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Comparing human and animal antimicrobial usage: a critical appraisal of the indicators used is needed

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Comparisons between antimicrobial usage (AMU) in humans and food-producing animals are regularly made. The accuracy of such comparisons depends on the indicators used to quantify AMU. Indicators for AMU quantitatively relate use data (the numerator) to population data (the denominator). The denominator should be a proxy for the population at risk in a certain period when comparing the exposure of different populations to antimicrobials. Denominators based on numbers of animals slaughtered, such as the commonly used population correction unit, do not consider the time at risk of antimicrobial treatment. Production-based indicators underestimate animal AMU. Additionally, production-based indicators are fundamentally different from indicators used to quantify human AMU. Using such indicators to compare human and animal AMU therefore leads to biased results. More caution should be taken in selecting the indicator to quantify AMU when comparing AMU in food-producing animals and humans.

Introduction

Several studies have shown that antimicrobial usage (AMU) is associated with the development, selection and spread of antimicrobial resistance in animals and humans.[1–4] Limiting AMU in humans and animals is therefore crucial. Quantifying AMU is important in guiding and evaluating measures taken to reduce AMU in humans and animals. When comparing AMU between animals and humans, care should be taken in selecting the indicators used to quantify AMU, as the chosen indicator might affect AMU levels and therefore policy making. Comparisons between AMU in humans and food-producing animals using fundamentally different indicators to quantify AMU are often performed.[5–13] The outcomes of these analyses are accompanied by statements about the relative AMU in humans and animals, in some cases followed by communication in news media. In the most recent Joint Interagency Antimicrobial Consumption and Resistance Analysis report, it was concluded that AMU in food-producing animals in 2017 was lower than AMU in humans in 20 of 29 EU/EEA countries, and that overall AMU was lower in food-producing animals than in humans for the 2016–2018 period.[9]

Indicators used to compare antimicrobial usage

In studies comparing AMU in humans and animals, AMU in humans is often expressed as milligrams of active substance per kg of (average) body weight; that is, total mass of active substances divided by the number of individuals multiplied by the average weight in the population studied.[5–13]

AMU in food-producing animals is commonly expressed as milligrams of active substance per population correction unit (PCU) or kg of biomass of the animal population involved.[5–13] Both PCU and kg of biomass are production-driven denominators. Here we focus on the PCU. The PCU is used to obtain an estimate of the mass of the animal population for different animal species in a country. For meat-producing livestock, PCU is calculated by multiplying the number of animals slaughtered across species with an estimated treatment weight, while adjusting for import and export of fattening and slaughter animals. For primarily non-meat-producing livestock, such as dairy cattle, the PCU is calculated by multiplying the number of live animals with an estimated average weight at treatment.[14] The difference in indicators between human (mg/kg live body weight) and animal populations (mg/PCU, including slaughtered animals) complicates a direct comparison of AMU as is described next.

Limitations of a mass-based numerator

Indicators using milligrams of active ingredient do not account for differences in dosing between antimicrobial substances and between humans and food-producing animals. Considerable differences may exist in the proportion of low and high dosages,

respective to short- and long-acting antimicrobials between countries, in human and veterinary healthcare, creating systematic differences in AMU when quantified in total mass compared with a defined daily dose approach that accounts for the potency and pharmacokinetics of the antimicrobial used. Use of antimicrobial mass may therefore lead to biased comparisons when comparing countries where different (pharmaceutical formulations of) antimicrobials are being prescribed.

Fundamentally different denominators used to standardize antimicrobial usage

The denominators often used to adjust AMU for population size in humans (kg live body weight) and in food-producing animals (PCU) are fundamentally different, which also hampers an accurate comparison of AMU in animals and food-producing animals. The denominator used in humans estimates the population at risk of antimicrobial treatment within 1 year and is based on the number of citizens alive in a country in a certain year multiplied by an average weight for each citizen. The PCU, used to standardize the amount of antimicrobials used in food-producing animals, does not consider the lifespan of animals and so does not represent the population at risk of antimicrobial treatment within a year. This is best demonstrated for short-lived animals, such as broilers, veal calves and pigs. By using the numbers of slaughtered animals for meat-producing species, the PCU overestimates kilograms of animal at risk of antimicrobial treatment because animals slaughtered within a year are not at risk of antimicrobial treatment for the entire year, resulting in an underestimation of AMU in food-producing animals.[15,16] This issue was already highlighted in the first ESVAC (European Surveillance of Veterinary Antimicrobial Consumption) report when veterinary AMU in Denmark was discussed: 'As lifespan is not considered, the chosen denominator (PCU) overestimates the population at risk in Denmark, as opposed to countries with a large cattle population, in particular countries with large young-beef, beef or dairy productions. Overestimating the population at risk leads to underestimating the usage, particularly in broilers and pigs.'[14] It is also stated in the first ESVAC report that reporting AMU in mg/PCU does not provide information on real exposure to antimicrobials, but may be used to assess trends in AMU. This denominator is therefore also less suitable for comparison of AMU between countries or species or human versus veterinary. To overcome the issue that the PCU does not represent an approximation of the population at risk for antimicrobials treatment, the PCU for animals slaughtered within 1 year of age could be adjusted by animal lifespan, as suggested by Radke.[16]

Conclusions

Accuracy of comparisons made between AMU in humans and food-producing animals depend on the indicators used to quantify AMU. Comparisons based on fundamentally different indicators can lead to biased results. By using a production-based indicator, such as mg/PCU, AMU in food-producing animals is underestimated. This is most apparent for countries with a large contribution of relatively short-lived animals to the overall animal population. Against this background, it is worrying that the use of the mg/PCU indicator is now, next to country-to-country comparisons of overall usage, also proposed for animal sector comparisons between countries by the European Medicines Agency.[17] Caution should be taken when comparing AMU in food-producing animals to AMU in humans using fundamentally different indicators to quantify AMU. The use of more adequate and accurate epidemiological indicators, such as the defined daily dose based on a denominator that accounts for the period of antimicrobial exposure or risk period ('time at risk' based denominators), is thereby warranted.

