Relevant knowledge is the prerequisite for the proper use of antimicrobials and the correct handling of multidrug-resistant pathogens. In the population, as well as among medical and veterinary specialists and livestock raisers, there is a significant need for information and gaps in knowledge are prevalent that must be filled in.

What was achieved

Various training offers are available to doctors on the topic of antimicrobial resistance. The training in prudent antimicrobial therapy has special significance (Antibiotic Stewardship, ABS). The S3 guideline on ensuring prudent antimicrobials use in hospitals sees the function of an ABS Appointee or ABS Expert as necessary for clinics. In November 2017, the existing certified ABS training programmes were transferred into a structured curricular training programme “Antibiotic Stewardship (ABS)” of the German Medical Association. The qualification of ABS Appointee or ABS expert can be acquired via the training.

Comprehensive information and training materials for various target groups are made available via the RAI “Rational Antimicrobial Use through information and communication”, which is funded by the InfectControl 2020 Consortium.[15] The project is aimed equally at antibiotics-prescribing actors such as GPs, surgeons and intensive care specialists, as well as patients. RAI is also including veterinarians and farmers.

15 http://www.rai-projekt.de/rai/startseite/

Consumer monitoring carried out by the BfR shows that there is a marked, long-term awareness of the problem of antimicrobial resistance in the population.

The BMEL-funded E-learning offering VetMAb [16] was extended as VetMAb II and has been supplemented with a training block for farmers and for official veterinarians active in controlling the antimicrobial-minimisation concept. This eLearning offer supplements the large number of in-person training events currently addressing the topic of antimicrobial resistance.

Outlook

Measures to strengthen the training of medical personnel, in particular, on antimicrobial resistance and the prudent use of antimicrobials will be continued. For Autumn an expert discussion focusing on the outpatient sector is planned with the ART Commission.

Experts working in the higher federal authorities will continue to pass on the latest knowledge about antimicrobial resistance through publications in specialist magazines and presentations at training events. In autumn 2018, the BfR will again organise a symposium on antimicrobial resistance along the food chain.

GOAL 6: Supporting research and development

Research makes an important contribution to gather the data required to create the bases for evidence-based measures against AMR. The goal of DART 2020 is therefore to strengthen all relevant research areas in human and veterinary medicine – from basic research via clinical research into public health issues to research done in conjunction with the healthcare, agriculture and food

16 https://www.vetmab.de/

industries. Alongside better understanding about the emergence and spread of resistance there is a major need for new antimicrobials. Nationally and internationally, coordinated initiatives will enhance the research and development of anti-infectives.

What was achieved

National activities

Antimicrobial resistance is studied by scientists at universities and non-university research institutions. Particularly worthy of mention here are the Helmholtz Centre for Infection Research (HZI) in Braunschweig with the Helmholtz Institute for Pharmaceutical Research (HIPS) in Saarbrücken and the German Centre for Infection Research (DZIF).

At HZI, research aimed to discover and develop new antimicrobials focuses on natural antibiotics, which are then optimised with medicinal chemistry to retain the most promising candidates for later development as drugs. The new antibacterial candidate amidochelocardin was discovered during this process, for example. The effectiveness of amidochelocardin against gram-negative bacteria has already been demonstrated in an animal model for urinary tract infections.

The DZIF is developing new strategies to counter the emergence and spread of resistance. These include improved monitoring of spread of infection, more responsible use of antibiotics (e. g. Antibiotic Stewardship) and the development of new vaccines and medicines. To monitor and control the spread of multi-drug-resistant bacterial strains in hospitals, their appearance must be efficiently monitored. An important basis for this is the so-called R-Net of the DZIF: A network for recording multi-drug-resistant pathogens, with six DZIF sites participating. In Cologne and Gießen, for example, multi-drug-resistant strains can be identified quickly via gene sequencing. An early warning system for clinics, that indicates the first signs of nosocomial bacteria spreading, is currently being developed in Berlin. Patient decolonisation is another strategy: This

means eliminating multi-drug-resistant bacteria that the patients are carrying. The DZIF has already found a promising substance, lugdunin, which in many people produces a natural protection against *Staphylococcus aureus* in the nose.

