

WORLD HEALTH ORGANISATION



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.

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 2016, the main focus was set on the collaboration with partners from other scientific disciplines. Research and training in the field of 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 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 2016: In addition to the annual networking meetings, consolidation of the comprehensive samples and isolates database of RESET (see below) was an important objective in 2016. One issue addressed were missing entries and, if necessary, completion of those. Furthermore, the possibilities for additional use of the database were discussed.

Moreover, it was discussed how the German RESET project can be integrated into the WHO-AGISAR international actions (see 2.2). 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). The task of the ongoing project is to use an approach that encompasses all animal species to examine whether there are connections between holding properties and isolate characteristics.

Project progress 2016: The epidemiological data from the cross-sectional study about the occurrence of cefotaxime-resistant *E. coli* in 160 farm animal holdings in Germany were linked to the data from corresponding isolates. Thus, the isolate characteristics (ESBL genes, phylogroup and phenotypical resistances) can now be tested for association to epidemiological factors such as farm size, presence of other animal holdings in the neighborhood or the use of antibiotics. Multivariate, distance-based permutation tests are used for these analyses. Initial results show that characteristics profiles from isolates of broiler holding farms significantly differ from isolates of farms with fattening pigs or cattle.

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 2016: The database is actively used by the project partners and contains information on 12,861 samples and 3958 isolates as of the end of 2016. In the past year, approximately 850 new isolates have been entered into the database and information on the existing data has been deepened. The data input and output options were further elaborated by the associated partner Leipzig University-Pharma in coordination with the other project partners and supplemented by new input fields. The display of specific data analyses was extended. The fact that this collection presents a valuable resource for current scientific questions became particularly obvious by the detection of the new mcr-1 resistance gene.

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.

Project progress 2016: In October 2016, an initial project meeting for the development of the ESBL-EC project protocol took place; the WHO-CC HAEI also participated. It was discussed whether the protocol developed in the scope of the RESET project can also be used for this global project.

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

2.3 Development of the research consortium "*Integrated Surveillance of Transfer of Antimicrobial Resistance within the Human-Animal-Environment Interface*" - ISTAR

On January 29, 2016, the research agreement on diseases transmissible between humans and animals (zoonoses) was renewed between the Federal Ministry of Education and Research (BMBF), the Federal Ministry of Food and Agriculture, the Federal Ministry of Health and the Federal Ministry of Defense. The BMBF announced the establishment of an interdisciplinary "national research network of zoonotic infectious diseases" as well as corresponding funding guidelines.

The ISTAR research consortium developed after these guidelines has the goal to identify and reduce the risks arising from zoonotic, multiresistant, gram-negative bacteria (MDRGN). Existing data on the spread of MDRGN in human and veterinary medicine as well as in environmental research are fragmented and not generally accessible. Thus, they are unavailable for joint, cross-sectoral analyses. In the scope of ISTAR, data from surveillance and monitoring programs, from previous studies on human and veterinary healthcare and on the prevalence and transmission of MDRGN should be integrated and supplemented by new, targeted studies. In doing so, survival mechanisms of bacteria in different environments, as well as the role of colonisation and persistence, should be investigated in particular.

This approach helps to develop strategies for the early detection of pathogen clones as well as for the control of MDRGN. In addition, utilization of existing data should allow new, practical concepts for the exchange and application of epidemiological and microbiological information. Therefore, clarification of the legal framework for the scientific use of data that goes beyond the original goal is essential.

Project progress 2016: The WHO Centre initiated and coordinated the development of the concept for the new ISTAR research consortium. In May 2016, a meeting of all project partners took place in the WHO Centre to complete the elaboration and application of the project. The project outline was submitted on schedule. Unfortunately, the project is not supported.

2.4 Planning of a study on animal health, hygiene and biosafety in German dairy farms - PraeRi

A case-control study carried out in dairy farms in North Germany on the significance of *Clostridium botulinum* for chronic disease showed that deficiencies in the areas of breeding, hygiene, feeding and management are possible risk factors for the occurrence of chronic, mostly nonspecific diseases. It can be assumed that the identified deficits exist not only in North Germany but nationwide. Thus, a Germany-wide representative prevalence study in dairy farms on the status quo of animal health in calves, heifers and cows as well as on breeding, feeding, hygiene, management and biosafety is being carried out in three dairy cow-intensive regions in Germany (North, East, South). Based on the results, options for actions will be developed for occupational groups of dairy cow farms, which will also serve as the basis for discussion for policy decision-makers.

