

WORLD HEALTH ORGANIZATION



COLLABORATING CENTRE

FOR RESEARCH AND TRAINING FOR HEALTH AT THE HUMAN-
ANIMAL-ENVIRONMENT INTERFACE

AT THE UNIVERSITY OF VETERINARY MEDICINE HANNOVER

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1 State of the WHO Collaboration Centre for Research and Training for Health at the Human-Animal-Environment Interface

1.1 Personnel and re-designation

The work on the scientific tasks of the WHO Collaboration Centre for Research and Training for Health at the Human-Animal-Environment Interface (WHO CC HAEI) was carried out by the employees of the Institute for Biometry, Epidemiology and Information Processing.

The Department of Food Safety and Zoonoses of the WHO headquarters is currently responsible for the cooperation between WHO and our institute. The contact persons are Dr. Awa Aidara-Kane and Dr. Jorge R. Matheu Alvarez.

After intensive consultation with the WHO beginning in the fall of 2014, an application for re-designation as WHO CC HAEI was submitted in spring 2015, which was approved in a letter dated December 15, 2015. The current period of re-designation started on December 17, 2015 and ends on December 17, 2019.

1.2 Terms of reference

With the re-designation requested in spring 2015, the terms of reference for basic, advanced and follow-up training as well as research at the human-animal-environment interface was redesigned in coordination with the WHO and structured as follows:

1. Studying antibiotics use and resistance in animal populations to assess its impact on resistance in humans;
2. Studying animal health and animal welfare as the basis for improving human health (with a focus on food-borne infections in humans);
3. Methods for regional, national and global strategies for surveillance, prevention and control of zoonoses and food-borne infections.

2 Research

The WHO CC HAEI conducts research activities in several areas. In 2017, the main focus was set on the collaboration with partners from other scientific disciplines. Research and training in the field of animal health, zoonoses and antibiotic resistances represent the core of our work. These activities are directly linked to the work of the WHO Advisory Group on Integrated Surveillance of Antimicrobial Resistance (AGISAR).

The following short reports summarize all of the projects performed by the institute. Projects which could only be conducted with the additional support from the WHO CC HAEI are indicated separately.

2.1 The research consortium RESET: "*ESBL and Fluoroquinolone Resistance in Enterobacteriaceae*"

Enterobacteriaceae play an important role in the spread of antimicrobial resistance. Caused by the production of extended spectrum beta-lactamases (ESBL) and (fluoro-) quinolone, resistance to beta-lactam antibiotics presents new resistance characteristics which dramatically restrict therapeutic possibilities in veterinary and human medicine.

The RESET consortium consists of nine partners and 13 associated partners from human and veterinary medicine, basic and applied research and epidemiology. RESET includes different complementary studies on factors linked to the spread of emerging resistance characteristics in *Enterobacteriaceae* from humans, animals and the environment.

As the coordinator of the network, the WHO Centre faces a number of special tasks. The project management has to organise conferences, meetings and conference calls, but also to prepare reports and monitor the budget. In addition, the homepage of the network is maintained by the institute (www.reset-verbund.de).

Project progress 2017: Between April 26 and 28, 2017, the final conference of the RESET consortium took place at the BfR, Berlin, jointly with the MedVetStaph consortium. Here, the main findings from both consortia were presented and discussed.

Data collected in the joint consortium data base were used for further analyses and networking in the international context (see 2.1.1).

The RESET activities are possible only through additional support from federal funds for the WHO CC HAEI.

2.1.1 Project 1: Overarching assessment of epidemiological information and isolate characteristics

The research task of the WHO Centre within the scope of the RESET network is to link data about the occurrence of ESBL-producing *E. coli* with potential risk factors in farm animals. Therefore, a cross-sectional study was carried out in pigs, cattle and poultry in four districts

in Germany. Within the scope of this study, a total of 194 holdings with pig and poultry fattening and holdings with dairy and beef cattle were included in 2011 and 2012.

Samples with cefotaxime-resistant *E. coli* were detected in a very high proportion of the investigated farm animal holdings (100% at broilers; 85% at pigs; 85% at dairy cattle and 70% at beef cattle holdings). During the year 2017, associations between holding properties and isolate characteristics were analysed in the frame of a Master's thesis.

Project progress 2017: 469 isolates from 150 holdings (34 broiler, 38 fattening pig, 43 dairy cattle and 35 beef cattle holdings) were included into the analyses. The ESBL gene family, phylogroup and phenotypical susceptibility against several antimicrobial substances were determined. These data were used to develop different characteristics profiles for the isolates. Associations between characteristics profiles of isolates and holding-related influencing factors (e.g. management, housing, surroundings of the holding) were investigated with the help of non-parametrical, distance-based, multivariate analyses.

In none of the tested isolates, genes of more than one ESBL family could be detected. Sixty-eight percent of the isolates carried *bla*_{CTX-M} gene variants. Different phylogroups occurred with the following frequencies: A (55%), B1 (35%), D (17%) and B2 (3%). The phenotypical non-wildtype profile occurring most often was the one with none-wildtype status solely from Cefepim (27% of the isolates). Characteristics of isolates from broiler holdings were clearly different from those of all other isolates. Associations between holding properties and characteristics profiles differed, depending on the isolate characteristics included in the analysis. Some factors describing the surrounding of holdings, like water fowl in the proximity of the holding, were associated with all characteristics profiles investigated. Associations between holding factors and isolate characteristics elucidate the importance of biosecurity measures in livestock holdings.

These results were submitted for publication.

2.1.2 Project 2: Database

The central database of the consortium (www.reset-datenbank.de) should document all significant information on the obtained samples and isolates.

Project progress 2017: In 2017, the possibilities of the database for data entry and output were further developed and supplemented with new input boxes for isolates in coordination with the project partners.

The database is actively used by the project partners and contained information on 11 371 samples and 3534 isolates originating from RESET as of the end of 2017 (<http://datenbank.reset-verbund.de>).

In the frame of the consortium it could not be finally clarified, if and how a sustainable usage of the data base infrastructure and the enclosed information could be secured after the end of the project. The WHO centre will therefore continue to endeavour to maintain this research data infrastructure.

