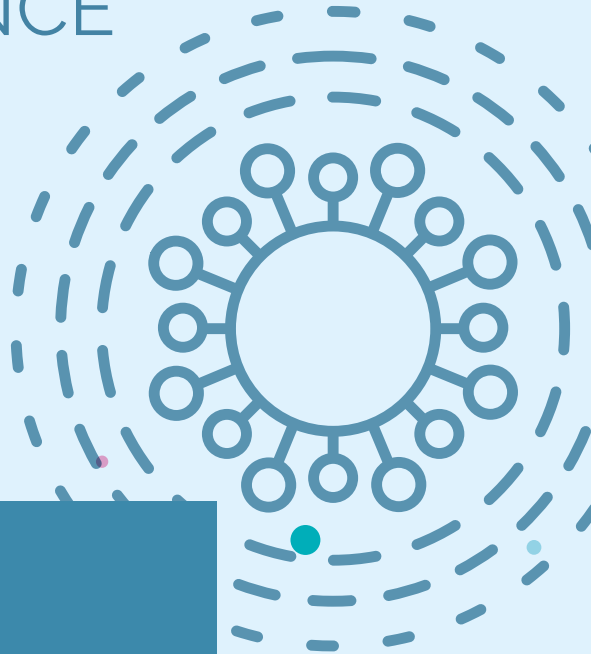




The
Federal Government

AVOIDING ANTIBIOTIC RESISTANCE



DART 2020

Fourth interim report 2019

Introduction

The German Antimicrobial Resistance Strategy “DART 2020” was developed in 2015 by the Federal Ministry of Health (BMG), the Federal Ministry of Food and Agriculture (BMEL) and the Federal Ministry of Education and Research (BMBF). Due to its fundamental significance, it was then approved by the Federal Cabinet. With the DART 2020, Germany set out a national plan of action in 2015, which also complies with that which has been stipulated by the World Health Organisation (WHO) in this area.

The primary goal of DART 2020 is to prevent antimicrobial resistance from occurring and spreading in Germany. A key aspect of this is the “One Health approach” – an interdisciplinary collaboration aimed at combating antimicrobial resistance. The activities which are being carried out to this end within the fields of human and veterinary medicine and the agriculture sector are outlined in the form of six individual goals. This interim report shall pick up on these six goals and present those activities which have been carried out since the third interim report, published in May 2018.

In 2018, following its G20 presidency in 2017, Germany further developed those international activities which were initiated as part of the presidency (for more on this, please see Goals 1 and 6 in particular). Bilateral cooperation aimed at containing antimicrobial resistance were also created and expanded upon as part of the “Global Health Protection Programme” (GHPP). What’s more, a range of pilot projects were initiated at the national level to provide a closer look at into the particular aspects involved in containing the spread of antimicrobial resistance. In addition, the “Global Antimicrobial Resistance Research and Development Hub (Global AMR R&D Hub)”, an international initiative for carrying out research and development (R&D) in the field of antimicrobial resistance (AMR) sponsored by both governmental and non-governmental institutions, was officially launched during the 2018 World Health Assembly.

GOAL 1: Strengthening the One Health approach nationally and internationally

Human health and animal health must be considered as one. Controlling the emergence and spread of antimicrobial resistance can only be achieved through a cross-sector approach.

This requires the close cooperation among 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 global action plan set out by the WHO, the Food and Agriculture Organization (FAO) and the World Organisation for Animal Health (OIE), which emphasises a One Health approach, is the prerequisite for this.

What was achieved

National activities

Zoonoses are caused by pathogens which can be spread from animals to humans and vice versa. By researching zoonoses, we can protect the health of both humans and animals. Since January 2019, the BMG has funded three projects as part of their “zoonoses” funding priority. Among other things, these projects focus on antimicrobial resistance and/or nosocomial infections:

- “The genome-based surveillance of communicable colistin and carbapenem resistance in Gram-negative pathogens” (GÜCCI) By means of two types of antimicrobial resistance which are particularly problematic, among other things, existing methods of analysis should be harmonised and the manner in which epidemiological information is gathered standardised. Doing so would thus enable data to be compared between the animal, food and human sectors.

- “Zoonotic *Clostridium difficile* Infections Acquired in the Community (ZODIAC)”
This project investigates the epidemiological significance and risk factors of the transmission of *Clostridium difficile* in the field of outpatient treatment. This project’s findings are needed in order to be able to develop and/or adapt preventative and control measures.
- “Antimicrobial-resistant pathogens transmitted via pets (AMRPet)”
This project investigates whether pets play a role in humans becoming colonised with ESBL-producing *Enterobacteriaceae* (3MRGN), methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant enterococci (VRE).

As an umbrella organisation for zoonoses and One Health research, the National Research Platform for Zoonoses continues to receive funding from four federal departments: the BMBF, BMG, BMEL and the Federal Ministry of Defence (BMVg). In January 2019, the BMBF declared its intention to provide funding for an additional four years. Pilot and cross-sectional projects – and, most recently, doctoral projects – which deal with the subjects of zoonotic agents and AMR can apply for funding as part of this scheme. For example, as of the end of 2018, the BMBF has been sponsoring a pilot project aimed at establishing a new type of system for visualising and investigating electric impulses in the biofilms of antibiotic-resistant bacteria.

The platform for zoonoses continues to carry out regular workshops. In February 2018, a workshop on “Networking research and public health services – combating AMR together” was carried out in Düsseldorf in cooperation with the Academy of Public Health Services. Another workshop in this series on multi-drug-resistant pathogens in veterinary and human medicine was carried out in February 2019.

In October 2018, the Symposium on Zoonoses Research, an annual event held in Berlin, was hosted jointly for the first time by the platform for zoonoses and the Research Network for Infectious Zoonotic Diseases, which was founded in 2017.

The aim of the research network is to continue to reinforce the One Health approach within research, as well as to build up a closer relationship between research and health services so as to promote a more rapid incorporation of research findings into public health services within the fields of human and veterinary medicine. In order to achieve this goal, the work of the research network has been supported by a coordination project since September 2017. To date, public health service-related projects have been initiated on topics such as the investigation of the occurrence of antibiotic-resistant pathogens in the meat production and processing chain, as well as in environmental samples.

