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Comparison of different antimicrobial use indicators and antimicrobial resistance data in food-producing animals

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Objectives: To explore the effects of using different indicators to quantify antimicrobial usage (AMU) in livestock and compare outcomes with antimicrobial resistance (AMR) data.

Methods: Three indicators were used to quantify AMU, two indicators in which the denominator varied: defined daily doses per average mass of the animals present per year (DDD/AY) and defined daily doses per population correction unit (DDD/PCU) and one in which the numerator varied: milligrams of active ingredient per PCU (mg/PCU). AMU was compared with antimicrobial resistance data from the national monitoring programme from 2013 to 2018 with the proportion of *Escherichia coli* isolates fully susceptible to a predefined panel of antimicrobials for the broiler, dairy cattle and pig farming livestock sectors in the Netherlands.

Results: The ranking of livestock sectors differs between sectors when using different indicators to express AMU. Dairy cattle rank lowest when expressing AMU in DDD/AY, followed by pigs and broilers corresponding to the rankings of the sectors for AMR. When changing the denominator to PCU, the ranking in AMU is reversed: use ranks highest in dairy cattle and lowest broilers.

Conclusions: Using different denominators in AMU indicators has a major impact on measured use. This might result in misinterpretation of effects of interventions on AMU and the associations of AMU with AMR across animal sectors. From an epidemiological perspective, indicators that take into account time at risk of exposure to antimicrobials are to be preferred and reflect the AMR risk most accurately.

Introduction

Quantitative monitoring of antimicrobial use (AMU) is important for optimizing AMU and ultimately limiting antimicrobial resistance (AMR). To estimate AMR by quantifying AMU, the used indicator should have a high correlation with AMR data. Indicators for AMU quantitatively relate use data (the numerator) to animal population data (the denominator).[1] The numerator can be mass-, dose- or count-based. Here, two approaches were used: milligrams of active ingredient (mass based) and defined daily doses (dose based), which takes into account differences in the dose rate of antimicrobials. The denominator is a proxy for the target animal population. The average mass of the animals present and the biomass produced, both within a year, were used as denominators.

These different numerators and denominators are used interchangeably in monitoring systems and scientific publications. A discussion emerged about which measure to use to monitor AMU.[2–6] The optimal choice depends on the purpose of AMU monitoring. Different units may be applicable for trend analysis than for studying the association with AMR data or when studying the effect of AMU interventions on AMR.[7]

To explore the effect of using different methods to quantify AMU we used two indicators in which we varied the denominator: defined daily doses per average mass of the animals present per year (DDD/AY) and defined daily doses per population correction unit (DDD/PCU) and one in which we varied the numerator: milligrams per PCU (mg/PCU). We applied these proxies on usage data from three Dutch livestock species to explore the effect on the relative ranking in AMU of these sectors. A comparison between results of AMU measured with these three indicators and AMR data was explored, using AMU and AMR data from the Netherlands.

Materials and methods

AMU and AMR data

National AMU monitoring data from Dutch dairy cattle, pigs and broilers were used. For the purpose of comparing indicators, AMU was expressed in DDD/AY, DDD/PCU and mg/PCU. For the DDD/AY denominator we multiplied the average number of animals present per year by a standardized weight that represents the average weight of an animal during its lifespan (Table S1, available as Supplementary data at *JAC-AMR* Online). The produced biomass is expressed as the number of PCU. PCU by species was calculated according to the EU method described in Appendix 2 of the report on AMU sales between 2005 and 2009.[8] In short, for meat-producing livestock sectors the PCU is calculated by multiplying the number of animals slaughtered with an estimated treatment weight while adjusting for import and export of fattening and slaughter animals (Table S2). For non-meat-producing livestock sectors, such as dairy cattle, the PCU is calculated by multiplying the number of live animals with an estimated average weight at treatment. For the DDDs the same dose rates were used for both indicators (DDD/AY and DDD/PCU). Milligrams of active ingredient of antimicrobials used in Dutch livestock were calculated based on full coverage data for each sector. Appendix S1 provides more information on methods used to calculate AMU.

To compare AMU across livestock sectors using different indicators, AMU was standardized by dividing by the mean usage across all species and years. This was done to avoid scaling issues when presenting results for all animal sectors and AMU indicators in one graph that would have arisen when results were presented without standardization.

AMR data of the indicator organism *Escherichia coli* was obtained from the annual 'Monitoring Antimicrobial Resistance and Antibiotic Use in Animals in the Netherlands' (MARAN) reports.[9] In accordance with the AMR indicators proposed by ECDC, European Food Safety Authority (EFSA) and EMA, the proportion of isolates fully susceptible to a panel of antimicrobials, as defined in Decision 2013/652/EU, was used as primary indicator for AMR.[10]

In this study AMU and the proportion of fully susceptible *E. coli* were evaluated for broilers, dairy cattle and pigs for the 2013–18 period, corresponding to the period for which detailed data on AMU were available.

