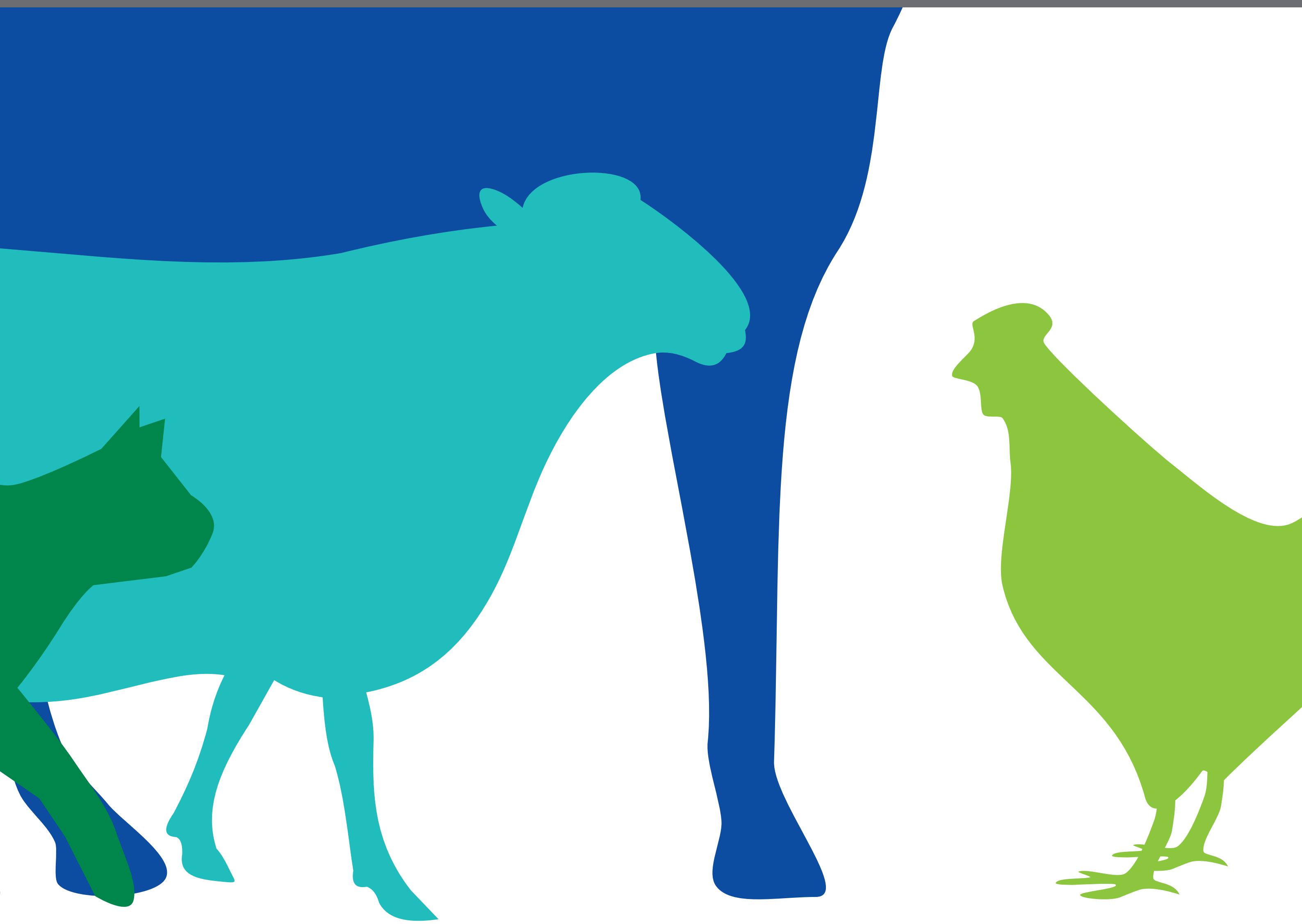
ANTIMICROBIAL USAGE IN COMPANION AND FOOD ANIMALS: METHODS, SURVEYS AND RELATIONSHIPS WITH ANTIMICROBIAL RESISTANCE IN ANIMALS AND HUMANS, VOLUME II

EDITED BY: Carolee Anne Carson, Miguel Ángel Moreno and Lucie Collineau
PUBLISHED IN: Frontiers in Veterinary Science



frontiers Research Topics

ISSN 1664-8714
ISBN 978-2-88971-308-0
DOI 10.3389/978-2-88971-308-0

About Frontiers

Frontiers is more than just an open-access publisher of scholarly articles: it is a pioneering approach to the world of academia, radically improving the way scholarly research is managed. The grand vision of Frontiers is a world where all people have an equal opportunity to seek, share and generate knowledge. Frontiers provides immediate and permanent online open access to all its publications, but this alone is not enough to realize our grand goals.

Frontiers Journal Series

The Frontiers Journal Series is a multi-tier and interdisciplinary set of open-access, online journals, promising a paradigm shift from the current review, selection and dissemination processes in academic publishing. All Frontiers journals are driven by researchers for researchers; therefore, they constitute a service to the scholarly community. At the same time, the Frontiers Journal Series operates on a revolutionary invention, the tiered publishing system, initially addressing specific communities of scholars, and gradually climbing up to broader public understanding, thus serving the interests of the lay society, too.

Dedication to Quality

Each Frontiers article is a landmark of the highest quality, thanks to genuinely collaborative interactions between authors and review editors, who include some of the world's best academicians. Research must be certified by peers before entering a stream of knowledge that may eventually reach the public - and shape society; therefore, Frontiers only applies the most rigorous and unbiased reviews.
Frontiers revolutionizes research publishing by freely delivering the most outstanding research, evaluated with no bias from both the academic and social point of view. By applying the most advanced information technologies, Frontiers is catapulting scholarly publishing into a new generation.

What are Frontiers Research Topics?

Frontiers Research Topics are very popular trademarks of the Frontiers Journals Series: they are collections of at least ten articles, all centered on a particular subject. With their unique mix of varied contributions from Original Research to Review Articles, Frontiers Research Topics unify the most influential researchers, the latest key findings and historical advances in a hot research area! Find out more on how to host your own Frontiers Research Topic or contribute to one as an author by contacting the Frontiers Editorial Office: frontiersin.org/about/contact

ANTIMICROBIAL USAGE IN COMPANION AND FOOD ANIMALS: METHODS, SURVEYS AND RELATIONSHIPS WITH ANTIMICROBIAL RESISTANCE IN ANIMALS AND HUMANS, VOLUME II

Topic Editors:
Carolee Anne Carson, Public Health Agency of Canada (PHAC), Canada
Miguel Ángel Moreno, Complutense University of Madrid, Spain
Lucie Collineau, Agence Nationale de Sécurité Sanitaire de l'Alimentation, de l'Environnement et du Travail (ANSES), France

Citation: Carson, C. A., Moreno, M. Á., Collineau, L., eds. (2021). Antimicrobial Usage in Companion and Food Animals: Methods, Surveys and Relationships With Antimicrobial Resistance in Animals and Humans, Volume II. Lausanne: Frontiers Media SA. doi: 10.3389/978-2-88971-308-0

Table of Contents

05 ***Editorial: Antimicrobial Usage in Companion and Food Animals: Methods, Surveys and Relationships With Antimicrobial Resistance in Animals and Humans, Volume II***
Lucie Collineau, Carolee A. Carson and Miguel A. Moreno

07 ***Antimicrobial Usage in Horses: The Use of Electronic Data, Data Curation, and First Results***
Anne Schnepf, Astrid Bienert-Zeit, Hatice Ertugrul, Rolf Wagels, Nicole Werner, Maria Hartmann, Karsten Feige and Lothar Kreienbrock

18 ***Antimicrobials Used in Backyard and Commercial Poultry and Swine Farms in the Philippines: A Qualitative Pilot Study***
Toni Rose M. Barroga, Reildrin G. Morales, Carolyn C. Benigno, Samuel Joseph M. Castro, Mardi M. Caniban, Maria Fe B. Cabullo, Agnes Agunos, Katinka de Balogh and Alejandro Dorado-Garcia

26 ***Standardization of Therapeutic Measures in Antibiotic Consumption Monitoring to Compare Different Livestock Populations***
Katharina Hommerich, Charlotte Vogel, Svetlana Kasabova, Maria Hartmann and Lothar Kreienbrock

35 ***Monitoring of Farm-Level Antimicrobial Use to Guide Stewardship: Overview of Existing Systems and Analysis of Key Components and Processes***
Pim Sanders, Wannes Vanderhaeghen, Mette Fertner, Klemens Fuchs, Walter Obritzhauser, Agnes Agunos, Carolee Carson, Birgitte Borck Høg, Vibe Dalhoff Andersen, Claire Chauvin, Anne Hémonic, Annemarie Käsbohrer, Roswitha Merle, Giovanni L. Alborali, Federico Scali, Katharina D. C. Stärk, Cedric Muentener, Ingeborg van Geijlswijk, Fraser Broadfoot, Lucie Pokludová, Clair L. Firth, Luís P. Carmo, Edgar Garcia Manzanilla, Laura Jensen, Marie Sjölund, Jorge Pinto Ferreira, Stacey Brown, Dick Heederik and Jeroen Dewulf

51 ***Small and Large Animal Veterinarian Perceptions of Antimicrobial Use Metrics for Hospital-Based Stewardship in the United States***
Laurel E. Redding, Brandi M. Muller and Julia E. Szymczak

61 ***Agreement of Benchmarking High Antimicrobial Usage Farms Based on Either Animal Treatment Index or Number of National Defined Daily Doses***
Dolf Kuemmerlen, Thomas Echtermann, Cedric Muentener and Xaver Sidler

74 ***Does the Use of Different Indicators to Benchmark Antimicrobial Use Affect Farm Ranking?***
Lorcan O'Neill, Maria Rodrigues da Costa, Finola Leonard, James Gibbons, Julia Adriana Calderón Díaz, Gerard McCutcheon and Edgar García Manzanilla

87 ***Antimicrobial Use Indices—The Value of Reporting Antimicrobial Use in Multiple Ways Using Data From Canadian Broiler Chicken and Turkey Farms***
Agnes Agunos, Sheryl P. Gow, David F. Léger, Anne E. Deckert, Carolee A. Carson, Angelina L. Bosman, Stefanie Kadykalo and Richard J. Reid-Smith

107 ***Antibiotic Use in Organic and Non-organic Swedish Dairy Farms: A Comparison of Three Recording Methods***
Gabriela Olmos Antillón, Karin Sjöström, Nils Fall, Susanna Sternberg Lewerin and Ulf Emanuelson

120 ***Comparing Farm Biosecurity and Antimicrobial Use in High-Antimicrobial-Consuming Broiler and Pig Farms in the Belgian–Dutch Border Region***
Nele Caekebeke, Franca J. Jonquiere, Moniek Ringenier, Tijs J. Tobias, Merel Postma, Angelique van den Hoogen, Manon A. M. Houben, Francisca C. Velkers, Nathalie Sleeckx, J. Arjan Stegeman and Jeroen Dewulf on behalf of the i-4-1-Health Study Group

131 ***Quantifying Antimicrobial Exposure in Dogs From a Longitudinal Study***
María Méndez and Miguel A. Moreno

138 ***Antimicrobial Usage Among Different Age Categories and Herd Sizes in Swiss Farrow-to-Finish Farms***
Thomas Echtermann, Cedric Muentener, Xaver Sidler and Dolf Kuemmerlen

148 ***A Cross-Sectional Study of Antimicrobial Usage on Commercial Broiler and Layer Chicken Farms in Bangladesh***
Tasneem Imam, Justine S. Gibson, Mohammad Foysal, Shetu Bhusan Das, Suman Das Gupta, Guillaume Fournié, Md. Ahasanul Hoque and Joerg Henning

159 ***Antimicrobial Use Surveillance Indicators for Finfish Aquaculture Production: A Review***
Jacob A. Narbonne, Brian R. Radke, Derek Price, Patrick C. Hanington, Amreen Babujee and Simon J. G. Otto

frontiers in Veterinary Science

EDITORIAL
published: 23 July 2021
doi: 10.3389/fvets.2021.728267

Editorial: Antimicrobial Usage in Companion and Food Animals: Methods, Surveys and Relationships With Antimicrobial Resistance in Animals and Humans, Volume II

Lucie Collineau[1], Carolee A. Carson[2] and Miguel A. Moreno[3,4]*

[1] Epidemiology and Surveillance Unit, Laboratory of Lyon, French Agency for Food, Environmental and Occupational Health & Safety (ANSES), Lyon, France, [2] Public Health Agency of Canada (PHAC), Guelph, ON, Canada, [3] Department of Animal Health, Veterinary Faculty, Complutense University, Madrid, Spain, [4] VISAVET Health Surveillance Centre, Complutense University, Madrid, Spain

Keywords: antibiotic use, metrics, livestock, pets, monitoring, surveillance

OPEN ACCESS

Edited by:
Salome Dürr,
University of Bern, Switzerland

Reviewed by:
Lothar Kreienbrock,
University of Veterinary Medicine Hannover, Germany

***Correspondence:**
Lucie Collineau
lucie.collineau@anses.fr

Specialty section:
This article was submitted to Veterinary Epidemiology and Economics, a section of the journal Frontiers in Veterinary Science

Received: 21 June 2021
Accepted: 29 June 2021
Published: 23 July 2021

Citation:
Collineau L, Carson CA and Moreno MA (2021) Editorial: Antimicrobial Usage in Companion and Food Animals: Methods, Surveys and Relationships With Antimicrobial Resistance in Animals and Humans, Volume II. Front. Vet. Sci. 8:728267. doi: 10.3389/fvets.2021.728267

Editorial on the Research Topic

Antimicrobial Usage in Companion and Food Animals: Methods, Surveys and Relationships with Antimicrobial Resistance in Animals and Humans, Volume II

The best way to quantify antimicrobial use (AMU) in animals has raised wide research interests over the past years. Following the success of the first edition of the Research Topic on "Antimicrobial Usage in Companion and Food Animals: Methods, Surveys, and Relationships with Antimicrobial Resistance in Animals and Humans" Moreno et al., a second edition was launched. The objective was to continue the discussion on AMU metrics and expand the topic to other geographical regions (beyond North American and European Union countries), as well as other animal species (other than cattle, pigs, poultry, cats, or dogs).

A total of 14 articles contributed to this collection, including 12 original research papers and two review papers. Among the original research papers, geographical areas covered included Europe ($n = 8$), North America ($n = 2$), and Asia ($n = 2$). Animal species covered included pigs ($n = 5$), poultry ($n = 4$), multiple animal species ($n = 3$), dairy cattle ($n = 1$), dogs ($n = 1$), finfish aquaculture ($n = 1$), and horses ($n = 1$).

Out of the various research questions proposed in the Research Topic scope, the large majority of contributing studies aimed to compare different metrics to characterize AMU in animals ($n = 10$), while others primarily intended to compare AMU between countries ($n = 4$), between animal populations or farms, i.e., benchmarking ($n = 3$), or to monitor AMU trends over time ($n = 1$). None of the published studies addressed the aspects of linking AMU to antimicrobial resistance (AMR), or linking AMU between human and animal sectors, suggesting there is still room for more integrated and One Health approaches in the AMU metrics area.

Most studies relied on end-user (farms or veterinarians) data ($n = 12$), while only a few studies relied on national ($n = 1$) or supra-national data ($n = 1$). This suggests a recent shift from national to end-user data, which are closer to "actual" AMU. Interestingly, this shift was also described by Sanders et al. who reported the development of multiple farm-level monitoring systems in Europe and Canada over the recent years. These are public or private monitoring programs (~50% each), which for some of them manage to achieve full sector coverage.

Sanders et al. also reviewed the different AMU indicators being used by farm-level monitoring systems, defined as the amounts of antimicrobials consumed (numerator) normalized by the population at risk of being treated in a defined period of time (denominator). The authors demonstrated a clear lack of harmonization between farm-level indicators across countries and systems. The same observation was made by Narbonne et al. who systematically reviewed AMU indicators in finfish aquaculture. In addition, the calculation of AMU indicators in finfish aquaculture raised specific issues, e.g. related to the lack of average weight at treatment available in this sector.

Several contributing studies quantified the gap between different indicators applied to the same dataset, and discussed the impact this had on the study results. Depending on the indicator applied to broiler chicken and turkey farm-level data, Agunos et al. observed variations in reported quantity of use, temporal trends, and relative ranking of the antimicrobials. Discrepancies were also observed by Kuemmerlen et al. and O'Neill et al. when ranking Swiss and Irish pig farms using various AMU indicators, highlighting the fact that different methods of measuring AMU can affect a benchmarking system. Discrepancies appeared higher when comparing weight-based vs. dose-based metrics, while comparisons within dose-based metrics appeared relatively concordant. Similarly, Schnepf et al. reported little deviation when comparing Used Daily Doses with Defined Daily Doses in horses presented at a veterinary university clinic in Germany. Comparisons between populations, e.g., between countries, could be improved by applying a standardization procedure to correct for differences in the composition of livestock demographics, as suggested by Hommerich et al.

Some contributing studies also explored associations between AMU quantities and farm management practices. Caekebeke et al. studied associations between AMU and biosecurity levels in broilers and pig farms in Belgium and the Netherlands, and showed that Dutch farms overall had higher biosecurity and lower AMU than Belgian farms. In addition, Echtermann et al. reported positive significant associations between AMU and farm size, as well as between AMU in sows and piglets in Swiss farrow-to-finish pig farms. Olmos Antillón et al. explored variations in AMU between conventional and organic dairy farms in Sweden; while AMU for injectable and lactating cow intramammary treatments statistically differed between production systems, no difference was found for dry-cow therapies.

One study by Redding et al. looked at perceptions of AMU indicators by small and large animal veterinarians in the USA. While respondents were quite positive about being part of a benchmarking system, they also reported AMU indicators, and especially dose-based indicators to be confusing, and recommended further guidance on how to interpret the metrics. Hence, the authors stressed the importance of selecting AMU indicators that are meaningful to clinicians for AMU monitoring to have a positive impact on antimicrobial stewardship.

Beyond generating meaningful indicators, the issue of accessing detailed data that are necessary to calculate advanced indicators such as dose-based indicators was also raised. In their longitudinal study on AMU in Spanish dogs, Méndez and Moreno called for a pragmatic approach to use the simplest indicators based on the most frequently available information, as a compromise for permitting certain AMU data analyses. This is also the approach that has been used by Imam et al. and Barroga et al. in Bangladesh and the Philippines, where quantitative AMU data are not routinely recorded. The analysis of the proportion of farms using selected antimicrobial classes showed the frequent use of critically important antimicrobials in pigs and poultry in both countries, highlighting the critical need to improve antimicrobial stewardship in the region. Among others, this could be achieved via stronger AMU monitoring systems.

Between April 2019 and March 2021, there were substantial contributions (29 articles) to the two article collections. Both article collections highlighted the diversity of approaches to data collection and reporting of AMU information, with resulting implications for interpretation and communication of the findings. Within the article collections were themes of pragmatism in AMU reporting, a need for harmonization and transparency in documentation of methods, and reporting AMU in a way that is meaningful to the target audience to improve antimicrobial stewardship.

AUTHOR CONTRIBUTIONS

LC produced the first draft of the editorial. All authors edited and approved the editorial.

ACKNOWLEDGMENTS

Authors thanks all the reviewers and authors of this collection for helping to improve knowledge about antimicrobial use and to trigger discussions about best practices for quantification of antimicrobial use in animals.

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

frontiers in Veterinary Science

ORIGINAL RESEARCH
published: 29 April 2020
doi: 10.3389/fvets.2020.00216

Antimicrobial Usage in Horses: The Use of Electronic Data, Data Curation, and First Results

Anne Schnepf[1]*, Astrid Bienert-Zeit[2], Hatice Ertugrul[1], Rolf Wagels[3], Nicole Werner[1], Maria Hartmann[1], Karsten Feige[2] and Lothar Kreienbrock[1]

[1] Department of Biometry, Epidemiology and Information Processing, WHO Collaborating Centre for Research and Training for Health in the Human-Animal-Environment Interface, University for Veterinary Medicine Hannover, Hanover, Germany, [2] Clinic for Horses, University for Veterinary Medicine Hannover, Hanover, Germany, [3] Information and Data Service (TiHo-IDS), University for Veterinary Medicine Hannover, Hanover, Germany

OPEN ACCESS

Edited by:
Carolee Anne Carson,
Public Health Agency of Canada (PHAC), Canada

Reviewed by:
Laurel Redding,
University of Pennsylvania, United States
Jana Schulz,
Friedrich Loeffler Institute, Germany

***Correspondence:**
Anne Schnepf
anne.schnepf@tiho-hannover.de

Specialty section:
This article was submitted to Veterinary Epidemiology and Economics, a section of the journal Frontiers in Veterinary Science

Received: 05 December 2019
Accepted: 31 March 2020
Published: 29 April 2020

Citation:
Schnepf A, Bienert-Zeit A, Ertugrul H, Wagels R, Werner N, Hartmann M, Feige K and Kreienbrock L (2020) Antimicrobial Usage in Horses: The Use of Electronic Data, Data Curation, and First Results. Front. Vet. Sci. 7:216. doi: 10.3389/fvets.2020.00216

The usage of antimicrobial drugs (AMs) leads to an increase in antimicrobial resistance (AMR). Although different antimicrobial usage (AMU) monitoring programs exist for livestock animals in Germany, there is no such system for horses. However, with the increasing usage of electronic practice management software (EPMS), it is possible to analyze electronic field data generated for routine purposes. The aim of this study was to generate AMU data for German horses with data from the Clinic for Horses (CfH), University of Veterinary Medicine Hannover (TiHo), and in addition to show that different processes of data curation are necessary to provide results, especially considering quantitative indices. In this investigation, the number of antimicrobial doses used and the amount and percentage of active ingredients applied were calculated. Data contained all drugs administered between the 1st of January and the 31st of December 2017. A total of 2,168 horses were presented for veterinary care to the CfH and 34,432 drug applications were documented for 1,773 horses. Of these, 6,489 (18.85%) AM applications were documented for 837 (47.21%) horses. In 2017, 162.33 kg of active ingredients were documented. The most commonly used antibiotic classes were sulfonamides (84.32 kg; 51.95 %), penicillins (30.11 kg; 18.55%) and nitroimidazoles (24.84 kg; 15.30%). In 2017, the proportion of Critically Important Antibiotics (CIA)—Highest Priority used was 0.15% (0.24 kg) and the proportion of CIA—High Priority used was 20.85% (33.85 kg). Of the total 9,402 entries of antimicrobial active ingredients, the three with the largest number used were sulfonamides [$n = 2{,}798$ (29.76%)], trimethoprim [$n = 2{,}757$ (29.76%)] and aminoglycosides [$n = 1{,}381$ (14.69%)]. Comparison between Administered Daily Dose (ADA) and Recommended Daily Dose of CfH (RDD_{CfH}), showed that 3.26% of ADA were below RDD_{CfH}, 3.18% exceeded RDD_{CfH} and 93.55% were within the range around RDD_{CfH}. This study shows that data generated by an EPMS can be evaluated once the method is set up and validated. The method can be transferred to evaluate data from the EPMS of other clinics or animal species, but the transferability depends on the quality of AMU documentation and close cooperation with respective veterinarians is essential.

Keywords: antimicrobial consumption, individual animal, electronic practice management software, Germany, antimicrobial resistance

INTRODUCTION

Antibiotics have a long history of usage in human and veterinary medicine. In 1910, the first antimicrobial compound arsphenamine was introduced (1), and in 1929, penicillin was discovered by Sir Alexander Fleming (2). Curing bacterial infections without severe side effects was an important milestone in the history of medicine.

Today, mankind is facing one of the biggest problems in treating bacterial infections: the increase of antimicrobial resistance (AMR) that is correlated with the increasing use of antimicrobials (3–6). In particular, multiple drug-resistant pathogens will cause an increasing number of deaths in humans and animals. Recently, published numbers from the European Center for Disease Prevention and Control (ECDC) showed that cases of death caused by resistant pathogens increased from an estimated 25,000 fatalities in Europe in 2007 (7) to 33,000 fatalities (8) in 2015.

The increasing occurrence of resistant bacteria is a controversial issue. From the One Health perspective, using antimicrobial drugs (AMs) in farm animals is often thought to facilitate the spread of AMR, because of the dissemination of resistant bacteria through the food chain. In general, the roles of horses and companion animals as facilitators of AMR have been underestimated (9) and received less attention (10–13).

Today, horses live in close contact with humans. There are an estimated 1.3 million horses in Germany (14); these horses could be seen as a reservoir and vector for resistant bacteria (15, 16).

Despite playing a role in the development of AMR, there is very little information about antimicrobial usage (AMU) in horses in Germany. Official reports on antimicrobials sold for veterinary use are based on data from the register of veterinary medicinal products and do not include reports on specific animals. Additionally, many drugs are authorized for multiple animal species, making an assignment to specific animal species impossible, and off-label use of human medicinal products is not included (17–23).

Therefore, it is vital to develop a system for collecting and analyzing data on the usage of antimicrobial drugs in horses to provide useful information for veterinarians. So the aim of the study was to generate AMU data under the system for German horses, and in addition to show that different processes of data curation are necessary to provide results, especially regarding quantitative indices.

Abbreviations: ADA(s), Administered Daily Dose(s); ADF, Application and Delivery Forms; AM(s), Antimicrobial Drug(s); AMG, Medicinal Products Act ("Arzneimittel-Gesetz"); AMR, Antimicrobial Resistance; AMU, Antimicrobial Usage; CIA(s), Critically Important Antibiotic(s); ECDC, European Centre for Disease Prevention and Control; EPMS, Electronic Practice Management Software; EU, European Union; ID number, Identification number; RDD_{CfH}, Recommended Daily Dose of the Clinic for Horses, TiHo; $SD_{CfH,}$ Standard Dosage of the Clinic for Horses, TiHo; SPC, Summary of Product Characteristics; TiHoUniversity for Veterinary Medicine Hannover, Foundation (Stiftung Tierärztliche Hochschule Hannover); WHO, World Health Organization.

MATERIALS AND METHODS

In Germany, AMs for animals are, by law (AMG §56a), only available with a prescription from a veterinarian, so data from clinics or practices offer a good basis for evaluating AMU.

Data from the Clinic for Horses, University of Veterinary Medicine Hannover, Foundation (TiHo), on drugs used within the study period between the 1st of January and the 31st of December 2017 were evaluated. These data were generated in the electronic practice management software (EPMS) easyVet [Veterinärmedizinisches Dienstleistungszentrum (VetZ) GmbH, Isernhagen, Germany].

Only horses that had been prescribed at least one drug within the investigated time period were included in the study.

The Clinic for Horses, which is a university hospital, works mainly as a referral hospital without out-patient care. There are 20 veterinarians with different levels of experience at the Clinic for Horses.

Generating and Editing the Dataset

Data were extracted via export from easyVET. Extracted data were provided in Excel format (Microsoft, 2010) and imported into the statistical analysis software SAS 9.4 (SAS Institute Inc., Cary, NC, United States), where descriptive statistical calculations were performed.

For each horse, a unique animal identification (ID) number, breed, gender, date of birth, all documented weights, and status as food-producing animals were reported. For each drug, the following information was collected: treatment date, medicinal product name, amount and unit of the preparation and whether the drug was administered during the visit or dispensed to the owner. Further data collected were a unique case ID number and the corresponding diagnoses.

For this study, a few assumptions had to be made. First, it was assumed that all billed drugs were used to treat the horses, and only billed drugs were used. Second, it was assumed that only dosages based on a summary of product characteristics (SPC) and recent publications were applied and that every diagnosis verified by a veterinarian was documented in the system.

First of all, the following prescriptions were excluded (**Figure 1**): documented applications for species other than horse, documented applications without drug name, documented applications without amount of the drug.

Furthermore, in this study, AMs were defined as medicines that destroy or inhibit the growth of bacterial microorganisms (i.e., antibacterial drugs) and were authorized for systemic and topical use (24). Other AMs, such as antiviral or antifungal drugs or biocides, were excluded from this study (**Figure 1**).

A master table of AMs was developed using the product index of the clinic. All drug names were compared with different databases (vetidata.de, gelbe-liste.de, www.pharmnet-bund.de and drugs.com) to identify and extract all drugs containing at least one antimicrobial substance. In addition, products licensed for other species or humans, individually manufactured preparations and imported drugs were considered. The cascade principle [EU Regulation 37/2010, §56a (2), and in addition, §56a Abs. 2a AMG for equids]

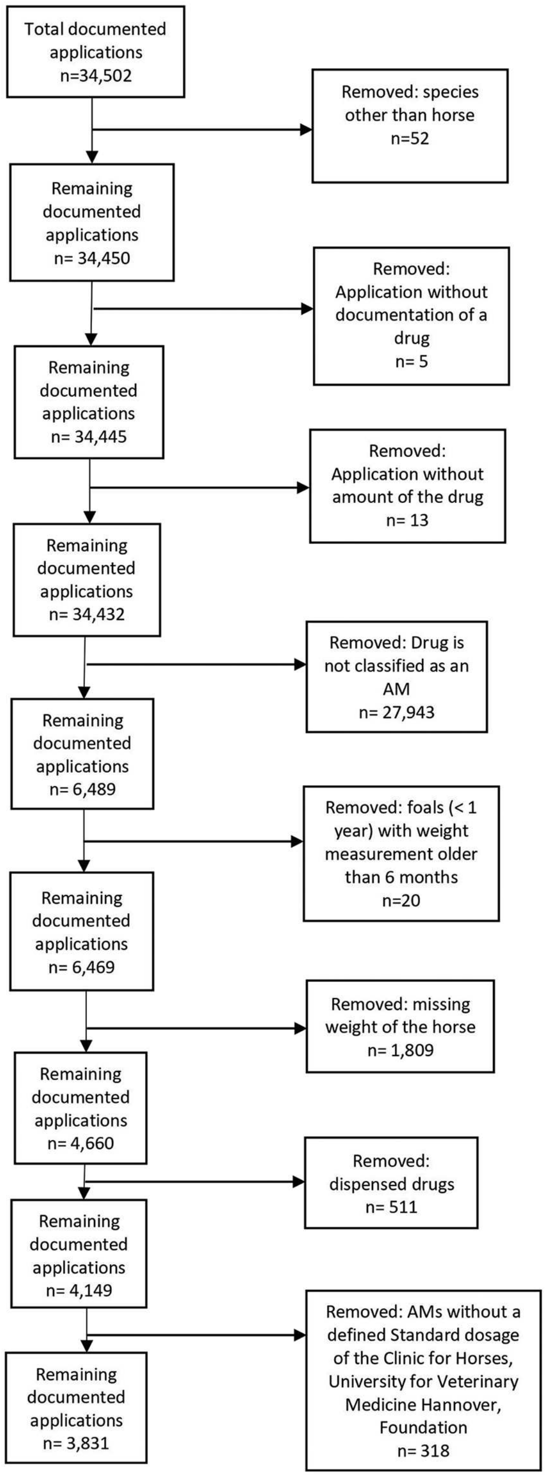


FIGURE 1 | Data cleaning process for drug applications in 2017 at the Clinic for Horses, University for Veterinary Medicine Hannover, Foundation.

allows the off-label use of medicinal products not licensed for horses in cases where there is no alternative drug licensed for horses that would provide an appropriate treatment, or the drug is not authorized for the field of application.