Since early 2019, two groups within the research network have been working together to investigate surface water in the vicinity of pig- and poultry-farming establishments. The water samples are being investigated for the presence of campylobacter and multidrug-resistant pathogens. In doing so, regions with little or no livestock farming (i. e. surface water in conservation areas) shall be included in the study to allow for a comparison.

The “German One Health Initiative (GOHI)”, a platform which networks the Robert Koch Institute (RKI), the Federal Institute for Risk Assessment (BfR), the Paul Ehrlich Institute (PEI) and the Friedrich-Loeffler-Institute (FLI), was also founded. This initiative supports multiple doctoral theses which, among other things, deal with data on AMR in humans and animals and the emergence of resistance. More specifically, the aim of the initiative is to compare resistance data from across the three systems which have been set up to monitor and survey AMR in animals and humans: ARS (Antibiotic Resistance Surveillance), for the human sector, Zoonoses Monitoring (zoonotic agents and commensal bacteria) and GERM-Vet (pathogenic

bacteria), for the veterinary field. Using *E. coli* resistance data from 2014 to 2017 as a model, the aim is to compare the systems and verify the extent to which the patterns of resistance resemble one another.

In their last meeting, the Interministerial Working Group on Antimicrobial Resistance (IMAG AMR) also discussed in great depth the incidence of antibiotics and antibiotic-resistant pathogens in the environment. At this occasion, the project coordinators of the BMBF-research project “Antimicrobial Resistance in the Water Cycle” (HyReKa) presented the initial findings of their research (for more on this, please see Goal 6).

International activities

An “Interagency Coordination Group” (IACG) was established following the high-level meeting on AMR at the United Nations (UN) General Assembly in September 2016 and the passing of a political declaration on AMR. This group is tasked with establishing guidelines for approaches which are necessary to guarantee global measures which can effectively combat AMR in the long term. In April 2019, the IACG reported their recommendations to the UN Secretary-General. Germany played an active role in developing the recommendations through its comments. At the same time, it strongly advocated the reinforcement of the “Tripartite Plus” (collaboration between the WHO, FAO, OIE and UNEP (United Nations Environment Programme)).

As it has done so in the past two years, in 2019, the WHO also used a questionnaire to enquire into the progress made by member states in implementing the global action plan presented by the WHO, FAO and OIE and/or the corresponding national action plans for combating AMR. Germany took part in this questionnaire; the results can be viewed in the WHO database.

At the second OIE Global Conference on Antimicrobial Resistance, the Federal Government presented on invitation of OIE secretary-general Monique Eloit the successes of DART 2020, as well as the challenges it raises for the fields of veterinary medicine and agriculture.

In December 2018, the sixth meeting of the Task Force AMR (TFAMR) of the Codex Alimentarius took place in South Korea. It was the second TFAMR meeting under the new mandate given in July 2017. During this meeting, the representatives of Germany supported the European Commission on site by once again advocating during consultations for the ambitious implementation of the mandate as well as convincing the delegations sent by third countries to do the same.

The EU Joint Action “Antimicrobial Resistance and Health Care associated Infections” (JAMRAI), which has been running since 2017, was set up to put the EU Action Plan against Antimicrobial Resistance into practice. Since 2017, the RKI – with financial support from the BMG – has been working on two work packages. In particular, these focus on implementing national AMR action plans and on the consumption of antibiotics. In this context, Germany took part in a country visit to France in October 2018. Plans have been made for Greece to visit Germany in 2019. These country visits, which cover aspects of both human and veterinary medicine, allow for the mutual exchange of experiences in areas which serve the interests of both sides. They supplement the formal One Health assessment visits which are carried out by the ECDC and the EU Commission to combat AMR.

The manner in which the One Health approach is being put into practice in Germany was presented at a meeting of the AMR One Health Network at the European Commission in Brussels in a joint presentation carried out by the BMG and the BMEL.

From 16th–18th October 2018, together with the Bill and Melinda Gates Foundation, Grand Challenges Canada, the Wellcome Trust and the United States Agency for International Development, the BMBF organised the Grand Challenges Meeting in Berlin. During this event, 1,500 scientists and representatives from politics, the economy and civil society came together to discuss how to strengthen global health. A main focus of the conference was the

subject of combating AMR. Particular emphasis was placed on the significance of interactions between humans, animals and the environment when it comes to the development of AMR, as well as on the potential represented by the One Health approach – which is yet to be fully realised. Those participating in the conference used specialist lectures, panel discussions and working groups to take a closer look at the innovative approaches being taken in the field of research and development, as well as at the interdisciplinary cooperations being carried out to prevent, contain and treat AMR.

Germany also continues to be involved in the Global Health Security Agenda (GHSA)'s AMR Action Package, thus also supporting the implementation of the global action plan set out by the WHO, the FAO and the OIE. In 2018, the initiative was extended by another five years. At the same time, the work plans – which have continued to develop since 2014 – were also adapted to the current situation.

Since 2016, as part of the GHPP initiated by the BMG¹, multiple countries in Africa and Asia have received support in establishing microbiological diagnostic procedures for detecting bacterial pathogens and testing them for resistance (see 3rd interim report from 2018). This programme was expanded in January 2019. As part of this expansion, additional projects which – among other things – focus on AMR, were initiated and existing projects were expanded upon. For example, the “Stand-AMR” project aims to develop a prototype for a functional, cost-effective bacteriological diagnostic laboratory in which blood, stool and urine samples, as well as cervical smears, can be tested and antimicrobial susceptibility testing can be carried out in accordance with the WHO's Global Antimicrobial Resistance Surveillance System (GLASS). The laboratory should be designed as a self-contained structure which is capable of functioning without an external electricity and water supply in regions which are difficult to access. The construction of two laboratories is planned to take place in rural regions in Ghana and Mali.

1 <https://ghpp.de/de/>

The BMBF is continuing to support research networks aimed at innovating health in sub-Saharan Africa. The “African Network for improved Diagnostics, Epidemiology and Management of Common Infectious Agents” (ANDEMIA) is also investigating the emergence of AMR in various regions and local settings, as well as the mechanisms through which these emerge, from a One Health perspective.