At the DZIF researchers are also looking for antibiotics with new mechanisms of action that do not lead to emergence of resistance. Examples are Corallopyronin A against worm infections and Aminochelocardine against urinary tract infections. The "Natural Compound Library" in the DZIF, which is coordinated at the HZI, currently offers 3000 extracts of microorganisms and 800 pure substances of natural origin, which are available to experts for large screening programmes. Possible antibacterial substances will be studied in the DZIF for their mechanism of effect, in order to determine their potential as antibiotics. New paths will also be sought to improve the action of antimicrobial substances: For example, researchers in Saarbrücken are attempting to manipulate *Pseudomonas aeruginosa* in biofilms.

The BMBF is providing around 45 million euros to the InfectControl2020 consortium. Universities, non-university research institutions, industrial partners and the departmental research institutions BfR, FLI and RKI are participating in around 30 research projects. The consortium is coordinated by the Leibniz Institute for Natural Product Research and Infection Biology – Hans-Knöll-Institute (HKI) in Jena. Within the programme, different professional groups, such as physicians, biologists, veterinarians, materials scientists or architects are drawing up solution approaches to prevent the emergence and spread of multi-drug-resistant bacteria and treat patients more quickly and more successfully. One of the largest projects of the consortium is dedicated to the prudent use of antibiotics through information and communication, in short RAI (see Goal 5).

The research work of the JKI deals with the environmental aspect of the One Health concept. The Julius Kühn-Institute (JKI) researchers are exploring the question of how different environmental factors

influence the resistance transmission of bacteria in the soil, in the rhizosphere, in organic fertilisers (manure, fermentation residue and sewage sludge) and in fresh products. Research results confirm that it is not only nutrients, important for plants, which are reaching the soil via organic fertilisers, but also traces of antimicrobials and bacteria with transferable resistance.

The BMBF-supported "National research network on zoonotic infectious diseases" began its work on 1st July 2017. The goal is to develop the One Health approach further and to build up a closer connection between research and the healthcare sector, so that the results can be used more quickly in the public health services in human and veterinary medicine. To achieve this goal, the work of the research network is supported by a coordination project that has been funded by BMBF since 1st September 2017.

The funded research collaboration "One Health Interventions to Prevent Zoonotic Spread of Antimicrobial Multidrug-Resistant Bacterial Microorganisms – #1Health-PREVENT", in which the BfR and RKI are involved, aims to study the zoonotic spread and transmission paths of multidrug-resistant microorganisms and to block this through suitable intervention strategies. Epidemiological studies on the zoonotic spread of multi-resistant bacterial pathogens in animals and humans will be carried out for this purpose. Consideration will also be given to measures that influence the direct transfer paths, such as changes in livestock husbandry for example. Interventions to control MRE in livestock, pets and companion animals will also be developed. This includes the use of antibacterials in animal clinics, vaccines for animals or alternative husbandry conditions for animals.

The funding measure "Clinical studies with high relevance for patient care" supports multi-centric, prospective, controlled clinical studies on proving the efficacy of therapy concepts. This includes several studies on antibacterial therapies, e.g. on the significance of a specific genotype for the prevention of infectious complications,

such as spontaneous bacterial peritonitis in cirrhosis of the liver. Another study seeks to demonstrate that patients with a moderate worsening of chronic obstructive pulmonary disease suffer no disadvantage if given no antibacterial in addition to the standard therapy. A new announcement of funding measures was published at the end of February 2018.

Since 2012, the BMBF has funded the clinical researcher group for clinical infectiology in the area of infections by multi-drug-resistant pathogens at the University Clinic of Jena. On 1st January 2018, the structure that began as a researcher group was transferred to an independent Institute for Infectious Medicine and Hospital Hygiene at the University Clinic of Jena. This has successfully stabilised the structures in Jena for research into antimicrobial-resistant bacteria.

