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Documentation of antimicrobial resistance data in veterinary practices in Germany

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Summary Antimicrobial resistance remains one of the greatest public health challenges of our time. By creating a selection pressure, the use of antimicrobials in general and the inappropriate overuse especially, fuels the emergence and spread of antimicrobial resistant bacteria in all sectors (human, veterinary and environment).
Therefore, numerous (inter-)national surveillance systems have been established to monitor the use of antimicrobial agents, yet the recording of antimicrobial resistance at the farm level remains scarce.
In Germany, the documentation of the use of antimicrobial agents in food-producing animals has been mandatory since 1975, with a standardised documentation and reporting format in place today. However, the reporting of susceptibility test results at the farm level is not subject to legal regulation. While there are some regulatory frameworks regarding documentation, we observe considerable heterogeneity in terms of content and format of the documented data.
The objective of this investigation is to provide a detailed account of the existing heterogeneity of documentation in German veterinary practices, in order to develop a data structure that can be used for future AMR monitoring at the farm level, based on routine veterinary diagnostic data.
To this end, the data transfer and processing are described, and the documentation of the individual components of the susceptibility tests in participating practices and laboratories is discussed. Based on this, it will be shown which components should be included in a monitoring system and why.
Finally, two possible paths for a monitoring system will be presented, along with recommendations.

Keywords resistance monitoring, heterogeneity, database, livestock

Dokumentation antimikrobieller Resistenzdaten in deutschen Tierarztpraxen

Zusammenfassung Antimikrobielle Resistenz stellt nach wie vor eine der größten Herausforderungen für die öffentliche Gesundheit dar. Der Einsatz von Antibiotika im Allgemeinen und der übermäßige Einsatz im Besonderen erzeugen einen Selektionsdruck, der das Auftreten und die Ausbreitung von antibiotikaresistenten Erregern in allen Bereichen (Human-, Veterinär- und Umweltbereich) begünstigt.
Daher wurden zahlreiche (inter-)nationale Monitoringsysteme zur Überwachung des Einsatzes antimikrobieller Substanzen etabliert, jedoch ist die Erfassung von Antibiotikaresistenzen auf der Ebene landwirtschaftlicher Betriebe nach wie vor unzureichend.
In Deutschland ist die Dokumentation des Einsatzes antimikrobieller Mittel bei Tieren, die der Lebensmittelgewinnung dienen, seit 1975 vorgeschrieben. Seitdem hat sich ein standardisiertes Dokumentations- und Berichtsformat etabliert. Die Meldung der Ergebnisse von Empfindlichkeitstests auf Betriebsebene unterliegt jedoch keiner gesetzlichen Regelung. Obgleich einige rechtliche Rahmenbedingungen für die Dokumentation bestehen, lässt sich eine erhebliche Heterogenität hinsichtlich des Inhalts und der Form der dokumentierten Daten beobachten.
Ziel dieser Studie ist es, die bestehende Heterogenität der Dokumentation in den deutschen Tierarztpraxen ausführlich zu beschreiben, um eine Datenstruktur zu entwickeln, die für ein zukünftiges Antibiotikaresistenzmonitoring auf Betriebsebene, basierend auf den veterinärdiagnostischen Routinedaten, genutzt werden kann.
Dafür werden der Datentransfer und die Datenaufbereitung beschrieben sowie die Dokumentation der einzelnen Komponenten der Empfindlichkeitsprüfung in teilnehmenden Praxen bzw. Laboren diskutiert. Darauf aufbauend wird aufgezeigt, welche der Komponenten zwingend in ein Monitoring aufgenommen werden sollten und warum.
Abschließend werden zwei mögliche Wege für ein Monitoringsystem vorgestellt und Empfehlungen gegeben.

Schlüsselwörter Resistenzmonitoring, Heterogenität, Datenbank, Lebensmittel liefernde Tiere

Introduction

Antimicrobial, or more precisely antibiotic, resistance is currently recognised as one of the biggest threats to public health. A systematic analysis conducted by several experts estimated that in 2019, 4.95 million deaths worldwide were associated with antibiotic resistance, with 1.27 million of those deaths directly attributable to the phenomenon (Murray et al. 2022). If left unchecked, this number might rise to 10 million deaths in 2050 (O'Neill 2014). Antimicrobial resistance (AMR) is primarily driven by the selection pressure exerted by antimicrobial use (AMU) – exacerbated by inappropriate overuse – in human and veterinary medicine, as well as the contamination of the environmental sector, which further promotes the emergence and spread of AMR (EFSA et al. 2021, WOAH 2021, European Commission 2022, Murray et al. 2022, WHO 2023).Therefore, a One Health approach (WHO 2015, European Parliament and the Council 2019) that includes these three sectors is essential to deal with this problem. Numerous initiatives worldwide address the implementation of AMU and AMR monitoring and surveillance systems (MOSS), as well as the standardisation and evaluation of collected data. For instance, the Global Antimicrobial Resistance and Use Surveillance System (GLASS [WHO 2023]), the Advisory Group on Integrated Surveillance of Antimicrobial Resistance (AGISAR [WHO 2017]), the European Antimicrobial Resistance Surveillance network in veterinary medicine (EARS-Vet [Mader et al. 2021]), and the Danish Integrated Antimicrobial Resistance Monitoring and Research Programme (DANMAP [National Food Institute 2021]) are such initiatives.

With regard to the veterinary sector, on 28th of January 2022, new EU legislation came into force that implements the collection of AMU data for food-producing animals, as well as companion animals, in all EU member states (European Parliament and the Council 2019). As specified in the Commission Implementing Decision 2020/1729 (based on Directive 2003/99/EC), AMR monitoring is conducted through an active sampling scheme of *Salmonella* and *Campylobacter* species, as well as commensal *Escherichia coli*, and, on a voluntarily basis, *Enterococci*, for healthy food-producing animals (e.g., fattening pigs and broilers) and meat in the EU (European Parliament and the Council of the European Union 2003, European Commission 2020). In Germany, the national zoonosis monitoring (Federal Office of Consumer Protection and Food Safety 2022b) is responsible for its implementation. However, Mader et al. (2021) state that "the[se] existing surveillance systems lack [antimicrobial resistance] data from clinical isolates of animals".

