The AACTING-network (www.aacting.org) presents:

GUIDELINES FOR COLLECTION, ANALYSIS AND REPORTING OF FARM-LEVEL ANTIMICROBIAL USE, IN THE SCOPE OF ANTIMICROBIAL STEWARDSHIP

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Herd level antimicrobial consumption in animals

Collect | Analyze | Benchmark | Communicate

1. BACKGROUND

The increasing occurrence of antimicrobial resistance (AMR) is one of the main health threats worldwide. AMR in animals may, among other things, compromise animal health and welfare, sustainable food production and food security. Furthermore, the environment and human health are affected. For this reason, AMR is considered a "One Health" issue, as resistant bacteria can be transmitted from animals to humans and vice versa via different transmission routes (e.g. direct contact, environmental contamination and consumption of animal products). As the use of antimicrobials is the main driver for AMR selection, a collaborative approach across all sectors to reduce antimicrobial use (AMU) is required in order to contain AMR.

At the national level, data on the sales of veterinary antimicrobial products have been shown to be important for guiding and supporting general policy making decisions. This may include implementing targets for reducing overall sales of veterinary antimicrobials or, more specifically, sales of particular antimicrobial classes such as critically important antimicrobials (CIAs) for human medicine (WHO, 2017), those of veterinary importance (OIE, 2015) or according to the degree of risk to public health due to resistance development following use in animals, which for the EU was assessed by the "Antimicrobial Advice Ad Hoc Expert Group (AMEG)" (EMA, 2014 and 2016).

Monitoring antimicrobial use at farm or prescriber level, however, is much more targeted than at the national level, as it offers the ability to pinpoint 'non-prudent' or excessive AMU and can help guide farm-specific preventive or corrective actions (Speksnijder *et al.*, 2015). The information arising from farm-level AMU monitoring is critical for driving antimicrobial stewardship, i.e. the establishment and implementation of measures aimed at combatting AMR by promoting responsible AMU practices (Dyar *et al.*, 2017).

These guidelines address: 1) data collection, 2) data analysis (i.e. the calculation of indicators to quantify AMU), 3) benchmarking and 4) reporting the results, as all are important elements in advancing antimicrobial stewardship. Each of these elements can be approached in different ways, with several decisions to be made along the way. These practical guidelines are intended to provide useful support when designing or revising farm-level AMU monitoring systems. In addition, they might provide a basis for future collection of harmonised farm-level data within and among countries, e.g. on the type and detail of the collected data, the indicators for reporting results and/or the benchmarking criteria for differentiating acceptable from excessive use.

2. PURPOSE OF THE GUIDELINES AND TARGET GROUPS

These guidelines summarise the key findings of a review paper that is currently in preparation by the AACTING consortium 'Monitoring of farm-level antimicrobial use to guide stewardship: overview of existing systems and practical guidelines based on a descriptive analysis of key components and processes'. To fully understand the background to these guidelines it is highly recommended to read the above-mentioned review paper when it becomes available, as it will describe the systems already in place and the experience gained following their implementation and use for antimicrobial stewardship, as well as explore the related scientific literature.

These guidelines are primarily based on experience in countries with established medicines registration and regulations, and might be difficult to translate in countries without these regulations. These guidelines are targeting all stakeholders involved in designing and setting up AMU monitoring systems at farm-level and using the AMU data for analysis and benchmarking. They also target parties that are involved with, have an interest in or are affected by the outcome of these systems (e.g. end-users of the data, such as farmers and prescribers or providers of antimicrobials, as well as competent authorities, wholesalers, slaughterhouses, consumers, etc.).

3. DEFINITIONS

In the context of these guidelines, the following definitions are used:

a. **Use of antimicrobials** – The actual administration of antimicrobials to the animals or any process that suggests the antimicrobials have been or will be administered, for example prescribing or delivering antimicrobials to the farm(er).
b. **Indicator** – A metric quantifying use of antimicrobials, usually expressed in relation to a denominator representing the population (at risk).
c. **Population/animals at risk** – All animals in a group (e.g. farm, house, flock) that can potentially be treated with antimicrobials in a corresponding period.
d. **Benchmarking** – The comparison of a party's AMU with AMU in a pre-defined population of similar parties.
e. **Antimicrobial stewardship** – A coherent set of actions that promotes using antimicrobials responsibly.
f. **Reporting** – The process of providing feedback about the farm-level AMU to the party in question.