Project progress 2016: The project started in July 2015. During the reporting period, the survey was planned and piloted. The WHO Centre is active as the lead epidemiological unit in the project network. In this regard, it coordinated the creation of the survey instruments and processed layout and question quality. In addition, the WHO Centre contributed to the preparation of SOPs and also initiated the creation of a SQL database in which data can be collected and processed. Furthermore, it developed a declaration of consent for participating farmers in collaboration with the partners. The WHO Centre carried out an initial observer-balance and evaluated it regarding possible interviewer bias through systematic survey differences among observers.

2.5 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 2001. 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 have shown that it is possible to quantify the use of antibiotics in Germany on the basis of a representative sample. The pilot study in 2013 serves as basis for the development of a continuous monitoring system.

This monitoring system has now been continued in the VetCAB-S sentinel study since the beginning of the year 2014. 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 behavior 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 2016: In addition to treatment frequency over time for the overall collective as well as for the panel farms, evaluations based on active substance group were also carried out. The antibiotic use per active substance class for each animal production type and over time was evaluated. Treatment frequencies per active substance group could be shown, as well as the percentage share of the individual active substance groups on the overall treatment frequency.

Currently, our work is focused on the evaluation of individual treatment profiles as well as a comparison of the Used Daily Doses determined in the study and the Defined Daily Doses published by the European Surveillance of Veterinary Antimicrobial Consumption (ESVAC) project in 2016.

2.6 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.

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

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

The research project “Survey on the treatment of certain farm animals (turkeys, pigs, beef cattle, veal calves) with veterinary drugs concerning the food chain information – stage 2” builds on the findings of the project with the same name and the amendment “stage 1:

method development". 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 2016: The relational, SQL-based drug database developed in stage 1 of the study was reviewed for currentness and supplemented with additional drugs for its use in stage 2. Currently, a total of 919 veterinary drugs with waiting time from 33 different drug categories are available for selection in the drug database. In order to ensure standardised collection and protection of all project-relevant information, the relational, SQL-based project database developed in stage 1 was used and supplemented with a section which allows the inclusion of information on slaughterhouses and carcass and organ findings of the respective lots delivered.

Based on an adaptive study design with stratified random selection, the sample size was adjusted in stage 2 based on the initial experiences. The updated sample planning for the farms to be included stipulates the following figures: turkeys 30 holdings, calves 58 holdings, beef cattle 60 holdings, piglets 30 holdings and fattening pigs 42 holdings. Since the end of 2016, collection of data on drug use and on carcasses and organ findings is being carried out simultaneously with the continuous acquisition of new project participants.

2.8 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 during the reporting period 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 2016: In January 2016, the veterinary staff was hired and the study portfolio for the farm visits was developed. The field work started in spring and all 30 farms were recruited and visited over the year. In addition, an occasion visit was carried out at 9 farms. The project database has been operational since the middle of the year and the first descriptive evaluations are being carried out.

2.9 PIG HEALTH LERN Network

Consumers protection, in particular consumers' concern about the use of antibiotics in livestock farming and antibiotic resistances, are growing issues. Pig holdings are encouraged to reduce the use of antibiotics in pig production (e.g. 16th amendment of the AMG). Based on the half-yearly evaluation of treatment frequencies, farms are compared with each other. Holdings with the highest treatment frequencies are affected by official measures like the obligation to write an action plan. 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 2016: In the reporting year, the LERN network was initiated and a concept for continuous information, discussion and adjustment of the behaviors of the individuals involved was established.

2.10 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 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 emphasis of the indicators corresponding to the practice situation will be carried out (avoiding of disorientations). 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 2016: A project application was submitted and approved. Work is likely to begin in early 2017.

2.11 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 2016: Within different work packages it was identified and analysed which data are available and suitable to describe animal health. Work initially started with the development of animal health scores by aggregation and intersection of individual indicators. Furthermore, initial deliberations on a data protection-compliant data information system have been made.