In order to address this issue, Germany implemented the national resistance monitoring of animal pathogenic bacteria (GermVet [Federal Office of Consumer Protection and Food Safety 2022a]). The programme collects and tests isolates from sick animals, focusing on predefined bacteria. However, the programme relies on voluntary submissions, which only cover a portion of all diagnostic laboratories in Germany, and excludes all bacteria outside the predefined scope. Furthermore, the data collected do not permit the drawing of conclusions about individual farms, thereby preventing benchmarking and the identification of farms with high AMR levels.

The value of farm-level monitoring for AMU MOSS has been demonstrated by the advantages it offers over monitoring systems that evaluate condensed data. These advantages include "[…] targeting unnecessary or inappropriate use, encouraging improvements in animal husbandry, disease prevention and control, and enabling detailed risk and trend analyses" (Sanders et al. 2020). With regard to AMR, on-farm data are essential to establish a comprehensive database, which can be used to describe the extent of the influence of an individual farm's antimicrobial treatment history on the development of AMR and to detect additional drivers of AMR at the population level. For this purpose, the Veterinary Antimicrobial Usage and Resistance project (VetAmUR) was initiated in 2021 with the objective of collecting AMU and AMR data (clinical samples from routine veterinary care) simultaneously from German livestock farms in a longitudinal approach (Bonzelett and Rehberg 2021).

The documentation of AMU data has been mandatory in Germany since 1975 and is currently subject to a legally standardised format (Bundesministerium der Justiz 1976, 2021). The mandatory reporting began in 2014. However, there are no regulations in place for the reporting of AMR data at the farm level, despite the existence of obligations to test for AMR in specific cases in accordance with § 12c of the amendment to the regulations of veterinary pharmacies (TÄHAV) (Bundesministerium der Justiz 2018). Such cases include the testing of animals prior to the administration of third- and fourth-generation cephalosporins and fluoroquinolones, as well as the switching of antimicrobial substances during the course of treatment. Furthermore, § 12d of the TÄHAV stipulates that isolated bacteria must be tested for susceptibility using recognised methods, that the sampled animals must be representative of the clinical signs, and that bacteria responsible for the disease must be isolated based on the clinical symptoms. In addition, § 13 of the TÄHAV defines the specific variables that must to be documented. Nevertheless, there is currently no harmonised format for collecting and reporting data on AMR testing, resulting in considerable heterogeneity in documentation at farm level.

Therefore, this investigation aims to describe the current concepts and structures of AMR documentation in German veterinary practices. The objective is to take a first step towards developing a practical, integrated AMU-AMR monitoring system at the farm level, taking into account the possibility that AMR reporting may become mandatory in the future.

Conceptual Framework

General Project Design

This investigation of the heterogeneity of AMR data in veterinary practices is based on the VetAmUR project, which focuses on the simultaneous collection of antimicrobial use and resistance data at the individual farm level in Germany to identify possible connections and the impact of AMU on AMR at the population level.

Veterinarians were recruited on a voluntary basis for data collection throughout Germany. Recruitment was conducted via a call for participation in the journal of the Federal Veterinary Surgeons' Association (BTK) (Kasabova et al. 2021), which is distributed to all approbated veterinarians in Germany. Additionally, direct recruitment was employed. The recruited veterinarians should cover a sample of farms as clients, representing the distribution of livestock across Germany. Generally, practices that treated the following animal species and production types were included in the project: pigs (piglets, weaner, fattening pigs, and sows), cows (dairy cows, calves (fattening, dairy), and fattening cattle), and chicken (broilers, and laying hens). The farm sizes varied depending on the animal species and production type. Information regarding the number of pig and cattle farms and their livestock units can be found in Table 1.

Due to a strict all-in/all-out procedure commonly employed in poultry farms, the data should be evaluated at the flock level if possible, taking into account the different farm and integration structures. Consequently, the data structure differs from that for pigs and cattle, and requires different comprehensive data management. Therefore, the results for poultry are subject to further analysis and have not been included here.

Data on AMU and AMR were provided by the veterinarians themselves, either from their electronic practice management software (EPMS) or via paper records. The AMU data were collected in accordance with the monitoring concept previously developed in the Veterinary Consumption of Antibiotics (VetCAb) project (Merle et al. 2012, Hemme et al. 2017), using the application and delivery forms that are currently mandatory in Germany. The provided information included animal identification, the number and type of animals treated, the drug name and dosage, the date and duration of treatment, the indication, the application route, and, if documented, the estimated weight of the animals (Bundesministerium der Justiz 1976, 2021). AMU data structures and trends between 2006 and 2020 have been described in detail within the VetCAb project. As this current investigation focuses on describing AMR data, there will be no further discussion of the AMU data obtained in this project.

AMR Data

As previously stated, §13 of the TÄHAV specifies the variables that must be documented when conducting a susceptibility test (Bundesministerium der Justiz 2018). These variables encompass the date of sample collection, the name and address of the farmer, the identity of the sampled animals, the material tested, the test used, the start date of testing and the date of the test result, as well as the original and interpreted test results. Nevertheless, since the reporting of AMR data at the farm level is not currently mandatory by law there are no standardised forms for documentation. Consequently, the data submitted by the participating veterinary practices are heterogeneous. However, for this project, data on AMR should include at least metadata and phenotyping data. Metadata should include farm ID, veterinarian ID, laboratory ID, order number and sample identification, animal species and production type, origin and type of sample, the reason for sampling (if available), and date of analysis. Phenotyping data should include the method of susceptibility testing, the isolated bacteria and antimicrobial substances tested, and the original (minimal inhibitory concentration and inhibition zone diameters) or already interpreted (susceptible, intermediate, resistant) AMR results from laboratory processing (with the used standard, if available). For further details, please refer to Table 2.

This investigation highlights the heterogeneity of the provided AMR data, both in terms of format and content. In order to assess the coverage of available veterinary breakpoints, we also compared participants' susceptibility test results with official CLSI documents, DVG recommendations, and the EUCAST list of expected resistant phenotypes (Fessler et al. 2022, EUCAST 2023c, CLSI 2024). As the majority of available breakpoints relate to bacteria that cause respiratory diseases, we focused our evaluation on this area.