4. PRACTICAL GUIDELINES

As a first and general step, it is vital to establish a clear vision of the goals of the entire system (including data collection, analysis, benchmarking and communication), even if not all the components can be developed at once. The expertise required by the team (e.g. veterinary medicine, epidemiology, pharmacology, information science and communication science) then needs to be defined and this group of people should be involved from the onset of the planning process. To help ensure understanding and build confidence, information should also be communicated to all relevant stakeholders as early as possible in the process e.g. by presenting the purpose and the draft protocol for the data collection, including suggestions for how it will be reported (indicators etc.). An overview of existing systems can be found on the AACTING website (www.aacting.org). It is strongly advised, as part of the planning process, that members of the team should visit one or more countries that already have systems in place to find more detailed information and learn from their experience. Finally, it is important to clearly define up front the roles and responsibilities of all parties involved (e.g. competent authorities and other stakeholders).

4.1. Data collection

The following points should be considered when setting up the data collection system:

a. **Determine the AMU monitoring objectives.** This will define the desired outputs, the extent of the data collection (e.g. comprehensive monitoring including all farms vs. a representative sample of farms, collection of data by animal species vs. by production stage or type) and the required resources. When aiming for a full coverage system, it might be helpful to start with a pilot study on a sample of farms first.

b. **Identify the data sources** (e.g. prescription records, farm records, veterinary practice records, delivery notes and/or invoices) that will achieve the stated objectives of the monitoring system.

c. **Determine the minimum required information needed to calculate the quantity of each antimicrobial active substance used,** i.e. the numerator data. This may include:

- Unique ID and name of the product
- Pack size
- Number of packages or amounts (e.g. g/ml/pieces) used
- Active ingredient
- Strength, for example mg (or IU)/g, mg(or IU)/ml, mg (or IU)/piece

Depending upon the goals of the data collection, the list can be extended to enable more detailed analyses. Examples include:

- Age at treatment
- The actual dose rate used
- Duration of treatment
- Route of administration
- Indication for treatment

However, in order to avoid over-complicating the analysis or collecting low quality data, additional information should only be collected if compatible with available resources (human and financial).

In preparation for future delivery of AMU data by species to OIE and, for example, EMA it is recommended that countries which set up a system for collecting data at farm level at least collect the variables for AMU suggested by EMA/OIE (OIE, 2017; EMA 2018).

d. **Determine the minimum required information needed to calculate the size of the population at risk for treatment**, i.e. the denominator data. This may include:

- The numbers of animals present at the farm in the different age categories (if relevant).
- The average duration of stay for each age category.
- The assumed biomass (weight) per animal for each age category, which could be based on the average weight at treatment or the average weight in the production period. Sometimes this information might be fully or partially obtained from the national identification and registration system.

e. **Define data collection time windows as well as data lock points**, e.g. four times a year AMU data should be provided for the past quarter (time window) and this data should be entered in the system at the latest 15 days after the end of the quarter (e.g. 15th April, 15th July, etc.).

f. **Determine how the data should be provided.** This can either be done automatically, by creating digital links between the data sources and the data collection system, or manually by providing a data input interface which needs to be used by the data providers to enter their information. Ideally, a combination of both should be made available to facilitate the users as much as possible.

g. **Determine who should provide the data.** This can either be the person delivering or administering the antimicrobials (e.g. veterinarian or pharmacies) or the person responsible for the animals (e.g. farmer). Ideally the party entering the data onto the system should also be responsible for its accuracy. However, when veterinarians or pharmacies are providing the data (as is very often the case in existing systems) and the animal owner (farmer) is the one responsible for the accuracy of the data provided to the database on AMU for the farm, there is a potential risk of conflict. It might therefore be advisable to build in an additional data validation step by the final responsible person (e.g. the farmer).

h. **Determine who can change the data.** It is recommended to limit access to the submitted data as much as possible. It therefore needs to be determined who can change (adapt, add, delete) the data, as well as which types of changes are allowed and during which time frame. It is also advisable to establish a logging system to track the changes in the data over time and enable any changes to be reversed.

i. **Install an active control with respect to completeness and accuracy of the collected data**. This might be carried out either at the source (farm) or at the data receiving end (before the start of the data analysis). Ensure data providers are aware of this control process for transparency and to achieve maximum adherence.

j. **Establish a confidentiality policy between the data providers and the system operators.** This should clearly define the levels of anonymity that are required. This is especially important in situations when the data collection and analysis is a joint effort between industry and competent authorities, e.g. where the competent authority performs the analysis.