With the Center for Sepsis Control and Care (CSCC), a centre with outstanding expertise in the sepsis field has also been established in Jena. The goal of the CSCC is to reduce the sepsis-related burden of disease through improved diagnosis and treatment. Numerous studies have shown that inadequate antimicrobial treatment, based on resistance, underdosing and / or the late start of therapy leads to a dramatic increase in mortality with sepsis. Together with the Institute for Infection Medicine and Hospital Hygiene at the University Clinic of Jena, the CSCC is currently carrying out two multi-centric studies on this focal area. In future, the results of the ongoing projects should contribute to a significantly more tailored use of antimicrobials.

In its “National Active Agent Initiative”, the Federal Government is currently funding pharmaceutical research and development to control infectious diseases. This should boost the development of new anti-infective medicines to be able to secure and further enhance medical care in Germany and worldwide, despite the increased development of resistance. Within the framework of the initiative, the BMBF has already started three funding measures:

1. The funding guidelines for “Diagnostics and new types of therapy to treat bacterial infections” were published in September 2016. The measure funds seven joint projects to develop new diagnostics and five joint projects on new therapy approaches primarily against bacterial infectious diseases.

2. Within the funding guidelines published in March 2017 on “Target validation for pharmaceutical drug development” the BMBF supports a total of 11 joint projects to study target structures for new antimicrobials against communicable and non-communicable diseases.

3. The BMBF funding guidelines “drug development based on natural substances for the control of infectious diseases” were published in March 2018 as the third measure.

The Health Research Forum and its “Value chain” working group, which were initiated in 2015 by the BMBF, explicitly support this effort. The working group has highlighted core problems at the interfaces in the value chain, identified barriers to innovation and built on this by drawing up solution approaches and implementation strategies. Strategies were elaborated to overcome barriers in the health research value chain and agreed at the Health Research Forum on 9th May 2017.

Since early 2016, the BMBF has been providing three-year funding for the collaborative project “Biological or hygienic-medical relevance and monitoring of antimicrobial-resistant bacterial pathogens in clinical, agricultural and municipal wastewater and their significance in raw water” (HyReKa). The interdisciplinary partners have set themselves the goal of qualitatively and quantitatively characterising the entry paths of antimicrobial-resistant bacteria, genes that confer antimicrobial resistance and antimicrobial residues of human or animal origin in the environment (Source Dissemination) and stopping their spread in the environment with suitable technical processes. How it

feeds back to humans through contact with water, wastewater or in clinics should also be studied (Microbial Dissemination). Ultimately, the traceability of antimicrobial-resistant pathogens and resistance genes from wastewater to their places of origin should be tested in accordance with Microbial Source Tracking. The BMBF joint project HyReKA is part of the BMBF funding measure “Risk management of new pollutants and pathogens in water (RiSKWa)” in the funding priority “Sustained water management (NaWaM)”.

In 2014, a cross-institution working group was formedat the MRI. The work of this cross-institution working group at the MRI on antimicrobial resistance focuses on studies on the appearance and characterisation of bacteria with (transferable) antimicrobial resistance in the foodstuff groups milk, meat, grain and fresh plant-based products. This includes precise identification and characterisation of the antimicrobial-resistant bacteria at the phenotypic and molecular levels. Their antimicrobial resistance and the genetic bases for their transfer will be studied, among other things.

At the national level, the MRI, together with the JKI, the TI, the BfR, the BLE and other institutions, is a member of the Human pathogens in plants working group that also cooperates on antimicrobial resistance.

International activities
In 2017, the Joint Programming Initiative on Antimicrobial Resistance (JPIAMR) published an announcement on support for transnational research projects within the ERANET COFUND (JPI-EC-AMR). The focal points of this announcement were prevention, monitoring and intervention strategies to control the development, transmission and infection with antimicrobial-resistant pathogens. 10 projects worth 11.5 million euros were selected, including three with German participation. The projects deal with Antimicrobial Stewardship in hospitals, manure treatment and hygiene in animal stables.

The aim of the newest announcement of the JPIAMR in January 2018 is the development of new targets, antimicrobials and tools against antimicrobial-resistant bacteria on the global WHO priority list including *Mycobacterium tuberculosis*. In total, 14.4 million euros are available. The expert review process is expected to finish in October 2018.