2.2 The "Tricycle" Project

The "Advisory Group on Integrated Surveillance on Antimicrobial Resistance" (AGISAR) and the Food Safety and Zoonoses Department of the WHO coordinate a project for global surveillance of ESBL-producing *E.coli* (ESBL-EC) whose aim is to introduce a simplified, integrated, trans-sectoral surveillance system for antibiotic resistance in bacteria on a global level. In doing so, the occurrence of ESBL-EC should be detected and compared annually on the basis of a uniform protocol in humans, animals/food as well as in the environment, where *E.coli* serves as an indicator for antibiotic resistance. The aim is to obtain robust, comparable and valid results from the three areas. In parallel, data on antibiotic consumption should also be collected. In addition to information about the occurrence of ESBL-EC, the data should also serve to show the effect of interventions as well as to investigate country-specific factors for the occurrence of ESBL-EC.

The protocol for the integrated surveillance of ESBL-EC in all three areas has to be highly standardized, and at the same time, the realization has to be feasible also in developing and threshold countries. Thus, the aim of the projects is to implement the One Health approach and to support these countries in the development of their National Action Plans on Antimicrobial Resistance.

Project progress 2017: The central WHO project started in 2017, beside others, in six African countries (Zambia, Zimbabwe and South Africa – pilot study; Ethiopia, Chad and Tanzania – focused project). During 2017, more countries were involved and trained.

In addition to the RESET project, the WHO CC HAEI elicited the possibilities in cooperation with the project partners to support the WHO Tricycle activities with epidemiological (database) expertise and microbiological laboratory analysis (see 4.2).

This activity has been possible only through additional support from federal funds for the WHO CC HAEI.

2.3 PraeRi – study on animal health, hygiene and biosafety in German dairy farms

In the frame of a Germany-wide representative prevalence study in dairy farms, the status quo of animal health in calves, heifers and cows as well as on breeding, feeding, hygiene, management and biosafety is surveyed in three dairy cow-intensive regions in Germany (North, East, South). For that purpose, 250 farms are randomly selected per region and during a farm visit, intensive investigations and data collections are carried out. On the one hand, the aim is to determine the Status Quo of animal health and, on the other hand, to develop options for actions for occupational groups of dairy farms, which will also serve as the basis for discussion for policy decision-makers.

Project progress 2017: During the reporting period, approximately 90 farms were visited in each region by the study teams. Additionally, the study database was developed, containing 35 main tables, 132 evaluation tables and 1 522 fields. Currently, the database is used by 37 users with different data access and user rights. Furthermore, im- and export

functions were established and a first version of an analysis plan for the comprehensive future evaluations was prepared.

2.4 VetCAb-Sentinel: Longitudinal capture of consumption quantities of antibiotics in food-producing animals at selected representative veterinary practices and holdings (participants - sentinel)

On behalf of the Federal Institute for Risk Assessment (BfR), the project "Veterinary Consumption of Antibiotics" (VetCAb) has been carried out since 2006. An initial feasibility study showed that the consumption of antibiotics could be captured in livestock farming. The results of this feasibility study and the subsequent pilot study, carried out in 2011, have shown that it is possible to quantify the use of antibiotics in Germany on the basis of a representative sample and formed the basis for the development of a continuous monitoring system. Since 2013, this monitoring system has been continued as a sentinel study (VetCAb-S).

In order to evaluate whether the consumption of antibiotics has changed over time, farms are observed over an extended period. Livestock holdings for which prescription data had already been collected in the pilot study were maintained as participants in the sentinel study and new participants are being recruited to sustain and expand the study cohort. In addition to yearly and half-yearly comparisons on the antibiotic use of the farms since 2011, the dosing behaviour of the veterinarians can be observed as well as the changes in frequency of use of different active substances or active substance classes. Via integration of the data with data on antibiotic resistances, this information can make an important contribution to understanding the development of resistances. Thus, the VetCAb Sentinel forms the basis for scientific risk assessment, which, according to the German Antibiotic Resistance Strategy (DART) as well as the WHO Global Action Plan on Antimicrobial Resistance, represents a substantial contribution to the reduction of antibiotic resistances.

Project progress 2017: In 2017, further cross-sectional studies and analyses of the core panel were carried out, including data of the year 2016. This entails the analysis of the distribution of the therapy frequency per production type within the whole study collective and the core panel, a categorised evaluation of each production type, related to the classes of active substances, for the whole study collective and the core panel, and the percentage therapy frequency, related to the classes of active substances, per production type. In addition, individual therapy profiles were generated and in-depth analyses of the used substances were performed. In the frame of multi-factorial model analyses, the influence of different factors on the development of the therapy frequency on cattle holdings was verified. Furthermore, different calculation methods for the treatment frequency were evaluated in the context of the benchmarking of farms.

2.5 Monitoring of antimicrobial drug usage in animals: methods and applications

Because the WHO Centre has dealt with the monitoring of antibiotic consumption in animals for many years, an overview of monitoring systems for the use of antibiotics in animals in different countries was created in cooperation with the Ontario Veterinary College of the University of Guelph, Canada.

One goal of this work is to summarise information on key figures and variables that can be used to describe the basic consumption of antibiotics. Furthermore, an overview of different monitoring systems in Europe, North America, Australia, New Zealand and Japan is given by way of examples. In addition to national activities, transnational initiatives are also described. To date, there are very little comparable data on antibiotic consumption in animals and there is a need for harmonisation of the data collection to allow comparisons among countries in future.

Further activities on harmonisation of reporting are being developed on the basis of this initiative.

Project progress 2017: The work was submitted for publication in March 2017.

This project has been possible only through additional support from federal funds for the WHO CC HAEI.

2.6 Survey on the treatment of certain farm animals (turkeys, pigs, beef cattle, veal calves) with veterinary drugs concerning the food chain information – stage 2

Because work is currently being carried out on a unified determination of the "safety-relevant period" at EU level, the objective of this project is to collect representative data about the use of veterinary drugs with withdrawal periods greater than zero in relation to respective slaughtering dates by means of a sample including turkey, pig, beef cattle and veal calf holdings representative for Germany. This data will be used to determine proposals for a reasonable "safety-relevant period" from epidemiological and meat hygiene points of view for any evaluated livestock species. In addition, the project involves an analysis of the connection between veterinary drug use during the rearing and fattening periods of the corresponding lots delivered and the occurrence of carcass and organ findings made in the framework of official meat inspections.