TABLE 1 | Active ingredients documented to be used in horses in 2017 at the Clinic for Horses according to the World Health Organization (WHO) classification, antimicrobial group and chemical structure.

WHO classification	Antimicrobial group	Substance
CIA*–Highest priority	Cephalosporins	Cefquinome (4th generation)
	Quinolones	Enrofloxacin
		Marbofloxacin
		Moxifloxacin
		Ofloxacin
	Macrolides	Azithromycin
	Polypeptides	Polymyxin B
CIA*–High priority	Aminoglycosides	Amikacin
		Gentamicin
		Neomycin
	Ansamycins	Rifampicin
	Penicillins	Amoxicillin
		Benzylpenicillin
Highly important	Amphenicols	Chloramphenicol
	Sulfonamides	Sulfadiazine
		Sulfadimethoxine
		Sulfonamide
	Tetracyclines	Chlortetracycline
		Doxycycline
		Oxytetracycline
	Trimethoprim	Trimethoprim
Important	Nitroimidazoles	Metronidazole

**CIA, Critically Important Antibiotics.*

If a product contained multiple active substances in the same preparation, substances other than antimicrobials were excluded from the calculations. Regarding amoxicillin plus clavulanic acid, only amoxicillin was included in the calculation, as clavulanic acid works as an adjuvant for penicillins and does not work as an antimicrobial by itself. In contrast, the quantity of sulfonamides and trimethoprim was calculated for each substance separately, as both are classified as antimicrobials. For any other compounded drug each substance by itself was included in the calculation with its own factor.

All antimicrobials were also categorized by their route of administration as per the SPC, resulting in three main groups: injection, oral and topical. The oral and topical routes were divided in several subgroups each (oral in tablets, capsules and oral—other; topical in eye, skin, ear and topical—other). Dividing injection into subgroups according to the exact route of administration (e.g., intravenously or intramuscular) was not possible with the extracted data or with the information given in the SPC.

Subsequently, the most recent WHO AM classification was applied: *Critically Important Antibiotics* (*CIA*)*—Highest Priority*, *CIA—High Priority*, *Highly Important* and *Important* (**Table 1**).

To smoothen the analysis processes, species, breed, gender and drugs were numerically encoded. With this step, misspellings and repeated entries, such as multiple breeds or drugs, were consolidated.

Choice of the Corresponding Diagnosis

Clinical diagnoses are manifold. To link the diagnosis and indication for antibiotic treatment, a decision tree based on the default catalog of diagnoses used by the Clinic for Horses was developed for choosing the diagnosis requiring AMU. Diagnoses in this catalog are composed of the affected organ system, detailed anatomic location, etiology and exact diagnosis. While developing this decision tree, primarily the etiology was used for choosing the diagnosis requiring AMU.

For cases where only one diagnosis was indicated, the single diagnosis was chosen for analysis. For cases with more than one diagnosis, choosing the diagnosis requiring for analysis was performed in an eleven-step process (see **Supplement 1**).

Using the unique animal ID number in combination with the unique case ID number, differentiation between recurring and distinct conditions was possible. The options for choosing a diagnosis in the EPMS can lead to different naming of the same condition; therefore, classification into distinct or recurring cases had to be performed manually.

Calculation of the Administered Daily Dose (ADA)

To calculate the amount used for each active ingredient, the master table was compared to a database with all veterinary drugs officially licensed in Germany. The information of each product in this database contains at least a pharmaceutical form, a quantity unit, the possible routes of administration and the active ingredients with international nonproprietary name, agent group (by chemical structure), and amount of active ingredients per quantity unit.

With this information, an ADA of each active ingredient, in grams, was calculated by transferring the amount given for each course.

$$ADA\ \left(Administered\ Daily\ Dose\right) = amount\ of\ drug\ \times\ proportion\ of\ active\ ingredient\ in\ this\ drug$$

Recommended Daily Dose (RDD_{CfH}) and Comparison With the ADA

The ADA of each active ingredient was compared to the Recommended Daily Dose internally defined by the TiHo Clinic for Horses (RDD_{CfH}) based on the weight of the horse and standard dosages to define whether the ADA was below the RDD_{CfH}, within a range around the RDD_{CfH} or exceeding the RDD_{CfH}. Standard dosages (SD_{CfH}) per kilogram per day were defined for each drug (see **Supplement 2**) with the information out of summary of product characteristics and recent research. For some active ingredients, such as amikacin, cefquinome, metronidazole, amoxicillin and ceftiofur, special dosages for foals were determined.

The calculated amount of active ingredient was defined as the RDD_{CfH} per animal for each active ingredient, and this value was calculated by multiplying the SD_{CfH} with the horses' weight measured at the closest date to treatment. If there was a weight entered before and after the day of treatment with the same time lag, the weight taken before treatment was chosen for analysis.

$$RDD_{CfH}\ \left(Recommended\ Daily\ Dose\right) = SD_{CfH}\ \times\ bodyweight$$

If SD_{CfH} consisted of a range of dosages and not a fixed value, the lowest and highest RDD_{CfH} were calculated with the lowest and highest SD_{CfH}, respectively.

Comparing ADA with RDD_{CfH} was done to evaluate whether the administered dosage was acceptable, below RDD_{CfH} or above RDD_{CfH}.

To compare ADA with RDD_{CfH} the ADA should be in the range of bioequivalence, e.g., from 80 to 125% of the RDD_{CfH}. To adjust for anomaly cases, a higher dosage of up to 2-fold was assumed to be acceptable. If the RDD_{CfH} was indicated by a dose range, the acceptable range of the active compound was within 80% of the lowest RDD_{CfH} and 125% of the highest RDD_{CfH}, considering the range of bioequivalence, i.e., ADAs between 80% of the lowest RDD_{CfH} and 250% of the highest RDD_{CfH} were defined as acceptable doses. If RDD_{CfH} consisted a fixed value, ADAs between 80 and 250% of this value were defined as acceptable doses.

In the dataset, certain drugs could be administered multiple times per day. Therefore, these drugs had to be classified differently on the first and last day of application, as the exact time of arrival and discharge or surgery were unknown. If a total given amount on the first and last day was lower than the $RDD_{CfH,}$ it was assumed that, due to the time of arrival or discharge, a full RDD_{CfH} was not possible. Therefore, we applied the same adjustment used for the range of bioequivalence for proportions of the daily dose on the first and last day of treatment for each drug.

For the calculation of the RDD_{CfH} and comparison with the ADA, only a part of the dataset could be used (**Figure 1**). Entries without a weight had to be excluded because calculation of the RDD_{CfH} and ADA was not possible. To avoid a misclassification, only drugs administered were evaluated, and entries of foals with a weight measurement that was older than 6 months were excluded. Only drugs where the SD_{CfH} was available and calculating the RDD_{CfH} was possible were included. In total, 2,658 entries (40.96%) were excluded; the majority of these entries (1,809 entries; 27.88%) were excluded because of missing weight.

RESULTS

In 2017, 2,168 horses were presented to the study clinic. Of these 1,733 (81.78%) horses had at least one documented drug application and 837 (38.60%) horses received at least one AM.

A total of 34,432 drug applications were documented for 1,733 horses in the study clinic in 2017. Of these 34,435 drug applications, 6,489 were AMs administered to 837 horses. Thus, 18.85% of all drugs given were AMs, and 47.21% of all treated horses received at least one AM. There were 43 different antimicrobial drugs with 22 different active ingredients used. The active ingredients were classified into twelve groups by their chemical structure and into four groups based on WHO classification (**Table 1**).

In this study, the cascade principle was used for eight veterinary drugs not licensed for horses, for 22 drugs only licensed for humans and for two drugs individually manufactured.

The 6,489 AM applications were split into 3,316 (51.10%) oral AM applications, 2,799 (43.13%) injections, and 374 (5.76%) topical AM applications. Seven hundred and fourteen (11.00%) of the AM applications were dispensed, and 5,774 (89.00%) were used for treatment in the clinic.

Using the unique case ID number, we determined that drugs were used in 2,178 different cases and, in 914 (41.97%) cases among 837 horses, AMs were prescribed. Fifty-nine (7.05%) of 837 horses had more than one case ID number, meaning that they were represented multiple times. Of these horses, 49 (83.05%) represented two cases, and ten (16.95%) horses represented three or more different cases; there was a maximum of seven cases per animal. Fifteen (25.42%) of the 59 horses were treated with antimicrobials because of distinct conditions, while 40 (67.80%) were treated for recurring conditions. Four horses (6.78%) had different case ID numbers because of recurring and distinct conditions.

In 585 (64.00%) of 914 cases, the animal was defined as a non-food-producing horse, while 103 (11.27%) were defined as food-producing horses. In 226 (24.73%) cases, the status was either unknown or was not entered into the system.

In 2017, a single AM was administered in 51.64% ($n = 472$) of the cases, two different AMs were administered in 22.65% ($n = 207$) three AMs were administered in 17.61% ($n = 161$), and between four and eight different AMs were administered in 8.1% ($n = 74$).

In total, 162.33 kg of antimicrobial ingredients were administered or dispensed in 2017 (**Table 2**). Sulfonamides (84.32 kg; 51.95%) had the largest share, with sulfadiazine (56.29 kg; 66.76%) used most often. Sulfonamides were administered mostly orally (83.94 kg; 99.55%). Penicillins (30.11 kg; 18.55%) were in second place in the ranking of the amount of active ingredients used. Benzylpenicillin was the penicillin used most often (20.14 kg; 66.89%), and injection was the main route of administration (29.66 kg; 98.51%). The 3rd place position was taken by nitroimidazoles with metronidazole as the only active ingredient used in this AM group. In total, 24.84 kg (15.30%) of nitroimidazoles were administered, mostly via the oral drug route (24.79 kg; 99.80%).

Of the total 9,402 entries, the three active ingredients with the largest amount used were sulfonamides [2,798 entries (29.76%)], penicillins [1,362 entries (14.49%)], and nitroimidazoles [292 entries (3.11%)] (**Table 3**). The ranking of drugs used by the number of entries showed sulfonamides in first place with 2,798 entries (29.76%), trimethoprim in second place with 2,757 entries (29.32%) and aminoglycosides in third place with 1,381 entries (14.69%).

Drugs licensed for horses had the largest share of the total amount of active ingredient used, with an amount of 109.83 kg (67.66%). The amount of drug used that was not licensed for horses was 52.50 kg (32.34%). Of the drugs not licensed for horses, 25.38 kg (48.34%) were originally licensed for humans, 2.73 kg (5.20%) were licensed for other animal species and 24.39 kg (46.46%) were individually manufactured. Out of the drugs licensed for human use only, the largest proportions were observed for benzylpenicillin (20.14 kg; 79.35%) and gentamicin (3.44 kg; 13.55%).

Referring to the WHO classification, 0.24 kg (0.15%; see **Figure 2**) of the drugs used were classified as *CIA—Highest Priority*; the drugs used in this category were mostly drugs licensed for animals other than horse, and polymyxin B as main active ingredient. Overall, 33.85 kg (20.85%) were classified as *CIA—High Priority*. Most of these drugs were licensed for humans, and benzylpenicillin accounted for the largest proportion. In the group classified as *Highly Important* (103.41 kg; 63.70%), the largest proportion of AM drugs used were licensed for horses, and sulfadimethoxine was the main active ingredient. Individually manufactured drugs provided the largest proportion of drugs classified as *Important* (24.84 kg; 15.30%), with metronidazole as the most common main active ingredient.

The comparison between the ADA and RDD_{CfH} showed that, of the 3,831 drug applications where the comparison was possible, only 125 drug applications (3.26%) were below the RDD_{CfH}, 122 (3.18%) drug applications exceeded the RDD_{CfH} and 3,584 (93.55%) drug applications were within the range around RDD_{CfH}.

DISCUSSION

Because of the increasing resistance of bacteria against antimicrobial compounds, there is a need to collect and evaluate data on AMU in companion animals such as horses and pets. To the best of our knowledge, this is the first study investigating the usage of antimicrobials in an equine clinic in Germany. Until now, such information has been scarce. Sales data of veterinary medicinal products are published annually (17), but these data do not refer to the species that the drug is used for, and off-label use of medicinal products licensed for humans or other animal species and individually manufactured AMs are not taken into account.

In this retrospective study, we used EPMS data that display the real usage of all kinds of antibacterial drugs. These large-scale data are generated within routine clinical work and do not require additional efforts from the veterinary practitioner involved. However, close cooperation with the respective veterinarians is crucial for a realistic evaluation, as errors in documentation are possible and can be found more easily when working with a close contact. In particular, when defining a standard dosage for each AM and choosing a corresponding diagnosis, knowledge in clinical work is essential.

This study presents the broad possibilities and benefits of analyzing data generated by EPMS, but also acknowledges the assumptions and adjustments that had to be made in advance.

In general, the results show that 47.21% of all horses treated with at least one drug, received at least one antimicrobial, but

TABLE 2 | Documented amount of antimicrobial active ingredients used in horses in 2017 at the Clinic for Horses, by route of administration.

Antimicrobial group and active ingredient	Injection Amount in kg	Oral Amount in kg	Topical Amount in kg	Total amount in kg (%)
Aminoglycoside	**3.62**	–	**0.00**	**3.63 (2.23%)**
Amikacin	0.19	–	–	0.19 (0.11%)
Gentamicin	3.44	–	0.00	3.44 (2.12%)
Neomycin	–	–	0.00	0.00 (0.00%)
Ansamycins	–	**0.11**	–	**0.11 (0.07%)**
Rifampicin	–	0.11	–	0.11 (0.07%)
Penicillins	**29.66**	**0.45**	–	**30.11 (18.55%)**
Amoxicillin	9.53	0.45	–	9.98 (6.15%)
Benzylpenicillin	20.14	–	–	20.14 (12.40%)
Cephalosporin	**0.03**	–	–	**0.03 (0.02%)**
Cefquinome	0.03	–	–	0.03 (0.02%)
Amphenicol	–	–	**0.00**	**0.00 (0.00%)**
Chloramphenicol	–	–	0.00	0.00 (0.00%)
Quinolones	**0.05**	**0.01**	**0.00**	**0.07 (0.04%)**
Enrofloxacin	0.01	0.01	–	0.02 (0.01%)
Marbofloxacin	0.04	–	–	0.04 (0.03%)
Moxifloxacin	–	–	0.00	0.00 (0.00%)
Ofloxacin	–	–	0.00	0.00 (0.00%)
Macrolide	–	**0.06**	–	**0.06 (0.04%)**
Azithromycin	–	0.06	–	0.06 (0.04%)
Nitroimidazole	**0.04**	**24.79**	**0.00**	**24.84 (15.30%)**
Metronidazole	0.04	24.79	0.00	24.84 (15.30%)
Polypeptide	**0.08**	–	**0.00**	**0.08 (0.05%)**
Polymyxin-B	0.08	–	0.00	0.08 (0.05%)
Sulfonamide	–	**83.94**	**0.38**	**84.32 (51.95%)**
Sulfadiazine	–	56.11	0.18	56.29 (34.67%)
Sulfadimethoxine	–	27.84	–	27.84 (17.15%)
Sulfonamide	–	–	0.20	0.20 (0.12%)
Tetracycline	**0.00**	**2.29**	**0.00**	**2.30 (1.42%)**
Chlortetracycline	–	–	0.00	0.00 (0.00%)
Doxycycline	–	2.29	–	2.29 (1.41%)
Oxytetracycline	0.00	–	0.00	0.00 (0.00%)
Trimethoprim	–	**16.78**	–	**16.78 (10.34%)**
Trimethoprim	–	16.78	–	16.78 (10.34%)
Total	**33.50**	**128.44**	**0.39**	**162.33 (100.00%)**

–, observed zero; 0, zero by rounding. The bold values are the summary per antimicrobial group, the corresponding active ingredients are underneath.

there was a very low frequency and amount of drugs classified as *CIA—Highest Priority* (0.15%; 0.24kg). The AMs used most often were classified as *Highly Important*, and the biggest proportion of the AMs used were licensed for horses.

Due to the lack of data, comparison of results with other studies or monitoring systems is difficult and only possible with reservations. Buckland et al. (25) showed that, in general, using EPMS data to study AMU in small animals is possible, but their way of evaluation is not applicable in our study because of the differences in investigated animal species between the studies and in the data that can be extracted from the particular EPMS. Furthermore, Buckland et al. (25) were working with a free text search to extract relevant treatment records, and it was only possible for these authors to extract a unique patient ID number (not a case ID number). As we were able to extract the drug name from easyVET, the source of errors related to AMU missing entries could be neglected in our study, while a free text search always bears a certain risk of drug misallocation. Therefore, these procedures are prone to information bias. In our study, it was possible to differ between prescriptions written for repeated vs. distinct conditions through the unique case ID number, which reduces this bias.

In our research in 41.97% of cases at least one AM was prescribed, which is comparable to results from Redding et al. (26) were AMs were prescribed in 38.4% of visits. Both proportions seem to be closely connected, but due to different definitions of cases and visits, detailed comparison is not possible.

TABLE 3 | Documented number of antimicrobial active ingredients used in horses in 2017 at the Clinic for Horses, by route of administration.

Antimicrobial group and active ingredient	Injection	Oral	Topical	Total documented applications (%)
Aminoglycosides	**1,222**	**–**	**159**	**1,381 (14.69%)**
Amikacin	141	–	–	141 (1.50%)
Gentamicin	1,081	–	3	1,084 (11.53%)
Neomycin	–	–	156	156 (1.66%)
Rifamycin	**–**	**70**	**–**	**70 (0.74%)**
Rifampicin	–	70	–	70 (0.74%)
Penicillins	**1,312**	**50**	**–**	**1,362 (14.49%)**
Amoxicillin	1,094	50	–	1,144 (12.17%)
Benzylpenicillin	218	–	–	218 (2.32%)
Cephalosporins	**61**	**–**	**–**	**61 (0.65%)**
Cefquinome	61	–	–	61 (0.65%)
Amphenicols	**–**	**–**	**3**	**3 (0.03%)**
Chloramphenicol	–	–	3	3 (0.03%)
Quinolones	**27**	**1**	**57**	**85 (0.90%)**
Enrofloxacin	4	1	–	5 (0.05%)
Marbofloxacin	23	–	–	23 (0.24%)
Moxifloxacin	–	–	53	53 (0.56%)
Ofloxacin	–	–	4	4 (0.04%)
Macrolides	**–**	**52**	**–**	**52 (0.55%)**
Azithromycin	–	52	–	52 (0.55%)
Nitroimidazoles	**8**	**242**	**42**	**292 (3.11%)**
Metronidazole	8	242	42	292 (3.11%)
Polypeptide	**168**	**–**	**156**	**324 (3.45%)**
Polymyxin-B	168	–	156	324 (3.45%)
Sulfonamide	**–**	**2,757**	**41**	**2,798 (29.76%)**
Sulfadiazine	–	1,672	25	1,697 (18.05%)
Sulfadimethoxine	–	1,085	–	1,085 (11.54%)
Sulfonamide	–	–	16	16 (0.17%)
Tetracyclines	**1**	**144**	**72**	**217 (2.31%)**
Chlortetracycline	–	–	62	62 (0.66%)
Doxycycline	–	144	–	144 (1.53%)
Oxytetracycline	1	–	10	11 (0.12%)
Trimethoprim	**–**	**2,757**	**–**	**2,757 (29.32%)**
Trimethoprim	–	2,757	–	2,757 (29.32%)
Total	**2,799**	**6,073**	**530**	**9,402 (100.00%)**

–, observed zero; 0, zero by rounding. The bold values are the summary per antimicrobial group, the corresponding active ingredients are underneath.

In general, it can be said that correctness of the documentation performed by the veterinarians is crucial in both methods. As clinical routine data are used for evaluating errors in documentation, plausibility checks are needed to reduce these errors to a minimum.

Schwechler (27) undertook a theoretical exercise where they asked veterinarians from Germany, Austria, and Switzerland which kind of AM they would prescribe in six different given hypothetical clinical cases in equine medicine.

The participants stated that they would prescribe cephalosporins of the 3rd and 4th generation in 11% of the hypothetical cases, and fluoroquinolones in 4% of the cases (27). These proportions take the results from Germany, Switzerland and Austria into account (27).

Depending on their *in vitro* spectrum of activity, cephalosporins can be categorized into four generations. The 3rd generation is composed among others of the active ingredients ceftiofur and ceftriaxone, the 4th generation of cefquinome and cefepime (28).

The authors also noted that in private equine clinics, cephalosporins of the 3rd and 4th generation are theoretically more often prescribed than in clinics of universities and private practice.

Results from De Briyne et al. (29) showed a similar theoretically prescription for horses in Germany. They asked veterinarians to name the five indications where AMs were prescribed the most and which group of AMs they would prescribe. Over all indications cephalosporins of the 3rd and 4th were mentioned in 9% and fluoroquinolones in 4% of theoretically prescriptions.

The results of this study show that only 0.65% of the drug applications at the Clinic for Horses were cephalosporins of the 4th generation. There was no application of cephalosporins of any other generation in the Clinic for Horses in 2017, as shown in **Table 1**. Fluoroquinolones were used in 0.90% of drug applications. There was a considerably lower usage of cephalosporins and fluoroquinolones in the Clinic for Horses than in the study of Schwechler (27) and in the study of De Briyne et al. (29).

In 2017, only a small amount (0.22 kg) of active ingredients with the WHO classification *CIA—Highest Priority* was used. This highlights that usage of these AMs was avoided, and *Highly Important* AMs were chosen instead. AMs licensed for horses were preferred (**Figure 2**). Active ingredients classified as *CIA-Highest Priority* were mostly used for specific ocular diseases. An exception is polymyxin B which is also classified as *CIA-Highest Priority*, but depending on the drug and indication, it is used either topically or injected. Injections were mainly administered during or directly after colic surgery in horses with signs of endotoxemia.

More detailed results with linkage between diagnoses and AMU could not be provided as documentation of diagnoses is not uniform between veterinarians.

Furthermore, the results from Schwechler (27) showed that 12% of the prescribed dosages were below the dosage recommended by the SPCs, and 72% of prescribed dosages were too low compared to dosages recommended in recent publications. The authors criticized that the recommended dosages of the SPCs were often obsolete and did not relate to recent publications.

In another study, Hughes et al. (30) sent a questionnaire to veterinarians in the United Kingdom and revealed that 5.8% of theoretical prescriptions were underdosed and 56.9% were overdosed compared to dosages issued by the VMD.

In the study from Schwechler (27) and the study from Hughes et al. (30) only the recommended dosages themselves were defined as acceptable dosages.

For comparison of the results of Schwechler (27), Hughes et al. (30) and the results of this study, it must be considered that the results of this study are based on routine treatment data and not theoretically prescribed AMs. It also has to

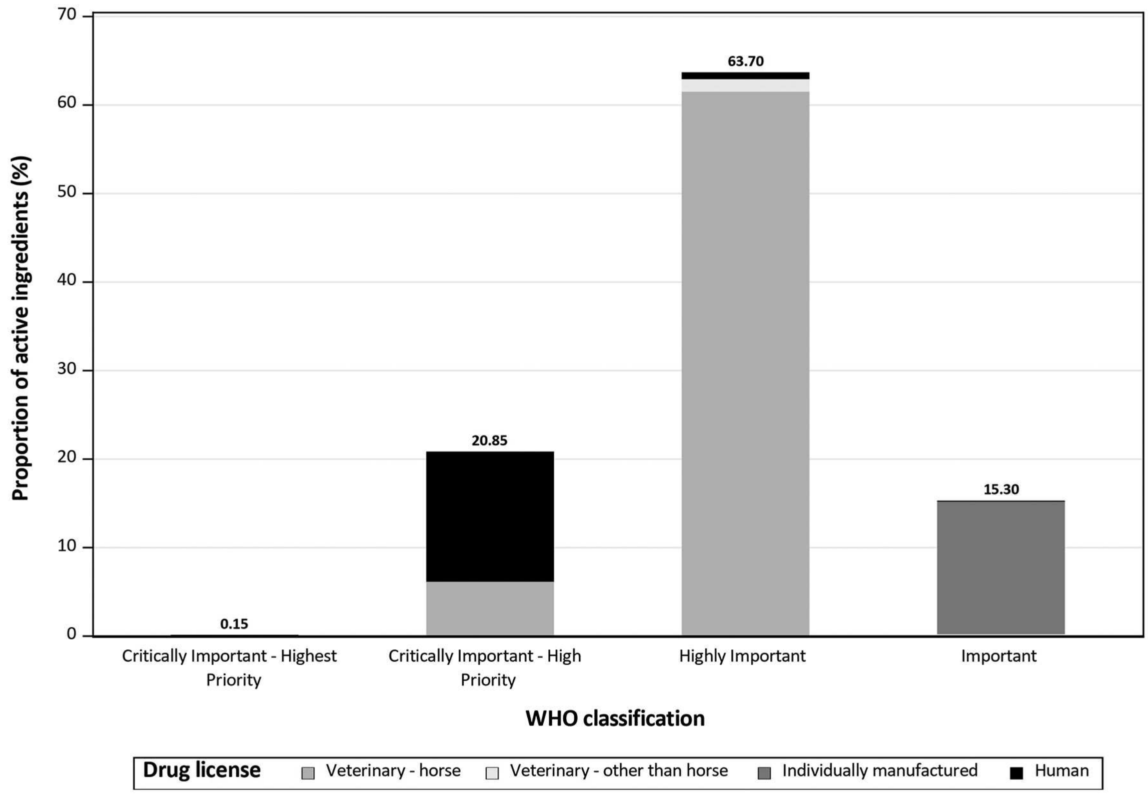


FIGURE 2 | Proportion of the amount of antimicrobial active ingredients reported to be used in horses in 2017 at the Clinic for Horses, University for Veterinary Medicine Hannover, Foundation, by drug license type and World Health Organization classification.

be noted that our study was based on data generated for accountancy and documentation purposes and not for research purposes. Therefore, the data must be examined for implausibility.

Possible sources for errors were not only falsely documented amounts of used AMs, but also outdated weights of treated animals, where the actual weight was used to calculate the dose but not entered into the system. Another possible source for errors was drugs falsely documented as being used in the clinic instead of being handed over to the animal owner. This led to a higher calculated ADA, as an amount for a few days dispensed to the owner was wrongly entered as a single treatment. Plausibility checks were performed, and a very high proportion of plausible data was found.

Dosages based on the SPCs and recent publications were used to define the SD_{CfH}. A mixture of both was used to formulate a realistic classification while comparing ADA to RDD_{CfH}, as recommended dosages in the SPCs could change after authorization because of recent research.

When comparing the UDD of the Clinic for Horses in 2017 to the RDD_{CfH}, there was very little deviation. Investigations of prescriptions of the Clinic for Horses in 2017 showed that with 3.26% of all entries below the RDD_{CfH} and 3.18% above the RDD_{CfH}, there was a high level of responsibility used when choosing the correct dosages.

In this study, calculation of the ADA was not possible for 1,809 entries because of missing weights, and these entries were excluded. For this study, the results of the comparison between the ADA and RDD_{CfH} need to be interpreted with caution, but it is assumed that missing bodyweights are purely by chance, and therefore, a change of proportions in the results is possible in both directions. It is assumed that this did not lead to a selection bias.

In total, 733 t of antimicrobial active ingredients were sold to the veterinary sector in Germany in 2017 (31). Here, the biggest proportion falls upon penicillins (36.7%), which was twice as much as the proportion used in the Clinic for Horses. Tetracyclines had the second biggest share with 25.94%. In contrast, in the Clinic for Horses, only 1.42% of the total amount used was tetracyclines. The difference in polypeptides is also obvious: in 2017, 10.1% of the total amount of active ingredients sold belonged to this group, while only 0.08% of the amount administered by the Clinic for Horses did.

To evaluate the results of the annual sales data in comparison to the amounts used in the Clinic for Horses, it is important to know that the biggest proportion of drugs sold is licensed for farm animals and only a relatively small amount was licensed for horses (32). Moreover, because of multiple approvals, an assignment to one species is not possible for most of the drugs. Additionally, off-label use is not considered in the sales data. In our study we could show, that off-label use should not be neglected: in the Clinic for Horses, 32.33% of the total amount of drugs used were not licensed for horses and, thus, affected the proportion and amount of active ingredients used.

As previously mentioned, there are different official and private monitoring systems in Germany for AMU in livestock [Herkunftssicherungs- und Informationssystem für Tiere (33); QS Qualität und Sicherheit GmbH (34)]. Both systems use information from official German Application and Delivery Forms (ADF) for evaluating AMU in livestock. An ADF must be filled out every time a food-producing animal is treated with a drug. In the European Union (EU), horses can be declared as food-producing or non-food-producing animals in the equine passport, and ADFs are mandatory only for food-producing horses. As long as it is not stated otherwise, horses count as food-producing animals, and only a limited number of antibacterial drugs can be used. In particular, the application of certain AMs, such as chloramphenicol, dapsone, dimetridazole, metronidazole, nitrofurans, and ronidazole, is prohibited by European law (35).

The status of a horse can be changed from food-producing to non-food-producing at any time to extend the possibilities of treatment, but once it is changed, it can never be withdrawn. A system using data from ADF can only be used for food-producing horses because these forms are only mandatory for animals entering the food chain. Furthermore, existing monitoring systems use treatment frequency for comparing AMU in different production types that relate to the reference population on the farm. In contrast, treatment in horses is always individualized, with a treatment plan for each single horse. Thus, transferring existing systems to horses is not possible, and a system to evaluate data on AMU in horses must be developed instead.

In 2017, 64.00% ($n = 585$) of the cases in the Clinic for Horses were non-food-producing horses, while 36.00% ($n = 329$) were treated as food-producing animals. Consequently, using the existing systems based on ADFs, only 1/3 of cases and the related drug applications in the Clinic for Horses in 2017 would have been taken into account, and the results would not have captured the real AMU picture in horses.