Results

Proportions of fully susceptible *E. coli* increased in all livestock sectors during the 2013–18 period, except for dairy cattle, which had very low resistance levels throughout the observation period (in dairy cows only 3.0% of all *E. coli* isolates in 2018 were not fully susceptible to the panel of antimicrobials).

Trends in AMU (expressed in the three indicators previously described) and fully susceptible *E. coli* isolates are shown in Figure 1. Table 1 shows the original data.

AMR was lowest in dairy cattle: the percentage of fully susceptible isolates ranged from 93.8% to 97.3% over the 2013–18 period (Figure 1). In both pigs and broilers AMR was more prevalent. In broilers the percentage of fully susceptible *E. coli* isolates was 32.4% in 2018, while 51.2% were fully susceptible in pigs in 2018.

A similar pattern is observed when AMU is expressed in DDD/AY. Use ranks lowest in dairy cattle, followed by pigs and broilers.

When changing the denominator to PCU (DDD/PCU) the AMU ranking of the sector reverses; due to the large number of production cycles per year broilers now rank lowest in AMU. Use in broilers is 8.1 times lower in 2018, corresponding to the number of production cycles in this livestock sector. Dairy cattle rank highest when expressing AMU in DDD/PCU; use is 3.4 times higher than in broilers. Dairy cattle use in DDD/PCU is higher than use in DDD/AY because a standardized weight of 425 kg is applied in the PCU calculations, while 600 kg is used in the Netherlands. The pig sector's DDD/PCU is 2.8 times higher than for broilers. In pigs, use measured

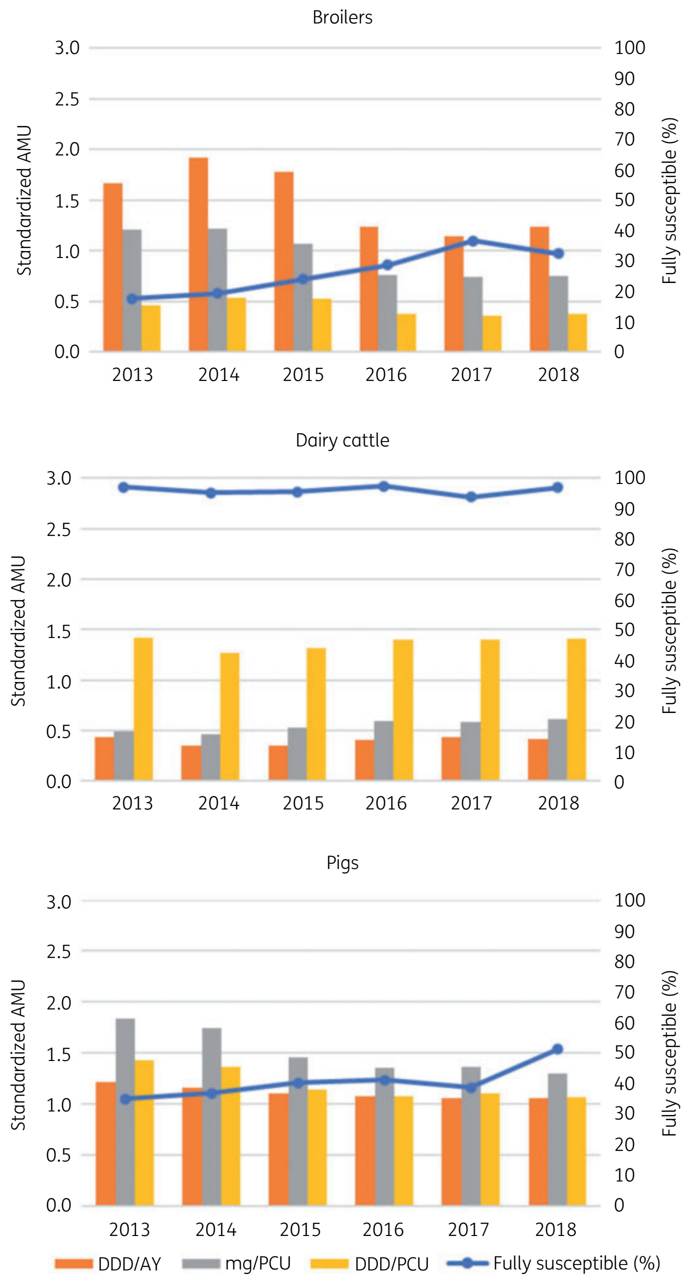

Figure 1. Trends in AMU and proportion of fully susceptible *E. coli* isolates for broilers, dairy cattle and pigs. AMU was divided by mean AMU in the three livestock sectors for each indicator. For example, a bar with value of 2 DDD/AY indicates that use in that livestock was twice the average use of the three described livestock sectors in DDD/AY.