A range of international research projects deal with the issue of AMR at the interface between human and veterinary medicine. As part of the SASSA (Genetic adaptation of non-typhoid Salmonella within human and animal reservoirs in sub-Sahara Africa) project, supported by the DFG and carried out by the Bernhard Nocht Institute for Tropical Medicine, the RKI and researchers from Tanzania and Ghana, non-typhoid Salmonella from clinical samples taken from both humans and animals in Tanzania and Ghana are being tested for resistance markers, among other things. The project also carries out an extensive teaching programme aimed at building capacity in Africa.

A main aim of the One Health European Joint Programme (OHE-JP)² is to reinforce cooperation between the participating scientific institutions through targeted joint research projects in fields such as AMR and food-borne zoonoses. Against this backdrop, a close cooperation is taking place between the BfR and the RKI, among others:

1. The ARDIG project is investigating the dynamics of AMR in humans, animals, food and the environment in six European countries (United Kingdom, Norway, France, the Netherlands, Germany, Spain), which differ from one another in terms of their consumption of antibiotics, the prevalence of AMR, their climate and management systems and their potential for the transmission of resistance.

More specifically, the aim of this project is to investigate the ecological effects of administering antibiotics to humans, animals and their environment as part of a One Health approach.

2 <https://onehealthjep.eu/>

This will enable a better understanding of types of resistance, their prevalence and how they vary in different populations over the course of time, allowing for the occurrence of multidrug-resistant bacteria to be monitored more easily. Furthermore, the work carried out as part of this project will contribute towards overcoming the limitations presented by comparing data from different sectors and countries.

2. As part of the NOVA (Novel approaches for design and evaluation of cost-effective surveillance across the food chain) project, the RKI – together with national and international partners – is investigating opportunities for identifying the transmission of pathogens via food more quickly.

The results from these projects should contribute to identifying factors which influence the transmission of AMR between animals, humans, food and the environment. This should not only serve as a basis on which to improve existing national surveillance, but also as one on which to develop new or improved global surveillance strategies for AMR, as well as for risk and transmission models aimed at evaluating future control measures and reducing those risks which come about as a result of AMR.

Outlook

In addition to its involvement in JAMRAI work packages through the RKI, the BMG is also represented in the Advisory Committee. The Advisory Committee's task is to strategically advise JAMRAI's General Assembly and the Executive Board, as well as to guarantee that the results of the Joint Action are taken into account when developing and implementing national AMR strategies. For this reason, the Advisory Committee is primarily made up of individuals who represent ministries. In March 2019, the BMG assumed chairmanship of the Advisory Committee on behalf of Germany.

Plans are currently underway to invite both the European Centre for Disease Prevention and Control (ECDC) and the European Commission (DG SANTE – the Directorate-General for Health and Food Safety) to Germany for a joint “One Health Country Visit” to discuss AMR issues. This visit aims to take into consideration all those areas involved in combating AMR and to evaluate these using a standardised method. The report which will be drawn up as a result will contain recommendations concerning the future orientation of Germany’s AMR policies.

The “VetCAB” research project, financed by the BfR, forms the scientific basis for the antibiotics minimisation concept which was introduced in Germany through the 16th amendment to the Medicinal Products Act. Since then, the project has caught the attention of international groups of experts. Thanks to funds provided by the BMG, the replication of this course of action is also being promoted in other countries under the name “VetCAB-International Documentation”. The project was launched at the end of 2018 as a three-month pilot study with partners in Chile, Japan and/or Zambia. The aim is to continue and expand this project in 2019. In doing so, expanding the project is understood to mean both with regard to a species of animal or user group found within a certain country as well as with regard to obtaining additional project partners. To this end, plans have been made for project partners to visit the WHO collaborating centre at the University of Veterinary Medicine Hannover in order to receive on-site training in inputting and evaluating data, as well as to discuss the study design and carry out any adjustments to the database.

As part of the G20 Agriculture Ministers’ Meeting, taking place in May 2019 in Niigata, Japan, Germany will present a report which takes stock of the extent to which those measures for combating AMR have been implemented which were set out in the Agriculture Ministers’ Declaration 2017, where Germany presided over the G20. In particular, this report shall address the fact that antibiotics should only be available upon prescription, as well as the fact that antibiotics should no longer be used as growth promoters.

The work of the Codex Alimentarius' TFAMR will be continued in the form of electronic working groups, in which Germany will play an active role. It will play an equally active role in the next meeting of the TFAMR, which will take place in December 2019.

GOAL 2: Recognising changes in resistance at an early stage

Representative data about the appearance of new pathogens and resistances are 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 continued to develop its laboratory-based Antimicrobial Resistance Surveillance system (ARS)³, which seeks to recognise the development of resistance at an early stage. The increased voluntary participation of laboratories in ARS is a trend which continues to grow. With this, the number of healthcare facilities which are covered by surveillance has also risen. In 2017, ARS combined data from 483 general hospitals. This amounts to 30 percent of all general hospitals. In the field of outpatient care, ARS evaluated resistance data from 18,129 doctor's practices. What's more, over the past three years, coverage has been greatly increased in those federal Laender which – until recently – tended to be under-represented. This has further strengthened the basis for a regional analysis of AMR data in Germany.

3 <https://ars.rki.de/>

In addition to participating in the European Antimicrobial Resistance Surveillance Network (EARS-Net), Germany has also transferred ARS data to the WHO's surveillance system (Global Antimicrobial Resistance Surveillance System – GLASS) since its inception (2016).

With the aim of improving laboratory diagnostics and the data situation surrounding gonococcal resistance in Germany, the BMG continues to support the Gonococci Resistance Network (GORE-NET)⁴ collaborative project being carried out between the RKI and the Consultant Laboratory for Gonococci. The data on gonococcal resistance in Germany which are obtained as part of this project form the basis for any evidence-based updates which are made to the AWMF's therapeutic guidelines on gonococci, as well as the therapy strategy that it recommends as part of these guidelines.