Data Processing and Storage and Exemplary Statistical Analyses

The project worked with data from veterinary practices participating in this investigation. Although almost all participants used EPMS for AMR and related outcomes, the data structures and physical formats were not harmonised. Only a few EPMS maintain AMR data structures directly within the software. From these, the data were provided in digital form, e.g., by Excel spreadsheets or similar, and could be integrated directly into a MOSS via an interface. Other veterinarians provided analogue handwritten documents or integrated scanned documents. These documents exhibited a variety of different data structures and formats, including different layouts of PDFs and disparate structures (e.g., susceptibility results in wide or long format). Consequently, a number of data extraction pipelines were

TABLE 1: Client farms of veterinary practices participating in the VetAmUR project: number of farms as well as the minimum, mean with 95% confidence limits, median, interquartile range and maximum number of livestock units kept at those farms, divided by animal species and production type

Animal species	Production type	Number of farms	Minimum	Mean ± 95% confidence limits	Median	Interquartile range	Maximum
pigs	piglets	289	10	1,773 ± 272	769	1400	102,480
	weaner	338	2	970 ± 36	680	850	7,000
	fattening pigs	778	2	932 ± 19	800	877	10,000
	sows	301	1	273 ± 27	150	222	10,000
cattle	dairy cows	118	1	152 ± 10	135	130	650
	dairy calves	114	2	45 ± 4	30	35	371
	fattening calves	365	1	371 ± 36	180	390	3,600

TABLE 2: Antimicrobial resistance data structure: variables and their descriptions

Variable	Description	Comment
Metadata		
Record ID	Unique number given by software	
Farm ID	Pseudonymised identity number	Assigned to the individual farmers by a member of the project team in ascending order
Veterinarian ID	Pseudonymised identity number	Assigned to the individual veterinarians by a member of the project team in ascending order
Laboratory ID	Pseudonymised identity number	Assigned to the individual laboratories by a member of the project team in ascending order
Order number	Identifier	Assigned to one or several samples from the same delivery upon arrival at the laboratory; alpha-numeric
Sample ID	Isolate-ID unique identifier	Assigned to a single isolate from a sample; alpha-numeric
Production type	For pigs: piglets, sows, weaner, fattening pigs For cattle: cow, heifer, dairy calf, fattening calf, beef cattle For chickens: broilers, laying hens	Number-coded
Sample material	Such as faeces, milk, blood	Number-coded
Reason for sampling	Such as therapy failure, TÄHAV	Free text
Date of sample taking	Date of sample taking	If available
Start date of testing	Date of arrival at laboratory	If available
Date of results	Date of test results	
Number of lactations	Number of lactations at the time of sample taking in case of milk samples	For dairy only; if available
Date of last calving	Date of last calving at the time of sample taking in case of milk samples	For dairy only; if available
Udder quarter	Udder quarter e.g. hind left quarter in case of milk samples	For dairy only; if available
Phenotyping Data		
Method of susceptibility testing	Either microdilution, agar diffusion or unknown/other method	
Sampling, Testing and Evaluation standards	Method used for sample taking, cultivation, and testing as well as evaluation standard such as CLSI, EUCAST or other	Including used version; free text
Pathogen	Such as *Escherichia coli*	Number-coded
Substances	Antimicrobial substances per isolate, such as Ampicillin	Number-coded
Interpreted results	S=susceptible, I=intermediate, R=resistant	
Original results MIC	Minimal inhibitory concentration	If available
Original results IZD	Inhibition zone diameter	If available

examined to harmonise data from this multitude of different data sources.

First, a target database for the AMR data was defined, containing the data structure shown in Table 2. The data structure was realised and maintained using REDCap (Research Electronic Data Capture, ©Vanderbuilt University, Nashville, 2004) (Anonymous 2004). REDCap includes a data storage, the presentation of the entered data, processing of the data, real data validation, data export functions for all common statistical programmes, and many more features (Harris et al. 2009, 2019).

In the event that data were entered manually, no additional steps were required. However, if data were uploaded, the original data needed to be restructured into the target data structure first. Data provided directly by the EPMS could usually be organised via an interface protocol. In contrast, if data were provided in graphical format, the information needed to be extracted and transformed using an ETL (Extract Transform Load) process.

The concept of ETL generally consists of three steps: the extraction of data, its transformation, and its (up-) loading into a target database (Farkisch 2011).

In order to test the feasibility of extracting data from text-based PDFs and similar documents at the population level (step 1 of the ETL), the software tool Tabula (Manuel Aristarán et al. 2012, Dougherty and Ilyankou 2021) was employed. The data could be extracted in the form of comma-separated values (csv), tab-separated values (tsv), or JavaScript Object Notation (json) files.

For the second ETL step, KNIME (Konstanz Information Miner) (KNIME AG 2004) was employed, which supports visual workflows and uses a flow diagram interface. The extracted data were transformed, rearranged into the REDCap structure, and exported for upload into the database.

For the purpose of evaluating preliminary results, the harmonised data from REDCap were exported in the form of flat files, such as csv, or in the form of proprietary formats to statistical evaluation programmes such as SAS (SAS 9.4 TS level 1M7 (SAS Institute Inc., Cary, NC, USA)).

The entire ETL process is depicted in Figure 1.

At this point, it should be noted that the software used in this project is merely provided as an example and does not represent product recommendations by the authors.