A comparison to other international reports, and therefore, a more detailed estimation of the consequences of using data from only food-producing horses is not possible, as these reports do not take the status of the horses into account (19).

Due to a series of missing values and dynamic changes in the status of food or non-food animals, presentation of analysis about AMU grouped by the status of the horse is not possible.

As a general rule, it can be stated that depending on the method of selecting data from an EPMS and the extent of these data, the developed method can not only be adapted to other species but also to data from EPMS other than easyVET. As EPMS always work as an accounting tool, information about the used amount of an AM is entered and can be used for calculating total amounts of active ingredients used. Other possible evaluations within this system are those in conjunction with the WHO classification, route of administration and the comparison between the ADA and RDD. The feasibility of evaluating diagnoses associated with the active ingredients used depends on the method of documentation of the diagnosis. If chosen from a given catalog, as in our study, the developed method can be used. If diagnoses are entered as free text, using this information in further investigations requires more effort, and a free text search has to be applied. This method bears certain risks; misspellings, abbreviations and special terms have to be taken into account, which increases the possibility of an information bias. However, easyVET is used in 5,000 clinics and practices worldwide (36), and therefore, large-scale data can be evaluated easily, as only the drugs used and the standard dosages have to be adapted.

For the corresponding clinics or practices, this evaluation enables valuable feedback on AMU and provides a baseline regarding AMU. Once a baseline has been set, data can be compared to it continuously, and changes in prescription habits can immediately be investigated. Thus, the developed method supports adherence to guidelines on antimicrobial usage in clinics and practices and facilitates compliance with standards such as good veterinary practice and quality management systems. The results can also be used for antimicrobial stewardship programs because the results of the developed method can illustrate room for improvement.

To better understand and combat AMR in the future, more validated information on AMU in different animal species is needed. It is vital to monitor and analyze data on AMU continuously, especially regarding the transmission of resistant bacteria between animals and humans. The method applied in our study offers a tool to monitor AMU not only in horses but also in other animal species, and it could facilitate the desired reduction in AMU. Because of the changing legal requirements in the EU about documenting AMU for all animal species, including companion animals, a tool for evaluating clinical routine data about AMU is needed (37).

CONCLUSIONS

Because of the threat of increasing AMR, it is crucial to make data about AMU available to preserve antimicrobial therapies. EMPS provides the possibility to extract large-scale data for analyses of AMU in clinics. Additionally, the corresponding veterinarians benefit without putting much effort into it, as the results provide very useful information that helps to improve their clinical work, such as adherence to guidelines on antimicrobial usage. In addition, this analysis allows comparison with AMU data from other animal species. Further investigations of AMU in combination with results of antimicrobial susceptibility testing, as well as analyses of data from clinics across the country, are necessary to provide a representative picture of AMU in horses in Germany.

DATA AVAILABILITY STATEMENT

The data were made available through internal cooperation. Therefore, any data transfer to interested persons is not allowed without an additional formal contract. Data are available to qualified researchers who sign a contract with the University of Veterinary Medicine Hannover. This contract will include guarantees to the obligation to maintain data confidentiality in accordance with the provisions of the German data protection law. A data access committee will be established on demand.

This committee will consist of the authors as well as members of the University of Veterinary Medicine Hannover. Interested cooperative partners, who are able to sign a contract as described above, may contact: Lothar Kreienbrock, Department of Biometry, Epidemiology and Information Processing, University of Veterinary Medicine, Hannover, Bünteweg 2, 30559 Hannover, Email: lothar.kreienbrock@tiho-hannover.de.

ETHICS STATEMENT

The data used in this study are based on data generated for accountancy and documentation purposes. Our research does not involve any regulated animals, and there were no scientific procedures performed on animals of any kind. For this reason, formal approval by an ethical committee was not necessary under the provisions of the German regulations.

AUTHOR CONTRIBUTIONS

AS and LK: conceptualization, formal analysis, investigation, methodology, and writing—original draft. AS, HE, RW, and MH: data curation. AS: project administration and validation. AS, HE, and MH: software. LK: supervision. AS, NW, AB-Z, KF, and LK: writing—review and editing.

FUNDING

This publication was supported by Deutsche Forschungsgemeinschaft and University of Veterinary Medicine Hannover, Foundation within the funding programme Open Access Publishing.

ACKNOWLEDGMENTS

We would like to thank Anja Seeman-Jensen from the Clinic for Horses, TiHo, for her support.

SUPPLEMENTARY MATERIAL

https://www.tiho-hannover.de/kliniken-institute/institute/bioepi/publikationen/zusatzmaterial-publikationen/

REFERENCES

1. Williams KJ. The introduction of 'chemotherapy' using arsphenamine - the first magic bullet. *J R Soc Med*. (2009) 102:343–8. doi: 10.1258/jrsm.2009.09k036
2. Fleming A. On the antibacterial action of cultures of a penicillium, with special reference to their use in the isolation of B. influenzae. *Bull World Health Organ*. (2001) 79:780–90.
3. Guardabassi L, Schwarz S, Lloyd DH. Pet animals as reservoirs of antimicrobial-resistant bacteria. *J Antimicrob Chemother*. (2004) 54:321–32. doi: 10.1093/jac/dkh332
4. Guardabassi L. Veterinary hospital-acquired infections: the challenge of MRSA and other multidrug-resistant bacterial infections in veterinary medicine. *Vet J*. (2012) 193:307–8. doi: 10.1016/j.tvjl.2012.04.005
5. Hillerton JE, Irvine CR, Bryan MA, Scott D, Merchant SC. Use of antimicrobials for animals in New Zealand, and in comparison with other countries. *N Z Vet J*. (2017) 65:71–7. doi: 10.1080/00480169.2016.1171736
6. Lloyd D, Page S. Antimicrobial stewardship in veterinary medicine. *Microbiol Spectr*. (2018) 6:ARBA-0023-2017. doi: 10.1128/microbiolspec.ARBA-0023-2017
7. Shallcross LJ, Davies SC. The world health assembly resolution on antimicrobial resistance. *J Antimicrob Chemother*. (2014) 69:2883–5. doi: 10.1093/jac/dku346
8. Cassini A, Hogberg LD, Plachouras D, Quattrocchi A, Hoxha A, Simonsen GS, et al. Attributable deaths and disability-adjusted life-years caused by infections with antibiotic-resistant bacteria in the EU and the European economic area in 2015: a population-level modelling analysis. *Lancet Infect Dis*. (2019) 19:56–66. doi: 10.1016/S1473-3099(18)30605-4
9. Barber DA, Miller GY, McNamara PE. Models of antimicrobial resistance and foodborne illness: examining assumptions and practical applications. *J Food Prot*. (2003) 66:700–9. doi: 10.4315/0362-028X-66.4.700
10. Weese JS, Caldwell F, Willey BM, Kreiswirth BN, McGeer A, Rousseau J, et al. An outbreak of methicillin-resistant *Staphylococcus aureus* skin infections resulting from horse to human transmission in a veterinary hospital. *Vet Microbiol*. (2006) 114:160–4. doi: 10.1016/j.vetmic.2005.11.054
11. Cuny C, Abdelbary MMH, Kock R, Layer F, Scheidemann W, Werner G, et al. Methicillin-resistant *Staphylococcus aureus* from infections in horses in Germany are frequent colonizers of veterinarians but rare among MRSA from infections in humans. *One Health*. (2016) 2:11–7. doi: 10.1016/j.onehlt.2015.11.004
12. German Federal Chamber of Veterinarians. *Synopse zur Zweiten Verordnung zur Änderung der Verordnung Über Tierärztliche Hausapotheken vom 21*. (2018). Available online at: https://www.bundestieraerztekammer.de/presse/archiv/3/2018/Synopse-zur-zweiten-Verordnung-zur-Aenderung-der-Verordnung-uebe/1308??pid=0 (accessed July 09, 2019).
13. Apostolakos I, Franz E, van Hoek A, Florijn A, Veenman C, Sloet-van Oldruitenborgh-Oosterbaan MM, et al. Occurrence and molecular characteristics of ESBL/AmpC-producing *Escherichia coli* in faecal samples from horses in an equine clinic. *J Antimicrob Chemother*. (2017) 72:1915–21. doi: 10.1093/jac/dkx072
14. German Equestrian Federation (FN). *German Olympic Committee for Equestrian Sport (DOKR)*. Jahresbericht 2017 (2017).
15. Islam MZ, Espinosa-Gongora C, Damborg P, Sieber RN, Munk R, Husted L, et al. Horses in Denmark are a reservoir of diverse clones of methicillin-resistant and -susceptible staphylococcus aureus. *Front Microbiol*. (2017) 8:543. doi: 10.3389/fmicb.2017.00543
16. Sieber S, Gerber V, Jandova V, Rossano A, Evison JM, Perreten V. Evolution of multidrug-resistant *Staphylococcus aureus* infections in horses and colonized personnel in an equine clinic between 2005 and 2010. *Microb Drug Resist*. (2011) 17:471–8. doi: 10.1089/mdr.2010.0188
17. Federal Office of Consumer Protection and Food Safety (BVL). Paul-Ehrlich-Society of Chemotherapy, Division of Infectious Diseases, University Medical Center Freiburg. *GERMAP 2012 – Bericht über den Antibiotikaverbrauch und die Verbreitung von Antibiotikaresistenzen in der Human- und Veterinärmedizin in Deutschland*. Rheinbach: Antiinfectives Intelligence Gesellschaft für klinisch-mikrobiologische Forschung und Kommunikation mbH (2014).
18. NORM/NORM-VET 2016. *Usage of Antimicrobial Agents ans Occurance od Antimicrobial resistance in Norway*. Oslo (2017).
19. National Institute for Public Health and the Environment (RIVM). *NethMap and MARAN-Report* (2017).
20. Finnish Food Safety Authority Evira. *FINRES-Vet 2013–2015, Finnish Veterinary Antimicrobial Resistance Monitoring and Consumption of Antimicrobial Agents*. Helsinki (2017).
21. Swesdres-Svarm 2017. *Consumption of Antibiotics and Occurence of Resistance in Sweden*. Uppsala (2018).

22. DANMAP 2016. *Use of Antimicrobial Agents and Occurrence of Antimicrobial Resistance in Bacteria From Food Animals, Food and Humans in Denmark*. (2017).
23. Netherlands Veterinary Medicines Authority. *Usage of Antimicrobial Drugs in Horses 2012-2014* (2017).
24. Giguère S. Antimicrobial drug action and Interaction. In: Giguère S, Prescott JF, Dowling, PM, editors. *Antimicrobial Therapy in Veterinary Medicine*. Ames, IA: John Wiley & Sons, Inc. (2013). p. 1–10.
25. Buckland EL, O'Neill D, Summers J, Mateus A, Church D, Redmond L, et al. Characterisation of antimicrobial usage in cats and dogs attending UK primary care companion animal veterinary practices. *Vet Rec*. (2016) 179:489. doi: 10.1136/vr.103830
26. Redding LE, Lavigne S, Aceto H, Nolen-Walston R. Characterization of antimicrobial prescription frequency and diversity in a large animal veterinary medical teaching hospital. *Prev Vet Med*. (2019) 68:66–74. doi: 10.1016/j.prevetmed.2019.04.012
27. Schwechler JE. *Antibiotikaeinsatz in der Pferdepraxis in Deutschland, in Oesterreich und in der Schweiz*. Switzerland: University of Zurich, Vetsuisse-Fakultät (2016).
28. Frey H-H, Richter A, Abraham G, Löscher W. *Lehrbuch der Pharmakologie und Toxikologie für die Veterinärmedizin*. 4. vollständig überarbeitete Auflage ed: Enke Verlag (2016). p. 429–30.
29. De Briyne N, Atkinson J, Pokludova L, Borriello SP. Antibiotics used most commonly to treat animals in Europe. *Vet Rec*. (2014) 175:325. doi: 10.1136/vr.102462
30. Hughes LA, Pinchbeck G, Callaby R, Dawson S, Clegg P, Williams N. Antimicrobial prescribing practice in UK equine veterinary practice. *Equine Vet J*. (2013) 45:141–7. doi: 10.1111/j.2042-3306.2012.00602.x
31. Federal Office of Consumer Protection and Food Safety (BVL). *Menge der Abgegebenen Antibiotika in der Tiermedizin Sinkt Weiter*. (2018). Available online at: https://www.bvl.bund.de/DE/08_PresseInfothek/1_FuerJournalisten_Presse/1_Pressemitteilungen/5_Tierarzneimittel/2018/_07_23_pi_Antibiotikaabgabemenge7.html (accessed May 06, 2019).
32. Federal Ministry of Food and Agriculture (BMEL) SJ, Kapitel CX. (2018). Available from: https://www.bmel-statistik.de/fileadmin/user__upload/monatsberichte/SJT-3100200-0000.xlsx (accessed May 07, 2019).
33. *Sechzehntes Gesetz zur Änderung des Arzneimittelgesetzes*. Bundesgesetzblatt Jahrgang 2013 Teil I Nr. 62, 16 AMG Novelle (2013).
34. Qualität und Sicherheit GmbH QS. *Antibiotikamonitoring bei Schweinen, Mastgeflügel und Mastkälbern*. (2015). Available online at: https://www.q-s.de/tieraerzte/antibiotikamonitoring-tieraerzte.html (accessed April 14, 2016).
35. COMMISSION REGULATION (EU) No 37/2010. *Pharmacologically Active Substances and Their Classification Regarding Maximum Residue Limits in Foodstuffs of Animal Origin*. COMMISSION REGULATION (EU) No 37/2010 (2009).
36. VetZ. *EasyVET*. Available online at: https://www.vetz.vet/de-de/easyVET (accessed June 10, 2019).
37. REGULATION (EU) 2019/6 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 11 December 2018. *Veterinary Medicinal Products and Repealing*. Directive 2001/82/EC (2019).

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Veterinary Science

ORIGINAL RESEARCH
published: 08 July 2020
doi: 10.3389/fvets.2020.00329

Antimicrobials Used in Backyard and Commercial Poultry and Swine Farms in the Philippines: A Qualitative Pilot Study

Toni Rose M. Barroga[1,2], *Reildrin G. Morales*[1,3], *Carolyn C. Benigno*[4], *Samuel Joseph M. Castro*[2], *Mardi M. Caniban*[2], *Maria Fe B. Cabullo*[2], *Agnes Agunos*[4†], *Katinka de Balogh*[4] and *Alejandro Dorado-Garcia*[5*]

[1] Food and Agriculture Organization of the United Nations—Philippine Component on the Global Efforts to Combat Antimicrobial Resistance Using One Health Approach (GCP/GLO/UK/710), Quezon City, Philippines, [2] Department of Agriculture, Bureau of Animal Industry, Quezon City, Philippines, [3] Department of Agriculture, National Meat Inspection Service, Quezon City, Philippines, [4] Food and Agriculture Organization of the United Nations Regional Office of Asia and the Pacific, Bangkok, Thailand, [5] Food and Agriculture Organization of the United Nations, Rome, Italy

OPEN ACCESS

Edited by:
Miguel Ángel Moreno,
Complutense University of Madrid, Spain

Reviewed by:
Cuong Nguyen,
Oxford University Clinical Research Unit, Vietnam
Marco De Nardi,
Safoso (Switzerland), Switzerland

***Correspondence:**
Alejandro Dorado-Garcia
alejandro.doradogarcia@fao.org

†Present address:
Agnes Agunos,
Center for Foodborne, Environmental and Zoonotic Infectious Diseases,
Public Health Agency of Canada,
Guelph, ON, Canada

Specialty section:
This article was submitted to Veterinary Epidemiology and Economics,
a section of the journal Frontiers in Veterinary Science

Received: 03 February 2020
Accepted: 12 May 2020
Published: 08 July 2020

Citation:
Barroga TRM, Morales RG, Benigno CC, Castro SJM, Caniban MM, Cabullo MFB, Agunos A, de Balogh K and Dorado-Garcia A (2020) Antimicrobials Used in Backyard and Commercial Poultry and Swine Farms in the Philippines: A Qualitative Pilot Study. Front. Vet. Sci. 7:329.
doi: 10.3389/fvets.2020.00329

Chicken and pork are the most frequently consumed meat products in the Philippines. Swine and poultry are reared in either commercial farms (CMf) or backyard farms (BYf); the latter production system is relatively common and essential to food security in low- and middle-income countries (LMICs) such as the Philippines. Similar to resource-limited LMICs, antimicrobial use (AMU) surveillance has not yet been established; thus, AMU in food animals is a knowledge gap in understanding the emergence of antimicrobial resistance (AMR) in zoonotic foodborne bacteria in the country. This qualitative AMU pilot study aims to describe the antimicrobial active ingredients (AAIs) used and associated AMU practices (e.g., source of AAIs and informed AMU decisions) by poultry and swine CMf and BYf in the Philippines. Ninety-three farms across four regions in the Philippines voluntarily provided AMU information as part of a larger biosecurity and good practices study. The percentage of farms using AAI over the total number of farms was the metric used to describe AMU. In total, there were 30 AAIs used (CMf: n =27 and BYf: n = 13); per farm, the number of AAIs used ranged from 1 to 7. The spectrum of AAIs was more diverse in swine (n = 24) compared to poultry (n = 18). Enrofloxacin was the most frequently reported AAI in poultry (33%) and swine (36%) farms. Respiratory diseases were the most frequently reported reason for AMU in both species. Between production systems, significant differences were observed in the percentage of farms using amoxicillin (27% CMf vs. 3% BYf), colistin (17% CMf vs. 3% BYf), and oxytetracycline (12% CMf vs. 39% BYf). In terms of AMU practices, of important concern was the over-the-counter access of AAIs at retail outlets and the limited veterinary oversight in BYf. Our data indicated that antimicrobials critically important for human medicine are frequently used in poultry and swine farms in the Philippines. This study can inform the development of guidelines for curbing AMR through prudent AMU and serves as a reference point for AMU surveillance capacity development in the Philippines.

Keywords: farm level, antimicrobials, surveillance, poultry, swine, Philippines, LMIC

INTRODUCTION

Low- and middle-income countries (LMICs) in certain regions of the world, such as Southeast Asia, are disproportionately burdened with enteric foodborne illnesses (1). Resistance to antimicrobials among zoonotic foodborne bacteria poses an additional concern (2). As such, LMICs have received special attention toward the mitigation of the impacts of antimicrobial resistance (AMR). Recent evidence suggests that antimicrobial use (AMU) in food and agriculture sectors is linked to the development of AMR in bacteria (3, 4). Furthermore, temporal correlations between AMR in zoonotic foodborne organisms in both animals and in people have also been reported (5, 6). Understanding AMU and associated practices in major food production sectors is an essential step to developing interventions to reduce the emergence and dissemination of AMR from animals to human populations.

In the Philippines, the agricultural sector contributes to 9% of its national gross domestic product (GDP), and 29% of the labor force is employed in agricultural services. Livestock and poultry production outputs rank second (25%; 27 million tons) next to crops (49%) in the country's total agricultural production. For the past 30 years, the 85% increase in the human population has been accompanied by a 195 and 332% increase in the volume of swine and poultry production, respectively (7). Similar to the Philippines, chicken and pork among the animal-sourced food are the most frequently consumed in Asia and are also implicated in foodborne illnesses (8). Increasing quantities of antimicrobials are expected to be used with the rapid growth of poultry and swine production in LMICs (9), emphasizing that these sectors are a priority for inclusion in AMU/AMR surveillance programs.

Veterinary services in the Philippines have established policies related to the sale, prescription, and distribution of antimicrobial veterinary medicinal products (VMPs) long before AMR became a global public health issue (10). However, similar to other resource-limited countries (11), weakness on implementation of standards for VMPs, lack of strict enforcement on issuing veterinary prescription to farmers, accessibility of farmers to purchase antimicrobial VMPs in local agriculture-veterinary (agrovet) supply/retail outlets, and lack of awareness on the prudent use of antimicrobials may fast-track the occurrence of AMR. Veterinarians employed by agrifood companies/integrators and allied industries such as feed and pharmaceutical industries, and diagnostic services/independent consultants provide diverse type of service to the livestock and poultry sectors and have established valid veterinary–client–patient relationships (VCPR), and thus have an important role in animal health and food safety. However, veterinarians servicing food animals in a rural setting such as villages within municipalities and cities are limited. Animal health services are typically provided by a network of regional and provincial veterinarians and paraveterinarians. Paraveterinarians are veterinary paraprofessionals commonly known as livestock inspectors, meat inspectors, and agricultural technicians employed by local government units (LGUs) who are trained by government veterinarians, though not yet recognized by the veterinary statutory body, to reach municipalities/cities that are located in remote areas. They have formal training in animal husbandry and some animal health and AMU dispensing training provided by national or regional veterinary authorities.

Gaps in VMP regulation might contribute to food safety (i.e., drug residues) and AMR-related health risks. Recent studies in the country have documented high prevalence and widespread distribution of bacteria resistant to certain antimicrobials (12–14). Of important public health concern is the detection of *Escherichia coli* harboring extended-spectrum beta lactamase-conferring genes (ESBLs) among swine (57.41%) (12) and poultry (66.67%) (13), and high prevalence of quinolone (nalidixic acid) resistant *Campylobacter* spp. from retail chickens (98.1%) (14) in the Philippines. Similarly, in pork products, a high prevalence of resistance to beta-lactams cefazolin (100%), cefuroxime (100%), and cefoxitin (100%) (15) and multidrug resistant *Salmonella* (15, 16) have been reported. In parallel to these findings, efforts to have a nationwide AMR surveillance have just started in 2018 as part of the Philippines AMR National Action Plan (NAP) (17). However, AMU surveillance in the animal sector in the Philippines is yet to be established. Information on the extent of AMU is an indispensable step to tackle AMR. In other countries with well-established AMU programs, integration of AMU and AMR data across multiple surveillance components and sectors (humans, animals) informs the development of One Health evidence-based policies for AMR and enables the monitoring of interventions (17) whether these are industry- or government-driven (18). Global requirements to submit data on antimicrobials intended for use in animals will therefore enable the evaluation of impacts from various directives to reduce AMU in animals (19–21). Built onto NAPs, refinements of husbandry practices, on-farm biosecurity, and management of bacterial infections are complementary preventive approaches to improve production while reducing the need of antimicrobials (22). An understanding of AMU practices and other drivers for AMR are fundamental for the enhancement of food safety programs in the poultry and swine production continuum.

In the context previously described, this qualitative pilot study aims to describe the antimicrobial active ingredients (AAIs) used and AMU practices (e.g., source of AAIs and informed AMU decisions) by poultry and swine CMf and BYf in the Philippines. This study can inform the development of guidelines for curbing AMR through prudent AMU and serves as a reference point for AMU farm surveillance capacity development in the Philippines.

MATERIALS AND METHODS

This pilot study on AMU is part of a larger project delivered by the Food and Agriculture Organization of the United Nations (UN FAO) in the Philippines and globally (Fleming Fund II GCP/GLO/710/UK "Engaging the food and agriculture sectors in sub-Saharan Africa and South and South-east Asia in the global efforts to combat antimicrobial resistance using a One Health approach").

Pilot Study Design

The Philippines is an archipelagic country located in Southeast Asia and consists of 7,641 islands. The country is divided into three major islands—Luzon, Visayas, and Mindanao. The study was conducted in representative provinces from the Luzon and Visayas group of islands, where the total population of swine and poultry is estimated at 12 and 197 million, respectively. Approximately 65 and 80% of the poultry and pigs, respectively, are raised in these two islands (7).

Ninety-three farms (four regions) across the Philippines voluntarily provided AMU information as part of a larger biosecurity and good practices study. Farms were enrolled with the assistance of a network of provincial veterinarians, extension service staff (LGUs), and regional AMR coordinators. Information sessions were held to discuss the study. The number of farms per region (Central Luzon, South Luzon, Central Visayas, and Western Visayas) was allocated based on their relative contribution to the national swine and poultry production. Within each province, farms were selected proportional to the species and production profiles. The categories of production systems were defined to classify farms into backyard farm operation (BYf) or commercial farm operation (CMf). For this study, BYf were defined as those having ≤500 layer or 1,000 broiler birds or ≤10 sows. On the other hand, CMf were defined as operations having ≥11 sows or ≥501 layer or 1,001 broiler birds. Depending on the province, researchers ensured that swine commercial grower operations varied in herd sizes to ensure representativeness.

Prior to participation in the interview, the researcher administered an informed consent form to the participating producer/designated farm staff. Interviews were conducted in English and Filipino. The questionnaire collected various pieces of information (please refer to **Supplementary Materials I** for additional details), but for the purposes of this study, reasons for AMU, AAIs, routes of administration, and stage of production where the AAIs were used (page 10 of the questionnaire) were extracted for analysis. Antimicrobials used pertain to the current cycle of broiler chickens, layers, and grower-finisher pigs, and other applicable stages, such as breeders, sows, and piglets for farms that have mixed production stages at the time of the study as indicated on page 3 of the questionnaire. Quantitative data on antimicrobial used on farm were not collected. The study was conducted from April to May 2018.

Data Analysis

The data were entered in Microsoft Excel (Office 14) and analyzed descriptively using Microsoft Excel, Stata 15 (College Station, TX), and SAS version 9.4 (Cary, NC). The percentage of farms reporting using an antimicrobial over the total number of farms was the metric used to describe AMU. Proportions of the responses on AMU (i.e., the number of farms reporting use of each AAI) and AMU practices were compared between poultry and swine farms using either the Fisher exact test when there were five or fewer observations in any of the categories or the chi-square test in SAS 9.4. A *P*-value of ≤ 0.05 was considered significant, described as "significantly" or "statistically significant" throughout the text; actual *P*-values are specified in the tables. Comparisons of percentage of farms reporting use of each AAI between CMf and BYf were also made as detailed above. Reasons for use, categorized broadly by systems affected, the number of AAIs used by species, and production stage were analyzed descriptively. For this paper, the term "therapy" refers to both treatment and preventive uses. All AMU frequency and percentages information were organized by antimicrobial class.

RESULTS

The AMU data were voluntarily provided by a subset of farms ($n = 93$ farms) from 145 farms surveyed as part of the larger biosecurity study in the Philippines.

Respondents and Farm Characteristics

The vast majority of the respondents were distributed between the age of 16 and 60 years (86%) and comprised of farm staff (16 CMf, 8% BYf), farm owners (11% CMf, 8% BYf), and veterinarians (11% CMf); the rest of the respondents did not specify their position or role in the rearing of animals. The 93 farms surveyed comprised of 35% ($n = 33$) BYf and 65% CMf ($n = 60$). By species, 43% (39 flocks) were poultry and the remaining 57% (54 herds) were swine. The 39 poultry farms in the study comprised of broiler flocks ($n = 21$), layers ($n = 16$), a broiler breeder, and a mixed layer–broiler farm. As summarized in **Figure 1**, the 54 swine farms comprised of single production stage herds (growers, piglets, sows) or mixed production stages present (e.g., mixed growers and piglets) in the farm at the time of the study. Most of the respondents in CMf (72%) indicated that their establishment has been operational for ≥ 5 years, whereas this proportion was smaller in BYf (43%). The majority of CMf (77%) had ≥ 3 barns, whereas most of BYf (75%) have 1 or 2 barns on their premises. Significantly higher percentage of CMf (70%) compared to BYf (11%) practiced all-in–all-out systems.

AMU by Species

The spectrum of AAIs was more diverse in swine production (24 AAIs) compared to poultry (18 AAIs) (**Table 1**). Three AAIs were combination products (lincomycin-spectinomycin, trimethoprim-sulfamethoxazole, and trimethoprim-sulfadiazine). Significantly higher percentage of poultry farms used norfloxacin (poultry: 25% vs. swine: 6%). Erythromycin and fosfomycin were only used in poultry. In contrast, significantly higher percentage of swine farms used oxytetracycline (swine: 30% vs. poultry: 10%) and tylosin (swine: 25% vs. 8% poultry). Tiamulin and gentamicin were only used in swine. Enrofloxacin was the most frequently reported AAI in poultry and swine at 33% and 36%, respectively.

Number of Antimicrobials Used at Farm Level by Animal Production Stage and Reasons for Use

Figure 1 shows the percentage of farms using a different number of AAIs. The data were grouped according to species and the stage of production of the animals where the AAIs were used. One of the 93 farms was a broiler breeder farm that reported a

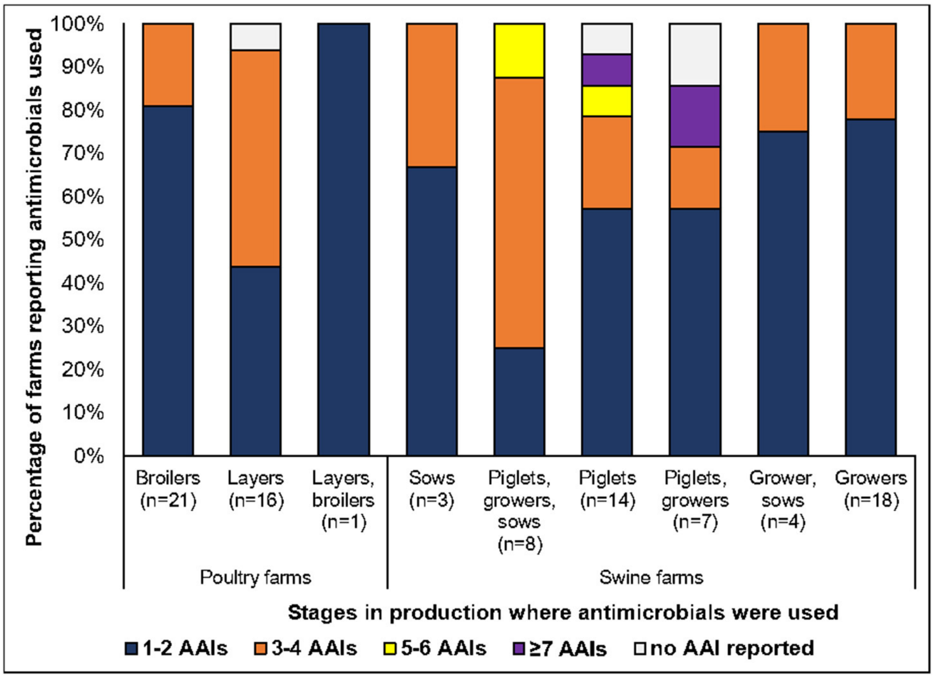


FIGURE 1 | Percentage of farms using the total number of antimicrobials by poultry and swine and production stages. AAI, antimicrobial active ingredients. Respondents were asked to indicate the stage where they used the AAI (please refer to page 10 of **Supplementary Materials I—Questionnaire**). Several respondents have animals in their farm that comprised of more than one production stage.

non-antimicrobial feed additive (not shown in the figure). Forty-four percent to 81% of farms across all production categories used one to two antimicrobials. The use of 5 to 6 AAIs and ≥7 AAIs were observed in swine farms, mostly in piglet and piglet-grower herds (**Figure 1**).