Both AMR monitoring programmes – (a) for zoonotic agents and commensal germs in the food chain (BfR) and (b) for animal pathogens (at the Federal Office of Consumer Protection and Food Safety, BVL) – have been continued. The results of these programmes have been published in written reports and presented in numerous presentations, on both a national and an international level. Additionally, the working group for AMR, which is attached to the BfR and BVL, developed an overview of the situation surrounding AMR and the use of antibiotics in farming and the food chain. This overview was published on the BMEL website⁵. Here, previously published data from 2011 to 2017 are combined in an overview which depicts various developments and trends in the use of antibiotics on animals. Among other things, it depicts the trend in resistance rates, which is, to some extent, decreasing.

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

5 https://www.bmel.de/SharedDocs/Downloads/Tier/Tiergesundheit/Tierarzneimittel/La-gebild%20Antibiotikaeinsatz%20bei%20Tieren%20Juli%202018.pdf?__blob=publicationFile

The second regulation amending the Regulation on Veterinary Pharmacies (TÄHAV), which came into force on 1st March 2018, includes the obligation to carry out antibiograms in specific cases, and also provides a framework for carrying these out. In the months after the TÄHAV came into force, associations, professional organisations and the BVL published documents explaining provisions, guidelines for sampling, sources for method protocols and the corresponding statutory limits required for interpreting the results of an antibiogram.

Outlook

Both AMR monitoring programmes which were established in the field of veterinary medicine were continued. The BfR is continuing to cooperate with a working group established by the European Food Safety Authority (EFSA). The aim of this group is to establish a scientific basis for the further development of resistance monitoring for zoonotic agents and commensal germs.

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 of targeted intervention measures and offers support for an assessment of their effectiveness.

What was achieved

Together with the Charité University Hospital, the RKI has built up a higher-level Antimicrobial Consumption Surveillance (AVS) system for hospitals. This aims to support hospitals when carrying out antimicrobial consumption surveillance in accordance with legal requirements, as well as when it comes to carrying out local

Antibiotic Stewardship (ABS) activities⁶. A total of 397 hospitals and rehabilitation facilities have registered with the system since the project began in 2014. Reference data from more than 180 institutions have been made publicly available in an interactive database on the AVS homepage. The database contains consumption data from general emergency hospitals which date back to 2015. The information is sourced from hospitals which have transferred data to AVS for at least one year, and comprises hospitals which provide primary and basic care as well as those which provide specialist and maximum care. Since the end of 2017, the database has also collected information on supply bottlenecks for antibiotics.

As part of the ARVIA (Antimicrobial Resistance and Consumption – an integrated Analysis) project, which is financially supported by the BMG, a model has been developed which allows for data from both the AVS and ARS (see Goal 2) surveillance systems to be analysed in relation to one another⁷. The first three-year phase of the project was completed in December 2018. Among other things, this phase was responsible for creating a new professional and content-based concept for ARVIA, establishing technical requirements for combining data from ARS and AVS, and piloting ARVIA at the first hospitals. The pilot testing demonstrated that there was still a need for improvement in terms of data quality and possibilities for analysis. As part of a second project phase, ARVIA will receive additional funding from the BMG until 2021. This will allow for it to be further developed in terms of its technology and content, and particularly with regard to the analysis it provides. ARVIA is already available online for anyone who is interested in taking part.

The regulations concerning reimbursement of the costs of diagnostic procedures were improved. The Evaluation Committee passed a resolution for adapting the uniform assessment standard (EBM) for medical services. With effect from 1st July 2018, new methods

6 <https://avs.rki.de/>

7 <https://ars.rki.de/Content/ARVIA/Main.aspx>

for identifying pathogens and testing for resistance were included within doctors' fee schedules. This allows for adjustments to be made to keep up with the latest scientific developments. In order to allow a clear distinction between bacterial and viral infections, the biomarker procalcitonin will be entered into the catalogue. Procalcitonin allows for a reduction in the use of antibiotics, particularly when it comes to infections of the respiratory tract – which are usually caused by viral pathogens and which are often unnecessarily treated with antibiotics. In addition, extrabudgetary funds will be used to remunerate the costs of the PCT test for three years, with no limit on quantity. In addition, the laboratory diagnostics for antimicrobial therapy will be taken from the profitability management.

The project “Ambulatory parenteral antibiotic therapy in the Cologne Metropolitan Region”, which is supported by the innovation fund, investigates the extent to which intravenously-supplied antibiotics can be administered in the home setting by a care person or the patient themselves. It would be beneficial if the patient were able to stay in their home environment despite undergoing therapy, and if they did not have to go into hospital.

In the field of human medicine, there are clear regional and age group-specific differences in how antimicrobials are prescribed. The causes of this are not completely understood. In February 2019, the BMG commissioned the Leibniz Institute for Prevention Research and Epidemiology – BIPS GmbH – with carrying out a study to identify the factors which influence the prescription of antimicrobials. The aim is to use the results of the study to develop measures which promote the prudent use of antimicrobials.

The amount of antimicrobials supplied by pharmaceutical companies and wholesalers to veterinarians is a statistic which has been recorded in Germany since 2011. This is a practice which has been continued. By 2017, these figures had dropped by 57% to 733 t.

Together with the BfR and the BVL, and supported by the company SAFOSO AG, the BMEL has compiled a report evaluating the effectiveness of the measures prescribed by the antibiotics minimisation concept, introduced through the 16th amendment to the Medicinal Products Act (AMG). The basis for this is the obligation to evaluate these measures in accordance with § 58g of the Medicinal Products Act. To this end, the Laender data reported by animal keepers for their animals from July 2014 to December 2017, and the antimicrobial treatments which were carried out on said animals, have been evaluated centrally by the BfR since March 2018 as part of the antibiotics minimisation concept. In doing so, official data from across Germany concerning the quantity of antibiotics which are actually consumed and the frequency of therapy carried out using specific classes of drugs have been made available for the first time for those types of animals which are subject to the antibiotics minimisation concept.

In summer 2018, a survey of animal keepers and veterinarians was carried out on behalf of the BMEL. This dealt with various aspects related to the 16th amendment to the AMG. The information obtained from evaluating data, the survey and a report compiled by the Laender on the enforcement of the 16th amendment to the AMG will be correlated with the results of the annual record of the dispensation quantities of antibiotics, as well as the results of both AMR programmes. These correlations were presented in an evaluation report and presented alongside the conclusions derived.