Results

Seven veterinary practices with the described characteristics were included in the evaluation. The practices were linked to 2,170 farms – including 934 pig farms and 596 cattle farms – and worked with 18 in-house and/or service laboratories. The prelimi-

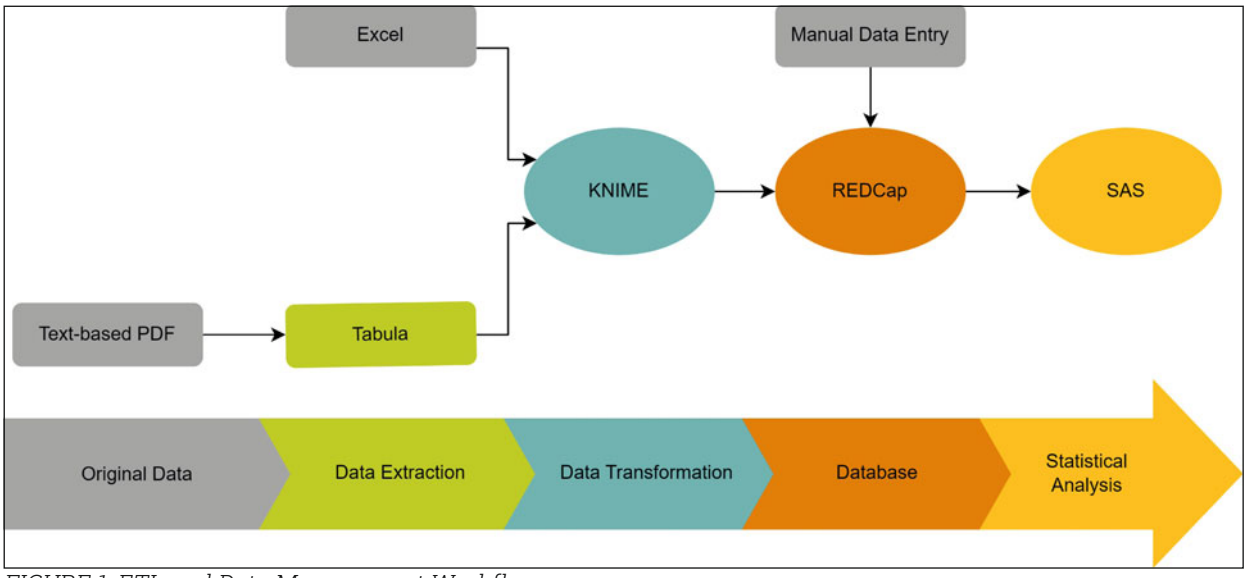

Figure: Clarissa Bonzelett

FIGURE 1: ETL and Data Management Workflow

nary results comprise 2,790 pig samples collected from 2017 to 2023 and 3,322 cattle samples collected from 2019 to 2023. Of the total samples, 142 were only isolated for the bacteria, without any susceptibility test being performed. The number of samples per farm varied between the years and animal species (see Table 3 for details). The overall median number of samples per farm and year was 1 for pigs (mean 1.99 ± 0.20) with an interquartile range (IQR) of 3 and 3 for cattle (mean 6.41 ± 1.24) with an IQR of 8. The median number of samples per farm per year also varied between the veterinary practices, ranging from 0 (mean 0.61 ± 0.15) with an IQR of 1 to 7 (mean 8.12 ± 4.78) with an IQR of 7.

The data provided varied considerably in terms of content and format. The following section presents the differences in documentation (some data were documented incomplete or missing), content of meta- and phenotyping data, as well as transmission and technical processing, giving an overview of the heterogeneity of AMR data from veterinary practices dealing with livestock.

Metadata

The documentation of AMR in veterinary practices represents an accompanying process of diagnosis and control of the treatment efficacy. Consequently, the selection of the laboratory facility and the methods employed for the evaluation of AMR is largely dependent on the specific objective of the test, which is reflected in the type of documentation generated.

In the course of our investigation, we found that five practices exclusively used service laboratories. Three practices used only one laboratory each, one practice used three and another practice used five different service laboratories. In contrast, two practices used a combination of one in-house laboratory and two or three service laboratories, respectively.

Furthermore, two laboratories did not provide unique identifiers for each isolate, but only for samples/laboratory orders. Subsequently, we then assigned a unique identifier to each isolate.

TABLE 3: Samples taken in the routine diagnostics of the participating veterinary practices: median and mean number of samples per farm as well as 95% confidence limits and interquartile range, divided by animal species and year

Animal species	Year	Median	Mean ± 95% confidence limits	Interquartile range
pigs	2017	0	1.04 ± 0.25	1
	2018	2	2.87 ± 0.40	3
	2019	2	3.35 ± 0.69	3
	2020	2	3.34 ± 0.87	3
	2021	1	2.71 ± 0.78	3
	2022	0	1.75 ± 0.45	2
	2023	2	2.67 ± 1.77	4
cattle	2019	2	4.37 ± 1.53	6
	2020	6	9.11 ± 2.94	8
	2021	4	9.55 ± 3.33	9
	2022	0	3.00 ± 2.06	1
	2023	2	5.00 ± 3.96	6

Information regarding the number of animals from which a sample originated was missing for samples from pigs and cattle, with the exception of samples from dairy cows, which were typically accompanied by a cow identification, ranging from pet names to transponder or ear tag numbers. Nevertheless, individual isolates could be traced back to their respective farms, specific dates, animal species, and even production types, since information on the type of production was only lacking in 2.8% of all samples.

Additionally, the reason for sample taking was rarely documented in the metadata, and therefore considered missing.

In contrast, in almost all cases (0.4% missing), information on the sample material was provided. In general, in our preliminary results, samples due to gastrointestinal (38.4%) and respiratory (25.9%) symptoms were tested most often for pigs. For cattle, milk samples (46.0%) and samples from the respiratory tract (48.0%) were tested most often. Depending on the production type, additional organ samples were collected regularly, including samples of the brain (piglets and weaners) and cervix (sows). For further information,

please refer to Supplement 1. In 78.9% of milk samples from dairy cows, the sampled udder quarter was documented, whereas the number of lactations and date of last calving were only available in 9.0% of all milk samples.

Lastly, with regard to the susceptibility tests, the data provided included up to three different dates: the date of sample taking, the date of arrival at the laboratory/start of the susceptibility testing, and the date of susceptibility results. In 57.8% of the samples, the date of sample taking was provided. The date of arrival at the laboratory was documented in 62.9% of the samples, and the date of the susceptibility test results was recorded in all cases.

Phenotyping Data

The detection of AMR was conducted using microdilution or agar diffusion. This information was provided by all participating practices. Specifically, the in-house or service laboratories of four practices used solely microdilution, while one practice used solely agar diffusion. Two practices employed agar diffusion in their in-house laboratories, while their service laboratories employed microdilution. In general, genotypic analyses were only sporadically used by two veterinary practices and therefore not documented in this project.