Project progress 2017: During the reporting period, the acquisition of holdings and the collection of data on the use of drugs and findings at meat inspection were continued. Indicators on drug usage were categorized for analysis. Approximately 50% of drugs were used to treat diseases of the respiratory tract. The second leading organ system was the intestinal tract. The acquisition of holdings and the collection of data are not finished yet. Further analyses, especially of the findings at meat inspection, were prepared.

2.7 VASIB – Reduction of antibiotic use in pig farming through the integration of epidemiological information from clinical, hygienic, microbiological and pharmacological veterinary consulting

Antibiotic-resistant pathogens represent a serious problem for animal and human health and consumer protection and are thus in the focus of the public. In the framework of this problem, treatment of livestock animals with antibiotics is a component for the emergence and spread of resistances. Each targeted antibiotic treatment will also treat the complete (remaining) microbiome of the animal in addition to fighting the pathogen. The resultant selection of resistant bacteria and persistence of pathogen genes bears the risk that animals can no longer be treated sufficiently in the future and that resistant bacteria are transmitted to humans via the food chain. Against this background, the administration of antibiotics to farm animals is a key source for the development of resistances and hence suitable concepts must be found for the reduction of antibiotics administration. This reduction can only be achieved sustainably if animal health is improved as a whole.

Therefore, a research approach was developed the aim of which is to optimise veterinary consulting. Piglet farms will be assessed for whether minimising of antibiotic use can be achieved through targeted diagnostic measures, optimising of treatment strategies as well as comprehensive, intensive management consulting. Thirty farms (from one veterinary practice) with recurring respiratory problems are being recruited and accompanied over a period of approximately one year. During this period, a status quo analysis of the farm is carried out with numerous questions to ask, observations to make and samples to collect. If the piglets come down with respiratory diseases, the farm will be visited again and findings and samples will be collected at the beginning of the antibiotic treatment and at the end of the treatment. A final visit will be made after approximately one year. The collected data and findings are consolidated and evaluated in a database to make a contribution to the integrated veterinary herd care.

Project progress 2017: According to schedule, all visits on demand and all final visits at the recruited farms were carried out during the reporting period. Hence, the stage of recording the situation on farms is concluded. Initial and final visits were carried out at all 30 farms participating in the project, one visit on demand took place on 16 farms and two visits on demand were done on four farms, respectively. The project database was successfully extended and all information on the farm visits (initial/on demand/final) as well as laboratory results can now be entered. Collected samples were stored and analyses on the content of antimicrobial substances are ongoing. Furthermore, first epidemiological and pharmacological evaluations and evaluations on animal health within the study collective have been done and results were already publicly presented at different conferences.

2.8 PIG HEALTH LERN Network

Consumers' concern about the use of antibiotics in livestock farming and antibiotic resistances is a growing issue. Pig holdings are encouraged to reduce the use of antibiotics in pig production. Because the use of antibiotics should be reduced to a minimum over the coming years, measures to reduce the use of antibiotics must be taken continuously. Since

the nature and extent of antibiotic use depend on many factors, farmers need an approach for reduction that addresses these various challenges.

In engineering, the learning factory is implemented for constant improvement of work processes (a customer-oriented order processing). Based on this knowledge, a LERN network consisting of pig farmers, specialised consultants, veterinarians and scientists is being developed for the reduction of antibiotic use to initiate realistic and innovative continuous improvement processes and to identify obstacles and fears in the development process.

Project progress 2017: The half-yearly therapy frequency of all participating holdings was calculated per production type for every holding/herd movement registration number. The median and the upper quartile of the therapy frequency were presented comparatively within the PIG HEALTH LERN network study collective and were also compared to the collectives of other studies. An individual therapy profile with relation to the drug classes used was compiled for every production type and provided for the participants. Thereby direct impulses could be given to the participating farmers that were included into discussions of the learning network.

2.9 MultiViS - Multivariate Assessment of animal welfare by integrative data collection and validation of animal welfare indicators in pig herds

Currently, a variety of indicators exist for the "pig value chain" from which conclusions for animal welfare should be drawn. To date, the large number of proposals has often been implemented only rudimentarily for various reasons; for example, indications were not validated against a practice background, correlation of the input indicators was not considered in particular for summary scores, the significance of the indicators was not sufficiently checked and the practical survey situation was not harmonised in the herd and at the slaughterhouse.

Against this background, a project is to be carried out taking into account these principles. Animal welfare and animal health will be described in a sufficiently large and representative collective of 200 pig fattening holdings. Existing animal welfare indicators will be recorded at pig holdings and slaughterhouses and included in an overall assessment in which redundancies in the indicators are avoided (improvement of the practicality), dependencies between the indicators will be considered (improvement of precision) and an assessing weighting of the indicators corresponding to the practice situation will be carried out (avoiding of bias). With an integrative approach, these steps will directly result in an innovative aggregation system that guarantees objective classification of animal welfare taking into account the different individuals involved. In addition, meeting of these objectives should lay the foundation for a national monitoring.

Project progress 2017: The official kick-off meeting of the project took place in April 2017. During the following half year, a questionnaire consisting of four sections was developed in cooperation with all project partners. It contains an interview section with the farmer and

three evaluation sheets on the environment and health of animals on the level of compartments, boxes and single animals. Field work started in November 2017.

Until the end of the year, the project database could almost be completed and data of the farms that had been already visited were entered. Additionally, routine data (key numbers and economic data) of the economic year 2016/2017 provided by the Association for promoting farming economics (Verein zur Förderung der bäuerlichen Veredlungswirtschaft, VzF GmbH) were transferred and plausibility checks were started.

2.10 PPP-InfoS - Study on integration of existing official and farm-produced data to improve animal welfare and animal health in pigs

During the rearing of animals for food production and the subsequent production processes, data are collected at different points that could provide information on the health and welfare of the animal. These data are recorded by the farmer himself, by the veterinarian involved, by the veterinary inspection offices or by the slaughterhouse operator; however, the data are currently not merged. In order to better describe and evaluate animal health at the level of the farm, targeted integration of existing official data (in particular from the veterinary inspection offices and official slaughter animal and meat inspections) with data from the operational and inter-operational production control and the economic-borne quality assurance seems very informative. Since 2015, the PPP-InfoS project has dealt with the development of animal health scores for fattening pigs from these routinely available data. A concept for a data information system is being developed to identify farm status by integration of information and to allow comparison between fattening farms. These functionalities are displayed in a demonstrator by way of example to illustrate how an effective tool for prevention, early warning and removal of deficiencies in animal keeping can be made using targeted integration of existing data.