4.2. Data analysis

The data analysis component essentially involves the calculation of an indicator quantifying the AMU. The indicator should consist of a numerator (amount of antimicrobials used) and a denominator (the animal population at risk of being treated). The following points should be considered when deciding on the methodology for quantifying AMU at farm level:

a. **Determine the numerator for analysing the data.** This can be count-based (e.g. number of days treated), weight-based (e.g. mg of active ingredient) or dose-based (e.g. number of defined daily or course doses). Dose-based measures have the advantage that they make it possible to correct differences in dosing between active ingredients and formulations and measure developments over time, despite changes in which active ingredients are used (Jensen 2004). Several dose-based units of measurement (UM) are in use for the analyses of AMU (Collineau *et al.*, 2017) and these are currently nationally or regionally defined, which is useful for monitoring trends at national or regional

level. However, approved dosing may vary substantially between countries (Postma *et al.*, 2014) resulting in differences between the UM. In the case of comparing populations beyond the national level, the use of a common UM (e.g. DDDvet/DCDvet for EU/EEA) is particularly useful.

b. **Determine the denominator for quantifying the size of the population of animals** in the farm that can potentially be treated. Various denominators could be used, leading to quite different results (Dupont *et al.*, 2016; Taverne *et al.*, 2016; Collineau *et al.*, 2017) and therefore assessing which denominator is most appropriate is a critical point in the decision making process. In some cases this will look at the farm as a whole and simply involve multiplying the average numbers of animals present (e.g. number of dairy cattle) over a pre-determined period of presence (e.g. one year) with an assumed biomass per animal (e.g. 500 kg). In other cases it is advisable to split the production process into several production stages (e.g. suckler pigs, weaner pigs, fattener pigs, sows), again with each having a specific assumed weight (e.g. 2, 15, 50, 240 kg). The assumed weight per animal may be based on the average weight at time of treatment or on the average weight during the production period. When more detailed data are available the exact weight of the population present at each moment of treatment (e.g. weight of broiler chicks based upon standard growth curves) can be used.

c. **Determine which AMU-indicator fits best with the goals of the entire system and the AMU monitoring objectives**. Several AMU indicators are available and all of them have different characteristics (Collineau *et al.*, 2017). It is not the aim of this guidance to recommend one particular indicator for analysing and reporting farm-level AMU, as the choice of indicator will reflect several considerations, such as the objectives of the monitoring system, the type of AMU data collected and the extent of data coverage.

The formula to determine the number of defined daily doses (DDD) per 100 animal days is provided below as an example (variations on this formula are discussed further).

$$\sum_{i=1}^{n} \frac{\text{amount AI}_i \text{ in period P (mg)}}{\text{DDD}_i \text{ (mg/kg/day)} \times \text{ \# animal days in period P (days)} \times \text{ standard or average weight (kg)}} \times 100$$

*Where AI_i = amount (in mg) of active ingredient i used in period P; i = 1, 2, …, n; DDD_i = Defined Daily Dose of active ingredient i (in mg/kg/day); # animal· days in period P = # animals present daily during P * P (in days); standard weight = standard animal weight at treatment (in kg) (Timmerman et al., 2006; Callens et al., 2012; Pardon et al., 2012; Persoons et al., 2012).*

The outcome of this formula provides the percentage of time an animal of a standard or average weight is treated during period P with a certain product. This measure is therefore an estimate of the percentage of animals treated daily at the farm for a given period (P). For example, if the outcome of this formula for tetracycline use in weaner pigs is 4.5 treatment days out of 100 days, it means that an average weaner pig on this farm is treated with tetracycline for 4.5% of the time it spent in the weaner phase. If different antimicrobial products are used, the sum of all these different number of treatment days will result in the total number of days under treatment over the defined period. In human medicine, daily doses are commonly expressed per 1000 days; the calculation above is therefore in line with antimicrobial quantifications in human medicine but with a factor 10 difference (http://www.who.int/medicines/ regulation/medicines-safety/toolkit_ indicators/en/).

Many variations on the illustrated formula are available. For example, if DDD_i is replaced by DCD_i (defined course doses) then the average number of courses per animal, rather than the number of treatment days, will be calculated. DDD_i and DCD_i may also be expressed in terms of number of items (e.g. intra-mammary tubes), in which case the number of items used in period P could be used in the formula instead of the amount of active ingredient. Another variation is that the usage could be expressed, for example, per 365 days to describe the number of treatment days per year. In addition the actual dose, rather than standardised, dose rates and weights at treatment can be used. This will provide a more accurate estimate, but also require more detailed data to be collected for each treatment. Furthermore, as well as calculating AMU per age category, AMU may also be calculated per species on a farm basis, in which case the sum of the farm weight at risk over all age categories can be used in the above calculation.