Table 1. Trends in AMU and AMR by species

Species	AMU/AMR	Indicator	Year					
			2013	2014	2015	2016	2017	2018
Broiler	AMU	DDD/AY	13.7	15.8	14.6	10.2	9.4	10.1
		DDD/PCU	1.5	1.8	1.8	1.3	1.2	1.3
		mg/PCU	38.9	39.1	34.3	24.3	23.7	24.0
	AMR	% fully susceptible	17.6	19.4	24.0	28.7	36.5	32.4
Pig	AMU	DDD/AY	10.0	9.5	9.0	8.9	8.7	8.7
		DDD/PCU	4.8	4.6	3.8	3.6	3.7	3.6
		mg/PCU	59.1	56.1	46.8	43.6	43.8	41.8
	AMR	% fully susceptible	34.9	36.7	40.3	41.1	38.7	51.2
Dairy cattle	AMU	DDD/AY	4.0	3.3	3.1	3.0	3.1	3.0
		DDD/PCU	5.7	4.7	4.4	4.3	4.3	4.3
		mg/PCU	19.3	17.3	17.1	16.6	16.2	16.8
	AMR	% fully susceptible	97.0	95.1	95.5	97.3	93.8	97.0

Three different indicators were used; AMR is described as the percentage of *E. coli* isolates resistant to at least one of the antimicrobials in the panel as defined in Decision 2013/652/EU.

in DDD/PCU is 2.4 times lower compared with DDD/AY. Pig farms have around two production cycles per year in the Netherlands, which largely explains this difference. The adjustment for import and export could be another factor that contributes to the observed differences, but this is secondary to the principal difference between denominators based on AY versus PCU.

The effect of using a different numerator, milligrams of active ingredient instead of DDDs, can be observed when comparing use in DDD/PCU with mg/PCU. Measured use in mg/PCU is relatively high for broilers compared with use in DDD/PCU, while use in dairy cattle is relatively low. This is caused by differences in dose rate. Broilers receive a higher dose on average than dairy cattle or pigs.

Discussion

Potential issues arise when drawing comparisons between countries and/or species when using AMU indicators that use a production-driven denominator in comparison with denominators based on average numbers of animals. The PCU does not account for differences in production cycle length and suggests that the produced kilograms of animals are exposed for a full year. Short-lived animals are not at risk of antimicrobial treatment for the entire year, but only for the course of their lifespan, clearly shorter than a year. This leads to scaling issues and might result in misinterpretations when comparing AMU between species or countries. AMU in countries with relatively large livestock sectors with short-lived animals, such as broilers, will be underestimated, as the PCU of these animal populations is heavily diluted in comparison to countries with more longer-lived animal species. Also, livestock sectors might be prioritized to reduce their AMU when using an indicator that standardizes use by a production-based denominator while this is not justified given their true exposure to antimicrobials and risk of developing AMR. Adjustment of the PCU for the lifespan of an animal has been suggested.[5] This issue is becoming more urgent as a new EU regulation has been adopted that sets out that all EU member states are to collect AMU data by animal species in the future.[11]

Using a weight-based numerator, like milligrams of ingredient, could lead to misclassification when benchmarking farms as it is favourable to use low-dose antimicrobials. O'Neill *et al*. indicated this could raise issues when critically important antimicrobials (CIAs), as defined by WHO,[12] have a higher potency than other classes of antimicrobial, as AMU could be underestimated when farms use relatively more CIAs.[4] Here, it was shown that using a weight-based numerator can result in misclassification of AMU on the species level.

Using different denominators in AMU indicators has a major impact on measured use. Using a denominator that contains meat production results in relatively low reported use for livestock sectors with short-lived animals, such as the broiler sector. Most AMU indicators express use per year, while animals with short production cycles are not at risk of antimicrobial treatment for the entire year. AMU expressed in DDD/AY ranks lowest in dairy cattle, followed by pigs and broilers corresponding to the rankings of the sector for AMR. The order changes when AMU is expressed in DDD/PCU or mg/PCU and the association with AMR (percentage of fully susceptible isolates) is less clear. When comparing associations between use and fully susceptible or resistance patterns across livestock sectors this might result in misinterpretation of effects of interventions on AMU and the associations of AMU with AMR. Moreover, using fundamentally different indicators for AMU may bias comparisons between veterinary use and use in humans and may bias associations between AMU in food-producing animals and AMR in humans, as recently explored.[13] From an epidemiological perspective, indicators that take into account time at risk of exposure to antimicrobials are to be preferred and reflect the AMR risk most accurately.

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Transparency declarations

None to declare.

Supplementary data

Appendix S1 and Tables S1 and S2 are available as Supplementary data at *JAC-AMR* Online.

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