Project progress 2017: After a profound analysis of all available routine data and in-depth interviews with farmers, slaughterhouse operators and veterinary services, application cases for a usage of the overarching system by these stakeholders were developed and evaluated. In addition, animal health scores were set up on the basis of multivariate statistical methods. These scores form the basis for the demonstrator that was developed in a first beta version.

2.11 Case description of patients in German veterinary practices

Various activities of the Royal College of Veterinary Surgeons Knowledge (RCVS Knowledge) or the European Association of Establishments for Veterinary Education (EAEVE) show that the concepts of evidence-based medicine (EbM) must be better established in veterinary medicine as well. Information on the type and numbers of animals presented in practices, diagnoses and the treatments administered form the basis of the EbMV. Supra-regional comparable information, however, is not currently available. Thus, the WHO Centre is also working on strengthening the methods and data of the EbVM.

Project progress 2017: For Germany, the WHO Centre HAEI collected data on the occurrence of practice cases. During the reporting year, the analysis of data was almost completed. Additionally, our institute continues to provide its expertise and knowledge on the usage of drugs for veterinary practices.

This project has been possible only through additional support from federal funds for the WHO CC HAEI.

2.12 Q fever - GermAn interdisciplinary Program for reSearch

Q-fever is a zoonotic disease caused by the bacterium *Coxiella burnetii* (*C. burnetii*). In the sense of the One Health approach, the national consortium Q-GAPS deals with open questions on epidemiology and pathogenesis of *C. burnetii* and wants to explore new methods for the surveillance, control and therapy of this disease in small ruminants and the human population. The aim of this project is to collect important information on *C. burnetii* and to pass it to people who deal with diagnosis and control of the disease. Besides a collection of existing information that is available online, guidelines for handling infections with Q-fever shall be developed. The close collaboration and exchange between partners of this interdisciplinary consortium form the basis for a successful research on the topic Q-fever.

In the frame of this consortium, the WHO centre is working on an individual project on the "Epidemiology of *C. burnetii* in small ruminants and in the human population." Thereby, an active monitoring and surveillance system for *C. burnetii* in herds of small ruminants will be designed, which shall be applied and evaluated in a possible second funding phase. In this context, the best combination of detection methods and sample matrices for *C. burnetii* in herds of small ruminants shall be identified. Research on the Q-fever associated chronic fatigue syndrome in human populations in Germany is another focus of our institute. Here, the WHO centre will collaborate closely with the public health service of Baden-Wuerttemberg, which is planning and conducting a cohort study on the risk of developing the chronic fatigue syndrome after an infection with *C. burnetii* in humans. Moreover, the WHO centre will participate in the development of

Project progress 2017: During the reporting period, the WHO Centre participated in the preparation of the project application. Participation as the epidemiology partner in the network and cooperation with one partner from veterinary medicine and one partner from human medicine is planned (case control study of chronic fatigue syndrome).

2.13 Collaborative research in rural and commercial farming of Chile

Since 2012, projects in close collaboration with the University of Chile, Santiago de Chile, are being conducted in the area of animal health and food production. The main focus is on scientific consulting in epidemiology of monitoring studies on animal health, antibiotic use in (productive) animals and research on antimicrobial resistance.

Progress report 2017: During the reporting year, studies on the occurrence of antimicrobial resistance in dairy farms in different regions of Chile were jointly analysed. Furthermore, a concept for the transfer of the VetCAB system of the WHO centre was developed at the University of Chile, and system catalogues were prepared in English and Spanish languages in order to facilitate establishment of a joint monitoring on antimicrobial use.

This work was possible only due to the additional funding as WHO CC HAEI.

2.14 Human exposure to contaminants through consumption of traded eggs: research on trade and structure data and sampling scheme for sampling traded eggs

In the scope of this project, pooled samples are to be prepared to determine the average content of dioxins and polychlorinated biphenyls (PBC) in eggs on the German market with the smallest possible analytical effort.

The objective of the analysis was to determine the boundary conditions for the preparation of representative pooled samples to describe the average concentration of dioxins and PBCs in eggs. Here, also a proportion of eggs with extremely elevated levels, as proved by limited evidence, as well as relevant influencing factors for concentration data are considered. The target population should be eggs produced in Germany from laying hens for human consumption.

For this purpose, investigations are to be carried out on egg production in Germany, sales figures as well as purchase and consumption habits to provide a data basis for sample calculation.

Project progress 2017: During the reporting period, this project was finished and handed over as a report to the Federal Institute for Risk Assessment. Additionally, a first draft of a scientific paper was developed.

2.15 Poultry farming restructured: integration of meat and egg production using the dual-purpose chicken as a measure for animal welfare (Integhof)

The task of the joint project is the multidisciplinary evaluation of the suitability of the dual-purpose chicken for fattening and egg production as a possible alternative to conventional genotypes. This project is to be carried out from the point of view of animal health, animal welfare, environmental and consumer protection as well as economic viability and consumer acceptance. The joint keeping of both genders of dual-purpose chicken in one holding requires a novel, integrated, especially animal-friendly and sustainable farming system for fattening and laying chickens, which will be tested and further developed in this project.

The aim of the studies is to test the feasibility of using a dual-purpose chicken for fattening as well as egg production from the point of view of animal, consumer and environmental protection and economic feasibility. By integrating the dual-purpose chicken at “Integhof” with farming systems adjusted to the needs of the animals, killing of day-old male chicks from the hen lines, a common practice up to date, could be prevented. Based on the results, a concept as well as recommendations for optimised keeping and feeding of these animals will be developed, taking into consideration and balancing potential conflicts of interest.

In collaboration with colleagues from animal hygiene and food safety, the WHO Centre is working on a sub-project investigating the hygiene barriers among animal groups (adult animals vs. young animals; male vs. female). Here, various indicator pathogens are being tested: *E. coli* (incl. ESBL), *Campylobacter spp.*, *Salmonella spp.* and MRSA.