In all cases, information on the isolated bacteria was provided. Overall, the most frequently isolated bacteria belonged to the families *Escherichia* (28.4%) and *Streptococcus* (23.5%). In addition, depending on the animal species and production type, other bacteria were isolated regularly, including *Staphylococcus* (e.g., dairy cattle and sows), *Clostridia* (piglets), or *Pasteurella* (fattening calves and fattening pigs). For further information, please refer to Supplement 2.

Ten laboratories explicitly used microdilution plate layouts for farm animals as recommended by the DVG (Fessler et al. 2022), whereas eight laboratories also used their own layouts (especially with agar diffusion), which resulted in discrepancies in the substances tested. In the susceptibility tests, Penicillin G, Ampicillin, Amoxicillin and Clavulanic Acid, Spectinomycin, Enrofloxacin, Tetracycline, Florfenicol, and Erythromycin were among the twelve most frequently tested substances in both agar diffusion and microdilution. Furthermore, Apramycin, Trimethoprim and Sulfonamides, Neomycin, and Colistin were used in 80.1% to 99.3% of agar diffusion tests, while Gentamicin, Tilmicosin, Tulathromycin, and Tiamulin were used in 70.8% to 71.0% of microdilution tests. Other substances were tested at varying frequencies or only tested in one of the methods, e.g., Gamithromycin (microdilution) and Paromomycin (agar diffusion). In all cases, the information pertaining to the tested substances was provided. For further information, please refer to Supplement 3.

Most data included in our investigation comprised original values – either minimum inhibitory concentration (MIC) or inhibition zone diameter (IZD) – while some in-house laboratories provided only interpreted data in the form of S (susceptible), I (intermediate), and R (resistant). The preliminary analysis revealed that interpreted data were missing in 6.6% of all cases. The majority of results (99.6%) were accompanied by original data in the case of microdilution, while only 14.1% were accompanied by original data in the case of agar diffusion. Four veterinary practices provided original data for 99.2% to 100% of samples tested with microdilution, whereas one practice provided original data for only 57.1% of samples tested with microdilution. In the case of agar diffusion, three veterinary practices did not provide original data, while two practices provided original data for 98.6% and 100% of samples, respectively.

An analysis of the AMR data structure of the participating veterinary practices showed that the methods of sampling, cultivation, and isolation of the bacteria were only known for one laboratory. In contrast, the standards for susceptibility testing and evaluation were provided in most cases, with only two laboratories lacking this information. The standards for AMR interpretation in our investigation could be divided into three categories: CLSI (CLSI 2024), recommendations by the German Veterinary Society (DVG; [Fessler et al. 2022]), and individual evaluation standards by the laboratories (with or without further information provided). In detail, of the 16 laboratories providing information on the standard used, ten laboratories exclusively employed CLSI and DVG recommendations, two laboratories used a combination of CLSI breakpoints and individual standards in the absence of breakpoints, two laboratories employed only individual standards but did not provide further information, and two laboratories used CLSI for microdilution and did not provide information on the standards used for agar diffusion.

As previously stated in the conceptual framework, the results of the susceptibility tests conducted on respiratory tract samples were analysed in order to ascertain the availability of breakpoints. In our data set, 15 different bacteria were isolated from respiratory tract samples of cattle and tested for susceptibility. Among these bacteria, *Pasteurella multocida* (66.41%) and *Mannheimia haemolytica* (24.39%) accounted for more than 90% of all cases. In accordance with the CLSI guidelines, breakpoints were available in 55.1% of the test results where the animal species, organ system, substance, and bacteria were a perfect match. In addition, other breakpoints were available: 6.03% for a different animal species, and 1.18% for humans. In 0.22% of cases, the bacterial subspecies was unknown, rendering it uncertain whether breakpoints were available or not, and in 37.47% of cases, breakpoints were missing. For further information, please refer to Supplement 4.

For pigs, our data set included susceptibility tests for 23 different bacteria, with different *Streptococcus* (47.8%), *Pasteurella* (19.02%), *Actinobacillus* (8.37%), and *Bordetella bronchiseptica* (9.89%) accounting for more than 85%. CLSI breakpoints were available in 19.16% of the tests where the animal species, organ system, substance, and bacteria were a perfect match. Additionally, other breakpoints were available: 8.9% for different animal species and 5.18% for humans. In 9.39% of cases, the bacterial subspecies was unknown, rendering it uncertain whether breakpoints were available or not, and in 57.37% of cases, breakpoints were missing. For further information, please refer to Supplement 5.

ETL-Pipelines

In veterinary practices, data are typically stored either in the EPMS or in handwritten files. In this investigation, the majority of veterinarians provided data on AMU and AMR in digital format, although a minority still used paper documentation exclusively. In the case of the application and delivery forms, two veterinarians used PDFs, four used Excel spreadsheets, and one used handwritten documentation. With regard to the susceptibility tests, two veterinarians used Excel spreadsheets, one used a combination of Excel spreadsheets and PDFs, and four used only PDFs.

In the case of document-based transmission of AMR data, the ETL pipeline is not homogeneous. In our investigation, eight practice-laboratory combinations transmitted data via (text-based) PDF documents. However, if the number of animals sampled (e.g., one to 55 samples per document, with different numbers of tables with susceptibility results) or the type or number of isolates tested differed, the PDF layout differed as well, resulting in up to 69 Tabula-KNIME-pipelines for one veterinary practice-laboratory combination. Within this framework, a technical transmission was possible, but the required time for processing corresponded to the time needed for manual data entry.

Discussion

Our investigations have revealed that while it is indeed possible to collect data from routine diagnostics for scientific purposes, the process is time-consuming and involves a number of additional difficulties when attempting to harmonise the evaluation of the data. These difficulties include different types of filing, sampling schemes, laboratory methods and missing values.

A joint AMU-AMR-MOSS is necessary to ascertain whether reduced use also leads to a reduced resistance situation and to identify the correlations at the farm level. Since no specifications have been provided thus far on how to collect and record data for this type of monitoring, the results of the VetAmUR project can provide an overview of the current structures and their heterogeneity and aid in the implementation of such a monitoring.