Following a long, intense series of negotiations at the EU level, the EU regulation on veterinary medicinal products and the EU regulation on the use of medicated feed came into force on 7th January 2019. Both regulations are to be applied by all member states by 28th January 2022. During the consultations in Brussels, the BMEL strongly advocated for regulations concerning a more restrictive use of antimicrobial veterinary medicinal products and explicitly welcomes the various measures which have been introduced with regard to the prudent and responsible use of

antimicrobial veterinary medicinal products. For example, these new regulations prohibit the future prophylactic use of antibiotics in groups of animals across the EU. The metaphylactic use of antimicrobial veterinary medicinal products will also be regulated more strictly in the future. With the new Regulation (EU) 2019/6 on veterinary medicinal products, EU legislators have laid down directly applicable, harmonised rules for veterinary medicinal products for the very first time. These rules make provisions for specific antibiotic agents to be reserved for treating people in the future. They contain regulations for a graded approach towards the collection of data on antimicrobial medicines which are used on animals across the EU.

Outlook

Although around 85% of all antibiotics in the outpatient sector are prescribed, to date, there is no comparable surveillance system for monitoring the consumption of antibiotics in the hospital sector which contains a structured feedback mechanism. A feasibility study for establishing such a system is being carried out at the RKI as part of a project supported by the BMG. The SAMBA (Surveillance of outpatient antibiotic consumption) feasibility study was launched in February 2019 and will run for three years.

Following the submission of the above-mentioned evaluation report on the effectiveness of the measures included within the 16th amendment to the AMG's antibiotics minimisation concept, the consequences thereof – including with regard to potential changes to the legal situation – will need to be discussed.

When the 16th amendment to the AMG came into force, many indications showed that the “veal calf” type of production was not differentiated enough. For this reason, a research project was launched which aims to characterise the various forms of calf rearing in Germany more closely, particularly with regard to the use of antibiotics, the feeding system and the resistance profile.

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 in hospitals and professional livestock owners is a crucial part of this. But timely diagnosis is also important in order to better target the use of antimicrobials and prevent the spread of resistant pathogens. Regional networks for the prevention and monitoring of multidrug-resistant infective agents can help identify and overcome local application obstacles and implementation problems.

What was achieved

The Commission for Hospital Hygiene and Infection Prevention (KRINKO)⁸ has set out recommendations aimed at recognising, preventing and combating nosocomial infections. Taking current analyses of the epidemiology of infectious diseases into account, these recommendations are constantly updated and developed further in order to keep them in line with the latest advances in medical science. KRINKO's recommendation on the "Prevention of surgical site infection" was revised and updated against this background; it was published in April 2018.

Another key aim of KRINKO's recommendations is to reduce the spread of pathogens with particular resistances in hospitals and other medical and care facilities. To this end, KRINKO created a recommendation for the prevention of infections caused by enterococci which exhibit special antibiotic resistance (e.g. vancomycin-resistant enterococci, VRE), which was published in October 2018. In addition, KRINKO is currently working on a recommendation for the prevention of *Clostridium difficile* infections (CDI). This is expected to be published in summer 2019.

Regional multidrug-resistant pathogen networks have been established in order to improve the exchange of knowledge and information when it comes to dealing with multidrug-resistant pathogens in medical facilities (hospitals, rehabilitation facilities, care home, doctor's practices, nursing services, etc.). These are moderated by the public health services. The RKI regularly organises a scientific symposium to support the moderators of the regional networks in exchanging their experiences.⁹ The sixth meeting of the multidrug-resistant pathogen network moderators took place at the RKI in November 2018 under the main topic of "vancomycin-resistant enterococci". A report on the meeting was published in July 2019.

In May 2017, the World Health Assembly passed a resolution on sepsis which was initiated by Germany. The resolution on sepsis places a series of demands on member states which include: improved awareness, particularly with regard to the early symptoms of sepsis; an increase in vaccination rates; reinforced infection prevention; the promotion of research and development into vaccinations; preventative measures; diagnostics and therapeutic substances; and increased measures for combating AMR. The BMG has already supported measures such as these for a long time, for example by increasing vaccination coverage as part of its national vaccination plan. Equally, the measures set out in the DART 2020 for preventing infection or the prudent use of antibiotics contribute towards avoiding cases of sepsis and/or improving the treatment thereof. In addition, multiple projects supported by the innovation fund deal with key issues, for example improving quality in the management of sepsis in hospitals or the provision of care in secondary complications of sepsis. Additionally, the RKI is working with the WHO to create a systematic review on the burden of disease of nosocomial sepsis. This review should be published in late 2019.

9 https://www.rki.de/DE/Content/Infekt/Krankenhaushygiene/Netzwerke/Netzwerke_node.html

Another project – also financed by the innovation fund – will, over the course of four years, investigate the effects of prevention strategies both horizontal, i.e. concerning all pathogens, and vertical, i.e. effective only for individual pathogens, which aim to prevent the spread of multidrug-resistant Gram-positive pathogens such as methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant enterococci (VRE). The aim of this project is to improve patient care through the more effective and efficient prevention of MRSA and VRE.

In Germany, the Standing Committee on Vaccination¹⁰ (STIKO), located at the RKI, develops national recommendations for the use of vaccines. This also includes recommendations for which vaccinations should be mandatory for staff employed in medical facilities – both to protect the employee and to avoid nosocomial infections (protection of third parties). A new working group for the vaccination of medical staff was established by STIKO in 2018.

The RKI also continues to collaborate with the Federal Centre for Health Education (BZgA) on the “We’ll beat the flu” national awareness campaign surrounding the influenza vaccination, as well as on “impfen60+”, a project supported by the BMBF.¹¹ In 2018, more than 140 clinics took part in the “OKaPII”¹² study, a national monitoring scheme for monitoring the vaccination coverage of medical staff in clinics which was initiated by the RKI.

10 <https://www.stiko.de>

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

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

Outlook

In addition to the measures for implementing the sepsis resolution which are already up and running, the BMG is also planning further research projects aimed at supporting the implementation of the sepsis resolution. In addition, it is planning to increase awareness and carry out more public relations work on the issue of sepsis.