Project progress 2017: In the reporting period, samples were collected at six time points to determine the so called indicator bacteria in different animal groups. These samples were investigated at laboratory by project partners and captured electronically. The WHO Centre conducted first analyses on questions of the hygiene status in the compartments of the system as well as on possible ways of carry-over regarding the exchange of pathogens characteristics between animal groups.

3 Training events

The WHO CC HAEI holds training events and scientific colloquia or supports these activities on a regular basis. In 2017, the following events were prepared or organised:

3.1 Seminar on Veterinary Public Health 2017: "Chemical hazards in the food chain – reality or fantasy?"

The "Seminar on Veterinary Public Health", held on February 3, 2017 at the University of Veterinary Medicine Hannover, made a contribution to the currently objective available standard of knowledge on the occurrence of residues and contaminants in food in Germany. Thus, the audience mainly consisted of veterinarians working at official (chemical and) veterinary laboratories, but also scientists from various fields of expertise, employees of the public veterinary service as well as diverse practicing veterinarians were among the participants.

In the first session, an overview on the current situation in Germany was given. Mr. Haunhorst, president of the Lower Saxony State Office for Consumer Protection and Food Safety (LAVES), started with an introduction of the legal framework on EU and national level and gave insight into the problems and questions in implementing these regulations in praxis.

Opportunities and problems in risk assessment were outlined by Prof Dr Dr Andreas Hensel, president of the Federal Institute for Risk Assessment (BfR). In his talk, he focused on the resources and other prerequisites needed to conduct risk assessments, e.g. existence of and timely access to required data, expertise, and legal frameworks. Also the understandable communication of results to risk managers and the public is very important. He showed in several examples, how the BfR is dealing with these problems.

Prof Dr Pablo Steinberg, Director of the Institute for Food Toxicology and Chemical Analytics of the University of Veterinary Medicine Hannover and designated president of the Max-Rubner-Institute, gave insight in "emerging toxins" as a new challenge in the field of chemical hazards in food. A possible effect of climate change, for example, might be the emergence of (new) mycotoxins and marine biotoxins, which partly are not regulated by law, and no testing procedures or maximum levels are determined for. Also changes in agricultural praxis, possible effects of floods and economic impacts, innovations in food production and risks from the trade via internet were explained by examples as new challenges.

The topic of the second, big block of the event was contaminants in the food chain. The block was opened by Prof Dr Josef Kamphues, director of the Institute for Animal Nutrition at the University of Veterinary Medicine Hannover. He explained the difference between accidental events and continuous contamination of soils that animals are feeding from (e.g. by grazing or picking). He presented studies that investigated the possibility of using green areas exposed to dioxins for feed production for productive animals. Results show that feed production in these areas is possible under certain conditions. For a practical implementation, important issues still have to be solved, e.g. administrative guidance as well as political and societal acceptance.

An assessment of the risk for consumers evolving from metal compounds in food was introduced by Prof Dr Andrea Hartwig, Executive Director of the Institute for Applied Biosciences at the Karlsruhe Institute for Technology, using cadmium and arsenic as current examples. She showed that exposure should be reduced in both cases.

Prof Dr Hans-Ulrich Humpf, Head of a Working Group at the Institute for Food Chemistry of the University of Münster, gave a lecture on food safety and mycotoxins. He explained the challenges for research in food chemistry using the example of Ochratoxin A and its thermic metabolites, which occur in coffee beans during the roasting process.

Natural plant substances as contaminants in the food chain were the topic of Prof Dr Alfonso Lampen, Head of the Department for Food Safety, BfR. Tropane alkaloids, of which up to 200 different alkaloids are known, and which are partly also used as drugs, may influence the heart rate and the nervous system. Maximum amounts were exceeded recently in several food items. Pyrrolizidine alkaloids are hepatotoxic, mutagen and carcinogenic and were recently detected as contaminants in teas. This could be critical for health in the case of chronic uptake.

Prof Dr Gerhard Eisenbrand, Head of the Department for Food Chemistry and Environmental Toxicology at the Kaiserslautern, presented a study on biomarkers and possibilities of their application in risk assessment of contaminants occurring during production processes. Here, different detection methods for acrylamide were investigated.

An overview on contaminants from materials that come into contact with food was given by Prof Dr Thomas Simat, Professor for Food Science and Commodities at the TU Dresden. Here, primary aromatic amines, synthetic oligomers and contamination by mineral oils were especially emphasized.

The last part of the seminar dealt with residues in the food chain. In her talk, Dr Britta Michalski, Leader of the working group "Residues and Analytical Methods", BfR, discussed the question whether residues of pesticides are a health risk. She contrasted the perception of consumers and the echo in media with the health risk assessment conducted by the BfR. In conclusion, with the exception of a few single substances, no health risks exist by residues of pesticides for consumers in Germany.

At the end of the seminar, Prof Dr Gerd Hamscher, Leader of the Analytics Working Group of the Institute for Food Chemistry and Food Biotechnology of the JLU Giessen talked about residues and contaminations of veterinary drugs. First of all he explained the situation regarding residues in food, showed different entry paths for (veterinary) drugs and also pointed on the problem of resistances. Furthermore, he introduced studies demonstrating a permanent contamination of soil and groundwater. At the end of his talk, he presented ways to reduce the contamination with drugs.

Subsequently, the event was closed with a discussion involving all speakers.

During the event, the 2017 Konrad Bögel Award was awarded to Dr med vet Sophia Johler-Ilić from the Institute of Food Safety and Hygiene of the Vetsuisse Faculty of the University of Zürich for her work entitled "Minimizing the Risk of Staphylococcal Food Poisoning". Every year, this seminar recognizes outstanding work in the field of "Veterinary Public Health" or veterinary medical epidemiology.

The seminar was evaluated positively by the participants.

This event has been possible only through additional support from federal funds for the WHO CC HAEI.

3.2 Course program: Epidemiology - Biometry 2017

The courses were held in February 2017 in collaboration with the WHO CC HAEI. The courses were intended for anyone who deals with the planning, analysis and evaluation of empirical studies within the scope of their work.