Data quality

Data enrolment for this project was shaped individually in order to ensure that all currently used procedures were accounted for and that the existing variations in documentation processes and formats could be documented. This involved tailoring the data transfer process to align with the software available in each practice as well as the type of filing (paper, PDF, Excel), whether by post, cloud, email or digital transmission on site. However, the project was dependent on the voluntary enrolment of veterinary practices, which may have introduced a degree of bias. The seven participating practices analysed in this investigation represent only a small proportion of all veterinarians in Germany and may have been a selective group who was very open to the topic of AMR and had sufficient time to participate in the project. Furthermore, non-responders were excluded without disclosing the reasons and attitudes behind their lack of participation, which could have varied from disinterest to inability. In addition, it should be noted that while the invitation to participate was sent to all veterinarians throughout Germany, the majority of participants were based in Northern Germany, which may have introduced a regional bias. Therefore, it is important to note that the reported results may only represent a subset of issues and may not necessarily reflect the overall situation in Germany.

However, the participating veterinarians met certain characteristics: They were not employed by farms, but by veterinary practices, and treated a considerable number of conventional farms of varying sizes that kept a variety of cattle and pig production types. Consequently, these results may represent common problems in practice and are suitable for forming hypotheses about the current state of resistance data documentation, which will need to be tested in further projects. Despite the limited sample size in this investigation, the considerable heterogeneity in testing behaviour and documentation observed in these practices made data processing complex, which could pose challenges in analysing a larger collective and should be taken into account in further studies. The restricted average number of available samples per farm and year represents an additional challenge in the evaluation of AMR at the farm level. Nevertheless, the results of this investigation could serve as an initial milestone in developing an integrated AMU and AMR monitoring system.

The proposed VetAmUR data structure is consistent with several international initiatives regarding AMU and AMR monitoring (WHO 2017, 2023, ECDC/EFSA/EMA 2024) and encompasses the most relevant data currently available in AMR data documentation in veterinary practices in Germany, including the variables specified in §13 of the TÄHAV (Bundesministerium der Justiz 2018). The feasibility project demonstrates that, when analysing AMR data from routine diagnostics, two general areas of data can be taken into account: metadata and AMR phenotyping results (see Table 2).

As previously stated, the participating veterinarians used a multitude of laboratories. Consequently, there were discrepancies in the methods and standards employed, as well as in the documentation of the results of susceptibility tests. This heterogeneity is a common problem described in several documents (WHO 2021, European Centre for Disease Prevention and Control 2022).

Metadata

It is often not possible to associate isolates with individual food-producing animals. This includes dairy cows, which may have identification in the provided data but lack uniform documentation. Therefore, conclusions cannot be drawn from individual treatment histories. As a result, the statistical unit of the analysis is the individual isolate, rather than the animal patient, and the analysis is limited to the overall situation of the production type on each farm.

As stated in other documents dealing with AMR monitoring systems, the reason for taking a sam-

ple greatly influences the results (Waldmann et al. 2018, Federal Office of Consumer Protection and Food Safety 2022a, Spronk et al. 2023). For instance, different AMR results are to be expected if samples are taken from animals after arriving at a new farm or entry into a new pen (lower resistance rates expected) compared to sampling of sick animals, particularly following treatment failure (higher resistance rates expected). Consequently, it is necessary to consider the potential for selection biases (over- and underestimation of AMR) to influence the results. To control for this influence, the reason for sampling is an essential information and needs to be documented as metadata.

In veterinary practice, samples are taken and analysed either due to specific (diagnostic and therapeutic) decisions made by the veterinarian and farmer or due to legal requirements. Tests conducted based on the decisions of the veterinarians or farmers are primarily due to reasons such as an acute health problem on the farm – affecting a larger group of animals – or treatment failure, as well as routine testing for certain production types such as herd status screening – e.g., in addition to somatic cell count for dairy cattle – or for the introduction of a new group of animals to the farm ("Einstalluntersuchung").

In contrast, susceptibility tests of animal bacteria conducted in accordance with legal regulations in Germany are mainly based on the TÄHAV and the guidelines for the prudent use of veterinary antimicrobial drugs. The reasons for testing include switching to another antimicrobial, treatment lasting longer than seven days or deviating from the licensed duration, treatment with more than one antimicrobial substance at the same time, or the need to test prior to treatment with a cephalosporin of the third and fourth generation or fluoroquinolone (Federal Veterinary Surgeons' Association [BTK] 2015, Bundesministerium der Justiz 2018).

Furthermore, additional individual reasons may apply.

Currently, documents rarely contain information on the detailed reason for taking samples for AMR testing. Accordingly, the named reasons in this manuscript were acquired by the authors via personal communications with the veterinarians and cannot be verified based on the provided data. Nevertheless, in an official MOSS, the reason for sampling should become a mandatory field of entry. We suggest the following distinction of main reasons for sample taking: sampling according to regulations, therapy failure, introduction of a new animal group to the farm (e.g., fattening calves, as observed in our data), AMR herd screening (e.g., dairy, as observed in our data), and a category for miscellaneous reasons.

Our results demonstrated a wide range of sampled organs and materials, which should be taken into account when interpreting the susceptibility test results. While sampling animals, it is crucial to consider the reason for sampling (as mentioned above) and the origin of the samples, as bacterial loads can vary considerably across different organs (Dünser et al. 2003), which can have a significant impact on the probability of detecting bacteria (Nieman et al. 2022). Sampling organs with low bacterial loads may cause a negative result with no bacterium isolated, thereby leading to an underestimation of the resistance rate. Similarly, the isolation and documentation of a commensal bacterium, even if it is not responsible for the clinical signs present, may lead to an overestimation of the resistance rate.