The PanACEA Consortium is dedicated to shortening and improving tuberculosis pharmacotherapy. It is financed by the European and Developing Countries Clinical Trials Partnership (EDCTP) and the BMBF, and LMU München is participating as a German partner.

The consortium can already show its first successes: Capacity-building by carrying out clinical studies in Tanzania, Gabon and Uganda, and carrying out four Phase II and one Phase III studies, and the identification of new antimicrobial candidates. PanACEA has access to a comprehensive portfolio of new antimicrobial candidates for tuberculosis treatment. With the current funding, which began in March 2017, the PanACEA II programme should be able to implement new study designs. The goal is to significantly shorten the duration of therapy. For this purpose, the clinical compatibility and bactericidal effect of two new medicines will be evaluated, and the effect of four new medicine combinations will be tested. In case of success, further clinical studies and medicine development leading to licensing are planned. Additional objectives are the improvement of the participating partners' diagnostic capacities and clinical management.

Until spring 2019, the BMBF will also support five German-African clinic partnerships, which will be funded within the framework of the ESTHER programme financed by the Federal Ministry for Economic Cooperation and Development (BMZ), with additional resources for handling research questions related to antibacterial resistance. The project's goals include collecting and analysing the spectrum of pathogens and their resistance profiles, researching transmission paths and developing action recommendations adapted to local circumstances. The African partner clinics are in Ethiopia, the Ivory Coast, Ghana, Kenya, Rwanda and Tanzania.

Outlook

The Global AMR R&D Hub, which was founded on the initiative of the G20 heads of state and government, will draw up cross-sector recommendations to enable efficient use, agreed upon by its members, of the funds available for AMR research and development. In the process, the Hub will also work with already existing research initiatives in the AMR field, such as GARDP and JPIAMR. The framework for the Hub is set by the WHO's recommendations (e.g. Priority Pathogen List) and other inter-state organisations. The Hub should lead to an increase in overall investment in research and development for AMR.

An interim board with representatives from 15 countries, the EU Commission, the Wellcome Trust, the Bill and Melinda Gates Foundation as well as the WHO and OECD as observers are currently preparing the foundation of the Global AMR R&D Hub. The official launch of the initiative is on 22nd May 2018 in Geneva, on the margins of the World Health Assembly (WHA). A secretariat should support the work of the Global AMR R&D Hub. For the first three years it will be housed at the DZIF. Over the next 10 years, the BMBF will support the Global AMR R&D Hub with up to 500 million euros.

Conclusion

The fight against antimicrobial resistance requires a package of interconnected measures. DART 2020 consolidates the activities required and represents the German framework for combating antimicrobial resistance. During its implementation, the structures successfully established in the last few years will be developed further.

Since publication of the last interim report in May 2017, additional important measures to combat antimicrobial resistance have been initiated. Other measures have been continued, adapted where required and developed further.

DART 2020 follows the One Health approach and takes agriculture into account alongside human and veterinary medicine. Current studies have shown that antimicrobial-resistant pathogens can also be found in the environment. Various research projects that are currently ongoing will bring additional insights that are required to minimise the entry and spread of drug-resistant pathogens into the environment. Here the responsible actors will further intensify their cooperation and in future the environmental sector will be integrated more strongly into the implementation of DART 2020.

Germany also benefits from the exchange of international experience and know-how. Alongside the focus provided within the framework of the German G7 presidency in 2015 and the German G20 presidency in 2017, other fora will also be systematically used to address specific aspects and draw up solution options.

In the years to come, the Federal Government will continue implementation of DART 2020's national and international activities and, by doing so, also contribute to timely implementation of WHO's Global Action Plan.

Legal Notice

Publisher
the Federal Ministry of Health
the Federal Ministry of Food and Agriculture as well as
the Federal Ministry of Education and Research

Contact
Federal Ministry of Health
Public Relations Division
D-11055 Berlin

As at
April 2018

Design
Atelier Hauer+Dörfler GmbH
10117 Berlin

Print
Druckerei des Bundesministeriums für Arbeit und Soziales

Photo
shutterstock.com