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Transparency declarations

None to declare.

References

1 Austin DJ, Kristinsson KG, Anderson RM. The relationship between the volume of antimicrobial consumption in human communities and the frequency of resistance. *PNAS* 1999; **96**: 1152–6. https://doi.org/10.1073/pnas.96.3.1152

2 Dorado-García A, Mevius DJ, Jacobs JJ *et al*. Quantitative assessment of antimicrobial resistance in livestock during the course of a nationwide antimicrobial use reduction in the Netherlands. *J Antimicrob Chemother* 2016; **71**: 3607–19. https://doi.org/10.1093/jac/dkw308

3 Dunlop RH, McEwen SA, Meek AH *et al*. Associations among antimicrobial drug treatments and antimicrobial resistance of fecal *Escherichia coli* of swine on 34 farrow-to-finish farms in Ontario, Canada. *Prev Vet Med* 1998; **34**: 283–305. https://doi.org/10.1016/S0167-5877(97)00095-0

4 Goossens H, Ferech M, Vander Stichele R *et al*. Outpatient antibiotic use in Europe and association with resistance: a cross-national database study. *Lancet* 2005; **365**: 579–87. https://doi.org/10.1016/S0140-6736(05)17907-0

5 Van Boeckel TP, Glennon EE, Chen D *et al*. Reducing antimicrobial use in food animals. *Science* 2017; **357**: 1350–2. https://doi.org/10.1126/science.aao1495

6 Carrique-Mas JJ, Choisy M, Van Cuong N *et al*. An estimation of total antimicrobial usage in humans and animals in Vietnam. *Antimicrob Resist Infect Control* 2020; **9**: 1–6. https://doi.org/10.1186/s13756-019-0671-7

7 ECDC (European Centre for Disease Prevention and Control), EFSA (European Food Safety Authority), EMA (European Medicines Agency). ECDC/EFSA/EMA first joint report on the integrated analysis of the consumption of antimicrobial agents and occurrence of antimicrobial resistance in bacteria from humans and food-producing animals. *EFSA J* 2015; **13**: 4006. https://doi.org/10.2903/j.efsa.2015.4006

8 ECDC (European Centre for Disease Prevention and Control), EFSA (European Food Safety Authority), EMA (European Medicines Agency). ECDC/EFSA/EMA second joint report on the integrated analysis of the consumption of antimicrobial agents and occurrence of antimicrobial resistance in bacteria from humans and food-producing animals—Joint Interagency Antimicrobial Consumption and Resistance Analysis (JIACRA) Report. *EFSA J* 2017; **15**: 4872.

9 ECDC (European Centre for Disease Prevention and Control), EFSA (European Food Safety Authority), EMA (European Medicines Agency).

Third joint inter-agency report on integrated analysis of consumption of antimicrobial agents and occurrence of antimicrobial resistance in bacteria from humans and food-producing animals in the EU/EEA: JIACRA III 2016–2018. *EFSA J* 2021; **19**: e06712. https://doi.org/10.2903/j.efsa.2021.6712

10 Hillerton JE, Irvine CR, Bryan MA *et al*. Use of antimicrobials for animals in New Zealand, and in comparison with other countries. *N Z Vet J* 2017; **65**: 71–7. https://doi.org/10.1080/00480169.2016.1171736

11 Moulin G, Cavalié P, Pellanne I *et al*. A comparison of antimicrobial usage in human and veterinary medicine in France from 1999 to 2005. *J Antimicrob Chemother* 2008; **62**: 617–25. https://doi.org/10.1093/jac/dkn213

12 Veterinary Medicines Directorate. UK One Health Report—Joint Report on Antibiotic Use and Antibiotic Resistance, 2013–2017. 2019. https://assets.publishing.service.gov.uk/media/5f6c4affe90e076c2055a8b2/Ted_Final_version__1318703-v45-One_Health_Report_2019_FINAL-accessible.pdf.

13 Veterinary Medicines Directorate. Third UK One Health Report—Joint Report on Antibiotic Use, Antibiotic Sales and Antibiotic Resistance. 2023. https://assets.publishing.service.gov.uk/media/656488f11524e60011a100f8/_2681096-v1-Third_UK_One_Health_Report.PDF.

14 EMA (European Medicines Agency). Trends in the Sales of Veterinary Antimicrobial Agents in Nine European Countries (2005–2009). 2011. https://www.ema.europa.eu/en/documents/report/trends-sales-veterinary-antimicrobial-agents-nine-european-countries_en.pdf.

15 Sanders P, Mevius D, Veldman K *et al*. Comparison of different antimicrobial use indicators and antimicrobial resistance data in food-producing animals. *JAC Antimicrob Resist* 2021; **3**: dlab172. https://doi.org/10.1093/jacamr/dlab172

16 Radke BR. Towards an improved estimate of antimicrobial use in animals: adjusting the "population correction unit" calculation. *Can J Vet Res* 2017; **81**: 235–40.

17 EMA (European Medicines Agency). Guideline on the Reporting of Antimicrobial Sales and Use 5 in Animals at the EU level—Denominators and Indicators. 2023. https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-reporting-antimicrobial-sales-and-use-animals-eu-level-denominators-and-indicators_en.pdf.