The hygiene promotion programme, introduced in 2013, supports hospitals when it comes to hygiene personnel staffing which complies with the Infection Prevention Act. In 2016, this programme was expanded and its term prolonged. Since then, the training in infectiology and consultancy services provided by infectiologists are eligible. Plans are underway to prolong the programme by another three years. It is currently being examined which adjustments to the subsidies are required to cover the needs as best as possible.

In a joint project being carried out by the BfR and the German Poultry Association (ZDG), which began in 2019, scientists from the BfR are evaluating data from antibiotics monitoring programmes and the German slaughter poultry industry's disease surveillance programme for chickens and turkeys. The aim is to use this information in the BfR's risk analysis and, where necessary, to identify potential weak spots. This has the potential to make a large contribution towards evaluating and communicating risks.

GOAL 5: Raising awareness and strengthening skills

Relevant knowledge is the prerequisite for the proper use of anti-microbials 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

With the support of the BMG, the workshop “Rational use of antibiotics in the outpatient sector”, run by the RKI, took place in Berlin on 28th November 2018. The workshop was an opportunity for people who are active in this field to network and exchange ideas, as well as to identify courses of action specifically aimed at increasing awareness of the problems surrounding AMR within the outpatient sector. Four working groups discussed the subjects “surveillance of antibiotic consumption”, “training in rational antibiotic treatment”, “effective interventions to reduce antibiotic consumption” and “the use of technical applications to manage the rational use of antibiotics” – all with a focus on the outpatient sector. The report, which was compiled as a result of this workshop, contains starting points for further measures to be carried out in this field.

In autumn 2018, the BMG provided information on measures for preventing infection and the prudent use of antibiotics as part of a social media campaign which lasted several weeks. This was carried out to mark Global Handwashing Day on 15th October, European Antibiotic Awareness Day on 18th November and World Antibiotic Awareness Week.

In addition to providing support for improving opportunities to gain the additional qualification of “infectiology” into all clinical subject areas, the Commission on Anti-Infectives, Resistance and Therapy (ART)¹³ is also working together with professional organisations and the German Medical Association to further develop Antibiotic Stewardship (ABS) programmes within hospitals.

In autumn 2018, the BfR once again hosted its well-established symposium on AMR in the food chain. The programme followed the One Health approach and featured the latest findings from human medicine, veterinary medicine and the environmental sector.

As part of the evaluation of the 16th amendment to the AMG, animal keepers and veterinarians were asked about their experiences in implementing the antibiotics minimisation concept (see also Goal 3). In January 2019, in order to be able to once again clarify individual questions through direct discussion, the BMEL arranged a workshop for all those who participated in the survey. One result of this process is that a large majority of veterinarians and animal keepers have been made aware of the problems presented by AMR and of the careful use of antibiotics. The legislation concerning the use of antibiotics on animals has also made a significant contribution towards achieving this outcome.

Outlook

A key focus for the coming years will be placed on increasing awareness among the general population, as well as on increasing awareness among medical staff when it comes to measures for avoiding nosocomial infections. Therefore, starting in 2019 target group-specific information and awareness campaigns will be carried out among the general population. It should also allow for campaigns to be carried out among medical staff which promote the prevention of infections, e.g. through increasing vaccination coverage, and which address hospital hygiene and AMR in particular.

13 https://www.rki.de/DE/Content/Kommissionen/ART/ART_node.html

GOAL 6: Supporting research and development

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

As of February 2017, the BMG supports seven projects under the funding priority “antimicrobial resistance and nosocomial infections” for a period of three years. In 2018, World Antibiotic Awareness Week from 12th–18th November and European Antibiotic Awareness Day on 18th November were taken as an opportunity to arrange a workshop in which the funded projects – halfway through their terms – would be able to present their initial findings and take part in scientific exchange. Methodological workshops which took place as part of the event were used to take a separate look at individual focus areas which were of particular interest. The results of this discussion are also contributing towards the creation of additional measures for implementing DART 2020.

As part of its “Twenty20 – Partnership for innovation” programme, the BMBF is supporting the “InfectControl2020” consortium with approximately 45 million euros. Here, universities, non-university research institutes, a range of industrial partners and the departmental research institutes BfR, FLI and RKI are involved in approximately 35 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 interdisciplinary research programme, different professional groups – such as doctors, biologists, veterinarians, materials scientists or architects – are developing approaches for preventing the emergence and spread of multidrug-resistant bacteria and treating patients more quickly and successfully. One of the consortium’s biggest projects is dedicated to the responsible use of antibiotics via information and communication, RAI for short.

Since the beginning of 2016, another collaborative project supported by the BMBF has been dealing with antibiotic-resistant bacteria in the environment – the “biological respectively hygienic-medical relevance and monitoring of antimicrobial-resistant pathogens in clinical, agricultural and communal waste water and its significance for raw water” (HyReKA). Here, the interdisciplinary partners have set themselves the target of qualitatively and quantitatively characterising the emission pathways of antibiotic-resistant bacteria, antibiotic resistance genes and traces of antibiotics from humans or animals to the environment (source dissemination) and of interrupting their spread into the environment through suitable technical measures. Equally, research shall also be carried out into how this feeds back to humans through contact with water or waste water or in clinics (microbial dissemination). Finally, the project aims to verify the traceability of antibiotic-resistant pathogens and resistance genes from waste water with regard to their original sources by performing microbial source tracking. The joint project will run until the end of 2019; however the researchers already presented their most important results to the public in Berlin at the beginning of April 2019. The initial findings of the project show a correlation between concentrations of antibiotic active agents and their abundance of resistant facultative pathogenic bacteria in waste water. In addition, discharge from combined sewer overflows exhibits similarly high numbers of resistant bacteria and resistance genes to those found in untreated waste water. In addition, resistant bacteria and resistance genes were

found in sewage treatment plant outflows. At the same time, it is necessary to make a distinction between sewage treatment plant outflows in a mixed rural and urban context and those in a purely urban context which are influenced by clinical waste water. In outflows of municipal sewage plants with or without influence of clinical waste water, different antibiotic drug spectra were found. Furthermore, sewage plants with influence of clinical waste water showed more complex and critical patterns of resistance (a higher incidence of 4MRGN with resistance to carbapenems (second-line antibiotics)). In addition to this, colistin resistance (*mcr-1*) genes (second-line antibiotic) were more frequently found in waste water from poultry processing plants.