2.12 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 2016: The WHO Centre HAEI collected the first data on the occurrence of practice cases and prepared an initial analysis. In addition, the institute introduced its expertise on the knowledge of drug use also in the veterinary practice and started a pilot project in small animal practice.

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

2.13 Q fever - GermAn interdisciplinary Program for reSearch

To date, there is no efficient treatment for chronic Q fever caused by *Coxiella burnetii* – nor for the Q fever fatigue syndrome. In order to develop new treatment methods, it will be essential to increase knowledge on pathogenesis of *C. burnetii*. In addition, specific precautions are crucial for preventing the spread of the pathogen and infections. However, it is not yet fully understood how *C. burnetii* is transmitted. In order to develop new diagnostic methods and a catalogue of countermeasures for the public health system, the Q-GAPS Network hopes to address unsolved questions concerning the epidemiology, pathogenesis, surveillance and control of *C. burnetii*. Clarification of the role of ticks as vectors for transmission is needed. Furthermore, antigen presentation will be examined to create the basis for new vaccines. By sequencing different isolates and association of the genome with virulence information, genes should be identified which are associated with certain host species and/or have specific pathogenic potential. Analysis of gene functions will allow the identification of candidate markers for the virulence of *C. burnetii*. The results of the network should provide a new understanding for infection in animals and throw light on the development of Q fever fatigue syndrome. All information will be integrated into a catalogue of countermeasures to help the public veterinary and human health care systems to better observe *C. burnetii* as well as to avoid and control outbreaks.

Project progress 2016: 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).

2.14 Collaborative research in rural and commercial farming of Chile

Since 2012, projects in close collaboration with the University of Chile, Santiago, and the Agricultural and Fisheries Services of 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 antibiotic use in livestock.

Progress report 2016: In close collaboration with our partners of the clinic for cattle, first attempts were made to set up a questionnaire. An investigation depository was developed to set up a tool box for investigations in livestock in Chile. To assist with these services, a training visit of students of the University of Chile was prepared and funding was asked for this activity.

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

2.15 Zoonosis research in the tropical rainforest of Guatemala

Interaction between human and animal population is a possible hazard for the spread of zoonotic agents. This is especially true for the strong interrelationship between wildlife and rural populations in semi-development countries like Guatemala, where villagers use and collect material from wildlife, cultivate maize and other crops for domestic consumption and raise pigs and poultry as sources of animal protein. In addition, hunting is a common and provides an interface between wildlife and domestic animals as well as humans.

Progress Report 2016: During the reporting period, project reports as well as international publications were finalised. Within this study, the first experiences on concepts and field work on methods in participatory epidemiology were made, which forms a basis for future activities in this field.

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

2.16 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 2016: This project was started during the reporting period. The WHO CC started data research and literature research for relevant sampling models.

2.17 Establishment of a veterinary medicine biobank

Biobanks as comprehensive collections of biological materials form an important basis for effective and sustainable medical, biomedical and veterinary medical research. In particular with regard to continually growing diagnostic possibilities, for example on molecular genetics level, long-term storage of biological material for future research purposes that are often largely undefined at the time of storage are vital for effective and sustainable research in terms of good scientific practice and conservation of resources. A comprehensive pool of relevant and representative samples is thus indispensable for many fields of veterinary medical research in the future.

A decisive advantage of biobanks over simple material collections is the linking of the physical samples with additional donor data relevant to medicine and research or, depending on the nature of the sample, data on the population or location where the material was sampled. This linking of information in turn allows a more effective and targeted planning of analyses. This is especially true regarding samples of different origin (human – animal – environment) that facilitate application of the one health approach in the first place.

Project progress 2016: In the reporting period, an application to the DFG was prepared to pilot a biobank using a one health concept. Therefore, monitoring aspects according to the WHO and EFSA criteria were integrated in addition to our own research focuses.

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

2.18 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). Various indicator pathogens are being tested: *E. coli* (incl. ESBL), *Campylobacter spp.*, *Salmonella spp.* and MRSA.

Project progress 2016: In the reporting period, the WHO Centre was involved in sampling. Furthermore, the WHO Centre collected additional information on visitors, materials introduced into the holding, productivity as well as climate data, and also performed initial evaluations.