The reported reason for AMU in poultry (**Supplementary Materials II**, **Annex 1**) was largely for respiratory diseases (17 AAIs) and a limited number (5 AAIs) were used for enteric diseases. Of note is the use of enrofloxacin (33%) and norfloxacin (25%) used for the therapy of respiratory diseases and colistin for both enteric and respiratory diseases. Similarly in swine, treatment of respiratory diseases was the most frequently indicated reason for use (20 AAIs). Enteric (17 AAIs), reproductive (4 AAIs), and non-specific (5 AAIs) diseases were additional reasons for use reported in swine. Of note is the use of enrofloxacin for the treatment of enteric, respiratory, and non-specific diseases.

Route of Administration

Supplementary Materials II, **Annex 2** summarizes the AAIs by routes of administration; this varied by species depending on the AAI. In poultry, the vast majority of the respondents indicated that they administered the AAIs largely via water, whereas in swine, the most common route reported was intramuscular.

AMU by Production System

Table 2 shows the percentage of farms from CMf and BYf production systems reporting specific AAIs. There were a total of 30 different AAIs belonging to 12 classes of antimicrobials documented. Overall, the spectrum of AAIs used among CMf was more diverse (29/30 AAIs) compared to those that were used in BYf (15/30 AAIs).

A significantly higher percentage of CMf reported use of amoxicillin and colistin (30% and 22% CMf vs. 3% BYf, respectively). Some AAIs such as norfloxacin were reported only in CMf. A significantly higher proportion of BYf used oxytetracycline (39% BYf vs. 12% CMf).

Access to Antimicrobials, Sources of Advice, and Related AMU Practices

When respondents were asked about the frequency of use, a vast majority indicated that they treat their animals only when the animals were sick or showed clinical signs (73% CMf and 83% BYf). In terms of access to antimicrobials, significantly higher proportion of BYf (30%) compared to CMf (9%) accessed AAIs over-the-counter from agrovet supply or retail outlets. Agrovet supply or retail outlets are local stores that typically sell VMPs, livestock, and farm equipment and supplies. CMf accessed antimicrobials largely from their integrator/company that supplied them with other farm inputs or directly from pharmaceutical companies (18%). A relatively small proportion of farms obtained VMPs with veterinary prescription from agrovet supply or retail outlets (6% BYf, 11% CMf).

For informed AMU decisions, a significantly higher percentage of CMf consulted with veterinarians (43% CMf vs. 18% BYf), whereas BYf more often consulted with

TABLE 1 | Percentage of farms reporting the use of different antimicrobial active ingredients by animal species (in 39 poultry farms and 54 swine farms).

Antimicrobial class	Antimicrobial active ingredient	Poultry farms n (%)	Swine farms n (%)
Aminoglycosides	Apramycin	0 (0%)	1 (2%)
	Gentamicin	**0 (0%)**	**7 (13%)***
	Neomycin	0 (0%)	1 (2%)
	Streptomycin	2 (5%)	2 (4%)
Cephalosporins	Ceftiofur	0 (0%)	2 (4%)
	Cephalexin	0 (0%)	1 (2%)
Fluoroquinolones	Ciprofloxacin	0 (0%)	1 (2%)
	Danofloxacin	0 (0%)	1 (2%)
	Enrofloxacin	13 (33%)	19 (36%)
	Levofloxacin	1 (3%)	0 (0%)
	Norfloxacin	**10 (25%)**	**3 (6%)***
Lincosamides and aminocyclitols	Lincomycin	0 (0%)	3 (6%)
	Lincomycin-spectinomycin	0 (0%)	1 (2%)
Macrolides	**Erythromycin**	**3 (8%)**	**0 (0%)***
	Kitasamycin	1 (3%)	0 (0%)
	Tilmicosin	2 (5%)	4 (8%)
	Tulathromycin	0 (0%)	1 (2%)
	Tylosin	**3 (8%)**	**14 (25%)***
Penicillins	Amoxicillin	8 (20%)	11 (21%)
	Penicillin	1 (3%)	1 (2%)
Phenicols	Florfenicol	4 (10%)	5 (9%)
	Thiamphenicol	1 (3%)	0 (0%)
Phosphonic acid derivatives	**Fosfomycin**	**4 (10%)**	**(0%) ***
Pleuromutilins	**Tiamulin**	**0 (0%)**	**12 (23%) ***
Polypeptides	Colistin	5 (13%)	6 (11%)
Tetraycyclines	Chlortetracycline	0 (0%)	2 (4%)
	Doxycycline	6 (15%)	11 (21%)
	Oxytetracycline	**4 (10%)**	**16 (30%)***
Trimethoprim and sulfonamides	Trimethoprim-sulfadiazine	5 (13%)	2 (4%)
	Trimethoprim-sulfamethoxazole	2 (5%)	0 (0%)

**Significant differences between poultry and swine farms ($P \leq 0.05$), Fisher exact test (represented in bold fonts).*

TABLE 2 | Percentage of farms reporting the use of different antimicrobial active ingredients by production type (in 33 backyard farms and 60 commercial farms).

Antimicrobial class	Antimicrobial active ingredient	Backyard farms n (%)	Commercial farms n (%)
Aminoglycosides	Apramycin	1 (3%)	0 (0%)
	Gentamicin	2 (6%)	5 (8%)
	Neomycin	0 (0%)	1 (2%)
	Streptomycin	2 (6%)	2 (3%)
Cephalosporins	Ceftiofur	0 (0%)	2 (3%)
	Cephalexin	0 (0%)	1 (2%)
Fluoroquinolones	Ciprofloxacin	0 (0%)	1 (2%)
	Danofloxacin	0 (0%)	1 (2%)
	Enrofloxacin	8 (24%)	24 (40%)
	Levofloxacin	0 (0%)	1 (2%)
	Norfloxacin	**0 (0%)**	**13 (22%)***
Lincosamides and aminocyclitols	Lincomycin	0 (0%)	3 (5%)
	Lincomycin-spectinomycin	0 (0%)	1 (2%)
Macrolides	Erythromycin	0 (0%)	3 (5%)
	Kitasamycin	0 (0%)	1 (2%)
	Tilmicosin	1 (3%)	5 (8%)
	Tulathromycin	0 (0%)	1 (2%)
	Tylosin	6 (18%)	10 (17%)
Penicillins	**Amoxicillin**	**1 (3%)**	**18 (30%)***
	Penicillin	1 (3%)	1 (2%)
Phenicols	Florfenicol	1 (3%)	8 (13%)
	Thiamphenicol	0 (0%)	1 (2%)
Phosphonic acid derivatives	Fosfomycin	0 (0%)	4 (7%)
Pleuromutilins	Tiamulin	2 (6%)	10 (17%)
Polypeptides	**Colistin**	**1 (3%)**	**10 (17%)***
Tetracyclines	Chlortetracycline	1 (3%)	1 (2%)
	Doxycycline	5 (15%)	12 (20%)
	Oxytetracycline	**13 (39%)**	**7 (12%)***
Trimethoprim and sulfonamides	Trimetoprim-sulfadiazine	3 (9%)	4 (7%)
	Trimetoprim-sulfamethoxazole	0 (0%)	2 (3%)

**Significant differences between backyard and commercial farms ($P \leq 0.05$), Fisher exact test (represented in bold fonts).*

paraveterinarians (28% BYf vs. 2% CMf). The rest of the BYf and CMf obtained advice from drug company representatives and relied on their own farm experiences in treating their animals and on the advice from agrovet supply staff or other producers.

Responses to the general reasons for using antimicrobials were relatively similar between the BYf and CMf where there was a relatively equal distribution of prevention or treatment alone, both prevention and treatment, and prevention, treatment, and growth promotion. In the event that the flocks or herds were unresponsive to antimicrobial therapy, a significantly higher proportion of CMf conducted necropsy (63% CMf vs. 21% BYf) or euthanasia followed by disposal of dead animals in designated sites within the farm (30% CMf vs. 13% BYf), whereas BYf took no action (40% BYf vs. 7% CMf).

DISCUSSION

This qualitative pilot study provides an overview of the AAIs used in poultry and swine CMf and BYf in the Philippines, the reasons why AAIs are used, and common AMU practices, including how producers access AAIs and whom they consult for AMU advice. Increasing demand for chickens and pork and the potential public health implications of the consumption of these products contaminated with antimicrobial resistant foodborne pathogens (12–16) emphasized that AMU surveillance in these food animals should be prioritized.

In this study, we used a simple count-based measurement indicating percentage of farms reporting the use of certain AAIs. Count-based measurements of AMU at the farm level such as the number of days and the number of medicated rations or water treatments and injections are commonly used as numerators in less sophisticated AMU surveillance programs (23). These measurements are useful to compare percentages of AAIs by species and between farms over time, to describe seasonal variations of use or shifts in AMU options (5), and to monitor the progress of interventions to reduce AMR (6). Our metric detected variations in the spectrum of antimicrobials used, the number of AAIs used in poultry and swine and in relevant production stages, and between BYf and CMf. An important finding is the use in poultry and swine CMfs of AAIs belonging to fluoroquinolones and polypeptides, classes categorized by the World Health Organization (WHO) as highest priority critically important antimicrobials (CIAs), and phosphonic acid derivatives, categorized as a high-priority CIA (24). Though at lower percentages, BYfs reportedly used the same classes. The spectrum of AAIs in our study is comparable to other LMICs in Southeast Asia with similar livestock farming systems (CMf and BYf) such as Indonesia, Vietnam, and Thailand (25, 26). The use of these AAIs is consistent with the detection of *E. coli* resistant to cephalosporins from poultry (13) and swine (12, 15, 16) and the detection of ciprofloxacin resistant *Campylobacter* from retail chickens (14) sampled within the same regions in our study. As evidenced by the relatively common practice of over-the-counter purchase of VMPs from agrovet shops or retail outlets (largely by BYf), enhanced veterinary oversight or VCPR and regulating access to these antimicrobials such as prescription-only use are required. This may involve monitoring the off-label use or restrictions on the metaphylactic use of antimicrobials belonging to WHO's Essential List of Medicines such as colistin (27).

Overall, respiratory disease was the most commonly reported reason for use in poultry and swine farms. The use of antimicrobials for enteric diseases was more common among swine farms, particularly in herds that comprised of piglets and growers. A proportion of swine producers indicated that they used AAIs, but the diseases they treated were not specified, emphasizing that the diagnosis and clinical assessments of the flock/herd conditions for informed AMU decisions need to be improved. These findings indicate that next to AMU data, more detailed information of diseases driving AMU in poultry and swine in the Philippines is needed to inform guidelines on prudent AMU and other interventions to curb AMU including refinements of vaccination and other preventive health programs.

From a surveillance standpoint, our study has certain limitations including the collection of more comprehensive data to enable quantitative estimation of farm-level AMU (23, 28, 29). However, our study provided a descriptive landscape of AMU practices (between production systems and stages of production). Commercial farms and BYf production systems both contribute to the national demand for poultry and swine products in the Philippines. The latter production system is relatively common as these farms are essential for food security in LMICs such as the Philippines for supplying local and remote areas and source of livelihood. The potential contribution of these production systems to the overall AMU quantity and food safety implications makes indispensable their inclusion in a national AMU surveillance program. Furthermore, the survey indicated that some farms constituted of mixed production stages (piglets/grower/sows, piglets/growers, layer/broiler), which may add complexity to a national AMU data collection, but the framework could target those stages that are closest to the consumer such as broiler chickens, layers, and growers, being more reflective of the potential AMR in foodborne pathogens from the meat and egg products. Our data also showed that diverse antimicrobials (up to seven AAIs) involved herds that contain young animals such as piglets, suggesting that this production stage should also be included in a national farm-level AMU surveillance for informing interventions to address health issues in young animals. Because national farm-level AMU surveillance would require human resources and ongoing national funding for operationalizing the farm data collection, future farm surveillance design may explore inexpensive farm-level AMU methodology, such as "garbage can audit" (30).

Our findings emphasized the urgent need for curbing the use of CIAs in poultry and swine farms in the Philippines and the need for changes in antimicrobial VMP regulations that pertain to their dispensation, in particular, where BYf frequently access these products (agrovet shops and retail outlets and their distributors). Enhanced veterinary oversight and ongoing national AMU monitoring will inform interventions to offset the need for AMU and reduction of AMR risks arising from food animals in the Philippines.

DATA AVAILABILITY STATEMENT

All datasets generated for this study are included in the article/**Supplementary Material**.

ETHICS STATEMENT

This farm-level survey involving producers is part of a larger study (good practices survey as part of the nationwide antimicrobial resistance [AMR] campaign in the Philippines IAMResponsible) and was reviewed and approved by the Bureau of Animal Industry-AMR program designates and the Regional AMR Coordinators. The participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

TB, RM, and CB conceived the study and developed the questionnaires and the sampling frame. TB, RM, MMC, and MBC contributed to the coordination of workshops, meetings with industry, and other stakeholders (industry and veterinary associations), the regional networks (veterinarians and staff from the local government units), and the recruitment of participants. TB, AA, and AD-G contributed to data validation and analysis. KB provided supervision and overall technical guidance to the project. All authors contributed to the writing and editing of the manuscript. All authors contributed to the article and approved the submitted version.

FUNDING

This research was funded by a grant from the Fleming Fund of the United Kingdom (https://www.flemingfund.org/) to the Food and Agriculture Organization of the United Nations

(GCP/GLO/710/UK). The funder had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

ACKNOWLEDGMENTS

The authors acknowledge the producers who participated in the study and voluntarily provided data. We are grateful to the provincial veterinarians, extension service staff, and regional AMR coordinators for their support.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fvets.2020.00329/full#supplementary-material

Supplementary Materials I | Questionnaire: informed consent form and farm questionnaire on antimicrobial use (page 10), good husbandry practices and biosecurity.

Supplementary Materials II | Other results: reasons for antimicrobial use and routes of administration in poultry and swine commercial and backyard farms in the Philippines.

REFERENCES

1. Havelaar AH, Kirk MD, Torgerson PR, Gibb HJ, Hald T, Lake RJ, et al. World Health Organization global estimates and regional comparisons of the burden of foodborne disease in 2010. *PLoS Med*. (2015) 12:e1001923. doi: 10.1371/journal.pmed.1001923
2. Collignon P, Beggs JJ, Walsh TR, Gandra S, Laxminarayan R. Anthropological and socioeconomic factors contributing to global antimicrobial resistance: a univariate and multivariable analysis. *Lancet Planet Health*. (2018) 2:e398–405. doi: 10.1016/S2542-5196(18)30186-4
3. Luiken REC, Van Gompel L, Munk P, Sarrazin S, Joosten P, Dorado-Garcia A, et al. Associations between antimicrobial use and the faecal resistome on broiler farms from nine European countries. *J Antimicrob Chemother*. (2019) 74:2596–604. doi: 10.1093/jac/dkz235
4. Van Gompel L, Luiken REC, Sarrazin S, Munk P, Knudsen BE, Hansen RB, et al. The antimicrobial resistome in relation to antimicrobial use and biosecurity in pig farming, a metagenome-wide association study in nine European countries. *J Antimicrob Chemother*. (2019) 74:865–76. doi: 10.1093/jac/dky518
5. Government of Canada. *Canadian Integrated Program for Antimicrobial Resistance Surveillance (CIPARS), Surveillance Bulletin. Reductions in Antimicrobial Use and Resistance: Preliminary Evidence of the Effect of the Canadian Chicken Industry's Elimination of Use of Antimicrobials of Very High Importance to Human Medicine.* (2016). Available online at: https://www.canada.ca/en/public-health/services/publications/drugs-health-products/canadian-integrated-program-antimicrobial-resistances-surveillance-bulletin.html (accessed June 6, 2020).
6. Hiki M, Kawanishi M, Abo H, Kojima A, Koike R, Hamamoto S, et al. Decreased resistance to broad-spectrum cephalosporin in *Escherichia coli* from healthy broilers at farms in Japan after voluntary withdrawal of ceftiofur. *Foodborne Pathog Dis*. (2015) 12:639–43. doi: 10.1089/fpd.2015.1960
7. Philippine Statistics Authority. *Selected Statistics on Agriculture 2019*. (2019). Available online at: https://psa.gov.ph/sites/default/files/Selected%20Statistics%20on%20Agriculture%202019.pdf (accessed June 5, 2020).
8. Li M, Havelaar AH, Hoffmann S, Hald T, Kirk MD, Torgerson PR, et al. Global disease burden of pathogens in animal source foods, 2010. *PLoS ONE*. (2019) 14:e0216545. doi: 10.1371/journal.pone.0216545
9. Van Boeckel TP, Pires J, Silvester R, Zhao C, Song J, Criscuolo NG, et al. Global trends in antimicrobial resistance in animals in low- and middle-income countries. *Science*. (2019) 365:eaaw1944. doi: 10.1126/science.aaw1944
10. Food and Drug Administration, Republic of the Philippines. *Rules on the Regulation of Veterinary Drugs and Products, Veterinary Biological Products, and Veterinary Drugs Establishments. Joint Department of Health-Department of Agriculture Administrative Order 2013-0026.* (2013). Available online at: https://ww2.fda.gov.ph/index.php/issuances-2/pharml-1/pharml-administrative-order/111167-joint-doh-da-ao-2013-0026 (accessed June 5, 2020).
11. Caudell MA, Dorado-Garcia A, Eckford S, Creese C, Byarugaba DK, Afakye K, et al. Towards a bottom-up understanding of antimicrobial use and resistance on the farm: a knowledge, attitudes, and practices survey across livestock systems in five African countries. *PLoS ONE*. (2020) 15:e0220274. doi: 10.1371/journal.pone.0220274
12. Gundran RS, Cardenio PA, Salvador RT, Sison FB, Benigno CC, Kreausukon K, et al. Prevalence, antibiogram, and resistance frofile of extended-spectrum beta-lactamase-producing Escherichia coli isolates from pig farms in Luzon, Philippines. *Microb Drug Resist*. (2019) 26:160–8. doi: 10.1089/mdr.2019.0019
13. Gundran RS, Cardenio PA, Villanueva MA, Sison FB, Benigno CC, Kreausukon K, et al. Prevalence and distribution of blaCTX-M, blaSHV, blaTEM genes in extended- spectrum beta- lactamase- producing *E. coli* isolates from broiler farms in the Philippines. *BMC Vet Res*. (2019) 15:227. doi: 10.1186/s12917-019-1975-9
14. Lim PW, Tiam-Lee DC, Paclibare PA, Subejano MS, Cabero-Palma JA, Penuliar GM. High rates of contamination of poultry meat products with drug-resistant Campylobacter in Metro Manila, Philippines. *Jpn J Infect Dis*. (2017) 70:311–3. doi: 10.7883/yoken.JJID.2016.309
15. Ng KC, Rivera WL. Antimicrobial resistance of Salmonella enterica isolates from tonsil and jejunum with lymph node tissues of slaughtered swine in Metro Manila, Philippines. *ISRN Microbiol*. (2014) 2014:364265. doi: 10.1155/2014/364265
16. Calayag AMB, Paclibare PAP, Santos PDM, Bautista CAC, Rivera WL. Molecular characterization and antimicrobial resistance of Salmonella enterica from swine slaughtered in two different types of Philippine abattoir. *Food Microbiol*. (2017) 65:51–6. doi: 10.1016/j.fm.2017.01.016
17. World Health Organization. *National Action Plan*. (2019). Available online at: http://www.who.int/antimicrobial-resistance/national-action-plans/en/ (accessed June 6, 2020).
18. European Centre for Disease Prevention and Control European Food Safety Authority and 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 bacterial from humans and food producing animals. Joint Interagency Antimicrobial Consumption and Resistance Analysis (JIACRA) Report*. (2017). Available online at: http://onlinelibrary.wiley.com/doi/10.2903/j.efsa.2017.4872/epdf (accessed June 6, 2020).
19. World Health Organization. *WHO Global Action Plan on Antimicrobial Resistance.* (2015). Available online at: https://www.who.int/antimicrobial-resistance/publications/global-action-plan/en/ (accessed June 6, 2020).
20. Food and Agriculture Organization of the United Nations. *The FAO Action Plan on Antimicrobial Resistance, 2016–2020*. (2018). Available online at: http://www.fao.org/fsnforum/resources/fsn-resources/fao-action-plan-antimicrobial-resistance-2016-2020 (accessed June 6, 2020).
21. World Organization for Animal Health (OIE). *Terrestrial Animal Health Code.* (2018). Available online at: http://www.oie.int/international-standard-setting/terrestrial-code/access-online/ (accessed June 6, 2020).
22. Food and Agriculture Organization of the United Nations. *Prudent and Efficient Use of Antimicrobials in Pigs and Poultry*. (2019). Available online at: http://www.fao.org/3/ca6729en/CA6729EN.pdf (accessed June 6, 2020).
23. AACTING network on quantification benchmarking and reporting of veterinary antimicrobial usage at farm level. *Guidelines for Collection, Analysis and Reporting of Farm-Level Antimicrobial Use, in the Scope of Antimicrobial Stewardship.* (2018). Available online at: https://aacting.org/aacting-guidelines/ (accessed June 6, 2020).

24. World Health Organization. *Critically Important Antimicrobials for Human Medicine 6th Revision*. (2019). Available online at: https://www.who.int/foodsafety/publications/antimicrobials-sixth/en/ (accessed June 6, 2020).
25. Coyne L, Arief R, Benigno C, Giang VN, Huong LQ, Jeamsripong S, et al. Characterizing antimicrobial use in the livestock sector in three South East Asian countries (Indonesia, Thailand, and Vietnam). *Antibiotics*. (2019) 8:10. doi: 10.3390/antibiotics8010033
26. Cuong NV, Phu DH, Van NTB, Dinh Truong B, Kiet BT, Hien BV, et al. High-resolution monitoring of antimicrobial consumption in Vietnamese small-scale chicken farms highlights discrepancies between study metrics. *Front Vet Sci*. (2019) 6:174. doi: 10.3389/fvets.2019.00174
27. European Medicines Agency. *Advice on Impacts of Using Antimicrobials in Animals*. (2019). Available online at: https://www.ema.europa.eu/en/veterinary-regulatory/overview/antimicrobial-resistance/advice-impacts-using-antimicrobials-animals (accessed June 6, 2020).
28. Collineau L, Belloc C, Stark KD, Hemonic A, Postma M, Dewulf J, et al. Guidance on the selection of appropriate iIndicators for quantification of antimicrobial usage in humans and animals. *Zoonoses Public Health*. (2016) 64:165–84. doi: 10.1111/zph.12298
29. European Medicines Agency. *Revised ESVAC Reflection Paper on Collecting Data on Consumption of Antimicrobial Agents per Animal Species, on Technical Units of Measurement and Indicators for Reporting Consumption of Antimicrobial Agents in Animals.* (2013) Available online at: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/12/WC500136456.pdf (accessed June 6, 2020).
30. Carson CA, Reid-Smith R, Irwin RJ, Martin WS, McEwen SA. Antimicrobial use on 24 beef farms in Ontario. *Can J Vet Res*. (2008) 72:109-18.

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Veterinary Science

ORIGINAL RESEARCH
published: 23 July 2020
doi: 10.3389/fvets.2020.00425

Standardization of Therapeutic Measures in Antibiotic Consumption Monitoring to Compare Different Livestock Populations

Katharina Hommerich, Charlotte Vogel, Svetlana Kasabova, Maria Hartmann and Lothar Kreienbrock*

Department of Biometry, Epidemiology and Information Processing, WHO Collaborating Centre for Research and Training for Health at the Human-Animal-Environment Interface, University for Veterinary Medicine Hannover, Hanover, Germany

OPEN ACCESS

Edited by:
Lucie Collineau, Agence Nationale de Sécurité Sanitaire de l'Alimentation, de l'Environnement et du Travail (ANSES), France

Reviewed by:
Nico Bondt, Wageningen University and Research, Netherlands
Anne Hemonic, Institut du Porc (IFIP), France
Fraser Keith Broadfoot, Veterinary Medicines Directorate, United Kingdom

***Correspondence:**
Katharina Hommerich
katharina.hommerich@tiho-hannover.de

Specialty section:
This article was submitted to Veterinary Epidemiology and Economics, a section of the journal Frontiers in Veterinary Science

Received: 10 December 2019
Accepted: 12 June 2020
Published: 23 July 2020

Citation:
Hommerich K, Vogel C, Kasabova S, Hartmann M and Kreienbrock L (2020) Standardization of Therapeutic Measures in Antibiotic Consumption Monitoring to Compare Different Livestock Populations. Front. Vet. Sci. 7:425. doi: 10.3389/fvets.2020.00425

Using sales data, information on antimicrobial consumption in animals is collected cumulatively across the European Union and member countries of the European Economic Area, which is documented and reported by every country and published within annual reports by the European Surveillance of Veterinary Antimicrobial Consumption (ESVAC). These serve to perform cross-border comparisons of antimicrobial consumption, despite their ambiguity due to the different units and key figures used. To improve comparability, the European Medicines Agency has introduced the population correction unit (PCU), which represents the biomass of a livestock population and is related to antibiotic consumption. However, the PCU does not consider the variability of how a livestock population is composed structurally regarding the proportions of production types contained therein. To achieve better comparability between the different geographical areas, we therefore applied a system of standardization in different examples and in real antimicrobial consumption data. This was done by quantifying the consumption of antibiotics by livestock in exemplary regions and countries (Denmark, Germany, France) by means of the active substance used (mg/kg) and subjecting it to a direct and indirect standardization procedure to identify and measure differences in consumption in relation to the composition of livestock demographics. The consideration of livestock demographics results in substantial effects when comparing antimicrobial usage in livestock. To achieve a more compelling comparability in the context of monitoring antibiotic consumption in livestock populations, we recommend using an indirect standardization method, to control potential confounding effects caused by different livestock demographics. This assumes that animal populations can be structured accordingly well. Correspondingly, detailed information on antimicrobial usage by species should be available for this type of stratification.

Keywords: antimicrobial usage, livestock, confounding, stratification, animal demographics, population correction unit

INTRODUCTION

The monitoring and surveillance of antimicrobial usage (AMU) is essential for identifying factors that drive the development of antimicrobial resistance in humans and animals, one of the major issues defined by the World Health Organization that threatens global health (1). For Europe, there is no binding legislation with regard to the implementation of monitoring programs at the national level. Different countries use their own specifications with regard to collection and evaluation of AMU data at the farm level and the definition of standard weights and populations (2). With respect to the implementation of synchronized monitoring programs at the national level, countries are still at different levels (3). In a comparison of AMU data from European countries and the United States of America, large differences have been found, which were attributed to the availability of data and differences in livestock demographics (4). Other stakeholders have also drawn attention to the need for the harmonization and standardization of AMU data at the farm level. For instance, the AACTING network has issued guidelines to provide useful support when designing or revising farm-level AMU monitoring systems (5). However, at this point, if data are available, they are usually not standardized internationally and are therefore not unambiguously comparable due to the differences in calculation methods and units (6).

Therefore, to perform cross-border comparisons of AMU, sales data are typically used, documented and reported by every country (7). Information on which antimicrobial agents are sold across the European Union (EU) are collected, evaluated and published in annual reports (8). The ESVAC project (European Surveillance of Veterinary Antimicrobial Consumption) was launched by the European Medicines Agency (EMA), following a request from the European Commission, to develop a harmonized approach for the collection of data on the AMU in animals from the EU and the European Economic Area Member States (9). The quantities of active substances are expressed in mg/PCU (population correction unit, a representation of the biomass of all farm animals within an entire national livestock), and thus, a comparison between the countries is possible (9). Suggestions have already been made to adjust the PCU by reevaluating the standard animal weight and including farm animal lifespan (10). Bondt et al. compared the overall exposures of the animals using model calculations and the assumption of varying treatment incidences in two countries. This comparative analysis of sales figures from Denmark and the Netherlands showed that reliable results can only be obtained based on consumption per species and that it is therefore necessary to have information on the animal population separated by species (11). Nevertheless, the antibiotic use and consumed amounts of almost all active substance groups differ between countries, which can also be attributed to the fact that the proportions of the various animal species differ between countries. As the types and incidences of infectious diseases vary considerably between animal species and production category (e.g., beef vs. dairy cattle), consequently, the sales of veterinary antibacterial agents are thought to be influenced by animal species demographics (7). Because livestock populations of the different countries are composed differently, comparisons may be biased to higher consumption for countries that maintain more treatment-intensive production types of livestock. As an example, countries with a high proportion of fattening pigs had a higher consumption per PCU (12). Although sales data are available in most European countries, there is a lack of AMU surveillance at the animal species level in many countries. Therefore, at present, population-based evaluations are carried out with regard to their distribution of the PCU by animal species and country (13), but these are not linked to information on species-related antimicrobial consumption.

To illustrate the effect of the population composition and the corresponding variation in the use of the active ingredients in international comparisons of AMU, we applied standardization techniques to several data sets, i.e., to artificial data to illustrate the strategy, to real antibiotic consumption data, which were documented within the VetCAb-S study (Veterinary Consumption of Antibiotics—Sentinel), a German antibiotic monitoring sentinel, and to international data from some European countries.

MATERIALS AND METHODS

Compelling comparisons of AMU between two different populations can only be made if the populations are similar with respect to characteristics that might affect AMU. If the populations are dissimilar with respect to such characteristics, erroneous conclusions might be drawn because these characteristics may act as confounders (14). These confounders can be prevented by standardization (15). Standardization is a method used to compare observed and expected rates of a given outcome by removing the influence of factors that may confound the comparison (16). To achieve a better comparability between the consumption of antibiotics in different geographical areas regarding their different populations and corresponding exposure (17), we applied the systematics of direct and indirect standardization in example data and subsequently transferred these to real AMU data from a German antibiotic monitoring sentinel (VetCAb-S) as well as to AMU-data derived from national reports from Denmark (18) and France (19).

Basic Example - Which Data Are Required?

Consider two hypothetical regions A and B with different livestock demographics. **Table 1** shows the characteristics of the standard population in Region A (hereafter marked with an asterisk "*") and of the study population in Region B. For the selection of the standard population, sufficient information on the characteristic to be examined should be known. The choice of the reference population should be realistic and relevant with regard to the planned evaluations (14), e.g., that the region is considered reasonably representative at regional or national

Abbreviations: AMU, Antimicrobial usage; CTF, Comparative Treatment Figure; EMA, European Medicines Agency; ESVAC, European Surveillance of Veterinary Antimicrobial Consumption; PCU, Population Correction Unit; STR, Standardized Treatment Ratio; TR, Treatment Ratio; VetCAb-S, Veterinary Consumption of Antibiotics – Sentinel.