Four courses were offered, each consisting of three days training: Descriptive Epidemiological Methods, Analytical Epidemiological Methods, Application of Dynamic Models for Epidemiological Considerations and Introduction to Risk Analysis.

The "Descriptive" and "Analytical Epidemiology" courses imparted the methodical knowledge necessary for epidemiological studies and explained them by means of examples. Concepts for the construction and collection of epidemiological measured values, the most important collection methods, evaluation and correction of error sources and basic evaluation methods for epidemiological studies were described.

The course "Application of Dynamic Models for Epidemiological Considerations – a practical introduction" was offered for the first time in 2017. Participants were taught both background knowledge and practical experience in the development and application of models. Here, compartment models on infectious diseases in certain host groups were introduced, developed and tested in NetLogo. Afterwards, a model for the dissemination of an infectious disease based on individuals was developed and variegated depending on different practical questions. In a practical exercise, participants were given the possibility to apply disease modelling to solve real problems in decision making.

In the course "Introduction to Risk Analysis", held in English language, the terminology of risk analysis (standards according to OIE, Codex Alimentarius) and of risk modelling (deterministic, stochastic models, simulation) was explained. Additional topics were modelling tools and qualitative risk assessment on the application model animal protection. These were imparted theoretically and on the basis of example applications (modelling, data availability, validation).

All courses received positive evaluations from participants.

3.3 Symposium in remembrance of Prof Dr Günter Klein

Prof Dr Günter Klein, Director of the Institute for Food Quality and Safety and Head of the Centre for Animal Health and Food Quality at the University for Veterinary Medicine Hannover, Foundation, passed away at the end of 2016 after severe illness. On May 5, 2017, a scientific symposium was held in remembrance of him, entitled "Career stages –

Findings – Cooperation". The symposium took place at the University of Veterinary Medicine Hannover.

In the first part of the programme, the floor was given to colleagues from various career stages of Prof Klein. Thus, Dr Christine Bonaparte (TZL MiTec GmbH, Detmold) spoke about bifidobacteria in the course of time, Dr Lüppo Ellerbroek (NRL Campylobacter, BfR, Berlin) about preventive measures in slaughter hygiene, and Dr Ulrich Schotte (Central Institute of the Sanitary Services of the German Armed Forces, Kiel) about wildlife as a reservoir for hepatitis E viruses.

The second session of the event dealt with the scientific work of Prof Klein at the University of Veterinary Medicine Hannover. Within this session, colleagues from the Institute of Food Quality and Safety presented their research outcomes. The first two presentations covered the use of high pressure technology for safe food items (Dr Nadine Sudhaus und Dr Birte Ahlfeld). They were followed by Dr Sophie Kittler, who talked about the application of bacteriophages in food production. The problem of *Campylobacter* in poultry meat production and possible interventions and perspectives was the topic of Dr. Felix Reich. Finally, Prof Dr Corinna Kehrenberg, PhD, presented the latest findings on transmission of antimicrobial resistance in bacteria relevant for food hygiene.

During the last part of the symposium, cooperation partners of Prof Klein took over. Prof Dr Diana Meemken (Martin-Luther-University Halle) started the session, talking about risk orientation along the food chain. Prof Dr Matthias Greiner (BfR, Berlin) continued with a presentation about spatio-temporal investigations on the occurrence of infections with *Campylobacter* and *Salmonella* in Germany. The last talk of the symposium was held by Melanie Eger, PhD, from the Institute of Physiology of the University of Veterinary Medicine Hannover, about *in-vitro* studies on the ruminal microbiome and metabolome.

The symposium in remembrance of Prof Klein was, besides others, organised substantially by the WHO CC HAEI. This event has been possible only through additional support from federal funds for the WHO CC HAEI.

3.4 Symposium on Antimicrobial Resistance in Animals and the Environment (ARAE)

The 7th Symposium on Antimicrobial Resistance in Animals and the Environment (ARAE) took place from June 26 to 28 2017 in Braunschweig, Germany. The ARAE Symposium is an international, interdisciplinary event for scientists from the research areas of microbiology, animal and environmental hygiene, epidemiology and molecular biology dealing with zoonoses and resistance research.

During the three days, 161 participants from 23 countries of 6 continents discussed recent developments in antimicrobial resistance (AMR), one of the most important One Health challenges in the world.

Participants of the ARAE 2017 were given a warm welcome by the organisers and the mayor of Braunschweig, Dr Helmut Blöcker, at the evening of June 25 in the old town hall (Altstadtrathaus). This historical location is a remarkable example of Gothic architecture in

the city of Braunschweig and provided a perfect atmospheric and impressive frame for the opening of the meeting.

The scientific programme was subdivided into ten oral and two poster sessions.

In the first session "Monitoring and epidemiology of AMR", Prof Séamus Fanning from the University College Dublin, Ireland, gave an insight into the characteristics of *Salmonella* isolates from China. In his keynote speech, he presented studies that identified and characterized multidrug-resistant *Salmonella enterica* subsp. *enterica* serovars from the food chain, including the characterization of a bla_{NDM-1}-carrying multiresistance plasmid from a *S. Indiana* isolate of poultry origin. The following presentations, given by speakers from France and Germany, focused on the occurrence and characteristics of mobile, mainly plasmid-borne (fluoro)quinolone or linezolid resistance genes from *Proteae* and enterococci, respectively.

In his keynote lecture opening the session "AMR in the environment", Prof Thomas Berendonk, Technical University of Dresden, Germany, showed that when comparing in- and outflow of wastewater treatment plants no significant reduction in the relative abundances of key resistance genes was observed. However, a change in the bacterial community appeared. Reports on the frequent occurrence of antibiotic-resistant bacteria in wastewater from Ireland and The Netherlands completed this session.

René Hendriksen, PhD, from the Technical University of Denmark spoke about AMR genes in sewage from airplanes, urban slums and wastewater treatment plants. As keynote lecturer of the session on "Novel diagnostic tools", his focus was on the use of metagenomic analyses to improve the surveillance of AMR in large human and animal populations. These methods can be applied to characterise the entity of genetic material obtained directly from a specimen. Another sequence-based approach, developed by working groups from the UK, was also presented in this session. The so called ARIBA (Antimicrobial Resistance Identification By Assembly) uses a combined mapping/alignment and targeted local assembly approach to identify AMR genes and variants thereof efficiently and accurately from Illumina paired sequencing reads. In addition, new methods for susceptibility testing of *Haemophilus parasuis* and biocide susceptibility testing were introduced by two speakers from Germany.