2.19 Research and development for the application of epidemiological methodology

Various different methods for modeling and analysis of veterinary epidemiological data are explored. The data are obtained from internal study data or from counseling cases of the institute and include general modeling and specific applications of contingency table analyses, logistic regression cluster analyses, multiblock redundancy analyses and processing of modern diagnostic data structures of the "Next Generation Sequencing".

Project progress 2016: Statistical methods were developed that can be used to describe the use of drugs. Here, a main focus was the comparison of differently defined measured values to describe the frequency of use; among other issues, different definitions in dosing (UDD = used daily doses vs. DDD = defined daily doses) were discussed.

3 Training events

The WHO-CC HAEI holds training events and scientific colloquia or supports these activities on a regular basis. In 2016, the following events were prepared or organised:

3.1 Seminar on Veterinary Public Health: "Zoonoses in the food chain – incidence and real risks"

The "Seminar on Veterinary Public Health", held on February 5, 2016 at the University of Veterinary Medicine Hannover Foundation, made a contribution to the currently objective available standard of knowledge on the incidence of zoonotic diseases in Germany. The main focus was the cooperation of human and veterinary medicine from health care and scientific authorities. Scientists from various fields of expertise, employees of the public veterinary service as well as diverse practicing veterinarians were among the 130 participants.

An overview of new projects in the battle against zoonoses on both the national and EU level was presented by Dr. Wiemer from the Federal Ministry of Food, Agriculture and Forestry. The results of zoonoses monitoring show that the incidence of *Campylobacter spp.* in the food chain still poses a considerable problem and further measures for risk minimisation are required. After the EHEC crisis in 2011, the European Commission asked the European Food Safety Authority and the European Centre for Disease Prevention and Control to establish a joint database for molecular typing data of pathogens. Another ongoing national project is the further development of official slaughter animal and meat inspections for poultry.

In his lecture, PD Dr. Tenhagen (BfR) explained the structure of zoonosis monitoring in food. Monitoring begins already in livestock, which represents a source for zoonotic pathogens as well as a point for potential interventions. Monitoring continues in the slaughterhouse, where transmission and reproduction of zoonotic pathogens is possible. The product meat can in turn be contaminated on its way to the consumers and also in their kitchen and ultimately cause an infection. Monitoring of zoonotic pathogens mirrors these different steps of the various food chains precisely, so that over the past years, a relatively clear picture of the prevalence of different zoonotic pathogens at the different levels has emerged. New questions have arisen, in particular with regard to resistant pathogens as a zoonotic problem within the last years.

Dr. Janson from the Robert Koch Institute explained the epidemiology and surveillance of zoonoses in the area of human medicine. Surveillance and outbreak investigations as well as epidemiological studies are among the tasks of the RKI. Dr. Janson illustrated the problem of passive surveillance and underreporting using the example of diarrheal diseases. Molecular surveillance plays an important role in the examination of outbreaks and tracing of food along trade chains. Finally, two epidemiological studies of the RKI on zoonoses were presented.

In the second block of the event, which focused on the current situation in Germany with regard to zoonotic pathogens in food-producing animals, Prof. Dr. Bülte (JLU Gießen) first

gave a lecture on bacterial zoonotic pathogens in animals. Then he transitioned from the important zoonoses tuberculosis and brucellosis in the post-war period to the topical problem of food-associated diseases caused by *Campylobacter spp.* and salmonellae.

Dr. Anheyer-Behmenburg (TiHo Hannover) discussed viral zoonotic pathogens and explained the different possible transmission paths, although food-borne infections are rather less frequent. FSME virus and Rift Valley fever virus, for example, can be transmitted by raw milk. Autochthonous infections are becoming more common for the Hepatitis E virus in Germany, probably caused by food made from infected domestic pigs and wild boars.

Dr. Ludewig from the University Leipzig explained the most important parasitic pathogens. Globally, the most significant parasitic-caused zoonosis is toxoplasmosis, although it rarely results in a clinical disease. In food hygiene matters, probably the best known zoonotic parasite is *Trichinella spp.* In the second part of her lecture, Dr. Ludewig explained the effect of food technology procedures on the infectivity of zoonotic pathogens.