TABLE 1 | Livestock demographics and treatment in Region A and Region B.

REGION A (STANDARD POPULATION)				
Production type	**k**	$w_k{}^*$	$AMU_k{}^*$ **in mg/kg**	**Weighted AMU***
Pigs	1	$w_1{}^* = 0.70$	80	56
Cattle	2	$w_2{}^* = 0.30$	20	6
				$AMU^* = 62$
REGION B (STUDY POPULATION)				
Production type	**k**	w_k	AMU_k **in mg/kg**	**Weighted AMU**
Pigs	1	$w_1 = 0.40$	60	24
Cattle	2	$w_2 = 0.60$	30	18
				$AMU = 42$

TABLE 2 | Direct standardization of Region B.

Production type	**k**	$w_k{}^*$	AMU_k **in mg/kg (Region B)**	**Weighted, standardized AMU**
Pigs	1	$w_1{}^* = 0.70$	60	42
Cattle	2	$w_2{}^* = 0.30$	30	9
				$AMU_{st} = 51$

level. The populations to be compared were divided into animal strata (15). The term "strata" defines the livestock demographics broken down into different layers of production types of livestock animals. The expression "production type" hereafter describes the type of use of the livestock animal within an animal species, for example: dairy cows kept for milk production or beef cattle reared for meat production. In the example considered, livestock within one region is composed of K strata, where here K = 2, consisting in this case of pigs (k1) and cattle (k2). The different strata each make up a proportion of $w{*}_k$ (k = 1 … K) in the total population. By definition, $w_k{*}$ denotes the proportion of the k-th production type in Region A (standard population) and w_k in Region B (population under study). Note that proportions add up to 1, i.e., $\sum w_k{*} = 1$. Suppose that pigs are usually treated with 80 mg/kg ($AMU_1{*}$) active substance in Region A, whereas cattle are treated with 20 mg/kg ($AMU_2{*}$). This antimicrobial consumption information AMU_k is also required for the study population, with which the comparison will be performed. For each stratum, weighted AMU-amounts can be calculated by multiplying the proportion by its production-type specific quantity of antimicrobials used. Then, the overall amount of active treatment equals the sum over all weighted AMU-amounts from the total population (see **Table 1**).

$$AMU^* = \sum w_k{}^* \cdot AMU_k{}^* \qquad (1)$$

Similarly, in the study population, the overall amount is determined as

$$AMU = \sum w_k \cdot AMU_k \qquad (2)$$

This forms the basis for the calculation of the "Treatment Ratio" (TR), which compares the individual overall amount by forming a ratio as

$$Treatment\ Ratio = \frac{AMU}{AMU^*} \qquad (3)$$

Here, the Treatment Ratio = 42/62 = 0.68; the overall amount is lower in the study population in Region B than in the standard population in Region A. Thus, without considering the livestock demographics as a confounding factor, Region B consumes 0.68 of the antibiotic active ingredients consumed in Region A (i.e., Region B consumes 32% less than Region A).

Implementation of Standardization Procedure

For direct standardization, the observed proportions in the individual strata of the standard population are assumed to be fixed as the true underlying distribution of the production types to identify population-structural differences and their impact on antibiotic consumption. In **Table 2**, the region-specific proportions of the production types of the standard population within Region A are applied to the study population within Region B. The transferred population stratification is weighted with the applied amount of active ingredients in mg/kg of the study population (Region B). The sum of these values is

$$AMU_{st} = \sum w_k{}^* \cdot AMU_k \qquad (4)$$

which yields the total amount of active ingredients that would be estimated if the study population had the livestock demographics

TABLE 3 | Indirect standardization of Region B.

Production type	k	w_k	AMU^* in mg/kg (Region A)	Weighted, expected AMU
Pigs	1	$w_1 = 0.40$	80	32
Cattle	2	$w_2 = 0.60$	20	12
				$AMU_{expected} = 44$

as our standard population. This is therefore denoted as AMU_{st} for the standardized AMU-amount.

Following (4), the "Comparative Treatment Figure" (CTF) is determined by comparing the directly standardized AMU of the study population with the total AMU of the standard population.

$$CTF = \frac{AMU_{st}}{AMU^*} = \frac{\sum w_k{}^* \cdot AMU_k}{\sum w_k{}^* \cdot AMU_k{}^*} \tag{5}$$

This measure indicates the ratio in the population stratification when assuming the same structural proportions as in the study population.

Here, the Comparative Treatment Figure = 51/62 = 0.82; considering the population stratification as in the standard population, Region B consumes 0.82 of the antibiotic active ingredients consumed in Region A (i.e., Region B consumes 18% less than Region A).

Similarly, the procedure can be performed using an indirect standardization technique. This technique appears more suitable here, as it is easier to assume similar treatment regimens in different regions. In this regard, we weight the region-specific proportions of the production types of the standard population (Region B) with the applied amount of active ingredients in mg/kg of the study population (Region A) (see **Table 3**).

$$AMU_{expected} = \sum w_k \cdot AMU_k{}^* \tag{6}$$

By now comparing the nonstandardized AMU with the $AMU_{expected}$, the "Standardized Treatment Ratio" (STR) is obtained by

$$STR = \frac{AMU}{AMU_{expected}} = \frac{\sum w_k \cdot AMU_k}{\sum w_k \cdot AMU_k{}^*} \tag{7}$$

In the present example, this precisely means that the AMU rate of the study population is related to the expected AMU rate. This indicates the rate in overall therapy when assuming the same treatment regime as in the standard population.

Here, the Standardized Treatment Ratio = 42/44 = 0.95; assuming the same treatment regimen in Region B as in Region A, Region B consumes 0.95 of the antibiotic active ingredients consumed in Region A (i.e., Region B consumes 5% less than Region A).

Transferring the Method to VetCAb-S Data

To quantify antibiotic consumption, real AMU data collected within the scientific project VetCAb-S were used. The aim of the study is to evaluate and describe the use of antibiotics in farm animals in Germany and to assess it on a scientific basis (20, 21). Since 2013, the project has continued as a longitudinal study with ongoing participant recruitment and data collection (22, 23). Participating veterinarians and farmers voluntarily provide information on AMU at the farm level by official application and delivery forms, which are transferred into a database that maintains information about the species, production type, number of animals treated, the treatment date and duration and the name and amount of the medicinal product used.

For this exercise, subsets from real antibiotic consumption data from the VetCAb-S study were formed. To ensure a cross-sectional study-like study population, the data were checked for representativeness by investigating the demographic characteristics of the participating farms by comparing this data with official data from agricultural statistics (24).

Here, we systematically selected areas with a high density of pig farms and a low density of cattle farms and vice versa from the VetCAb-S population. For this purpose, the county codes of all VetCAb regions, defined by Merle et al. (25), were analyzed with regard to the number of participating cattle and pig farms and their stable capacities. To determine the total biomass of livestock kept in the defined subregions within the considered time period (half a year), the numbers of livestock animals kept on the considered farms were multiplied by the estimated weight at treatment. Therefore, the standard weights defined by ESVAC were used; i.e., for fattening pigs 65 kg, for calves 140 kg, and for beef cattle and dairy cows 425 kg (9). In addition, in order to adjust the determined biomass of fattening pigs, it was multiplied by the usual passage rate for Germany for half a year of 1.425 (26). Based on the determined biomass, the corresponding proportions (k) of the total livestock were determined. The quantities of antimicrobial active substances consumed were determined for the corresponding period and subregions to be compared. The consumption of antibiotics by livestock in the exemplary subregions was measured by the ratio of the biomass in kg and the amount of active ingredients used in mg. After addition of the respective average AMU of the individual production types, the overall AMU of the active ingredient for the entire livestock population was obtained (see **Table 4**) to then determine the treatment ratio of the two regions.

VetCAb Study Population

In accordance with the example above, the direct and indirect standardization method was applied (see **Tables 5**, **6**), and the "Comparative Treatment Figure" and "Standardized Treatment Ratio" were determined according to Equations (5) and (7). For the analyses, data from the second half of the year 2014

TABLE 4 | Livestock demographics and treatment, VetCAb-S Subregion 1 and Subregion 2.

SUBREGION 1					
Production type	**Biomass (kg)**	**w_k^***	**Active ingredients (mg)**	**AMU_k^* in mg/kg**	**Weighted AMU***
Fattening pigs	17,685,910	76.9	1,416,595,566	80.1	61.6
Dairy cows	3,224,900	14.0	32,157,300	10.0	01.4
Calves	946,820	04.1	26,669,911	28.2	01.2
Beef cattle	1,150,900	05.0	13,126,236	11.4	00.6
∑	23,008,530	100.0	1,488,549,013		64.7
SUBREGION 2					
Production type	**Biomass (kg)**	**w_k**	**Active ingredients (mg)**	**AMU_k in mg/kg**	**Weighted AMU**
Fattening pigs	5,142,633	52.4	294,047,708	57.2	30.0
Dairy cows	3,077,425	31.3	24,432,104	07.9	02.5
Calves	1,011,140	10.3	34,603,400	34.2	03.5
Beef cattle	586,500	06.0	1,213,250	02.1	00.1
∑	9,817,698	100.0	354,296,462		36.1

TABLE 5 | Direct standardization of VetCAb-S Subregion 2.

Production type	**w_k^* Subregion 1**	**AMU_k in mg/kg Subregion 2**	**Weighted, standardized AMU**
Fattening pigs	76.9	57.2	44.0
Dairy cows	14.0	07.9	01.1
Calves	04.1	34.2	01.4
Beef cattle	05.0	02.1	00.1
∑	100.0		46.6

TABLE 6 | Indirect standardization of VetCAb-S Subregion 2.

Production type	**w_k Subregion 2**	**AMU_k^* in mg/kg Subregion 1**	**Weighted, expected AMU**
Fattening pigs	52.4	80.1	42.0
Dairy cows	31.3	10.0	03.1
Calves	10.3	28.2	02.9
Beef cattle	06.0	11.4	00.7
∑	100.0		48.7

were selected to demonstrate the method with real-application data. The two selected subregions are located in the middle and northwest of Germany, both of which employ intensive pig farming. Within these subregions, one was identified with a small and one with a large proportion of cattle. Subregion 1 is made up of 79 dairy farms, 41 beef cattle farms and 179 pig farms with 17,059 livestock places for dairy cows, calves and beef cattle (hereafter summarized as "cattle") and 190,941 livestock places for fattening pigs. Subregion 2 comprises 69 dairy farms, 25 beef cattle farms and 52 pig farms, with 15,772 livestock places for cattle and 55,521 for fattening pigs. Biomass (in kg) is defined here as the inventory of livestock that was kept at the farms within the defined regions during the study period.

The biomass of Subregion 1 is accordingly divided into 77% pigs and 23% cattle and is hereafter referred to as the "pig dense region." The biomass of Subregion 2 is distributed into approximately equal parts with 52% cattle and 48% pigs, hereafter referred to as the "species balanced region." The respective overall amount of active substance used per production type and subregion are shown in **Table 4**.

Transferring the Method to EU AMU Data

As a last exercise the standardization technique presented is applied to European antibiotic consumption data. For this purpose, it was assumed that livestock demographics are composed of pigs and cattle only and their percentages shown in **Table 7** were extrapolated, to 100% therefore (see **Table 8**) (27). It should be noted that after extrapolation to 100%, the stratification of the livestock population no longer corresponds directly to the real country-specific French, German or Danish livestock population. Data on antibiotic consumption for Germany were obtained from the VetCAb collective, Subregion 1 (see **Table 4**). Due to the clear differences in the percentage distribution of the species cattle and pig within **Table 7**, AMU-data data suitable for the application of the methodology for France and Denmark were obtained from reports published annually (18, 19). Germany artificially serves as the trial standard for the calculations; France and Denmark form the study populations.

RESULTS

Standardization of VetCAb Data

After multiplying the amount of active substances per production type in each subregion by the percentage distribution of production types, the weighted amount of active substances was 64.7 mg/kg in Subregion 1 and 36.1 mg/kg in Subregion 2, with a resulting Treatment Ratio of 0.56 (see **Table 4**). This quotient means that in Subregion 2, in relation to Subregion 1, slightly

TABLE 7 | Livestock in tons and percentages of total population in BE, DK, DE, ES, FR, NL, and the UK in 2014 (27).

Country	Cattle		Pigs		Poultry		Sheep		Total livestock (tons)
	tons	%	tons	%	tons	%	tons	%	
Belgium	1,052,725	71.4	412,750	28.0	8,442	0.6			1,473,917
Denmark	660,025	44.3	826,085	55.5	3,260	0.2			1,489,370
Germany	5,415,350	72.9	1,842,035	24.8	50,849	0.7	120,075	1.6	7,428,309
Spain	2,583,575	46.9	1,726,920	31.4	39,182	0.7	1,157,400	21.0	5,507,077
France	8,190,175	85.0	864,500	9.0	47,306	0.5	537,600	5.6	9,639,581
Netherlands	1,771,825	66.4	784,225	29.4	31,356	1.2	80,250	3.0	2,667,656
United Kingdom	4,119,525	67.0	293,150	4.8	37,853	0.6	1,701,525	27.7	6,152,053

The following estimated weights at treatment by ESVAC were used: Cattle 425 kg, Pig 65 kg, Poultry 1 kg, Sheep 75 kg (7).

TABLE 8 | Livestock demographics (27) and AMU-data, German Subregion 1 (VetCAb-S), France (19) and Denmark (18).

Production type	w_k^*	AMU_k^* in mg/kg	Weighted AMU*
Germany (Standard population)			
Pigs	0.25	80.1	20.0
Cattle	0.75	13.5	10.1
			$AMU^* = 30.2$
France (Study population)			
	w_k	AMU_k in mg/kg	Weighted AMU
Pigs	0.10	64.3	6.4
Cattle	0.90	14.1	12.7
			$AMU = 19.1$
Denmark (Study population)			
Pigs	0.56	91.0*	50.9
Cattle	0.44	19.0*	8.4
			$AMU = 59.3$

**source of data: biomass (27), kg active compound (18).*

more than half as much active substance is consumed (i.e., Subregion 2 consumes 44% less than Subregion 1).

Following direct standardization, the biomass distribution in Subregion 2 is set the same as in Subregion 1 (see **Table 5**). Consequently, the resulting Comparative Treatment Figure was 0.72; i.e., considering the same population stratification as in the standard population, Subregion 2 consumes 72% of the antibiotic active ingredients consumed in Subregion 1 (in other words Subregion 2 consumes 28% less than Subregion 1).

If the concept of indirect standardization is used for Subregion 2, the treatment habits of Subregion 1 are assumed. This yield expected overall AMU outlined in **Table 6**. Subsequently, the resulting Standardized Treatment Ratio was 0.74, which means that assuming the same AMU in species balanced Subregion 2 as in the standard population in Subregion 1; the total amount of active substance consumed is 0.26% lower in Subregion 2.

Standardization of EU AMU Data

The comparison between Germany (standard population) and Denmark (study population) results in a TR of 59.3/30.2 = 2.0 i.e., in the example Denmark consumes 2 times the antibiotic active ingredient consumed in Germany. After applying the direct standardization method, the CTF = 37.0/30.2 = 1.2. Considering the population stratification as in Germany, Denmark consumes 120% of the antibiotic active ingredients consumed in Germany. After applying the indirect standardization method, the STR = 59.3/50.8 = 1.2. Assuming the same treatment regimen in Denmark as in Germany, Denmark consumes 120% of the antibiotic active ingredients consumed in Germany.

The comparison between Germany (standard population) and France (study population) results in a TR of 19.1/30.2 = 0.6 (i.e., France consumes 40% less than Germany). After applying the direct standardization method, the CTF = 26.6/30.2 = 0.9 "(i.e., France consumes 10% less than Germany). After applying the indirect standardization method, the STR = 19.1/20.2 = 0.9 (i.e., France consumes 10% less than Germany) (see **Tables 8–10** respectively).

DISCUSSION

To assess the risk of the development of antimicrobial resistance, a precise quantification of AMU is indispensable. It is therefore necessary to generate access to detailed information on antimicrobial usage. Generally, to report the antimicrobial

TABLE 9 | Direct standardization of AMU-data, France and Denmark.

Production type	w_k^*	AMU_k in mg/kg	Weighted, standardized AMU
France			
Pigs	0.25	64.3	16.1
Cattle	0.75	14.1	10.6
Total			$AMU_{st} = 26.6$
Denmark			
Pigs	0.25	91.0	22.7
Cattle	0.75	19.0	14.3
			$AMU_{st} = 37.0$

TABLE 10 | Indirect standardization of AMU-data, France and Denmark.

Production type	w_k	AMU^* in mg/kg	Weighted, expected AMU
France			
Pigs	0.10	80.1	8.0
Cattle	0.90	13.5	12.2
			$AMU_{expected} = 20.2$
Denmark			
Pigs	0.56	80.1	44.9
Cattle	0.44	13.5	5.9
			$AMU_{expected} = 50.8$

consumption of a country, national requirements, such as the quantification of use data, as well as international documentation and comparison of quantities of antimicrobial active ingredients sold must be followed (28). According to these, the overall amount of the active ingredient sold in target animal populations is recorded cumulatively and published in annual reports in the context of the ESVAC project by the European Medicines Agency (7). To quantify livestock, in the monitoring of AMU, the biomass or another equivalent, such as the PCU, is usually calculated (7). The PCU figure is a harmonized average weight in kilograms of all animals at the time of treatment multiplied by the number of animals based on national statistics (7). Regardless of the species in question, the weight in kilograms of the livestock is consequently considered as equal.

Since data collection by production strata is recommended by the EMA (29) but has not yet been implemented, the classical standardization procedure is to adjust for the confounding of a stratification variable. This established method has thus served in many fields of standardization within human populations (15). Using this standardization technique, different rates are determined to allow more in-depth comparisons of the antibiotic consumption of a population based on its composition. The generated key figures are artificial measures that cannot be interpreted on their own but only make sense in comparison with a second rate (15).

By using the direct standardization method, a standard distribution of the population in each stratum of the confounder for the factor of interest is needed. This approach is very popular in human medicine and demography, e.g., for the standardization of mortality rates. By nature of the method, the standard population is arbitrary, but usually "average populations" are used to calculate standard rates, which are close to the real world. A well-established standard therefore is Segi's world population (30), but other standards like European or African standard populations are used as well. Here, the selection of the populations to be compared made is intended only to illustrate the methodology.

Applying the indirect standardization method and computing standardized ratios (STR) is a more often used method to control potential confounding effects when comparing rates from different populations (15). These are based on a set of stratum-specific rates from the standard population (here the species-specific rates) together with the observed proportion of the treatment behavior in each of the strata of the study population. This method is especially useful if the actual stratum-specific rates (in this case the species-breakdown) are not available for the study population (15). The indirect standardization method could therefore be used to predict antibiotic consumption in regions where at the one hand detailed information on antibiotic consumption by species is not available, but where at the other hand enough data on how animal populations are structured is given. This is usually the case for all international data sets comparing AMU by country.

Both standardization techniques, direct and indirect, in general represent an artificial process. For the direct standardization livestock demographics of the standard population are assumed to be livestock demographics of the study population, i.e., treatment is compared in similar populations. Vice versa the same applies to the indirect standardization, where the treatment regime is assumed the same, which implies the comparison of a population with an expected result under a given treatment regimen. This indirect approach is more closely related to the intended purposes in the context of a harmonized approach of cross-border AMU comparisons. While interpreting the present results, it should be noted that each antibiotic treatment is composed of different drugs and components, respectively. Because the applied amounts of active ingredients are summed up, these differences in potencies are not considered in the outcome.

Regardless of which of the two methods is used, applying the standardization technique leads to a control for confounding biases resulting from different livestock demographics. After considering the stratification, the previously existing bias has decreased. Accordingly, the calculation indicates that there is an effect, and its extent can only be determined with detailed information at the level of the individual animal species. In order to integrate evaluations of this kind into the reports of ESVAC, appropriate information on the AMU at species level is required in addition to the already existing "estimated PCU in tons of the population by species and country," which could serve as data basis for the strata. This information could be derived in the form of active substance-related recommended dose per species (Defined Daily Doses Animal) either from country-specific summaries of product characteristics or from scientific studies such as Sjölund et al. (31). As long as more detailed country specific antibiotic consumption data are not available, the proposed standardization technique could serve as an interim solution to improve the comparison of AMU of livestock in different countries.

If structural differences within a population are not considered, there is a risk of possible bias in the comparison of antimicrobial consumption data of individual countries at the general PCU level. **Table 7** clearly shows the variability in the proportions of livestock animals within selected animal species and selected member states of the EU (27). The application of the methodology to selected European livestock demographics and AMU-data shows that the standardization technique has substantial effects on the ratios calculated.

Within the example, more than half of Denmark's biomass is comprised of pigs, which have higher AMU than, for example, cattle. In contrast to this the German population is 25% pigs only. As a consequence, the resulting treatment ratio of 2.0 comparing Denmark and Germany is 2-fold higher, which is largely due to the higher proportion of pigs and not to different treatment regimes. This bias could be reduced with standardization. If it is assumed that in Denmark is the same proportion of animals as in Germany, the CTF is 1.2 only. However, it should also be taken into account that regions with a high livestock density may have a higher consumption of antibiotics because of greater health problems caused by high density of farms. For the example, this means that Denmark could have a lower AMU if the density of pig farms would be lower. Consequently, this would also have a reducing effect on the CTF. If on the other hand, in Denmark the same treatment is assumed as in Germany the STR is 1.2. Both standardized rates therefore approach 1, i.e., the non-standardized treatment ratio is strictly biased and heavily overestimate the true ratio of both countries. Taking into account that within the example 85 % of the biomass o France is made up of cattle, the results of the comparison between France and Germany can be interpreted equivalently.

This implies that comparing countries and disregarding the corresponding proportions of the individual animal species may lead to biased results in terms of the overall assessment of antibiotic consumption. By taking into account the livestock demographics or transfer of treatment regimes, a potential confounding can be reduced.

CONCLUSIONS

Within this paper, comparisons of antimicrobial usage in different livestock populations showed that the structural composition of the livestock population has an impact on total consumption. Therefore, we recommend an indirect standardization method for cross-population comparisons to achieve a more compelling comparability and obtain deeper insight in the context of monitoring antibiotic consumption in livestock populations. Corresponding detailed information on antimicrobial usage by species should be made available for this type of stratification so that animal populations can be structured accordingly well.

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding author.

ETHICS STATEMENT

The data used for the VetCAb-example are based on mandatory application and delivery forms, which were provided voluntarily by farmers and veterinarians, signing individual written consent for the data to be used by the study team only. Our research does not involve any regulated animals, and there were no scientific procedures performed on animals of any kind. For this reason, formal approval by an ethical committee was not necessary under the provisions of the German regulations.

AUTHOR CONTRIBUTIONS

KH and LK: conceptualization, formal analysis, investigation, and writing—original draft. KH and MH: data curation and validation. LK: funding acquisition and supervision. KH, CV, and LK: methodology. KH and SK: project administration. MH: software. KH, CV, SK, and LK: writing—review and editing. All authors contributed to the article and approved the submitted version.

FUNDING

This study was supported by research grants from the Federal Institute for Risk Assessment (BfR), Max-Dohrn-Str. 8-10, D-10589 Berlin (Grant Nos. 1329-525 and 1329-504). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript. This publication was supported by Deutsche Forschungsgemeinschaft and University of Veterinary Medicine Hannover, Foundation within the funding programme Open Access Publishing.

ACKNOWLEDGMENTS

We would like to thank all the farmers and veterinarians who participate in the VetCAb-S-project.

REFERENCES

1. WHO. *Global Action Plan on Antimicrobial Resistance*. Geneva: World Health Organization (2015).
2. Carmo LP, Schüpbach-Regula G, Muntener C, Chevance A, Moulin G, Magouras I. Approaches for quantifying antimicrobial consumption per animal species based on national sales data: a Swiss example, 2006 to 2013. *Euro Surveill.* (2017) 22:30458. doi: 10.2807/1560-7917.ES.2017.22.6.30458

3. Collineau L, Belloc C, Stark KD, Hemonic A, Postma M, Dewulf J, Chauvin C. Guidance on the selection of appropriate indicators for quantification of antimicrobial usage in humans and animals. *Zoonoses Public Health*. (2017) 64:165–84. doi: 10.1111/zph.12298
4. Geijlswijk, van IM, Bondt N, Puister-Jansen LF, Mevius DJ. Use of veterinary antibacterial agents in Europe and the United States. In: Keen PL, Montforts MMHM, editors. *Antimicrobial Resistance in the Environment*. Oxford: Wiley-Blackwell (2011).
5. AACTING-network. *Systems for Quantification of Antimicrobial Usage.* (2018). Available online at: http://www.aacting.org (accessed November 21, 2019).
6. Rennings L, Merle R, Münchhausen C, Stahl J, Honscha W, Käsbohrer A. Variablen zur Beschreibung des Antibiotikaeinsatzes beim Lebensmittel liefernden Tier. *Berl Münch Tierärztl Wschr*. (2013) 13:297–309. doi: 10.2376/0005-9366-126-297
7. ESVAC. Sales of veterinary antibacterial agents in nine European countries during 2005-09: trends and patterns. *J Antimicrob Chemother*. (2012) 67:3001–8. doi: 10.1093/jac/dks298
8. ESVAC. *Sales of Veterinary Antimicrobial Agents in 30 European Countries in 2016.* European Surveillance of Veterinary Antimicrobial Consumption (2018).
9. ESVAC. *Trends in the Sales of Veterinary Antimicrobial Agents in Nine European Countries (2005-2009)*. (EMA/238630/2011). European Medicines Agency (2011).
10. 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.
11. Bondt N, Jensen VF, Puister-Jansen LF, M I. van Geijlswijk, Comparing antimicrobial exposure based on sales data. *Prev Vet Med*. (2013) 108:10–20. doi: 10.1016/j.prevetmed.2012.07.009
12. Grave K, Torren-Edo J, Mackay D. Comparison of the sales of veterinary antibacterial agents between 10 European countries. *J Antimicrob Chemother*. (2010) 65:2037–40. doi: 10.1093/jac/dkq247
13. ESVAC. *Sales of Veterinary Antimicrobial Agents in 31 European Countries in 2017*. (EMA/294674/2019). European Medicines Agency, European Surveillance of Veterinary Antimicrobial Consumption (2019).
14. Thrusfield MV. *Veterinary Epidemiology*. Oxford: Blackwell Science (2007).
15. Dohoo I, Martin W, Stryhn H. *Veterinary Epidemiologic Research.* Charlottetown: VER (2010).
16. Tripepi G, Jager KJ, Dekker FW, Zoccali C. Stratification for confounding – Part 2: direct and indirect standardization. *Nephron Clin Pract*. (2010) 116:c322–5. doi: 10.1159/000319591
17. Sarrazin S, Joosten P, Van Gompel L, Luiken RE, Mevius DJ, Wagenaar JA. Quantitative and qualitative analysis of antimicrobial usage patterns in 180 selected farrow-to-finish pig farms from nine European countries based on single batch and purchase data. *J Antimicrob Chemother*. (2018) 74:807–16. doi: 10.1093/jac/dky503
18. DANMAP. *Use of Antimicrobial Agents and Occurrence of Antimicrobial Resistance in Bacteria from Food Animals, Food and Humans in Denmark*. (2017). Available online at: https://www.danmap.org/-/media/arkiv/projekt-sites/danmap/danmap-reports/danmap-2017/danmap2017.pdf?la=en
19. ANSES. Agence Nationale de Sécurité Sanitaire de l'alimentation, de l'environnement et du Travail. *Sales Survey of Veterinary Medicinal Products Containing Antimicrobials in France in 2017*. Annual report. Scientific Edition. Maisons-Alfort Cedex 14 (2018)
20. Merle R, Robanus M, Hegger-Gravenhorst C, Mollenhauer Y, Hajek P, Kasbohrer A, et al. Feasibility study of veterinary antibiotic consumption in Germany–comparison of ADDs and UDDs by animal production type, antimicrobial class and indication. *BMC Vet Res*. (2014) 10:7. doi: 10.1186/1746-6148-10-7
21. van Rennings L, von Münchhausen C, Ottilie H, Hartmann M, Merle R, Honscha W. Cross-sectional study on antibiotic usage in pigs in Germany. *PLoS ONE*. (2015) 10:e0119114. doi: 10.1371/journal.pone.0119114
22. Hemme M, Ruddat I, Hartmann M, Werner N, van Rennings L, Kasbohrer A, et al. Antibiotic use on German pig farms - A longitudinal analysis for 2011, 2013 and 2014. *PLoS ONE*. (2018) 13:e0199592. doi: 10.1371/journal.pone.0199592
23. Hommerich K, Ruddat I, Hartmann M, Werner N, Käsbohrer A, Kreienbrock L. Monitoring antibiotic usage in German dairy and beef cattle farms—a longitudinal analysis. *Front Vet Sci*. (2019) 6:244. doi: 10.3389/fvets.2019.00244
24. Statistisches Bundesamt. *Land- und Forstwirtschaft, Fischerei - Viehbestand und tierische Erzeugung 2013, (2014)*. Wiesbaden (2015).
25. Merle R, Busse M, Rechter G, Meer U. Regionalisation of Germany by data of agricultural structures. / Regionalisierung Deutschlands anhand landwirtschaftlicher Strukturdaten. *Berl Münch Tierärztl Wschr*. (2012) 125:52–59. doi: 10.2376/0005-9366-125-52
26. KTBL. *Betriebsplanung Landwirtschaft 2016/17. Daten für die Betriebsplanung in der Landwirtschaft*. Darmstadt: Kuratorium für Technik und Bauwesen in der Landwirtschaft (2016).
27. EUROSTAT, AMI, Statistisches Bundesamt, MEG, BLE (414), BMEL (723). *Ernährung, Landwirtschaft und Forsten in den Mitgliedstaaten der EAMI U*. Statistisches Bundesamt (2018). Available online at: https://www.bmel-statistik.de/landwirtschaft/tierhaltung/ (accessed November 20, 2019).
28. Anonymous. *Regulation (EU) 2019/6 of the European Parliament and of the Council of 11 December 2018 on Veterinary Medicinal Products and Repealing Directive 2001/82/EC*. Strasbourg (2019).
29. EMA. *Questions and Answers for the Guidance on Collection and Provision of National Data on Antimicrobial Use by Animal Species/Categories*. (EMA/489035/2016-Rev.1): 3/6 (2018)
30. Segi M. *Cancer Mortality for Selected Sites in 24 Countries' (1950-1957)*. Sendai: Department of Public Health, Tohoku University of Medicine (1960).
31. Sjölund M, Postma M, Collineau L, Lösken S, Backhans A, Belloc C, et al. Quantitative and qualitative antimicrobial usage patterns in farrow-to-finish pig herds in Belgium, France, Germany and Sweden. *Prev Vet Med. (*2016) 130:41–50. doi: 10.1016/j.prevetmed.2016.06.003