In order to prevent the spread of AMR, and with the aim of protecting public health, an enhanced form of waste water treatment could be meaningful at selected sewage treatment plants. Continuing to process waste water from clinical departments with a high antibiotic usage and sewage from the meat processing chain and the retrofitting of sewage treatment plants that discharge into sensitive waters (such as bathing water, sewage treatment plants in the vicinity of raw water supply points) could prove to be worthwhile. Some anecdotal evidence does exist in this regard, but closer investigation is required. Ultrafiltration processes are more suitable for reducing resistance genes and resistant bacteria than processes which use ozon or UV radiation. For the simultaneous reduction of antibiotic residues (and other trace substances), however, process combinations are required. One aspect which is particularly relevant to hygiene concerns the frequent detection of multi drug-resistant strains of bacteria in aeroplane toilets.

The BMBF joint project HyReKA is part of BMBF's "Risk management of new harmful substances and pathogens in the water cycle (RiSKWa)" support measure within its "Sustainable water management (NaWaM)" funding priority.

As part of its “Clinical studies with high relevance for patient care” funding priority, the BMBF supports multicentric, prospective, controlled clinical studies which are aimed at proving the effectiveness of therapy concepts. This includes multiple studies on antibiotic treatments, e.g. on the significance of a particular genotype for preventing infectious complications such as spontaneous bacterial peritonitis in cirrhosis of the liver. Another study is testing the hypothesis that patients with an acute exacerbation of chronic obstructive pulmonary disease suffer no disadvantage when not given an antibiotic in addition to the standard therapy. This was re-announced as a funding priority in March 2019.

Since 2012, the BMBF has supported the clinical research group for clinical infectiology which carries out research in the field of infections caused by multi drug-resistant pathogens at Jena University Hospital. On 1st January 2018, the structure – which began as a research group – was transferred to an independent Institute for Infectious Medicine and Hospital Hygiene at Jena University Hospital. This has successfully stabilised those structures at Jena which are involved in clinical research into AMR bacteria. Some examples of topics being researched here are the development of a technique for measuring the concentration of antibiotics in blood, or the search for substances which destroy bacterial biofilms. The BMBF is supporting the work of the infectious medicine specialists at Jena until the beginning of 2020 with a total sum of more than 4 million euros.

A centre with expertise in the field of sepsis has also been established in Jena in the form of the Center for Sepsis Control and Care (CSCC). The aim of the CSCC is to reduce the burden of disease of sepsis through improved diagnostics and treatment (see 3rd interim report from 2018). Funding for the CSCC will cease in 2020. Results from the clinical studies which are currently being carried out at the CSCC are expected at the end of the funding period.

Together with the Leibniz Institute of Photonic Technology (Leibniz IPHT), the Biophotonics core unit at the CSCC was able to develop a light-based process which enables pathogens to be diagnosed quickly and cost-effectively. Within three and a half hours, the new quick test provides information on which available antibiotic would still be effective in this specific case. This enables the success rates of therapies for multidrug-resistant bacteria to be improved and also reduces the unnecessary use of antibiotics.

The Federal Government is currently funding pharmaceutical research and development into combating infectious diseases in the form of its “National Active Agent Initiative”. This initiative aims to boost the development of new anti-infective medicines for the purposes of guaranteeing and further enhancing medical care in Germany and around the world, despite increased antibiotic resistance. The BMBF has already begun three support measures which form part of this initiative (see Interim Report 2018).

In March 2018, the third BMBF funding guideline “Drug development based on natural substances for combating infectious diseases” was published. The projects derived from these measures will begin in early 2019. Due to the positive reception of the second guideline published in March 2017 to promote “Target Validation for the Pharmaceutical Drug Development”, it was re-launched in February 2019.

International activities

In 2018, the European Commission’s Joint Programming Initiative on Antimicrobial Resistance (JPIAMR) published three bulletins to promote transnational research projects into AMR. The call for transnational research partnerships was on the subject of “new targets, compounds and tools; fundamental, translational research, with the exception of clinical trials”. Ten projects were selected to receive a share of the 12.8 million euros in funding, eight of which featured German researchers. These projects are concerned with developing new strategies to fight bacteria which are on the WHO priority list – including *Mycobacterium tuberculosis*. In addition,

there were two calls to found transnational networks on the subjects of surveillance and the JPIAMR's virtual research institute. Four of the 18 total networks which were selected will be led by researchers from Germany. The networks met for an introductory workshop on 19th/20th February 2019. The aim of this workshop was to allow them to identify common activities.

JPIAMR's latest announcement, from December 2018, is aimed at improving the diagnosis and surveillance of antibiotic-resistant bacteria: Projects which develop new tools, technologies and methods for global use can receive funding of up to 20.06 million euros in total. The involvement of new funding agencies will, for the first time, entitle research groups from low- and middle-income countries in Africa and Asia to submit applications for funding. The proposal review process is expected to be completed in October 2019. To date, the BMBF has provided approximately 6.6 billion euros for research projects carried out by German researchers in JPIAMR networks.

Since 2009, the European and Developing Countries Clinical Trials Partnership (EDCTP) and the PanACEA consortium, financed by the BMBF and featuring the LMU Munich as a German partner (see 3rd interim report from 2018), has been dedicated to improving medication therapy for tuberculosis, as well as to shortening the duration thereof. BMBF will continue to support PanACEA.

As part of the ESTHER programme, financed by the Federal Ministry for Economic Cooperation and Development (BMZ) and the BMG, the BMBF will be supporting five German-African clinic partnerships until autumn 2019. The African partner clinics are located in Ethiopia, Ivory Coast, Ghana, Kenya, Rwanda and Tanzania. The research funds will be used to address questions on AMR. Among other things, the aim of the project is to collect spectra of pathogens and their resistance profiles, to research transmission routes, and to develop recommendations for action which are adapted to meet local conditions.