Our preliminary results indicated that the organs sampled and bacteria tested were correlated with the most common diseases – treated with antimicrobials – in animals in general (e.g., gastrointestinal and respiratory diseases) and in certain animal species and production types in particular, as described in the literature (Zimmerman et al. 2019, Craig 2022). The majority of samples for dairy cattle consisted of milk samples, which is in alignment with the frequency and importance of mastitis (Jamali et al. 2018, Cheng and Han 2020). It can therefore be assumed that the data collected are a reliable reflection of routine veterinary practice. Additionally, documenting the udder quarters in a monitoring programme appears to be feasible and may prove useful for practical – e.g., improving hygiene management for quarters with a higher risk and selective dry cow management – and scientific – some authors have suggested that the prevalence of quarter-level mastitis may vary between quarters (Guarín and Ruegg 2016, Belay et al. 2022) – purposes. Conversely, the number of lactations and the day of last calving are often missing, and should not become mandatory.

Phenotyping Data

In our data, the methods used for susceptibility testing differed and included agar diffusion and microdilution. Microbiologists recommend microdilution as the gold standard (Schwarz et al. 2003, Humphries et al. 2018, International Organisation for Standardisation 2019, EUCAST 2023b), yet it is not implemented in all veterinary practices. This may be attributed to a number of factors, including the higher costs associated with microdilution compared to agar diffusion (Balouiri et al. 2016, WOAH 2022, Lazou and Chaintoutis 2023). In addition, conducting agar diffusion is "[…] easy to perform […]" (Putatunda et al. 2023), "[…] require[s] little specialised equipment and [is] easily customizable […]" (Hoelzer et al. 2011) and is therefore frequently employed in in-house laboratories. Furthermore, the unavailability of microdilution plates in general, or covering certain antimicrobial substances, e.g., individual selection of active substances depending on the isolated bacteria and veterinarian's treatment preferences (personal communication with participating veterinarians), restricts the practical use of microdilution. Although many of the antimicrobial substances tested are the same in both agar diffusion and microdilution, there can be significant differences in the substances between the two methods. Additionally, some antimicrobials are exclusively tested using one of the two methods. As a result, agar diffusion "[…] remains one of the most widely used methods[…]" of susceptibility testing (EUCAST 2023a) "[in] many veterinary diagnostic laboratories […]" (CLSI 2024).

Based on our preliminary results, we may guess an overall ratio of 2:1 for the relation between microdilution and agar diffusion tests for all animal species combined. However, when examining individual

production types, this ratio can vary considerably. For example, agar diffusion was employed more frequently for isolates from sows (ratio of 9:1) in our data, whereas microdilution was used more often for dairy cows (approx. 5:1). By limiting our investigation to microdilution, we would have had to exclude a third of our data, thereby preventing a comprehensive analysis of all production types.

In addition to the method of testing, the standards for evaluating the results can differ as well. Furthermore, there are often no breakpoints available in CLSI or EUCAST (European Committee on Antimicrobial Susceptibility Testing) for veterinary medicine in general or for individual animal species and their respective indications (CLSI 2021, EUCAST 2021), which creates a knowledge gap for the susceptibility testing, or rather for the evaluations. Consequently, veterinarians and laboratories utilise human breakpoints (EUCAST 2023b, CLSI 2024) as well as recommendations from literature without accredited breakpoints (Schwarz et al. 2008, Fessler et al. 2012), or even devise their own breakpoints/interpretation rules (EUCAST updated 2021).

EUCAST as a European approach is currently not suitable, as almost no specific breakpoints are available for veterinary medicine (Toutain et al. 2017, EUCAST 2023b). In contrast, CLSI has established 54 breakpoints for cattle (65% for respiratory diseases, 33% for mastitis, and 2% for metritis), and 32 breakpoints for pigs (94% for respiratory diseases and 6% not specific for one disease complex) (CLSI 2024). Focussing on the breakpoints for respiratory diseases, the susceptibility test results from the participating practices showed that CLSI breakpoints were missing in 37.47% of cases in cattle and 57.37% of cases in pigs. In conclusion, while respiratory diseases have the most available breakpoints, indicating an even lower coverage for other disease complexes, a high percentage of cases in our data still lack breakpoints. Therefore, the evaluation of results within an AMR MOSS is hampered and this issue must be addressed in the future.

Moreover, from a practical point of view, the test range for microdilution may vary. It is usually determined by the laboratory performing the test and is based on clinical relevance, cost, feasibility, and effort and is always limited (dilution series). In the event that the tested values are outside the specified range, they are documented as being above or below a certain concentration, thereby representing censored results (CLSI 2021, Fessler et al. 2022). From the perspective of a MOSS, this mechanism of censoring weakens the accuracy of the system and may introduce an information bias. This is a challenging aspect to regulate, particularly when alterations to breakpoints and test ranges do not align. Furthermore, the censored values cannot be used directly in calculations comparing dilution value distributions for monitoring purposes. Therefore, a rule must first be defined on how to process them.

In addition, there are frequently no officially recognised standards for sampling, cultivation, and isolation. If other recommendations – such as those of the DVG (Fehlings et al. 2009, Waldmann et al. 2018) – are applied, they are not documented in the patient's record and therefore remain unknown for monitoring purposes. In contrast, the standard for susceptibility testing and evaluation of the results is most often provided, but only as general information on laboratory methods and not for each susceptibility test. Therefore, potential deviations from the standard operating procedures in individual cases (e.g., for specific bacteria) cannot be accounted for. In the event that original values are available, the results may be used directly for in-between comparisons in the monitoring data. However, since the evaluation standard should only be employed when the appropriate standard for cultivation and testing is also used, this may potentially introduce further biases (Mesa Varona et al. 2020). Consequently, in a monitoring system, it is necessary to document whether a standard is used for sampling, testing, and evaluation, and if so, which standard, as a direct comparison of different methods is not possible.

The evaluation focused on the interpreted results S-I-R, which may have introduced an information bias, potentially narrowing the results of a monitoring system. Then again, there are also numerous other monitoring systems that collect MIC and/or IZD data, as well as interpreted data (Mesa Varona et al. 2020, WHO 2021), but only report S-I-R, "[…] since original susceptibility test results are missing for a large part of the data […]" (European Centre for Disease Prevention and Control 2022). In our data, original results were available for almost all microdilution susceptibility tests, but missing for a large part of agar diffusion tests. Focussing solely on original results would have excluded a large part of the agar diffusion data currently provided, which would have narrowed the data evaluation even further. In a monitoring system, it would be necessary to either increase the data coverage of the original results or conduct data interpretation at the S-I-R level.