Of the 16 countries identified to have systems in place for collecting farm-level AMU data by species (http://www.aacting.org/monitoring-systems/), dose based indicators are currently applied in 8 – Austria, Belgium, Canada, Denmark, France, Italy, the Netherlands and Switzerland.

d. **Clearly document the data analysis method** and make sure it is understood and accepted by all parties concerned.

4.3. Benchmarking

Benchmarking is a powerful tool for raising awareness and promoting antimicrobial stewardship. When benchmarking farms or other parties, e.g. veterinarians, based on farm-level AMU, the following aspects should be considered:

a. **Decide who to benchmark.** Are only farms benchmarked or will veterinarians or other parties also be included.

b. **Determine the reference group**. This is the group against which the result of the specific farm is compared to. Ideally each farm is compared to a reference group that is as representative as possible (e.g. comparable production system for the animal species in question, region, etc.). Keep the sample size and the representativeness of the reference population in mind when extrapolating the benchmarking results towards estimating sector or national use, especially in systems with partial sector coverage.

c. **Decide whether to use AMU thresholds.** These are defined levels above which the use is considered elevated. If thresholds are used, a single cut-off value (e.g. below the value use is acceptable, above the value use is unacceptable) allows for a more straightforward interpretation of results, whereas two thresholds (e.g. acceptable, elevated, unacceptable) allows the system to focus efforts on the highest users of antimicrobials, yet also allows the large group of 'elevated attention' users to be kept under observation. The determination of the threshold levels should be based upon the distribution of AMU in the reference group. An undesired side effect of establishing threshold levels is that some producers might adapt their use in relation to the threshold to ensure that they are just below a certain level, whereas they might have the potential to go lower.

d. **Define the outcome of exceeding the thresholds, if any** – e.g. require improvement measures, fines, loss of quality assurance label, etc. The nature of the consequences should be different for exceeding the lower and higher thresholds, and for when thresholds are exceeded once or repeatedly.

e. **Consider the "lifetime" of the thresholds.** Thresholds kept steady for a longer period (e.g. a few years) have both technical and practical advantages over thresholds that are regularly changing as they provide stability, for the system users and data analysts, and help build trust. After some years, however, circumstances may have changed and therefore thresholds may need to be adapted. If this is done, it is important to provide sufficient information and go through this process in consultation with the parties involved.

f. **Decide on benchmarking frequency.** This could be consistent with the life-cycles of the animal species and/or production type(s) involved or, for example, could be on an annual basis. An adequate frequency should keep enough pressure on the benchmarked parties and this is also related to the frequency of reporting (see below).

4.4. Reporting

Reporting on the outcome of the AMU quantification is of critical importance; otherwise the data cannot be used by stakeholders. Farm level AMU data, when explained and communicated properly, is very useful for guiding the antimicrobial stewardship efforts.

a. **Determine the target groups** for reporting. Different types of reporting are required when communicating to 1) the individual farmer or veterinarians on their specific use, 2) the animal industry and 3) the broader (national) audience.
   - Individual farmers/veterinarians should receive clear reports describing their use in comparison to a certain reference population if possible (see benchmarking above). Ideally the report should also provide an indication of the evolution of the use over time.
   - The animal industry should be provided with detailed statistics describing the evolution of the AMU in the population (mean, median, quartiles, percentage of farms above a certain limit, etc.).
   - A broader, national audience should be provided with a simpler summary of statistics describing the general trends.

b. **Determine the frequency of reporting** to the target group. The greater the frequency of reporting, the easier it is to maintain awareness and the closer the results are to the recent AMU. If benchmarking is applied, then the reporting and benchmarking frequency should be aligned.

c. **Determine the units of measurement to report with**. Using quantitative data from the data analysis is very powerful if the results are well explained. However, qualitative information can also be reported, such as the type of antimicrobials used (e.g. proportion of highest priority CIAs for human medicine) as this information can be very helpful when providing stewardship advice.

d. **Determine how to report the data to relevant parties**. Whenever possible provide reports in graphical form (e.g. using clear colours) to ensure effective transfer of information to all relevant parties. Infographics, appropriate to the data and stakeholder group, can be powerful knowledge translation tools in communicating key findings. The use of business intelligence tools to process the data might prove to be very helpful for creating automated graphs. Whenever a standard report has been designed, make sure this is pre-tested on a representative group of the target audience to ensure correct understanding of the message.

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