In addition, the scientists from the individual projects have networked in order to collect compatible data and develop solutions as a team.

Since October 2018, the BMBF has been supporting the research and development portfolio of the Global Antibiotic Research and Development Partnership (GARDP) with a total sum of 50 million euros. GARDP is a joint initiative from the Drugs for Neglected Diseases initiative (DNDi) and the WHO. GARDP is a not-for-profit research and development initiative which develops new treatments for bacterial infections. Its main focus is on infections which are frequently caused by pathogens with AMR or for which only inadequate treatment is possible. The BMBF supports four research programmes carried out by GARDP.

All programmes primarily address needs in the field of public health, taking into account measures to ensure sustainable, fair and affordable access to those substances which are developed in the course of these programmes.

In 2019, the BMBF joined the “CARB-X” initiative, an international public-private partnership whose aim is to accelerate the development of innovative antibiotics and other therapeutic substances, vaccinations, rapid diagnostic tests and devices for combating drug-resistant bacterial infections. The BMBF will support this global partnership for the next four years with the sum of approximately 40 million euros. This funding includes supporting a so-called “CARB-X-Accelerator”. This is a cooperation between the German Center for Infection Research (DZIF), the Federal Institute for Drugs and Medical Devices (BfArM) and the PEI which advises German and European researchers and companies who are applying for funding opportunities from CARB-X or who have already received funding from CARB-X. The CARB-X Accelerator assists applicants and projects in an advisory capacity when it comes to scientific and regulatory issues and problems, and also accompanies researchers along the path to potential CARB-X funding.

The Global AMR R&D Hub was founded following the G20 Summit in 2017. This was done on the initiative of the G20 heads of state and government. Currently, this hub is made up of 15 countries, the European Commission, the Wellcome Trust and the Bill and Melinda Gates Foundation, with the WHO, OIE and OECD acting as observers. The main goal of the Global AMR R&D Hub is to develop general recommendations in order to allow its members to use the funding available for research and development into AMR – in a manner which is efficient and which has been agreed upon by the members themselves. In addition, it is on this basis that the total investments made in carrying out research and development on AMR should be further increased. Provisions have not been made for the Global AMR R&D Hub to carry out its own calls for proposals or funding activities. The hub follows the One Health approach and will encompass aspects from the fields of human medicine, veterinary medicine and the environment. The Global AMR R&D Hub will follow the recommendations given by the WHO and other relevant organisations with regard to its activities and analyses. Over the next 10 years, the BMBF will contribute towards fulfilling the goals of the Global AMR R&D Hub by providing up to 500 million euros in funding.

During the first three years of its existence, the secretariat of the Global AMR R&D Hub was based at the DZIF in Berlin. Germany agreed to bear the costs of the secretariat during this time. An initial work programme for 2018–2020 was approved in September 2018 and should now be implemented without undue delay. A key element of the work plan is the creation of a “dynamic dashboard”, a database which displays up-to-date information on the flow of funding and R&D activities which are within the remit of the hub. Preliminary information should be published on the dashboard at the end of 2019.

Outlook

In December 2018, the BMBF and the French Ministry for Higher Education, Research and Innovation (Ministère de l'Enseignement supérieur, de la Recherche et de l'Innovation, MESRI) published a joint announcement declaring their support for collaborative German-French projects aimed at researching AMR. This measure has created funding for collaborative German-French projects to be carried out on microbiome-based prevention and treatment strategies, as well as on antibiotics with new effect mechanisms. In addition, research into the emergence and spread of AMR, as well as into the burden of disease with antibiotic-resistant pathogens, or into investigating pathogenic mechanisms, the development of diagnostic methods and treatment strategies for resistant fungal infections is also eligible for funding as part of this measure.

In 2019, the BMBF will initiate a “research networking platform for global health” in order to fundamentally strengthen German research into the field of global health. The networking platform aims to build up an overarching structure which provides researchers with support when it comes to improved networking across disciplines, working together more effectively, and making an efficient, sustainable contribution to solving global health issues. In particular, the platform aims to provide researchers from disciplines which, up to now, have not been prominently represented in health research in Germany (e.g. social sciences, public health) with the opportunity to make a substantial contribution to research.

Over the coming years, the BMBF will increase the amount of financial support it provides with regard to capacity building and promoting young researchers who are undertaking research into the field of infectious diseases in Germany. The corresponding funding guidelines are expected to be published in 2019.

Conclusion

The fight against AMR demands a combination of different measures. By passing the global action plan to tackle AMR at the 2015 World Health Assembly and the Political Declaration on AMR at the UN General Assembly in 2016, member states have committed themselves to developing national action plans. The key elements which make up these action plans (surveillance, the prudent use of antibiotics, infection prevention and control, research and collaboration on the basis of the One Health approach) are specified in the global action plan on AMR drafted by the WHO, the FAO and the OIE and must be underpinned by measures which have been adapted to the specific situation in each country.

However, the decisive factor here is not the creation of these national action plans, but rather their strict implementation. This present report represents the fourth interim report which has been compiled since the DART 2020 was published in 2015. Taken as a whole, the interim reports depict the progress which has been made in implementing the DART 2020 since May 2015, thus demonstrating the continuously high priority which the Federal Government has placed on combating AMR.

Since 2018, more important activities have been carried out. With regard to humans, these activities involve aspects such as the outpatient sector, which is becoming increasingly more involved. The measures which have been initiated in this sector will be continued over the coming years. The key focus of activities carried out in the field of veterinary medicine and agriculture was on evaluating the effectiveness of the antibiotics minimisation concept, which was introduced in the 16th amendment to the AMG.

The DART 2020 is scheduled to end in 2020. Both the special health policy importance of the topic “AMR”, which has high priority for the Federal Government, as well as international commitments to implement the global action plan, e.g. in the context of G7 and G20 agreements, as well as EU Council conclusions, argue that a continuation of this successful strategy is needed. In order to not only take stock from a national point of view with the interim reports, the Federal Government has invited the ECDC and the EU Commission to a joint “One Health Country Visit”. This independent expertise can help to identify which measures have been particularly successful and could be exemplary for others. Their recommendations may, if appropriate, be used to decide which established measures should be continued or modified and which new measures should be taken.

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