As demonstrated by other authors, genome sequencing "[…] is currently a valuable diagnostic tool employed in outbreak investigation, tracking and surveillance[…]" (Maunsell et al. 2021), providing results within hours (Bard and Lee 2018, Gajic et al. 2022), and is used for specific forensic investigations in veterinary medicine, predicting AMR through the presence of genes or mutations (Banerjee and Patel 2022). However, it is not performed as a routine diagnostic test in clinical veterinary laboratories, and was only sporadically observed in our data. This may be attributed to its higher costs and the need for specialised equipment compared to phenotypic methods and that it "[does not predict] susceptibility, and therefore cannot rule in antimicrobial therapy options unless there is a singular genetic mechanism of resistance for a particular antibiotic/bacterial species combination." (Banerjee and Patel 2022). Consequently, genotyping was not included in this project, and should not become mandatory in a national farm-level AMR monitoring programme, which focuses on collecting routine diagnostic data.

Technical Issues for Implementing a Monitoring System

Currently, many veterinarians use electronic practice management software for the storage and retrieval of patient files. However, our findings indicated that this

does not always result in the digital documentation of AMU and AMR data. Additionally, while some service laboratories offer interfaces between laboratory and practice systems, most veterinarians use electronic summaries such as PDFs to connect patient and AMR data.

As a result, there is often no direct link between patient, AMU and AMR data. Consequently, the data submitted (by the veterinarians) must be adapted using workflows – relying on several different software applications – in order to enable centralised storage and evaluation.

The investigation demonstrated the feasibility of transferring data from EPMS and laboratory information systems. In VetAmUR, the following tool were used for data curation: Tabula, KNIME, and REDCap. It was demonstrated that information from PDF documents can generally be uploaded, although significant variation exists in laboratory protocols. Therefore, utilising these pipelines outside of scientific investigations can be highly time-consuming and is currently not applicable to a population-wide MOSS. Nevertheless, the target data structure implemented in REDCap has proven to be a suitable database for this project, indicating the general feasibility of a MOSS. Moving forward, the implementation details need to be determined.

Derivations for Implementing a Monitoring System

Currently, there is no legal obligation in Germany to report or harmonise AMR data at the farm level. Although there are legal requirements for the documentation of susceptibility test results, this investigation shows that the required variables are documented to varying degrees. The resulting heterogeneity of AMR documentation raises a number of practical issues that must be considered in the preparation of a monitoring system based on veterinarians' routine diagnostic. Generally, two options may be considered: a relatively fixed data structure or a more flexible one.

The first option is implemented, for example, in the AMU surveillance system in Germany (Bundesministerium der Justiz 2021). The mandatory and harmonised documentation of AMU in veterinary practices and farms was introduced through the use of application and delivery forms. Since 2014, the AMU data for several production types must be reported to a central database (Federal Ministry of Food and Agriculture (BMEL) 2019). Therefore, standardised data structures with defined variables and formats could be utilised by implementing technical interfaces across various systems used by veterinarians in their daily work. This approach offers the advantage of maintaining consistent variables and formats over time, thereby improving data quality. However, it is debatable whether a strict data structure can adequately reflect the current heterogeneity of AMR data in practice and avoid substantial limitations in the reporting of routine diagnostic data.

The second option for establishing a MOSS is to define simple and flexible rules that merge heterogeneous data into a common format. This approach to establishing a monitoring system has been implemented in numerous international systems as well, including the WHO-GLASS system for reporting antimicrobial resistance in humans (WHO 2023). The general advantage of this option is that existing data can be used directly and with minimal additional effort by the participating veterinarians. However, transformation rules can be complex and may result in rough formatting, potentially introducing information bias throughout the database. Therefore, it is of the utmost importance to implement rigorous data curation processes in order to guarantee the quality of the data.

Apart from the question of data structure, the variation in test routines should also be taken into account. Ideally, a monitoring system should include representative data from both healthy and sick animals alike in order to avoid under- or overestimating the actual resistance rates. It is also important to distinguish between different types of production and age groups of animals, given the differing sampling schemes, bacteria, and treatments used.

Outlook/Conclusion

A MOSS must find an easy and efficient way to document the most important information. The metadata should include at least the animal species and production type, a structured categorisation of the reasons for sampling – with information on previous antimicrobial treatments – the material sampled, and information on the methods used for sampling, testing, and evaluation. The phenotyping data should include at least the bacteria isolated, the substances tested, and an interpretation of the results based on clinical breakpoints in the form of S-I-R (and/or original results, if available).

However, the current availability of samples per farm and year is limited. To evaluate the development of resistance rates over time at the farm level and the impact of antimicrobial use on the development of resistance, an increase in the number of samples would be desirable. Moreover, analysing the data from poultry farms is necessary to provide a basis for further assessments of all three main food-producing animal species in Germany.

Abbreviations

AMR	Antimicrobial resistance
AMU	Antimicrobial use
CLSI	Clinical and Laboratory Standards Institute
DVG	German Veterinary Society
EPMS	Electronic Practice Management Software
ETL	Extract Transform Load
EUCAST	European Committee on Antimicrobial Susceptibility Testing
GLASS	Global Antimicrobial Resistance and Use Surveillance System
I	Intermediate
IQR	Interquartile Range
IZD	Inhibition Zone Diameter
KNIME	Konstanz Information Miner
MIC	Minimum Inhibitory Concentration
MOSS	Monitoring and Surveillance Systems
R	Resistant
REDCap	Research Electronic Data Capture

S	Susceptible
TÄHAV	Amendment to the regulations of veterinary pharmacies in Germany (Verordnung über tierärztliche Hausapotheken)
VetAmUR	Veterinary Antimicrobial Usage and Resistance
VetCAb	Veterinary Consumption of Antibiotics
WHO	World Health Organization
WOAH	World Organization for Animal Health

Ethical approval

The authors hereby declare that they have followed the universally accepted guidelines of good scientific practice while preparing the present article.

Conflict of interest

The authors hereby declare that they have no proprietary, professional or other personal interests in any product, service and/or company that could have influenced the contents or opinions expressed in this publication.

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Data collection, analysis and interpretation: CB, BR.
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