In the session on the "Use of antimicrobial agents", an overview on comparability of data from monitoring systems and the consequences of differences in the calculation of variables describing the use of antibiotics in food-producing animals was given in talks from Germany and Italy. Two speakers from Belgium and the USA discussed the association between veterinary antibiotic use and resistance in commensal *E. coli* from livestock. In summary, the continuous decrease in antibiotic use appears to have a positive effect on the levels of resistance. However, it is important to differentiate between antibiotics, bacterial species and animal species. At the end of this session, results on AMR in Norwegian red foxes and their role as indicators of AMR in the environment were presented.

Two sessions dealt with AmpC-, carbapenemase- and ESBL-producing *Enterobacteriaceae*. Speakers from The Netherlands, Germany, France, New Zealand, USA and Canada presented data on prevalence and characteristics of these bacteria isolated from livestock,

horses, companion animals, seal pups, or food. A research group from the Netherlands studied the occurrence of ESBL- and AmpC-producing *E. coli* in calves. They found a prevalence of 24% in calves aged three to four days but this prevalence strongly decreased after day five. The authors of a longitudinal study from The Netherlands concluded that the dissemination of ESBL-producing *E. coli* on the investigated broiler farm was not due to the spread of one specific *E. coli* clone, but due to horizontal transfer of a specific plasmid carrying certain ESBL-genes. This finding was in line with the results of other studies presented at the conference.

The topic "Colistin resistance" was introduced by Associate Professor Dr. Laurent Poirel, University of Fribourg, Switzerland. He explained that the impact of the use of polymyxins in agriculture was not seriously taken into account as long as there was no critical need for colistin in human medicine. This situation has changed due to rapid emergence of multidrug-resistant gram negatives in human medicine. Therefore, colistin is now one of the last resort antibiotics to treat human infections. Poirel pointed out difficulties in the determination of polymyxin susceptibility. The talks in this session and the following session reported on occurrence and characteristics of mcr-gene carrying strains from China and Europe.

Results on characteristics of methicillin-resistant *Staphylococcus aureus* (MRSA) from a German research consortium were presented in the "MRSA" session. Presence of MRSA in wild hedgehogs from Sweden was reported. A speaker from Denmark explained that although farmers are often persistent carriers of MRSA, visitors of livestock farms lost the livestock-associated MRSA strains in their nose soon after the farm visits. Moreover, that the nasal microbiome of farmers and visitors differs.

The session "Novel and alternative Approaches in Fighting AMR" started with a keynote lecture given by Prof Scott McEwen, Ontario Veterinary College, Canada. He explained the criteria which are used from the WHO to categorise antimicrobials with respect to importance for human health. These criteria are also used to develop risk management strategies for antimicrobial use in food-producing animals. A speaker from New Zealand showed that a novel veterinary intervention programme could reduce the antimicrobial usage on dairy farms. Cationic antimicrobial peptides (AMPs) were introduced by a speaker from Germany and are promising candidates for future alternative treatment strategies of mastitis in dairy cattle.

The scientific programme was concluded by a keynote lecture held by Engeline van Duijkeren, PhD, National Institute for Public Health and the Environment, The Netherlands. She gave an overview on recent research on the epidemiology of ESBL-producing *E. coli* among animals, humans and the environment and pointed out the necessity of a One Health approach to fight AMR.

During the two poster sessions, 89 posters were presented and discussed. In addition, 15 selected posters were introduced within three-minute speed presentations in the lecture hall. A best poster award, sponsored by Veterinary Sciences, was handed over at the last day of the conference by Kristina Kadlec, PhD and Prof Dr Patrick Butaye, Ross University School of Veterinary Medicine, Saint Kitts and Nevis, Editor-in-Chief of "Veterinary Sciences". The poster from Cindy Dierikx showing that eating meat does not increase the

risk to carry ESBL-producing *E. coli/Klebsiella pneumoniae* convinced the jury and was considered as the best poster.

A special issue of the journal *Veterinary Microbiology* will give participants the chance to publish their results presented at ARAE 2017.

The evaluation of the conference by the participants was very positive.

The WHO CC HAEI had the lead in planning, organization and realization of the ARAE. Besides other, conference calls with the organizing committee were organized on a regular basis and the conference website was maintained and kept up-to-date during the reporting period.

This event could only be organized due to additional funding of the WHO CC HAEI.

4 Ongoing activities

4.1 Visit of a delegation from Japan

In the frame of a visit to Germany for several days, the WHO Centre hosted a delegation from Japan on February 27, 2017. The delegation consisted of three scientists of the University of Tokyo and was led by Prof Katsuaki Sugiura. The colleagues had a special interest in monitoring of antibiotic usage in livestock. Therefore, Prof Kreienbrock presented an overview on the different monitoring systems in Germany and subsequently, the VetCAB-S project was introduced and discussed. Furthermore, information on data collection of antimicrobial usage in livestock in Japan was exchanged.

This visit was followed by a lively communication with the aim of supporting members of the Japanese delegation in the frame of the training offers of the WHO Centre.

This activity could only be organised due to additional funding of the WHO CC HAEI.

4.2 Zambia

Following an invitation of the German Research Community (Deutsche Forschungsgemeinschaft, DFG) in the frame of its Africa concept, Prof. Kreienbrock took part in an event jointly organised by the DFG and the research funding organisations of Zambia and Malawi in Livingstone, Zambia, from 21. until 26. November 2017. The aim of this event was not only scientific exchange, but also the promotion of international research cooperation. The "Symposium on Animal and Livestock Sciences" accompanied the African Regional Conference of the Global Research Council and the annual meeting of the Science Granting Councils Initiative, the network of the African research funding organisations. Scientists from participating countries, England, South Africa and other African countries were invited.

In the frame of this event, intensive contacts with the African partners were established that shall lead to collaboration with the WHO Centre.