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Veterinary Science

REVIEW
published: 21 August 2020
doi: 10.3389/fvets.2020.00540

Monitoring of Farm-Level Antimicrobial Use to Guide Stewardship: Overview of Existing Systems and Analysis of Key Components and Processes

Pim Sanders [1*†], *Wannes Vanderhaeghen* [2†], *Mette Fertner* [3], *Klemens Fuchs* [4], *Walter Obritzhauser* [5], *Agnes Agunos* [6], *Carolee Carson* [6], *Birgitte Borck Høg* [7], *Vibe Dalhoff Andersen* [8], *Claire Chauvin* [9], *Anne Hémonic* [10], *Annemarie Käsbohrer* [5,11], *Roswitha Merle* [12], *Giovanni L. Alborali* [13], *Federico Scali* [13], *Katharina D. C. Stärk* [14‡], *Cedric Muentener* [15], *Ingeborg van Geijlswijk* [1], *Fraser Broadfoot* [16], *Lucie Pokludová* [17], *Clair L. Firth* [5], *Luís P. Carmo* [18], *Edgar Garcia Manzanilla* [19,20], *Laura Jensen* [21], *Marie Sjölund* [22], *Jorge Pinto Ferreira* [14‡], *Stacey Brown* [16], *Dick Heederik* [1] and *Jeroen Dewulf* [23]

[1] The Netherlands Veterinary Medicines Institute (SDa), Utrecht, Netherlands, [2] Centre of Expertise on Antimicrobial Consumption and Resistance in Animals (AMCRA), Brussels, Belgium, [3] Department of Veterinary and Animal Sciences, University of Copenhagen, Frederiksberg, Denmark, [4] Department for Data, Statistics and Risk Assessment, Austrian Agency for Health and Food Safety, Vienna, Austria, [5] Unit of Veterinary Public Health and Epidemiology, Institute of Food Safety, Food Technology and Veterinary Public Health, University of Veterinary Medicine, Vienna, Austria, [6] Public Health Agency of Canada, Guelph, ON, Canada, [7] Division for Risk Assessment and Nutrition, National Food Institute, Technical University of Denmark, Lyngby, Denmark, [8] Research Group for Genomic Epidemiology, National Food Institute, Technical University of Denmark, Lyngby, Denmark, [9] Epidemiology, Health and Welfare Unit, French Agency for Food, Environmental and Occupational Health & Safety, Ploufragan, France, [10] IFIP-Institut du Porc, Domaine de la Motte au Vicomte, Le Rheu, France, [11] Unit for Epidemiology, Zoonoses and Antimicrobial Resistance, Federal Institute for Risk Assessment (BfR), Berlin, Germany, [12] Institute for Veterinary Epidemiology and Biostatistics, Freie Universität Berlin, Berlin, Germany, [13] Istituto Zooprofilattico Sperimentale della Lombardia e Dell'Emilia Romagna, Brescia, Italy, [14] SAFOSO AG, Bern, Switzerland, [15] Institute of Veterinary Pharmacology and Toxicology, University of Zurich, Zurich, Switzerland, [16] Veterinary Medicines Directorate, Addlestone, United Kingdom, [17] Institute for State Control of Veterinary Biologicals and Medicines, Brno, Czechia, [18] Vetsuisse Faculty, Veterinary Public Health Institute, University of Bern, Bern, Switzerland, [19] Moorepark Animal and Grassland Research Center, Teagasc, Irish Agriculture and Food Development Authority, Cork, Ireland, [20] School Veterinary Medicine, University College Dublin, Dublin, Ireland, [21] Danish Veterinary and Food Administration, Glostrup, Denmark, [22] Department of Animal Health and Antimicrobial Strategies, National Veterinary Institute, Uppsala, Sweden, [23] Veterinary Epidemiology Unit, Faculty of Veterinary Medicine, Ghent University, Merelbeke, Belgium

Edited by:
Fernando O. Mardones, Pontificia Universidad Católica de Chile, Chile

Reviewed by:
Laurel Redding, School of Veterinary Medicine, University of Pennsylvania, United States
Laura Hardefeldt, The University of Melbourne, Australia

****Correspondence:***
Pim Sanders
p.sanders@uu.nl

† These authors share first authorship

‡ Present address:
Katharina D. C. Stärk, Federal Food Veterinary Office, Bern, Switzerland
Jorge Pinto Ferreira, World Organisation for Animal Health (OIE), Paris, France

Specialty section:
This article was submitted to Veterinary Epidemiology and Economics, a section of the journal Frontiers in Veterinary Science

Received: *01 May 2020*
Accepted: *10 July 2020*
Published: *21 August 2020*

Citation:
Sanders P, Vanderhaeghen W, Fertner M, Fuchs K, Obritzhauser W, Agunos A, Carson C, Borck Høg B, Dalhoff Andersen V, Chauvin C, Hémonic A, Käsbohrer A, Merle R, Alborali GL, Scali F, Stärk KDC, Muentener C, van Geijlswijk I, Broadfoot F, Pokludová L, Firth CL, Carmo LP, Manzanilla EG, Jensen L, Sjölund M, Pinto Ferreira J, Brown S, Heederik D and Dewulf J (2020) Monitoring of Farm-Level Antimicrobial Use to Guide Stewardship: Overview of Existing Systems and Analysis of Key Components and Processes. Front. Vet. Sci. 7:540. doi: 10.3389/fvets.2020.00540

The acknowledgment of antimicrobial resistance (AMR) as a major health challenge in humans, animals and plants, has led to increased efforts to reduce antimicrobial use (AMU). To better understand factors influencing AMR and implement and evaluate stewardship measures for reducing AMU, it is important to have sufficiently detailed information on the quantity of AMU, preferably at the level of the user (farmer, veterinarian) and/or prescriber or provider (veterinarian, feed mill). Recently, several countries have established or are developing systems for monitoring AMU in animals. The aim of this publication is to provide an overview of known systems for monitoring AMU at farm-level, with a descriptive analysis of their key components and processes. As of March 2020, 38 active farm-level AMU monitoring systems from 16 countries were identified. These systems differ in many ways, including which data are collected, the type of analyses conducted and their respective output. At the same time, they share key components (data collection, analysis, benchmarking, and reporting), resulting in similar challenges to be faced with similar decisions to be made. Suggestions are provided with respect to the different components and important aspects of various data types and methods are discussed. This overview should provide support for establishing or working with such a system and could lead to a better implementation of stewardship actions and a more uniform communication about and understanding of AMU data at farm-level. Harmonization of methods and processes could lead to an improved comparability of outcomes and less confusion when interpreting results across systems. However, it is important to note that the development of systems also depends on specific local needs, resources and aims.

Keywords: antimicrobial use, livestock, overview, indicator, benchmarking, monitoring, antimicrobial stewardship, antimicrobial resistance

INTRODUCTION

Antimicrobial resistance (AMR) is acknowledged as one of the main threats to human health worldwide. It is widely recognized that antimicrobial use (AMU) leads to the selection of resistant bacteria (1), and that animals may constitute one of the reservoirs of resistant bacteria and resistance genes (2–4). Recently, an association between the use of certain antimicrobials in animals and the occurrence of AMR in certain clinical isolates from humans has been shown (5–7). Consequently, reducing AMU in both humans and animals is an essential step toward limiting the prevalence of AMR in both humans and animals.

At the end of the previous millennium, the concept of antimicrobial stewardship (AMS) was established as a set of "responsible use" policy measures aimed at combatting AMR in human hospitals (8). AMS programs have since become common tools in human medicine (9). Following an increased focus on "One Health"; which emphasizes the interconnection between human, veterinary and environmental health, the need for more prudent use practices in veterinary medicine has become more widely accepted, i.e., using antimicrobials "only when necessary" and with treatment decisions based on the diagnosis, including pathogen and relevant resistance data (10).

Collection of reliable AMU data is crucial for the establishment of AMS programs and to measure their effectiveness. In veterinary medicine, major steps have been taken in many countries regarding the development and implementation of systems for collecting national sales data of antimicrobial medicinal products. At the European Union (EU)/European Economic Area (EEA) level, these data are collated by the European Surveillance of Veterinary Antimicrobial Consumption (ESVAC) project at the European Medicines Agency (EMA). The latest ESVAC report included sales data from 31 countries (11), having increased from nine countries in the initial ESVAC report (12). Data is provided voluntarily to ESVAC. In the future collecting data on the volume and use of antimicrobials will become mandatory for EU member states (13). The data published in ESVAC reports has been shown to be important for policymaking, including AMS at the national level, such as setting targets for reducing overall sales and, in particular, of critically important antimicrobials (CIAs). However, accurately determining AMU by animal species using sales data is complicated by the fact that VMPs are labeled for use in multiple species and often used off-label in other species. Furthermore, antimicrobial sales quantification typically does not take dosing differences between antimicrobials into consideration. Moreover, availability of reliable AMU data at the level of the end-user and/or prescriber or provider of the medicinal products (farmer, veterinarian, pharmacies, or feed mills), is vital for guiding farm- and/or sector-specific AMU practices (14–16), targeting unnecessary or inappropriate use, encouraging improvements in animal husbandry, disease prevention and control, and enabling detailed risk and trend analyses.

Many countries are at the initial or advanced stages of setting up systems for monitoring AMU at farm-level by animal species in all or some (food-producing) animal species. Setting up such systems involves various challenges to be faced and decisions to be made, for example, how to organize the data collection, the type and detail of the collected data, choice of indicators for reporting results, benchmarking criteria for acceptable or non-acceptable use, etc. The aim of this paper is to describe known farm-level AMU monitoring systems and discuss their key components and processes. This should provide support for establishing or working with a system and lead to a better implementation and evaluation of stewardship measures. Furthermore, it could be a step toward an improved understanding and sharing of knowledge as well as a more uniform communication across systems and countries. This would make it easier to identify and understand the effects of factors influencing AMU, such as animal health status, presence or absence of certain diseases, biosecurity levels, vaccination programs, historically developed practices, cultural differences, etc., and ultimately, AMR.

This paper was written within the framework of the AACTING project (a Global "network on quantification of Antimicrobial consumption in animals at farm-level and Analysis, CommunicaTion and benchmarkING to improve use"), which was funded by the Joint Programming Initiative on Antimicrobial Resistance (JPI-AMR, project number 270610). A detailed overview of the characteristics of the current systems in each country is available on the AACTING website[1].

OVERVIEW OF EXISTING SYSTEMS FOR AMU MONITORING AT FARM-LEVEL

As of March 2020, 38 active farm-level AMU monitoring systems (further referred to as "systems") from 16 countries were identified by the authors. **Figure 1** lists all systems, including inactive systems, by year of official implementation and, if applicable, stratifies them by animal species. The oldest systems are those of the Swedish Board of Agriculture (SBA) and the Danish VetStat monitoring tool. Since 2010, many new systems have been set up in many countries and several existing systems were extended to additional animal species. As shown in **Table 1**, pigs and broilers are most frequently monitored, followed by calves and dairy cows.

Three general features of the systems merit closer attention. The first is coverage, i.e., the proportion of the animal population included from the animal sector(s) targeted by a system. The identified systems can be divided into sample surveys ($N = 11$), partial coverage systems ($N = 15$), and full coverage systems ($N = 12$) (**Figure 1**). Full coverage systems aim to include all farms in an animal sector. Partial coverage systems include a substantial part of a sector, often on a non-random and possibly compulsory basis (e.g., adherence to a quality assurance scheme). For example, in the UK using the eMB-pigs system is a requirement under the farm assurance scheme "Red Tractor," which represents 94% of UK pig farms. Sample surveys target a small and ideally random and representative sample of a sector. Alternatively, stratified sampling can be applied and, by weighting the results by stratum, a representative result for AMU in a sector can be obtained. Sample surveys are often intended to estimate the AMU within the sector and/or can be pilots to gain knowledge for establishing monitoring systems with broader coverage. For example, the MARAN data collection system in the Netherlands was used as the basis for the sector quality assurance systems that at present provide full coverage AMU monitoring (17). Participation in these systems can be a requirement for farmers to allow access to certain markets or customers. The German "VetCab" sample survey was the pilot for the implementation of the module for AMU in the "HIT" system and is now used to collect data for detailed analyses and to test options for methodological changes (18). The "HIT" system collects AMU data for almost all food-producing animal farms (although selection criteria on farm size are applied for major fattening livestock species). In France, the "INAPORC" surveys will continue to be used until the "GVET" monitoring system is more widely implemented (19). In the Czech Republic, pilot schemes are currently being used to plan for the establishment of broader systems later. Furthermore, in Italy data from the national electronic prescription system, which became mandatory in May 2019, is currently under processing and it will be used to improve 2020 pharmacosurveillance controls in pigs, cattle, and poultry. Despite their relatively limited scope, sample surveys can inform decision making, ideally when a representative sample is reached. In Canada, for example, data from a sample of sentinel farms was used to eliminate the preventive use of ceftiofur and fluoroquinolones in the poultry sector, as well as to reduce the use of some nationally defined medically important antimicrobials (20).

A second general aspect of the systems is their main funder, being either "private" or "governmental." This is relevant for the "management role" in a system (i.e., who is operating the system?), as well as data ownership. **Figure 1** shows that most systems are primarily government funded. Some systems, e.g., CLIPP in France, are jointly funded by private organizations and the government. Private organizations include quality assurance organizations, industry levy boards, or professional bodies.

When combining coverage and funding, it appears that the government is the main funder for most sample survey and full coverage systems. In contrast, private organizations are the main funders of almost all currently existing partial coverage systems. These systems generally target only farms that adhere to the respective quality assurance scheme and/or professional bodies.

The third general aspect, linked to coverage and funding, is the participation in the system, which can be "voluntary" or "compulsory" (**Figure 1** and **Table 1**). Most systems with full coverage are compulsory, primarily by law/regulations. Several partial coverage systems are also compulsory as a requirement of quality assurance schemes. Caution should be exercised when interpreting data or extrapolating results from voluntary systems as these may represent the more conscientious and proactive farmers, and usually cannot be regarded as being representative of the population at large.

ANALYSIS OF KEY COMPONENTS AND PROCESSES OF MONITORING SYSTEMS FOR FARM-LEVEL AMU

Four key components were distinguished for farm-level AMU monitoring systems: (1) data collection and quality control, (2) data analysis, (3) benchmarking, and (4) reporting.

Data Collection and Quality Control

Data collection includes the process of entering raw data into the data collection system. Within the specific scope of monitoring farm-level AMU data, some aspects are particularly relevant.

At least two types of data need to be collected per identified farm: use data (also referred to as the "numerator," see section "Data analysis") and the animal population to standardize the use data (also referred to as the "denominator," see section "Data analysis"). Use does not always constitute real administration of antimicrobials to animals; prescriptions, deliveries or sales at farm-level are often the only convenient data-source in practice. It is essential to record the time of use or date of delivery, in order to allocate the AMU to a certain time interval (see section "Benchmarking").

[1] www.aacting.org

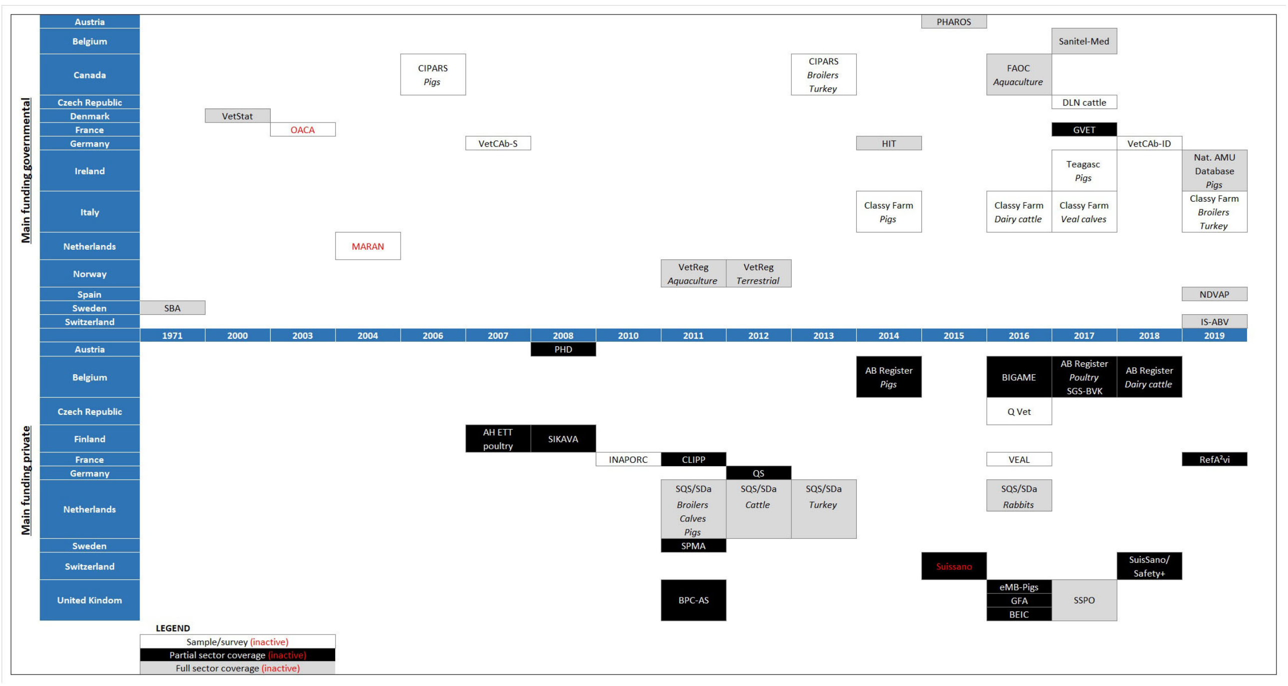


FIGURE 1 | Data collection systems in each country, shown by start year of data collection and divided according to the coverage of the sectors included in each system (see "LEGEND"). A species below a system name is to indicate that the species was included in the system from that year on; no species indicated has no specific meaning—see further in the text for information on which species are covered in each system.

Data collection can be automatic or manual. The former means the data are delivered digitally through software-linked data sources, e.g., from veterinary practice or farm management software, while the latter requires the data to be actively entered, e.g., by typing into an online interface, using prescription sheets, medicine books, as the data source. A pragmatic approach for data input is to offer both an automatic and a manual option. Automatic input will reduce the risk of typing errors and will significantly reduce the administrative burden for the parties providing the data. However, automatic input and transfer may require investment, training, and an adjustment of existing software. Manual input and transfer may therefore be offered as an alternative. In addition, if mistakes occur, manual correction of the automatic data input should be possible. When allowing manual retrospective corrections, a time-lock for accepting such changes should be considered, after which data entry cannot be altered by primary users. Allowing traceability of subjects uploading as well as altering the data is also considered useful. Data input in general (including "new" data) could be subjected to a time-lock, after e.g., a 1-year period. This may trigger users to frequently interact with the system and prevents continuous changes in the outcomes of the analyses, which is not desirable as the data might also be used for trend analysis and future calculations of AMU indicators. Note that a time-lock should not preclude correction of data errors. System administrators should always have the possibility to correct data errors, e.g., when obvious discrepancies are identified, and data quality could be considerably improved. In addition to using a time-lock, a logging system will be indispensable for enabling follow-up of the data-input. Data logs are useful for retrieving facts and figures for later analyses and for quality assurance.

To minimize the risk of data manipulation, careful consideration is required when determining which parties are authorized to alter the data, and which changes are allowed. Authority for alterations could, for example, be given only for data that the party has provided. Additionally, or alternatively, "party-over-party" checks could be required before accepting changes. For example, if the veterinarian provides the number of medication packages delivered and the farmer is permitted to make changes to that number, then the system might require final approval from the veterinarian. By imposing quality checks upon data input, the need to alter data at a later stage—and possible problems associated with such changes (e.g., changed benchmarking results)—might be avoided or minimized. This can be done by defining mandatory information to be included and running plausibility checks before the dataset can be submitted. Requiring active confirmation of a farmer that their data are correct might also be an option. This approach is particularly relevant for parties that actively register zero AMU, in order to distinguish true zero-users from farms with incorrect data or non-active farms. In the Belgian AB Register, farms that do not report any use over a certain period, without confirming this, are targeted by certified control agencies.

A quality check can also be implemented after sending the data. Standard quality measures should include plausibility

TABLE 1 | Core characteristics of the currently existing systems for farm-level data collection of antimicrobial use data.

Country[a]–system		Collection														
		Animal type[b]													Input of AMU data[c]	Compulsory by[d]
Austria	PHAROS	Pi	Da	Be	Ca	Br	La	Tu	Go	Sh					Vet	Legislation
Austria	PHD					Br	La	Tu							Vet	QAS
Belgium	AB Register	Pi	Da			Br	La	Tu							Vet·FM·PH	QAS
Belgium	BIGAME	Pi	Da	Be	Ca	Br	La		Go	Sh					Vet	QAS · voluntary
Belgium	Sanitel-Med	Pi			Ca	Br	La								Vet	Legislation
Belgium	SGS-BVK				Ca										Vet	QAS
Canada	CIPARS	Pi				Br		Tu							Farmer·Vet	NA: survey
Canada	FAOC											Fi			Farmer	Legislation
Czech Republic	DLN cattle		Da												Farmer·Vet	NA: voluntary
Czech Republic	Q VET pigs	Pi													Farmer	NA: voluntary
Denmark	VetStat	Pi	Da	Be	Ca	Br	La	Tu	Go	Sh		Fi		Ot: Mi	Vet·FM·PH	Legislation
Finland	AH ETT poultry					Br		Tu							Vet	NA: voluntary
Finland	SIKAVA	Pi													Farmer·Vet	QAS
France	CLIPP													Ot: Ra	Farmer·Vet·TN	NA: voluntary
France	GVET	Pi													Farmer	NA: voluntary
France	INAPORC	Pi													Farmer·Vet·FM·TN	NA: survey
France	RefA²vi					Br		Tu						Ot: **	Farmer·Vet	NA: voluntary
France	VEAL				Ca										Farmer·Vet	NA: voluntary
Germany	HIT	Pi		Be	Ca	Br		Tu							Farmer·Vet	Legislation
Germany	QS	Pi			Ca	Br		Tu						Ot: Du	Vet	QAS
Germany	VetCAb-ID	Pi	Da	Be	Ca	Br	La	Tu	Go	Sh	Ho	Fi	Pe	Ot	Not specified	Not specified
Germany	VetCAb(-S)	Pi	Da	Be	Ca	Br									Farmer·Vet	NA: survey
Ireland	Teagasc	Pi													TN	NA: survey
Ireland	Nat. DB pigs	Pi													Farmers	QAS
Italy	ClassyFarm	Pi	Da		Ca	Br	La	Tu							Researcher	NA: survey
Netherlands	SQS|SDa	Pi	Da	Be	Ca	Br		Tu						Ot: Ra	Vet	QAS
Netherlands	SDa*								Go	Sh	Ho		Pe	Ot: Mi	Vet	NA: survey
Norway	VetReg	Pi	Da	Be	Ca	Br	La	Tu	Go	Sh	Ho	Fi	Pe	Ot: De	Vet·FM·PH	Legislation
Spain	NDVAP	Pi	Da	Be	Ca	Br	La	Tu	Go	Sh	Ho				Vet	Legislation
Sweden	SBA	Pi	Da	Be	Ca	Br	La	Tu	Go	Sh	Ho	Fi		Ot: #	Vet	Legislation
Sweden	SPMA					Br									Vet	QAS
Switzerland	IS ABV	Pi	Da	Be	Ca	Br	La	Tu	Go	Sh	Ho	Fi	Pe	Ot: Ra	Vet	Legislation
Switzerland	SuisSano|Safety +	Pi													Farmer	QAS
United Kingdom	BEIC						La								Farmer	QAS
United Kingdom	BPC-AS					Br		Tu						Ot: Du	Vet	PB
United Kingdom	eMB-Pigs	Pi													Farmer·Vet·FM	QAS
United Kingdom	GFA													Ot: Ga	Vet·FM	NA: voluntary
United Kingdom	SSPO											Fi			Vet	NA: voluntary

(Continued)

TABLE 1 | Continued

Country[a]–system		Analysis[e]			Benchmarking[f]		Reporting at farm level (Y/N)[f]
		Weight-based	**Dose-based**	**Count-based**	**Y/N**	**Parties**	
Austria	PHAROS	–	DDDvet	–	Y	(Farmers) Vets	N
Austria	PHD	mg	–	Herds	Y	Farmers	Y
Belgium	AB Register	–	$DDDA_{bel}$	–	Y	Farmers	Y
Belgium	BIGAME	mg/kg	$DDDA_{bel}$	–	Y	Farmers	Y
Belgium	Sanitel-Med	mg/kg	$DDDA_{bel}$	–	Y	Farmers·Vets	Y
Belgium	SGS-BVK	–	$DDDA_{bel}$	–	Y	Farmers	Y
Canada	CIPARS	mg/PCU	DDDvetCA	Flocks/herds	N		Y
Canada	FAOC	mg			N		Y
Czech Republic	DLN cattle	mg	–	–	Y	Farmers	Y
Czech Republic	Q VET pigs	–	ADD	–	Y	Farmers	Y
Denmark	VetStat	–	ADD	–	Y	Farmers	Y
Finland	AH ETT poultry	–	–	Flocks	N		N
Finland	SIKAVA	–	–	–	(Y)		N
France	CLIPP	–	–	Days	Y	Farmers	Y
France	GVET	mg	UDD·UCD·DDD (vet) ·DCD(vet)	Days/animals	Y	Farmers	Y
France	INAPORC	mg	DDD(vet)·DCD (vet)	–	N		Y
France	RefA^{2}vi	–	DDD_{FR}·DCD_{FR}	–	N		Y
France	VEAL	mg/animal	DCD_{FR}	Days/animals	N		Y
Germany	HIT	–	–	Days/animals	Y	Farmers	Y
Germany	QS	–	–	Days/animals	Y	Farmers	Y
Germany	VetCAb-ID	–	–	Days/animals	N		N
Germany	VetCAb(-S)	–	–	Days/animals	N		Y
Ireland	Teagasc	mg/kg	–	–	Y	Farmers	Y
Ireland	Nat. DB pigs	mg/kg	–	–	N		Y
Italy	ClassyFarm	–	$DDDA_{IT}$	–	Y	Farmers	Y
Netherlands	SQS|SDa	–	$DDDA_{NL}$	–	Y	Farmers·Vets	Y
Netherlands	SDa*	–	$DDDA_{NL}$	–	N		N
Norway	VetReg	mg	–	–	N		N
Spain	NDVAP	mg	–		N		N
Sweden	SBA	–	–	–	N		N
Sweden	SPMA	–	–	Flocks	N		N
Switzerland	IS ABV	–	PDD·DDDvet·DCDvet	Animals	(Y)	Farmers·Vets	(Y)
Switzerland	SuisSano|Safety +	–	DCDvet·DCD_{CH}	Animals	Y	Farmers	Y
United Kingdom	BEIC	–	ADD	–	N		N
United Kingdom	BPC-AS	mg/kg	–	–	N		N
United Kingdom	eMB-Pigs	mg/kg	–	–	Y	Farmers	N
United Kingdom	GFA	mg	–	–	N		N
United Kingdom	SSPO	mg/kg	–	–	N		N

[a] *AT, Austria; BE, Belgium; CA, Canada; CH, Switzerland; CZ, the Czech Republic; DE, Germany; DK, Denmark; FI, Finland; FR, France; IE, Ireland; IT, Italy; NL, the Netherlands; NO, Norway; SE, Sweden; SP, Spain; UK, United Kingdom.*

[b] *Pi, pigs; Da, dairy cattle; Be, beef cattle; Ca, calves (veal and/or conventional); Br, broilers; La, laying hens; Tu, turkeys; Go, goats; Sh, sheep; Ho, horses; Fi, fish; Pe, pets; Ot, other, which can be De, (rein)deer; Du, ducks; Ga, game birds; Mi, mink; Ra, rabbits; in case of the SBA system in Sweden, # stands for geese, ostriches, mink and reindeer, *stands for all poultry production species including duck, guinea fowl, pigeon.*

[c] *Vet, veterinarian; FM, feed mills; PH, pharmacies; TN, technician.*

[d] *NA, not applicable; PB, Professional Body; QAS, quality assurance scheme.*

[e] *ADD, animal daily dose; $DDDA_{bel}$, defined daily dose for animals as defined for Belgium; DCD_{CH}, defined daily dose for animals as defined for Switzerland; DCD_{IT}, defined course dose for animals as defined for Italy; DDD_{FR}/DCD_{FR}, defined daily/course dose for animals as defined for France; $DDDA_{NL}$, defined daily dose for animals as defined for the Netherlands; DDDvet/DCDvet, defined daily/course dose for animals as defined by EMA (EMA, 2015); DDDvetCA, defined daily dose for animals as defined for Canada; PCU, population correction unit, as defined by EMA (EMA, 2011); PDD, prescribed daily dose; UCD, used course dose; UDD, used daily dose; DCD, defined course dose.*

[f] *Y/N, yes/no; (Y), planned for the (near) future.*

checks of whether the reported variables are within the expected range, whether the identification numbers of core-variables are unique and whether the combination of categories is valid. In the latter case, for example, age groups, and disease groups should match the intended animal species, e.g., weaners should always be recorded in the animal category "pig" while the disease "goldfish ulcer disease" should only apply to "fish." By processing the data into the anticipated result or by cross-checking with corresponding information in other databases or previous submissions, suspected mistakes can also be identified. After this checking step, validation should be requested, for example, by requiring additional (manual) confirmation or requiring input of the corrected data instead. For example, in the Netherlands, quality systems are notified of outliers by the Netherlands Veterinary Medicines Institute, and confirmation or correction is requested.