Dr. Käsbohrer (BfR) talked about antibiotics, resistances and transfer along the food chain. Summarizing, it could be made clear that clonal spread of resistant germs is particularly important for certain pathogens. These pathogens seem to follow the same transmission paths as observed for other zoonotic pathogens or their non-resistant variants. In contrast, horizontal gene transfer is significant for certain resistance characteristics, in particular in *Enterobacteriaceae*. This not only complicates tracking of infection chains along the food chain but also gives hope that reduction of selection pressure slows down spread. A wide range of human and veterinary medicine measures must be complementary and engage together in order to impede the development of resistance. A one-health approach must be developed and followed stringently.

Dr. Wichmann-Schauer, also from the BfR, explained how outbreak investigations along the food chain are carried out. Since local outbreaks are quickly recognized and notified in most cases, supra-regional outbreaks caused by contaminated food are rarely discovered. To detect an outbreak, the health authorities compare current case numbers with the expected value of prior years. Supra-regional food-caused outbreaks usually require a complex outbreak investigation with the participation of the federal authorities. This in particular aims to identify the food involved in the outbreak and determine its spread in order to then withdraw it from the market. A good cooperation between health, veterinary and federal food control authorities is essential for successful clarification of the outbreak.

The last part of the seminar was started by Dr. Pulz (Lower Saxony Health Authority, NLGA, Hannover), with an outlook on regional perspectives of the cooperation between human and veterinary medicine in Lower Saxony from the point of view of the public health service. For many years, there has been very good cooperation between the NGLA and the Lower Saxony Office for Consumer Protection and Food Safety (LAVES) in Lower Saxony. Based on the last outbreaks (Leptospirosis 2014, EHEC 2015), the nature of cooperation was discussed in detail. It was concluded that standardised data collection instruments are essential. Surveillance systems should be sought that allow a joint evaluation of corresponding human and veterinary medical data on a regional level as well.

Subsequently, Prof. Haunhorst (LAVES, Oldenburg) presented his point of view on regional perspectives in Lower Saxony. The cooperation between human and veterinary public health authorities in Lower Saxony has proven successful since the EHEC crisis in 2011 and has been continually developed since then. Reduced time delays for the notification of special outbreaks between LMÜ and ÖGD, increased exchange of epidemiological data, improved epidemiological reconconditioning of food-caused outbreaks as well as the yearly joint training sessions on zoonoses outbreaks and antibiotic resistance were mentioned by way of examples. In the future, the focus will include continued improvement of coordination of the cooperation as well as communication. Among other objectives, this also includes direct reconciliation regarding analytical parameters and the handing over of isolates as well as the establishment of a joint database with typing criteria of pathogens.

At the end of the seminar, the focus moved from regional to global: Prof. Kreienbrock explained the One Health Approach of the WHO and the cooperation with OIE and FAO in the fight against antibiotic resistances. In addition to the Global Action Plan adopted in May 2015 on the World Health Assembly, he presented the work of the WHO Advisory Group on Integrated Surveillance of Antimicrobial Resistance (AGISAR) as well as of the WHO Collaborating Centres.

During the event, the 2016 Konrad Bögel Award was awarded to Dr. phil. Stephanie Mauti, med. vet., from the Department of Epidemiology and Public Health of the Swiss Tropical and Public-Health-Institute in Basel for her work entitled "*A contribution to dog ecology and dog-related zoonoses in Bamako, Mali*". Every year, this seminar recognizes outstanding work in the field of "Veterinary Public Health" or veterinary medical epidemiology.

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

3.2 Course program: Epidemiology - Biometry 2016

The courses were held in February and March 2016 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.

Three courses were offered, each consisting of three days training: Descriptive Epidemiological Methods, Analytical Epidemiological Methods and Evaluation of Diagnostic Tests.

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 "Evaluation of diagnostic tests" course imparted knowledge on study planning, sample collection, evaluation and critical interpretation of the different study types for the

evaluation of diagnostic tests. The required statistical and epidemiological concepts were explained.

All courses received positive evaluations from participants.

4 Ongoing activities

4.1 Work plan WHO-CC HAEI

In the course of the re-designation of the WHO Centre, a new work plan was developed. Since the complete process up to and including acceptance of the redesignation took longer than expected, the work plan must be updated and supplemented. Thus, a number of conference calls between WHO and the WHO Centre have been held in the reporting year to coordinate the work plan and supplements. In particular, the original schedules for the individual activities had to be adjusted and some content-related clarifications had to be included.