4.3 Website redesign

With the re-designation as the WHO CC HAEI, there is a strong new orientation of the Centre towards the One Health concept. Thus, the WHO Centre considers it important to redesign the present website for the topic Veterinary Public Health/One Health. Thus, the domain www.One-Health-Hannover.de has already been reserved. During the year 2017, the concept of the internet presence was renewed and focused on a One Health approach. Here, the contents were completely revised and terminology from One Health and Veterinary Public Health was defined and explained. Parts of these texts were taken over by the German Society for Veterinary Medicine (DVG) and included in a flyer introducing Veterinary Public Health as a discipline to the wider public.

This information service can only be offered through additional support from federal funds for the WHO CC HAEI.

4.4 Seminar Veterinary Public Health 2018

In the reporting period, the Veterinary Public Health 2018 Seminar on the topic "Pets in the One Health context" was planned and organised.

These event preparations could only be carried out through additional support from federal funds for the WHO CC HAEI.

5 Collaborations

5.1 International cooperation partners

At the international level, the WHO CC HAEI collaborates within the scope of its research and training activities with the following institutions:

- Veterinary Public Health-Institute, Bern, Switzerland
- Federal Food Safety and Veterinary Office, Bern, Switzerland
- Department of Biomathematics and Informatics, University of Veterinary Science, Budapest, Hungary
- Department of Population Medicine, Ontario Veterinary College, University of Guelph, Guelph, Canada
- Royal Veterinary College, London
- RCVS Knowledge, London
- London Department of Disease Control, University of Zambia, Lusaka, Zambia
- Department of Epidemiology, French Agency for Food, Environmental and Occupational Health & Safety (ANSES), Ploufragan, France
- Faculty of Veterinary Science, University of Pretoria, South Africa
- Faculty of Veterinary Medicine of the University of Chile, Santiago de Chile, Chile
- State Veterinary Services, Department of Agriculture, Stutterheim, Eastern Cape Province, South Africa
- Veterinary Faculty, Universidad Austral de Chile, Valdivia, Chile
- Austrian Agency for Health and Food Safety Vienna, Austria
- University of Veterinary Medicine Vienna, Austria
- Vetsuisse Faculty of the University of Zurich, Switzerland

5.2 National cooperation partners

On national level, the WHO CC HAEI collaborates within the scope of its research and trainings activities with the following institutions:

- Department of Veterinary Medicine at the Freie Universität Berlin
- Charité, Berlin
- Federal Institute for Risk Assessment, Berlin
- Federal Office of Consumer Protection and Food Safety, Berlin
- Robert Koch Institute, Berlin and Wernigerode
- QS Qualität und Sicherheit GmbH, Bonn

- Helmholtz Research Centre for Infection Medicine, Braunschweig
- Johann Heinrich von Thünen Institute, Federal Research Institute for Rural Areas, Forestry and Fisheries, Braunschweig
- Leibniz Institute of Prevention Research and Epidemiology - BIPS GmbH, Bremen
- Friedrich Loeffler Institute, Celle, Jena, Mariensee, Riems Island and Wusterhausen
- Max Rubner Institute, Detmold
- Bavarian State Office for Health and Food Safety, Erlangen
- University Hospital Erlangen
- Bavarian State Institute for Agriculture, Freising
- Marketing Service Gerhardy, Garbsen
- Veterinary and Medical Faculty of the Justus Liebig University Gießen
- Hannover Medical School
- Lower Saxony State Office for Health (NLGA)
- Lower Saxony State Office for Rural area, Food, Agriculture and Consumer Protection, Hannover (NML)
- University Hospital Jena
- Ministry of Energy, Agriculture, the Environment and Rural Areas, Schleswig-Holstein (MELUR), Kiel
- Veterinary Faculty of the University of Leipzig
- Fraunhofer Institute for Cell Therapy and Immunology, Leipzig
- Helmholtz Research Centre for Environmental Research, Leipzig/Halle
- BALVI GmbH, Lübeck
- Veterinary and Medical Faculty, Institute for Statistics of the Ludwig Maximilians University Munich
- Helmholtz Research Centre for Environment and Health, Munich
- Institute for Microbiology of the German Armed Forces, Munich
- Medical Faculty of the Westphalian Wilhelm University of Münster
- Lower Saxony Chamber of Agriculture, Oldenburg
- Lower Saxony State Office for Consumer Protection and Food Safety, Hannover and Oldenburg (LAVES)
- Veterinary Group Practice, Vet Team Reken, Reken
- Schleswig-Holstein Chamber of Agriculture, Rendsburg
- Health Authorities of the District of Stade
- Faculty of Agricultural Sciences at the University of Hohenheim, Stuttgart
- State Office for Health Baden-Wuerttemberg, Stuttgart

- Association for the Promotion of Rural Refining Economy, Uelzen
- Health Authorities of the District of Vechta

6 Publications

The following scientific writings were published by the WHO CC HAEI during the 2017 reporting period:

6.1 Scientific publications in journals

Amendt HL, Siedenburg JS, Steffensen N, Kordass U, Rohn K, Tipold A, Stein VM. Correlation between severity of clinical signs and transcranial magnetic motor evoked potentials in dogs with intervertebral disc herniation. *The Veterinary Journal* 2017;221:48-53.

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Habig C, Spindler B, Beyerbach M, Kemper N. Evaluation of footpad health and live weights in two lines of turkey hens kept under organic husbandry conditions in Germany [Evaluation der Fußballengesundheit und der Lebendgewichte von Putenhennen zweier Linien unter ökologischen Haltungsbedingungen in Deutschland]. *Berliner und Münchener Tierärztliche Wochenschrift* 2017;130(5-6):250-257.

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6.2 Academic works

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Eva D. Verzerrung von Studienergebnissen der Beurteilung von Haltungssystemen für Legehennen durch Haltung und Management. *Dissertationsschrift, Tierärztliche Hochschule Hannover, 2017*

Master theses:

Felski, M.-T. Analyse der Assoziation der Eigenschaftsprofile ESBL/AmpC- produzierender E. coli- Isolate aus nutztierhaltenden Betrieben mit Managementfaktoren dieser Betriebe. *Leibniz Universität Hannover, 2017*

Bachelor theses:

Warias, K.K. Power-Analyse für geringe Stichprobenumfänge bei Tierexperimenten. *Leibniz Universität Hannover, 2017*