Use Data

For use data some specific aspects apply. Restricting and/or standardizing the options per input field will help to improve data quality. For example, in the Netherlands, a template is sent to the respective sector quality systems, which states the variables to be reported and their range. In the French "GVET" system, drop-down lists are included in the software and farmers select the veterinary medicinal products from a standardized list of all products authorized in France, where all medicines are linked with a unique identifier. They then choose one of the pre-set units of dosage (g/animal or g/100 kg of body weight for example) and there are also lists for other treatment characteristics (dates of administration, duration, indication, etc.). A similar approach is used in the Swiss system "IS-ABV." The variables collected for the use data are dependent on the AMU indicator being calculated (see section "Data analysis"). As an example, the variables required in the Netherlands for the use data include the farm identification number, the delivery date of the antimicrobials, the European Article Number (EAN) of the antimicrobial and the number of packages delivered. The EAN is an identification number which is unique for every antimicrobial sold. In a database all antimicrobials used in livestock are recorded. This database also contains information on dosages (by animal species), administration routes, antimicrobial class, active ingredient(s), etc.

Animal Population Data

Depending on the AMU indicator being calculated, different types of animal population data can be collected (see section "Data analysis"). Within animal species, several animal categories can be distinguished to further refine AMU monitoring. For example, in Denmark and the Netherlands, three animal categories are defined for pigs: sows and piglets, weaned piglets and finishing pigs (21, 22). Animal population data per farm can be obtained internally or externally. Internally means that the data are collected specifically for the purpose of analyzing AMU data. For example, the monitoring system might require a farmer to provide the number of animals present (by production category) on his or her farm or the veterinarian might be required to record the number of animals on the farms visited. Regular inspections to obtain animal counts are also a possibility.

Externally acquired population data originate from sources established for purposes other than analyzing AMU data, typically not owned or managed by the AMU monitoring system, such as animal population data collected for epidemiological surveillance, for allocation of grants or for manure accounting. In the French GVET, for example, data from "GTE" is used, another French system whose goal is to yield technical-economic results to farmers. Data of produced biomass might also be obtained from slaughterhouses, which would have to register the number of animals slaughtered by farm. To improve data quality and for data management in general, it is advisable to minimize the number of "external" data sources. However, in many of the existing systems, animal population data are provided from external sources. In several systems, this is known to cause problems with retrieving updates or resolving problems in a timely manner. For example, in the Netherlands animal population data retrieved from the Central Board of Statistics were not always in line with animal population data collected by livestock sectors. Also updates in animal population data occurred after the annual report on AMU in the Dutch livestock sectors, leading to corrections in AMU figures after publication of the report. In Belgium, the SANITEL database for identification and registration of food producing animals does not contain animal numbers of all animal categories monitored in the AMU data collection systems. Furthermore, for several farms, SANITEL data are found to be incomplete or not up-to-date.

Additional data can be collected to allow for more detailed analysis and refined AMS. For example, use by animal production stage or type, the weight at treatment, indication(s) for treatment, and/or the prescribing veterinarian, type of administration (e.g., treatment, metaphylaxis, and prophylaxis) etc. However, the requested input should be of relevance to the analyses that will be carried out. Requesting too much or too detailed information will result in an unnecessarily high workload for the data provider and might lead to a subsequent lack of engagement.

It is also important to consider whether the data requires transformation prior to calculating AMU. For example, data on use of feed mixed with antimicrobials can be obtained directly by requesting the amount of premix delivered/mixed into the feed, or by requesting the amount of medicated feed delivered while also providing information on the concentration of premix in the medicated feed. Requesting untransformed data ensures a uniform calculation of AMU and is therefore preferred.

More practical information on data collection is provided in the guidelines (see AACTING website).

Data Analysis

Data analysis is conducted to establish the farm-level AMU. Three important aspects of this calculation exist: selection of unit of measurement (UM), the animal population at risk (or denominator) and the indicator (**Tables 1** and **2**).

Unit of Measurement

The UM is the unit in which the numerator is expressed. It can be mass-based, dose-based or count-based. Mass-based UMs express the numerator as milligrams, kilograms or tons (i.e., metric tons) of the active substance. Dose-based UMs express the numerator as the number of doses with several types being distinguished, e.g., defined daily dose animal (DDDA), used daily dose animal (UDDA), prescribed daily dose animal (PDDA), or defined course dose animal (DCDA) [(23–25); **Table 2**]. Typically, a dose-based UM is calculated from the amount of active ingredient using a mass-based UM. For example, if two 250 ml bottles of a medicinal product with one active antimicrobial substance at a concentration of 80 mg/ml have been used, a mass-based numerator indicates that 40,000 mg of active substance has been used. If these bottles have been used according to a prescription stating 8 mg/kg bodyweight per day, then a corresponding dose-based numerator indicates 5,000 PDDAs have been used (40,000/8 = 5,000).

For a count-based UM, the numerator can express the number of treatment days or treatment courses. Using the example above, if the medicinal product was used to treat a batch of 100 animals for 5 days, then the numerator would be 500 treatment days or 100 treatment courses. Hence, a count-based UM does not require data on the actual amount of antimicrobials used. It is worth noting that if, in the example given, each animal weighed ∼10 kg and the prescribed dose of 8 mg/kg bodyweight per day was given, then this will correspond to a mass-based numerator of 40,000 mg of active substance used (100*10*5*8 = 40,000) and a dose-based numerator of 5,000 UDDAs (40,000/8 = 5,000). These examples illustrate that, although they have a different meaning, mass-, dose- and count-based UMs are interlinked.

The value, meaning, usefulness and complexity of defining and using (dose-based) UMs for the quantification of veterinary AMU have been addressed before (25). At EU level, (23) published a list of standardized Defined Daily Doses (DDDvet) and Defined Course Doses (DCDvet) for pigs, poultry and cattle, defined at the level of active ingredient and administration route and based on the Summary of Product Characteristics (SPC) for products authorized for that period in nine European countries (26). **Table 1** illustrates the variety of UMs that are used. The choice of UM is highly dependent on the context (data availability, resources, surveillance objectives, etc.).

When working with mass-based UMs, farm-level AMU can appear to have improved by switching to medicinal products with a lower dose rate, whereas the level of animal exposure to antimicrobials may not have changed. Besides a lack of clarity around which species was treated, this is one of the main limitations of sales data. This is particularly true for some highest priority CIAs for human medicine, such as third and fourth generation cephalosporins, the use of which should be reduced in veterinary medicine.

When basing the analysis on the PDDA, automatic data input is only feasible if prescriptions are digitalized, which may require additional investment. Moreover, if the prescription does not specifically mention the dose in, for example, mg of active substance per kg bodyweight or mg of active substance per animal, the number of PDDA will require the data to be transformed first, particularly if an in-feed or in-water regimen is prescribed.

The UDDA can be calculated from administration data (treatment written/electronic treatment logbooks) and will, by definition, yield the most accurate reflection of the AMU on the farm. Depending on individual country regulations, working with the UDDA will often require the farmer/attending veterinarian to have a role in data input, either as a sole provider of the use data or for validating deliveries or prescriptions provided by another party (vet, feed-mill, etc.) based on what was actually used on farm. Count-based data, which are comparable to UDDA-based data in terms of outcome, can be determined from prescriptions, deliveries, as well as administration data and need input from farmers on what was really used for how many days and in how many animals.

If the intention is to be able to cross-check farm-level data with sales data on a national level, which are almost always mass-based, it must be possible to deduce the used mass of antimicrobials from the farm-level AMU data.

Denominator: The Animal Population

No matter what type of UM is used, the UM needs to be divided by a proxy for the targeted animal population to obtain comparable results. Different types of population data can be used, affecting the resulting indicator (25, 27).

The animal population is expressed as the mass of animals present over a defined period. This is either described as the biomass produced or the (average) mass of animals housed or a combination of both.

Biomass Produced

This can be based on the actual mass of meat produced or on the number of animals slaughtered multiplied by an estimated or standardized weight (standardized weights are discussed further in the text). For the calculation of farm-level AMU per year, it must be kept in mind that a denominator based on produced biomass does not reflect the true animal population at risk of antimicrobial treatment if multiple production cycles exist during that year. This is because slaughtered animals in high producing livestock sectors (such as swine and poultry), with multiple production cycles per year, have been at risk for antimicrobial treatment during their lifespan which is shorter than a year. This becomes evident when comparing AMU with species with longer production cycles (such as cattle) and/or countries where different farming practices apply (28). Therefore, biomass produced is not an appropriate denominator if the aim of a system is to calculate treatment incidences or frequencies at farm-level (estimating true exposure to antimicrobial treatment, see section about The Indicator). In contrast, it can be a useful denominator if, for example, the system aims for trend monitoring, e.g., for sector-level reduction targets, as exemplified by successful AMU reductions achieved in the UK (29). Also, if the aim is to compare AMU within a livestock sector per production cycle the biomass can be an appropriate denominator.

(Average) number or mass of animals at risk of treatment

The number of animals housed can be based on the maximum capacity of the barns (the maximum number of animals present on a farm), the number of animals present on average or the number of animals present at a given moment. This number of animals housed is then multiplied by an estimated or standardized weight in systems that use mass- and dose-based indicators. In contrast to produced biomass, the (average) number or mass of animals housed on farm is a suitable representation of the animal population at risk of antimicrobial treatment, hence, allows for calculation of treatment incidences or frequencies. The more the (average) number or mass of animals housed corresponds to the true number or mass of animals present at the time of treatment, the more accurate the calculation of exposure to AMU will be. To calculate this figure, capacity numbers are the least precise and accuracy increases when using stocking numbers, which need to be measured regularly.

Several options exist to determine the standardized or estimated weights that are used to establish the denominator (Estimated) liveweight at treatment will yield more precise results than an average weight (in a specific age category). For many animal categories, it is known that most antimicrobial treatments occur in the early stages of the animal's life (30–32). The estimated weight at treatment can be standardized, as suggested for example by EMA (EMA, ESVAC reflection paper 2013) and estimated standardized weights are applied in many countries (e.g., Belgium, the Netherlands, Denmark, United Kingdom). However, due to differences in production systems between countries and farms, animal weights at treatment might differ substantially and standardized weights may therefore be country- and livestock sector-specific. The estimated weight at treatment can also be determined based on age of the animal and a corresponding growth curve. This method will increase workload but will more accurately represent the animal liveweight at risk of antimicrobial treatment and will thus lead to more precise characterization of AMU.

For count-based systems, no weight is needed as either the UM is not reflecting the individual animals (i.e., number of farms using the drug is the UM) or the number of animals at risk is used in the calculation method. Kasabova et al. recently showed that differences in the weights used to calculate the population at risk have a substantial impact on the calculated AMU (31).

If the number of days at risk (i.e., the number of days each animal is present at the farm) is included in the denominator, i.e., the time interval during which AMU is assessed, the result will be a treatment incidence (33). The period at risk of treatment should correspond to the animal population at risk and to the period during which the numerator data are collected. As an example, if considering AMU over 1 year, the corresponding period at risk should be 1 year. In Denmark and Belgium 100 animal-days are used which is a proxy for the percentage of time an average animal is treated or the percentage of animals that are treated daily with one substance. In the Netherlands, the number of days an animal was treated in a year is calculated, which might be particularly useful for animals, such as dairy or beef cattle, with a longer production cycle.

The Indicator

The indicator is a technical unit used to quantify exposure to antimicrobials. Depending on the UM and the other parameters included in the calculation, different indicators will be obtained (23, 25, 27, 34). **Tables 1**, **2** illustrate the variety of indicators used in the different existing monitoring systems. Use of a mass-, dose-, or count-based UM will, respectively, lead to a mass-based indicator, such as mg/kg biomass or mg/PCU (population correction unit), a dose-based indicator, such as number of DDDA/1,000 animals produced or number of DDDA/animal year, or a count-based indicator, such as the treatment frequency. As indicated in **Table 1** most indicators included here are dose-based, a minority are mass-based, and some count-based indicators are calculated.

The choice of the indicator impacts on the interpretation of AMU monitoring results. However, deciding on which AMU indicator to use can be complex, given the range of existing options. The guidelines on the AACTING website highlight various aspects to consider when deciding which indicator to use for AMU monitoring.

Benchmarking

Benchmarking of AMU refers to the comparison of a party's AMU with the AMU of similar parties (the reference population), given that AMU for all parties is quantified in a comparable manner. To the authors' knowledge, benchmarking is currently carried out—or planned to be carried out as soon as good quality data are available and a methodology is developed—in 12 countries, encompassing 20 AMU monitoring systems (**Tables 1**, **2**). Most existing AMU monitoring systems benchmark farmers; three systems benchmark veterinarians (**Table 1**).

Benchmarking is performed with a certain frequency (for example, twice a year) and takes AMU within a certain time interval (for example, the preceding year) into consideration. The shorter the production cycle of the animal species or animal category for which the AMU is benchmarked, the greater the relevance of a high benchmarking frequency. The time interval should depend on the expected influence of recurring events (for example, seasonal influences) and needs to find a balance between allowing for frequent reporting of the benchmarking indicator (short time interval) and obtaining a longer-term view of AMU (long time interval). A longer time interval may be useful to achieve more sustainable use practices but could lead to issues with perceived "fairness" or "relevance" of the score if antimicrobial use distant in time still impacts the current benchmarking result.

Various aspects of AMU can be benchmarked using different indicators. A starting point at farm-level is the total AMU on the farm (per species or, if different age/weight categories of a species are present, per production stage). Furthermore, various qualitative aspects of AMU can be benchmarked, e.g., the use of certain classes or categories of (critically important) antimicrobials, the type of treatment [e.g., veterinary medical use vs. non-veterinary medical use (35)], the route of administration (e.g., oral, parenteral, and intramammary). It might be advisable not to benchmark too many aspects, as multiple benchmarking results for a single species (category) might become confusing and end up being counterproductive, especially if the results appear contradictory.

The reference population can be based on geography (e.g., country, region), economic traits (e.g., sector, quality assurance

TABLE 2 | Overview of count- and dose-based indicators calculated by different systems for analyzing AMU at farm-level.

Country[a]	System(s)	Type[b]	Indicator[c]	Formula of indicator[c,d]
Austria	PHAROS	Dose based	DDDvet/kg/year	mg AB used/DDDvet × n animals at risk × kg standard weight
	PHD	Count based	TH/UTH	n treated herds/n untreated herds
Belgium	All	Dose based	TD_{100}	(mg AB used/$DDDA_{bel}$ × kg animal at risk × n days at risk) × LA – factor × 100
	Sanitel-Med	Dose based*	Contract score	$\left[(\%\ \mathit{green\ ACU} \div 2) - (\%\ \mathit{red\ ACU} \div 2) + 0,5\right] \times 100$
Canada	CIPARS	Count based	pp TF|H	n treated flocks | herds/total n flocks | herds
		Dose based	DDDvetCA/PCU	$\left(\frac{\text{Milligrams active ingredient/DDDvetCA}_{mg/kg/day}}{\text{Total animals} \times \text{Standard weight at treatment}}\right)$
			DDDvetCA/1000 AD	$\left(\frac{\text{Milligrams active ingredient/DDDvetCA}_{mg/kg/day}}{\text{Total animals} \times \text{standard weight} \times \text{days at risk}}\right) \times 1,000$
Switzerland	IS ABV	Count based	ATI	n treated animals × n treatment days × n substances/n animals per year
		Dose based	Treatment intensity	(mg AB used/DDD_{vet} or DDD_{CH} × kg animal at risk × n days at risk) x 100
	SuisSano | Safety+	Count based	ATI	n treated animals × n treatment days × n substances/n animals per year $^{*LA\ Factor*}$HPCIA Factor
		Dose based	DCDvet/animal/year	(mg AB used/DCD_{vet} × standard weight × n animals at risk per year)
			DCD_{CH}/animal/year	(mg AB used/DCD_{CH} × standard weight × n animals at risk per year)
The Czech Republic	Q VET pigs	Dose based	ADD/100 animal-days	
Germany	HIT	Count based	Treatment frequency	n treated animals × n treatment days × n substances/n animals per day
	QS	Count based	Therapy index	n treated animals × n treatment days /total animal capacity
	VetCAb	Count based	Treatment frequency	n treated animals × n treatment days × n substances/total animal capacity
Denmark	VetStat	Dose based	ADD/100 animal-days	(mg AB used / technical daily dosage (ADD) × kg animal at risk × n days at risk) × 100
Finland	AH ETT poultry	Count based	pp TF	n treated flocks/total n flock
France	CLIPP	Count based	IFTA	$\sum_{t=1}^{z}$ (n treament days × n substances)$_t$/ n days in reproduction cycle or rearing period ↳ With t = the number of treatments
	GVET	Count based	Treatments/animal	$\sum_{t=1}^{z}$(n treated animals)$_t$/n animals at risk ↳ With t = the number of treatments
			Treatment days/animal	$\sum_{t=1}^{z}$(n treated animals × n treatment days)$_t$/n animals at risk ↳ With t = the number of treatments
	GVET | INAPORC	Dose based	CD/animal	mg AB used/$DCDA_{FR}$ × kg animals at riskn animals at risk
			DD/animal	mg AB used/$DDDA_{FR}$ × kg animals at risk/n animals at risk
	RefA²vi	Dose based	DDD_{FR}/kg slaughtered	mg AB used/DDD_{FR}/kg animals slaughtered
			DCD_{FR}/kg slaughtered	mg AB used/DCD_{FR}/kg animals slaughtered
	VEAL	Count based	Treatments/animal	$\sum_{t=1}^{z}$ (n treated animals)$_t$/n animals at risk ↳ With t = the number of treatments
			Treatment days/animal	$\sum_{t=1}^{z}$ (n treated animals × n treatment days)$_t$/n animals at risk ↳ With t = the number of treatments
		Dose based	ALEA	mg AB used/$DCDA_{FR}$ × n animals slaughtered × standard weight
Italy	ClassyFarm	Dose based	DCD_{IT}/animal/period	mg AB used /$DDDA_{IT}$ × kg animals at risk
The Netherlands	SQS/SDa	Dose based	$DDDA_{NL}$/yr	kg treatable animals/kg animals at risk
		Der	VBI	AUC of ln-transformed ratio $DDDA_{nl}$/yr and applicable thresholds over all 1-on-1-farms
Sweden	SPMA	Count based	pp TF	n treated flocks/total n flocks
The United Kingdom	BEIC	Count based	ADD/100 animal-days	
	BPC-AS	Mass based	mg/kg	mg AB used/kg animals at risk
	eMB-Pigs	Mass based	mg/kg	mg AB used/kg animals at risk
	SSPO	Mass based	mg/kg	mg AB used/kg animals at risk

[a] *AT, Austria; BE, Belgium; CA, Canada; CH, Switzerland; CZ, the Czech Republic; DE, Germany; DK, Denmark; FI, Finland; FR, France; IT, Italy; NL, the Netherlands; SE, Sweden; UK, United Kingdom.*

[b] **Derived from (dose-based) farm-level benchmarking results.*

[c] *ADD, animal daily dose; ATI, (animal treatment index); ALEA, Animal Level of Exposure to Antimicrobials; CD, course dose; DD, daily dose; DCD_{CH}, defined daily dose for animals as defined for Switzerland; DCD_{IT}, defined daily dose for animals as defined for Italy; DDD_{FR}/DCD_{FR}, defined daily/course dose for animals as defined for France; $DDDA_{NL}$, defined daily dose for animals as defined for the Netherlands; DDDvet/DCDvet, defined daily/course dose for animals as defined by EMA (EMA, 2015); DDDvetCA, defined daily dose for animals as defined for Canada; IFTA, Index of Frequency of Treatments with Antibiotics (number of treatment days related to rearing period); PCU, population correction unit, as defined by EMA (EMA, 2011); pp, proportion; TF\|H, treated flocks \| herds; UTH, untreated herds; VBI, Veterinary Benchmark Indicator.*

[d] *AB, active substance of an antibiotic; ACU, animal category unit, representing a single farm-level benchmarking result, with green being low use (= below the lower threshold as defined in the specific system) and red high use (above the higher threshold as defined in the specific system); AUC, area under the curve; $DDDA_{bel}$, defined daily dose for animals defined at Belgian national level; LA-factor, long-acting factor; the technical daily dosage is based on the ADD principle, where each registered antimicrobial product in Denmark is assigned a specific dosage.*

scheme), animal traits (e.g., species, age/weight category), or simply on selection criteria and the willingness of parties to co-operate (e.g., in a research study). In practice, combinations often occur, e.g., benchmarking within a group of farms adhering to a certain quality assurance scheme and raising fattening pigs. In systems with only partial coverage, special attention should be paid to defining the reference group to avoid drawing conclusions based on a few farms or particular farm types.

The more relevant the chosen reference group, the more practically useful benchmarking will be. For instance, in veal calves, it might be decided to benchmark among veal calf farms in general. Making a further distinction between production stages/types, for example starters and finishers or rosé and white veal farms (if applicable) might add important nuances to the result (36). However, defining too many reference groups, each with their own thresholds for (un)acceptable use, can be counterproductive. For example, if reference groups are chosen according to farm management characteristics (e.g., weaning age in pigs, breed), high use caused by using a vulnerable breed that is more prone to infectious diseases might be deemed acceptable by the benchmarking system.

Two types of benchmarking can be distinguished: "dynamic" and "fixed" benchmarking. We define "dynamic benchmarking" as a methodology where the benchmarking result depends on the distribution of AMU in the reference population. Ranking a party within the reference population (e.g., farm X is at the 40th percentile) is one form of dynamic benchmarking. Another is using one or more threshold values derived from the distribution of AMU in the reference population (e.g., the median and the 75th percentile) and categorizing farms relative to these thresholds. In contrast, "fixed benchmarking" uses reference values that do not (always) reflect the distribution of AMU in the reference population. Such threshold value(s) are typically set for a long(er) period. Generally, the distribution of AMU in the reference population is used to initially set or adjust the fixed threshold(s). However, "politically" motivated thresholds are also used, i.e., thresholds that are not related to the current distribution of use but state a fixed reduction target, e.g., reduction by 20% over a certain period.

Dynamic benchmarking is applied, for example, in Belgium and Germany, and the systems involved apply two threshold values. In Denmark, fixed benchmarking with one threshold is applied. This is also the case in the Netherlands, the latter having evolved recently from a fixed benchmarking method using two threshold values to now using only one. In Belgium, the pig sector has recently started working with fixed benchmarking with two threshold values.

A farm-level AMU distribution is in most cases right-skewed, with a long tail toward the high-user end of the distribution (22). For this reason, using the arithmetic mean AMU as a reference or threshold value may not be ideal. Therefore, the median value is often used as the lower threshold, for example, in Belgium and Germany. As the upper threshold, the third quartile (75th percentile) is used in Germany and the 90th percentile in Belgium.

Fixed benchmarking does not mean the threshold values will never change. Adaptations of thresholds according to changes in use or changes in policy are advisable. As described above, the Netherlands recently revised their threshold values, as the original benchmark values were no longer deemed to provide enough incentive to further reduce AMU in several livestock sectors (37). In Denmark, the threshold values have been revised five times since they were launched in 2010 (21). Furthermore, a differentiated benchmarking strategy was implemented in 2016, with certain antimicrobial classes being weighted with higher factors in the quantification of AMU in this country.

An advantage of dynamic benchmarking is that it is more difficult for the benchmarked parties to circumvent prudent usage policies by strategic changes in their AMU to comply with the threshold values. Dynamic values ensure that constant pressure is sustained for parties to keep reducing their AMU. However, this might have a discouraging effect, as reducing AMU does not necessarily mean that a party will reach a level below the threshold, because the threshold may have been lowered as well. A challenge of dynamic benchmarking is that data validation needs to be finalized and the data need to be fixed before benchmarking is applied. This avoids the reference group changing over the course of the process, as parties with incorrect data may be excluded (and later re-included) from the reference group during benchmarking periods, which would result in different benchmarking thresholds. This shows that working with dynamic thresholds can be technically harder and analyzing trends is more challenging. As a result, using dynamic thresholds in the design and communication of antimicrobial policy measures is generally more complex.

When applying fixed benchmarking, two thresholds might be set. With two thresholds, three zones are created: a zone with "desirable or accepted use," with AMU below the lower threshold; an "attention" zone, with AMU between the lower and the upper threshold and an "action" zone, with AMU above the upper threshold (see **Supplementary Figures 1, 2**). This approach allows the system to focus on the highest users of antimicrobials, yet allows the group of "elevated attention" users to be identified and alerted.

Ultimately, using only one fixed threshold value (per animal species or category) is the most straightforward approach (i.e., the level of AMU is categorized as acceptable or not) and administratively and technically the least complex. As shown in the Netherlands and in Denmark, this is particularly advisable if the distribution of the AMU in the reference population is generally low and less right-skewed. Adaptation to such a threshold will in this case not be such a problem. If this is not the case an "attention zone" might be useful, with farms within this zone receiving a warning but without warranting immediate action. The consequences of setting the level of a threshold, in terms of number of farms exceeding the threshold(s) and the corresponding workload, should be kept in mind.

For the purpose of AMS and to encourage behavioral changes, benchmarking is particularly relevant if the outcome has consequences for the benchmarked party. Across countries, different risk management measures or interventions are triggered when thresholds are exceeded. Examples include the requirement to draw up action plans to reduce AMU, detailing additional measures that will be taken to reduce disease incidence, additional veterinary or inspection visits, compulsory advice to be obtained from an external party, fines, or exclusion from quality schemes. Furthermore, more corrective measures could be foreseen if AMU levels remain above a certain threshold for an extended period. Ultimately, animals or their products could be considered unfit to enter the food chain. On the other hand, parties with prudent and responsible use might also be rewarded. Such positive consequences might be social, e.g., making the good results of farms visible through certification or other "signs of recognition," or financial, through for example a bonus for good results. However, very low or zero use should be validated, as use might not have been correctly reported. It is important to note that the goal should be to use antimicrobials prudently, which should lead to an overall reduction in AMU. This should be predominantly achieved by only using antimicrobials when necessary to ensure animal welfare.

Parties should be granted adequate time between receiving a benchmarking result and the deadline for subsequently achieving a reduction in AMU. For example, if benchmarking results are available every trimester, it is unfeasible to require a reduced AMU by the next reporting cycle when a single production cycle lasts 6 months. In the interests of fairness, it should also be possible to appeal against a result for a short period after receiving the benchmarking result.

The success of benchmarking in terms of AMS will increase if the analysis and benchmarking methodology are transparent and clearly communicated to the affected parties.

Considering the responsibility of veterinarians for prescribing antimicrobials and therefore directly influencing AMU in animals, benchmarking veterinarians is an important option from an AMS perspective. Depending on the country and its legislation, it is not necessarily the AMU of a veterinarian that is being benchmarked but rather their "antimicrobial prescribing behavior." For convenience, we will denote this as "AMU of veterinarians" for the remainder of this paper. Similar definitions and principles apply for benchmarking the AMU of veterinarians as outlined above for benchmarking the AMU of farmers. However, benchmarking the AMU of veterinarians is more complex. The benchmarking score of a veterinarian needs to be calculated from the AMU of multiple farms. This can be challenging, as differences exist between veterinarians in terms of the number and characteristics of the farms he or she is responsible for. In addition, compared to benchmarking farmers, who are (legally) responsible for actions taken regarding the health of animals on their farm, it is more difficult to make veterinarians feel responsible for the AMU on a farm if it is being serviced by other vets, i.e., if there is no strict one-to-one relationship.

Usage results may be biased due to different health status and size of farms serviced by a practice. The Netherlands was the first country to adopt benchmarking of veterinarians. The Dutch veterinary benchmark indicator (VBI) calculates the probability of the farms, for which a certain veterinarian is responsible, falling within the action zone [i.e., above a certain AMU threshold; (38, 39)]. This methodology is now under revision (22, 37). In 2019, the Belgian "Sanitel-Med" system launched its benchmarking of veterinarians. Two scores are applied: (1) a contract score, expressing, for farms on which the veterinarian is the designated "herd vet," the distribution of animal categories falling within the "low," "attention," and "high" AMU zones in the benchmarking at farm-level; (2) a management score. The latter expresses the proportion of the total AMU of a veterinarian that was used at farms where the veterinarian was not the designated herd veterinarian. Austria also recently implemented a benchmarking system for veterinarians. Switzerland and France have tools that may be used in the future to apply benchmarking of veterinarians, but the protocols are not yet established and implemented.

Benchmarking of AMU of farms and/or veterinarians can be a powerful tool in reducing AMU as shown in Denmark, Germany and the Netherlands (21, 22, 40).

Reporting

Within the scope of this review, reporting refers to the process of providing feedback about farm-level AMU to the farmer or other parties. Such a process is critical, especially in terms of AMS. Of the four processes discussed here, reporting is the most subjective one, and needs to be adapted to the target audience. Consequently, discussing the value of different reporting formats is beyond the scope of this paper. Examples are provided only to illustrate some of the possible options.

Three types of target groups can be broadly distinguished: farmers and veterinarians, regulators and stakeholders (government, industry, sector organizations, farm assurance schemes) and the general public/consumers. In terms of AMS, farmers and veterinarians are the group most suited for receiving individual benchmarking results. Summarizing reports, typically not containing individual results, are more useful for a wider audience. The latter reports focus on general trends, achieving policy targets, comparing AMU among different animal species, categories, or other subgroups, etc. Several countries have been publishing reports of antimicrobial sales data for many years, increasingly including AMU data and sometimes AMR data as well [examples from countries in the AACTING network (21, 22, 29, 41–44)]. Reports for regulators can fall in either of the two categories, i.e., the individual party and the anonymous summary reports. In Belgium, yearly summarizing reports, without individual farm results, are also made available for some quality assurance schemes. Regardless of the purpose of data collection and the report type, the ownership of the data and their confidentiality must be defined and strictly adhered to. Any communication of results to third parties must be approved by the data owner. Summary results such as general trends by sector can, however, generally be published. Data ownership by the government is another option.

In terms of policy making and auditing, reporting of farm-specific results should be periodic, i.e., at pre-defined times and for all farms. In the Netherlands, the "SDa" reports analyses on AMU to regulators, policy makers and the general public, while the quality systems report, in parallel, to their farmer members. Private quality assurance systems of the monitored livestock sectors report results and provide feedback to individual farmers about their AMU. Broiler farmers, for example, receive a report every 3 months in which several aspects of their AMU are compared to sector averages. If a farmer's AMU is considered too high, measures are required to reduce use. In this respect, it might be interesting to additionally provide means of evaluating the result in real-time (for example through an online portal), especially if the frequency of periodic reporting is low (for example once a year) and the animals' replacement rate is relatively high.

Reporting will have the greatest effect when the (quantitative) information is given in relation to a reference population, hence as a benchmarking result. Showing a specific farm's AMU within a distribution of AMU within that sector/animal category makes comparisons easier and more illustrative for farmers (**Supplementary Figure 1**). Moreover, this could lead to "social pressure," known to be one of the five cues for changing human behavior (45). Most systems that perform benchmarking also report the results to all the parties involved (**Table 1**).