4.2 Website redesign

Until now, the WHO Centre has operated the internet platform www.veterinary-public-health.de. However, 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. The plan is to develop new concepts in the scope of the TORs in 2017.

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

4.3 "Advisory group on Integrated Surveillance on Antimicrobial Resistance" (AGISAR)

The 7th Meeting of the AGISAR took place from October 17 – 20, 2016 at the North Carolina State University in Raleigh, USA. In addition to the Tricycle Project (see 2.2), the revision of the list of Critically Important Antibiotics for human medicine (WHO-CIA list), as well as the completion of the "WHO-AGISAR guidance on integrated surveillance of antimicrobial resistance" were the main topics. Furthermore, the progresses in some other AGISAR projects as well as international activities of OIE, FAO and WHO in the scope of One Health were presented.

The WHO Centre was represented by Prof. Kreienbrock at this meeting and at the ESBL-Ec Tricycle Project Meeting as resource advisor. This meant that various research activities from the WHO Centre HAEI could be directly included into the protocols.

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

4.4 7. Symposium on Antimicrobial Resistance in Animals and the Environment (ARAE)

The Antimicrobial Resistance in Animals and the Environment (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. ARAE offers the opportunity for interdisciplinary exchange in terms of One Health. It also supports the development of new research projects that lead to a better understanding of the spread of antibiotic resistances and thus can make an important contribution to the development of new control strategies. ARAE takes place every two years and will be held on June 26 - 28, 2017, for the first time in Germany.

The WHO-CC HAEI is significantly involved in the planning and organisation of the ARAE. In the reporting period, a first meeting of the organising committee was held in the WHO Centre, numerous conference calls with the organisation and scientific committee were organised and the ARAE website was created and put into operation. By the end of 2016, a substantial part of the preliminary work had already been completed.

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

4.5 Seminar Veterinary Public Health 2017

In the reporting period, the Veterinary Public Health 2017 Seminar on the topic “Chemical Hazards in the Food Chain – Reality or Fantasy?” 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 Meeting of the WHO-Collaborating Centres in Geneva

On May 16 and 17, 2016, a meeting of all WHO-CCs of the WHO Food Safety Departments and further stakeholders took place for the first time. The focuses of WHO activities for the next five years were first presented and it was explained where there is need for technical expertise, in the view of both WHO Headquarters as well as the Regional WHO Offices. Subsequently, a report of experiences on the networking between the WHO-CCs was presented.

In addition to an overview of what partners, such as FAO and OIE, as well as sponsors expect from WHO, there were two half days on which the following topics were discussed in smaller groups:

- Identification of gaps and synergies
- Identification of lack of resources and possibilities for resource mobilisation
- Exchange of success stories

The meeting received very positive evaluations. The WHO-CCs had the opportunity to establish contacts and to meet possible cooperation partners.

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

5.2 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 Epidemiology Unit, Department of Agriculture, Belfast, Northern Ireland
- 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
- Department of Epidemiology, French Agency for Food, Environmental and Occupational Health & Safety (ANSES), Ploufragan, France
- 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

5.3 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
- 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)
- Ministry of Energy, Agriculture, the Environment and Rural Areas, Schleswig-Holstein (MELUR), Kiel
- Veterinary Faculty of the University of Leipzig
- BALVI GmbH, Lübeck

- Veterinary and Medical Faculty, Institute for Statistics of the Ludwig Maximilians University Munich
- Helmholtz Research Centre for Environment and Health, 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, Oldenburg (LAVES)
- Faculty of Natural Sciences, University of Paderborn
- 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
- 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 2016 reporting period:

6.1 Scientific publications in journals

- Alajmi A, Klein G, Greiner M, Grabowski N, Fohler S, Campe A, Scheu T, Hoedemaker M, Abdulmawjood A. Potential role of real-time PCR for detecting *Mycobacterium avium* subsp. *paratuberculosis* in chronically diseased milking cows: a case control study. [Eignung der Real-Time PCR für den Nachweis von *Mycobacterium avium* subsp. *paratuberculosis* in Proben chronisch kranker Milchkühe: Ergebnisse einer Fall-Kontroll-Studie]. *Berl Munch Tierarztl Wochenschr* 2016;129(7-8):304-309 . doi: 10.2376/0005-9366-15103
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