In addition to the quantitative use results, reports may contain guiding information, such as directives, data on farm trends and more detailed qualitative analyses, creating more insight into farm-level AMU (**Supplementary Figure 2**). In the Netherlands, antimicrobials are classified as either first, second or third choice antimicrobials, depending on resistance inducing effects and importance to human health. A similar system exists in Belgium, using color codes (yellow, orange, and red antimicrobial classes, respectively). The use of different choices of antimicrobials is also reported to individual farmers. Other aspects of interest to report to farmers could include use of group treatments, use of medicated feed containing antimicrobials, use of intramammary tubes, age at treatment, indication for treatment, etc.

Ultimately sustained behavioral changes in veterinarians and farmers are needed to establish prudent AMU. Invoking behavioral changes is complex and dependent on the target audience. Speksnijder and Wagenaar described how sociopsychological models can provide insight into a farmers' and veterinarians' behavior regarding AMU practices and how behavioral changes can be motivated (46). Several studies report that veterinarians perceive their main role as a service provider, they do not feel a demand from their farmers for advice (47–49). Insights obtained from sociopsychological models might also support veterinarians in their advisory role toward improving a farmer's management (46). Communicating best practices to farmers as well as veterinarians might be a helpful tool to encourage farmers and veterinarians to reduce AMU (50).

DISCUSSION

This overview shows a very large variety across systems, especially at the level of analysis (choice of numerator, denominator and indicator). As AMU reduction figures for several countries have proven the principle of implementing farm level monitoring might be a more defining factor for success than the actual methods used. Furthermore, each system has its limitations, perhaps not so much in design as in execution: the results (calculated AMU) largely depend on the degree to which the data were provided to the system(s) correctly and in a timely manner. Hence, it could be argued that aiming for harmonization across systems is not only unfeasible but also unnecessary.

Nonetheless, a desire to compare, essentially between similar sectors in different countries, does exist (13). In this regard, it is remarkable that almost all systems deploying farm-level benchmarking in partial or full coverage systems use an indicator that reflects the (true) exposure of animals to AMU, by calculating a treatment incidence or treatment frequency (**Table 1**). It is for this reason that an indicator reflecting the number of treatment days out of 100 days present on the farm has been specifically brought forward in the AACTING guidelines, published in the scope of the AACTING project, and with the aim of assisting parties in setting up systems for monitoring of farm-level AMU (see www.aacting.org/aacting-guidelines). Although, as noted above, it is clear that various other indicators are just as valuable, the value of this particular indicator lies in the fact that its outcome is a meaningful parameter for the farmer and veterinarian, and that it is a flexible indicator, which makes it possible to calculate back to mg/kg or to transform to a treatment frequency (when using the UDD instead of the DDD). As a secondary effect, these guidelines might be a step toward more harmonized approaches for farm-level AMU monitoring. It should be recognized that there is potential for more harmonization. Currently, a lack of harmonization is one of the factors that limits comparisons of AMU between farms within countries and comparisons of farm-level AMU data between countries, even though such comparisons are important for improving AMU practices (25, 51). More harmonized approaches to monitoring AMU at farm-level will improve understanding, communication, and sharing knowledge regarding AMU monitoring and benchmarking. Yet, even if using harmonized usage indicators, comparing systems in different countries might be seriously limited by variations in health and husbandry conditions, for example, the production cycle length of animals, availability of medical products, and regulations. It remains the responsibility of the parties aiming for, or performing any, comparisons of systems to carefully address the differences between them, which will not be resolved by choosing a uniform indicator.

Apart from bringing forward the usefulness of a specific type of indicator for monitoring farm-level AMU, the AACTING guidelines had the aim of providing useful information as how to organize the data collection, what to take in consideration when choosing a methodology for analysis, principles of benchmarking, and critical factors for reporting. The rationale for many of the points raised in the guidelines is provided in this overview. It is therefore advised to jointly consider both documents.

In conclusion, quantifying AMU at the farm-level represents an important step toward AMS, as mirrored in the ESVAC vision for 2016–2020. Recently, an increase has been observed in the number of countries developing AMU quantifying systems. An important aim of the AACTING consortium is to provide information about existing systems and support in designing new systems or revising existing systems. In this paper, we investigated the necessary components of such systems and described the available options, taking into consideration a selection of systems that currently exist. Based on this overview and the combined expertise of the international authors, we proposed a set of guidelines on the collection, analysis, benchmarking and reporting of AMU. These guidelines represent a relevant tool for entities planning to establish new farm-level systems for quantifying AMU and shall ideally contribute to the standardization of methodologies.

AUTHOR CONTRIBUTIONS

WV drafted a first version of the manuscript. PS, MF, KF, WO, AA, CCa, BB, VD, CCh, AH, AK, RM, GA, FS, KS, CM, IG, FB, LP, CF, LC, EM, LJ, MS, JP, SB, DH, and JD give their initial comments on the first version. PS, WV, MF, DH, and JD reworked the manuscript to all its subsequent versions, with the others authors contributing equally in subsequent revisions, up to the final version. WV and PS have contributed equally to the final version and share first authorship. All authors contributed to the article and approved the submitted version.

FUNDING

This paper was written within the scope of the AACTING project, which received funding under the Joint Programming Initiative on Antimicrobial Resistance (JPIAMR). Individual authors were funded by their respective organizations. MF was funded by the Danish Pig Levy Fund.

ACKNOWLEDGMENTS

The authors acknowledge Kari Grave and Kay Torriani for their contribution to the initial versions of the manuscript.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fvets.2020.00540/full#supplementary-material

REFERENCES

1. Chantziaras I, Boyen F, Callens B, Dewulf J. Correlation between veterinary antimicrobial use and antimicrobial resistance in food-producing animals: a report on seven countries. *J Antimicrob Chemother.* (2014) 69:827–34. doi: 10.1093/jac/dkt443
2. Martel JL, Tardy F, Sanders P, Boisseau J. New trends in regulatory rules and surveillance of antimicrobial resistance in bacteria of animal origin. *Vet Res.* (2001) 32:381–92. doi: 10.1051/vetres:2001131
3. Schwarz S, Kehrenberg C, Walsh TR. Use of antimicrobial agents in veterinary medicine and food animal production. *Int J Antimicrob Agents.* (2001) 17:431–7. doi: 10.1016/S0924-8579(01)00297-7
4. Catry B, Laevens H, Devriese LA, Opsomer G, De Kruif A. Antimicrobial resistance in livestock. *J Vet Pharmacol Ther.* (2003) 26:81–93. doi: 10.1046/j.1365-2885.2003.00463.x
5. European Centre for Disease Prevention and Control (ECDC), European Food Safety Authority (EFSA), European Medicines Agency (EMA). 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. doi: 10.2903/j.efsa.2015.4006
6. European Centre for Disease Prevention and Control (ECDC), European Food Safety Authority (EFSA), European Medicines Agency (EMA). 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:e04872. doi: 10.2903/j.efsa.2017.4872
7. Mevius D, Heederik D, Duijkeren E, Veldman K, van Essen A, Kant A, et al. *Rapport ESBL-Attributieanalyse (ESBLAT): Op zoek naar de bronnen van antibioticaresistentie bij de mens.* De Stichting TKI AgriandFood (TKI) (2018).
8. Gould IM. Stewardship of antibiotic use and resistance surveillance: the international scene. *J Hosp Infect.* (1999) 43:S253–60. doi: 10.1016/S0195-6701(99)90095-6
9. Naylor NR, Zhu N, Hulscher M, Holmes A, Ahmad R, Robotham JV. Is antimicrobial stewardship cost-effective? A narrative review of the evidence. *Clin Microbiol Infect.* (2017) 23:806–11. doi: 10.1016/j.cmi.2017.06.011
10. Daeseleire E, De Graef E, Rasschaert G, De Mulder T, Van den Meersche T, Van Coillie E, et al. Antibiotic use and resistance in animals: Belgian initiatives. *Drug Test Anal.* (2016) 8:549–55. doi: 10.1002/dta.2010
11. European Medicines Agency. *Sales of Veterinary Antimicrobial Agents in 31 European Countries in 2017.* European Union. Regulation (eu) 2019/6 of the European parliament and of the council of 11 December 2018 on veterinary medicinal products and repealing Directive 2001/82/EC. Official Journal of the European Union, Doc. 32019R0006. (2019).
12. European Medicines Agency (EMA). *Trends in the Sales of Veterinary Antimicrobial Agents in Nine European Countries (2005–2009).* (2011).
13. EU. *Regulation (EU) 2019/6 of the European Parliament and of the Council of 11 December 2018 on Veterinary Medicinal Products and Repealing Directive 2001/82/EC.* (2018).
14. Carmo LP, Schüpbach-Regula G, Müntener C, Chevance A, Moulin G, Magouras I. Approaches for quantifying antimicrobial consumption per animal species based on national sales data: a Swiss example, 2006 to 2013. *Eurosurveillance.* (2017) 22:30458. doi: 10.2807/1560-7917.ES.2017.22.6.30458
15. Levy S. Reduced antibiotic use in livestock: how Denmark tackled resistance. *Environ Health Perspect.* (2014) 122:A160–65. doi: 10.1289/ehp.122-A160
16. Speksnijder DC, Mevius DJ, Bruschke CJM, Wagenaar JA. Reduction of veterinary antimicrobial use in the Netherlands. The Dutch success model. *Zoonoses Public Health.* (2015) 62:79–87. doi: 10.1111/zph.12167
17. SDa. *Beschrijving van het antibioticumgebruik bij vleeskuikens, zeugen en biggen, vleesvarkens, en vleeskalveren in 2011 en benchmarkindicatoren voor 2012* (2012).
18. Hemme M, Ruddat I, Hartmann M, Werner N, van Rennings L, Käsbohrer A, et al. Antibiotic use on German pig farms-A longitudinal analysis for 2011, 2013 and 2014. *PLoS ONE.* (2018) 13:e0199592. doi: 10.1371/journal.pone.0199592
19. Hémonic A, Chauvin C, Delzescaux D, Verliat F, Corrégé I. Reliable estimation of antimicrobial use and its evolution between 2010 and 2013 in French swine farms. *Porc Health Manage.* (2018) 4:1–11. doi: 10.1186/s40813-018-0084-7
20. Government of Canada. Public Health Agency of Canada. *Preliminary Evidence of the Effect of the Canadian Chicken Industry's Elimination of Use of Antimicrobials of Very High Importance to Human Medicine.* (2016). Available online at: https://www.canada.ca/en/public-health/services/publications/drugs-health-products/canadian-integrated-program-antimicrobial-resistances-surveillance-bulletin.html (accessed November 19, 2019).
21. DANMAP. *Use of Antimicrobial Agents and Occurrence of Antimicrobial Resistance in Bacteria from Food Animals, Food and Humans in Denmark.* (2019).
22. SDa. *Het gebruik van antibiotica bij landbouwhuisdieren in 2018: Trends, benchmarken bedrijven en dierenartsen*. SDa/1153/2019 (2019).
23. European Medicines Agency (EMA). *Revised ESVAC Reflection Paper on Collecting Data on Consumption of Antimicrobial Agents per Animal Species*,

on Technical Units of Measurement and Indicators for Reporting Consumption of Antimicrobial Agents In Animals (2012).
24. European Medicines Agency. *Principles on Assignment of Defined Daily Dose for Animals (DDDvet) and Defined Course Dose for Animals (DCDvet)* (2015).
25. Collineau L, Belloc C, Stärk KD, Hémonic A, Postma M, Dewulf J, et al. Guidance on the selection of appropriate indicators for quantification of antimicrobial usage in humans and animals. *Zoonoses Public Health.* (2017) 64:165–84. doi: 10.1111/zph.12298
26. European Medicines Agency. *Defined Daily Doses for Animals (DDDvet) and Defined Course Doses for Animals (DCDvet).* (2016).
27. Dupont N, Fertner M, Kristensen CS, Toft N, Stege H. Reporting the national antimicrobial consumption in Danish pigs: influence of assigned daily dosage values and population measurement. *Acta Vet Scand.* (2015) 58:1–9. doi: 10.1186/s13028-016-0208-5
28. 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. Available online at: https://www.ingentaconnect.com/content/cvma/cjvr/2017/00000081/00000003/art00012
29. UK-VARSS. *UK Veterinary Antibiotic Resistance and Sales Surveillance Report (UK-VARSS 2017).* Addlestone: Veterinary Medicines Directorate (2019).
30. Joosten P, Sarrazin S, Van Gompel L, Luiken RE, Mevius DJ, Wagenaar JA, et al. Quantitative and qualitative analysis of antimicrobial usage at farm and flock level on 181 broiler farms in nine European countries. *J Antimicrob Chemother.* (2019) 74:798–806. doi: 10.1093/jac/dky498
31. Kasabova S, Hartmann M, Werner N, Käsbohrer A, Kreienbrock L. Used daily dose vs. defined daily dose—contrasting two different methods to measure antibiotic consumption at the farm level. *Front Vet Sci.* (2019) 6:116. doi: 10.3389/fvets.2019.00116
32. Sarrazin S, Joosten P, Van Gompel L, Luiken RE, Mevius DJ, Wagenaar JA, et al. Quantitative and qualitative analysis of antimicrobial usage patterns in 180 selected farrow-to-finish pig farms from nine European countries based on single batch and purchase data. *J Antimicrob Chemother.* (2019) 74:807–16. doi: 10.1093/jac/dky503
33. Timmerman T, Dewulf J, Catry B, Feyen B, Opsomer G, de Kruif A, et al. Quantification and evaluation of antimicrobial drug use in group treatments for fattening pigs in Belgium. *Prevent Vet Med.* (2006) 74:251–63. doi: 10.1016/j.prevetmed.2005.10.003
34. Waret-Szkuta A, Coelho V, Collineau L, Hémonic A, Buy C, Treff M, et al. How input parameters and calculation rules influence on-farm antimicrobial use indicators in animals. *Front Vet Sci.* (2019) 6:438. doi: 10.3389/fvets.2019.00438
35. OIE. *Terrestrial Animal Health Code.* (2020). Available online at: https://www.oie.int/fileadmin/Home/eng/Health_standards/tahc/current/chapitre_antibio_monitoring.pdf (accessed April 14, 2020).
36. Bos ME, Taverne FJ, Van Geijlswijk IM, Mouton JW, Mevius DJ, Heederik DJ. Netherlands veterinary medicines authority SDa. Consumption of antimicrobials in pigs, veal calves, and broilers in the Netherlands: quantitative results of nationwide collection of data in 2011. *PLoS ONE.* (2013) 8:e77525. doi: 10.1371/journal.pone.0077525
37. SDa. *Het gebruik van antibiotica bij landbouwhuisdieren in 2017: Trends, benchmarken bedrijven en dierenartsen*. SDa/1152/2018 (2018).
38. SDa. *De 'Veterinaire Benchmarkindicator'. Naar een transparant en verantwoord voorschrijfpatroon van antibiotica in de veterinaire praktijk.* SDa/1144/2014 (2014).
39. Bos ME, Mevius DJ, Wagenaar JA, van Geijlswijk IM, Mouton JW, Heederik DJ. Antimicrobial prescription patterns of veterinarians: introduction of a benchmarking approach. *J Antimicrob Chemother.* (2015) 70:2423–5. doi: 10.1093/jac/dkv104
40. BMEL. *Report of the Federal Ministry of Food and Agriculture on the Evaluation of the Antimicrobials Minimisation Concept Introduced with the 16th Act to Amend the Medicinal Products Act (16th AMG Amendment).* (2019).
41. Anses. *Sales Survey of Veterinary Medicinal Products Containing Antimicrobials in France 2018* (2019).
42. BelVet-SAC. *Belgian Veterinary Surveillance of Antibacterial Consumption (BelVet-SAC) – National Consumption Report 2018.* (2019).
43. MARAN. *Monitoring of Antimicrobial Resistance and Antibiotic Usage in Animals in the Netherlands in 2017*. Lelystad: Wageningen Bioveterinary Research (WBVR).
44. Swedres-Svarm. *Consumption of Antibiotics and Occurrence of Resistance in Sweden.* Uppsala: Public Health Agency of Sweden and National Veterinary Institute (2018).
45. Lam TJGM, Jansen J, Wessels RJ. The RESET Mindset Model applied on decreasing antibiotic usage in dairy cattle in the Netherlands. *Irish Vet J.* (2017) 70:5. doi: 10.1186/s13620-017-0085-x
46. Speksnijder DC, Wagenaar JA. Reducing antimicrobial use in farm animals: how to support behavioral change of veterinarians and farmers. *Anim Front.* (2018) 8:4–9. doi: 10.1093/af/vfy006
47. Alarcon P, Wieland B, Mateus AL, Dewberry C. Pig farmers' perceptions, attitudes, influences and management of information in the decision-making process for disease control. *Prevent Vet Med.* (2014) 116:223–42. doi: 10.1016/j.prevetmed.2013.08.004
48. Coyne LA, Latham SM, Williams NJ, Dawson S, Donald IJ, Pearson RB, et al. Understanding the culture of antimicrobial prescribing in agriculture: a qualitative study of UK pig veterinary surgeons. *J Antimicrob Chemother.* (2016) 71:3300–12. doi: 10.1093/jac/dkw300
49. Gunn GJ, Heffernan C, Hall M, McLeod A, Hovi M. Measuring and comparing constraints to improved biosecurity amongst GB farmers, veterinarians and the auxiliary industries. *Prevent Vet Med.* (2008) 84:310–3. doi: 10.1016/j.prevetmed.2007.12.003
50. Ellis-Iversen J, Cook AJ, Watson E, Nielen M, Larkin L, Wooldridge M, et al. Perceptions, circumstances and motivators that influence implementation of zoonotic control programs on cattle farms. *Prevent Vet Med.* (2010) 93:276–85. doi: 10.1016/j.prevetmed.2009.11.005
51. Landers TF, Cohen B, Wittum TE, Larson EL. A review of antibiotic use in food animals: perspective, policy, and potential. *Public Health Rep.* (2012) 127:4–22. doi: 10.1177/003335491212700103
52. European Commission. *Directive 2003/99/EC of the European Parliament and of the Council of 17 November 2003 on the Monitoring of Zoonoses and Zoonotic Agents, Amending Council Decision 90/424/EEC and Repealing Council Directive 92/117/EEC.* OJ/325/31-40. Official Journal of the European Union (2003).
53. Weese JS, Page SW, Prescott JF. Antimicrobial stewardship in animals. *Antimicrob Ther Vet Med.* (2013) 117–132. doi: 10.1002/9781118675014.ch7
54. World Health Organization. *Critically Important Antimicrobials for Human Medicine*. 6th Revision (2018).

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

DEFINITIONS AND ABBREVIATIONS

AMU: Antimicrobial use.

AMR: Antimicrobial resistance; the ability of microorganisms of certain species to survive or even to grow in the presence of a given concentration of an antimicrobial agent that is usually sufficient to inhibit or kill microorganisms of the same species (52). Only acquired resistance is considered within the scope of this publication.

Benchmarking: The comparison of a party's AMU with the AMU of similar parties (the reference population), given that AMU for all parties is quantified in a comparable manner.

AMS: Antimicrobial stewardship; AMS is aiming for prudent and appropriate AMU, which is defined by the World Health Organization (WHO) as "use of antimicrobials, which maximizes therapeutic effect and minimizes the development of antimicrobial resistance"; according to the OIE, AMS consists of "a set of practical measures and recommendations intended to prevent and/or reduce the selection pressure of antimicrobial-resistant bacteria in animals" (53). This also includes preventive measures to avoid antimicrobial use.

CIA: Critically important antimicrobials as defined by the WHO. These antimicrobials are considered critically important for human health according to two main specific criteria (54).

Party: Any person, group of persons or organization involved in any of the processes of data collection, analysis, benchmarking, etc., such as farmers, herd managers, veterinarians, pharmacies, researchers, and system administrator(s).

DDDA: Defined daily dose animal; the assumed average dose of an antimicrobial per kg animal body weight by animal species. The EU standard is the DDDvet (24).

DCDA: Defined course dose animal; the assumed average dose of an antimicrobial per kg animal body weight per treatment course for a specific animal species. The EU standard is the DCDvet (EMA, 2015).

UDDA: Used daily dose animal; the actual dose used of an antimicrobial per kg animal body weight of active substance for a specific animal species.

PDDA: Prescribed daily dose animal; the dose of an antimicrobial (or active substance) that is on average prescribed per kg animal body weight per day for a specific animal species.

UM: Unit of measurement; the unit in which the amount of antimicrobials used is expressed.

Indicator: The parameter quantifying use of antimicrobials, generally calculated as "number of units of measurements" (the numerator) divided by the "animal population" to standardize the use data (the denominator).

frontiers in Veterinary Science

ORIGINAL RESEARCH
published: 08 September 2020
doi: 10.3389/fvets.2020.00582

Small and Large Animal Veterinarian Perceptions of Antimicrobial Use Metrics for Hospital-Based Stewardship in the United States

Laurel E. Redding[1]*, *Brandi M. Muller*[2] *and Julia E. Szymczak*[2]

[1] *Department of Clinical Sciences, University of Pennsylvania School of Veterinary Medicine, Philadelphia, PA, United States,* [2] *Department of Biostatistics, Epidemiology and Informatics, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA, United States*

Background: Robust measurement and tracking of antimicrobial use (AMU) is a fundamental component of stewardship interventions. Feeding back AMU metrics to individual clinicians is a common approach to changing prescribing behavior. Metrics must be meaningful and comprehensible to clinicians. Little is known about how veterinary clinicians working in the United States (US) hospital setting think about AMU metrics for antimicrobial stewardship.

Objective: To identify hospital-based veterinary clinicians' attitudes toward audit and feedback of AMU metrics, their perceptions of different AMU metrics, and their response to receiving an individualized prescribing report.

Methods: Semi-structured interviews were conducted with veterinarians working at two hospitals in the Eastern US. Interviews elicited perceptions of antimicrobial stewardship in veterinary medicine. Respondents were shown a personalized AMU Report characterizing their prescribing patterns relative to their peers and were asked to respond. Interviews were recorded, transcribed, and analyzed using the framework method with matrices.

Results: Semi-structured interviews were conducted with 34 veterinary clinicians (22 small animal and 12 large animal). Respondents generally felt positive about the reports and were interested in seeing how their prescribing compared to that of their peers. Many respondents expressed doubt that the reports accurately captured the complexities of their prescribing decisions and found metrics associated with animal daily doses (ADDs) confusing. Only 13 (38.2%) respondents felt the reports would change how they used antimicrobials. When asked how the impact of the reports could be optimized, respondents recommended providing a more detailed explanation of how the AMU metrics were derived, education prior to report roll-out, guidance on how to interpret the metrics, and development of meaningful benchmarks for goal-setting.

Conclusions: These findings provide important insight that can be used to design veterinary-specific AMU metrics as part of a stewardship intervention that are meaningful to clinicians and more likely to promote judicious prescribing.

Keywords: veterinarian, antimicrobial use, metric, antimicrobial stewardship, feedback

OPEN ACCESS

Edited by:
Lucie Collineau, Agence Nationale de Sécurité Sanitaire de l'Alimentation, de l'Environnement et du Travail (ANSES), France

Reviewed by:
Simon More, University College Dublin, Ireland
Angelina Louise Bosman, University of Guelph, Canada

***Correspondence:**
Laurel E. Redding
lredding@vet.upenn.edu

Specialty section:
This article was submitted to Veterinary Epidemiology and Economics, a section of the journal Frontiers in Veterinary Science

Received: *03 May 2020*
Accepted: *20 July 2020*
Published: *08 September 2020*

Citation:
Redding LE, Muller BM and Szymczak JE (2020) Small and Large Animal Veterinarian Perceptions of Antimicrobial Use Metrics for Hospital-Based Stewardship in the United States. Front. Vet. Sci. 7:582. doi: 10.3389/fvets.2020.00582

INTRODUCTION

Antimicrobial stewardship has been defined as "coordinated interventions designed to improve and measure the appropriate use of [antimicrobial] agents by promoting the selection of the optimal [antimicrobial] drug regimen including dosing, duration of therapy, and route of administration" (1). In people, antimicrobial stewardship programs (ASPs) have been shown to improve patient outcomes, shorten the length of stay, reduce antimicrobial resistance, and save money in the inpatient setting (2).

A frequently used stewardship initiative is the provision of periodic feedback on a prescriber's AMU, oftentimes situating their use relative to their peers'. In human medicine, this type of intervention has been shown to decrease AMU, improve clinical outcomes, and decrease costs in the outpatient clinical setting (3–6). In animal agriculture, AMU is tracked at the farm level in many (mostly European) countries, and individual AMU data are regularly provided to producers and veterinarians for purposes of benchmarking in the context of regulatory programs or quality assurance schemes. These types of initiatives are thought to be major contributors to the decline in AMU observed in many livestock sectors in these countries (7–9).

In veterinary hospitals, AMU data are rarely tracked and much less frequently fed back to clinicians. Veterinary hospitals represent fundamentally different prescribing ecosystems than farms, and very little is known about the attitudes of veterinary clinicians working in these settings toward antimicrobial stewardship initiatives involving tracking and reporting of antimicrobial use, especially in the United States (US). With increasing interest in antimicrobial stewardship within US veterinary hospitals (10, 11), more information is needed on best practices for implementing systems that involve the feedback of AMU prescribing data to veterinarians. In particular, there is no consensus on which metric(s) to use. In farm-level benchmarking schemes, a variety of metrics are used, including count-based, mass-based, daily dose-based, and course-based indicators (12). Each metric has advantages and disadvantages and may or may not be applicable to the hospital setting, where individual animals rather than herds are treated.

Because the goal of providing AMU prescribing data to clinicians is to effect behavior change related to antimicrobial prescribing, the best metrics to use will ultimately be those that are understood, accepted by individual clinicians, and make sense for the context in which they work (13). Feedback of AMU data to human medicine clinicians has mostly been successful in outpatient primary care settings (3–6). It has been less successful in improving the behavior of hospital-based clinicians (14). This may partially be explained by the fact that the social context of work in hospitals is different than in outpatient offices, where multiple clinicians may care for the same patient and responsibility for a prescription is not clearly linked to an individual clinician (15, 16). Sociobehavioral research on the way human medicine clinicians respond to AMU data targeted at them individually demonstrates that considerable skepticism and lack of trust can surround feedback reports, contributing to gaming and workarounds (17). Before implementing an ASP intervention, clinician confidence in the measurement system must be secured to boost clinicians' acceptance of feedback data and increase motivation to change (18, 19). The goal of this study was therefore to identify the perceptions that veterinary clinicians working in the US hospital setting hold toward different AMU metrics used for the systematic tracking and reporting of AMU for purposes of stewardship.

METHODS

Study Design, Setting, and Participants

We conducted in-depth, semi-structured interviews with a purposive sample of veterinary clinicians from two hospitals (one large animal and one small animal) within a health system in the Eastern US. The small animal hospital sees ∼35,000 patients per year and can house 250 inpatients at any time. The large animal hospital sees 4,900 patients per year and can house 200 inpatients at any time. The health system in which we gathered data did not have a formal stewardship program in place that utilized audit and feedback of AMU metrics at the time of data collection. However, both hospitals had implemented individual antimicrobial stewardship initiatives, had held educational sessions on AMU in veterinary medicine, and emphasized that improving the use of antimicrobials was an institutional priority.

This qualitative study was led by a medical sociologist (JES) with expertise in mixed-methods research on antimicrobial prescribing and stewardship interventions, in collaboration with a veterinary epidemiologist (LER) with expertise in developing novel stewardship measures and metrics in veterinary medicine. At each hospital, we sought to interview veterinary clinicians from different specialties who commonly prescribed antimicrobials including internal medicine, surgery, dermatology, and emergency medicine. To identify respondents, we worked with key contacts at each hospital to identify the names and email address of eligible clinicians. The study team recruited respondents by email. Respondents were offered a $50 Visa gift card as an incentive. Potential respondents were assured that their specific comments would not be shared with key contacts beyond a report of de-identified aggregated themes. Our protocol was approved by the University of Pennsylvania Institutional Review Board (IRB Protocol # 832630).

Data Collection

Data were gathered from April to July 2019. Interviews were conducted in person by the medical sociologist and a senior research associate (BMM) with graduate training in anthropology and advanced interview technique. A semi-structured interview guide was created based on a review of the literature and the authors' previous research (see **Supplementary Material** for the guide). Questions were designed to be open-ended in order to elicit in-depth responses from veterinarians with minimal prompting by the interviewer (20). Key thematic domains in the interview guide included respondent perceptions of antimicrobial resistance and overuse in veterinary medicine, the application of principles of antimicrobial stewardship to the veterinary hospital context, and perceptions of a personalized

Antimicrobial Use Report (described in more detail below). All interviews were, with permission, recorded. Respondents were made aware that the purpose of the study was to better understand their opinions and perceptions of antimicrobial stewardship interventions and AMU metrics in veterinary medicine in order to inform the development of future health system interventions. Interviewers kept ongoing data collection memos to monitor for identification of novel insights and saturation of key themes in order to determine sample size adequacy (21).

Personalized Antimicrobial Use Report

The last part of the interview involved presenting the respondent with a hard copy of a personalized Antimicrobial Use Report (see **Supplementary Material** for sample report). These reports were generated from our veterinary hospital administrative and electronic medical record databases as previously described (22). Briefly, individuals' antimicrobial prescribing patterns from 2013 to 2018 were characterized relative to their peers using metrics that are frequently used to characterize AMU, including count- and dose-based metrics involving the animal-defined daily dose [ADD—also known as the DDDvet (12)], a metric that represents the average maintenance dose of a drug for its main indication in a specified species (12, 23). Standard doses used for the calculation of the ADDs (i.e., the defined daily dose) were obtained either from the drug labels or based on convention in our hospitals. Specifically, the report provided data on (1) the percent of visits in which an antimicrobial or highest priority critically important antimicrobial (HP-CIA—an antimicrobial class that is the sole, or one of limited available therapies, to treat serious bacterial infections in people) (24) was prescribed; (2) the prescription rate, or number of antimicrobial ADDs per 1,000 patient-days; (3) the average number of antimicrobial ADDs per patient; (4) the average number of antimicrobial classes prescribed per visit; (5) and rankings of the most frequently prescribed classes and combinations of antimicrobials. Data were presented via both prose and graphics, and detailed definitions of the ADD metrics along with examples of its use were provided (see example report).

For the large animal hospital clinicians, prescribing patterns were situated relative to peers within their service. Because some of the small animal hospital clinicians were involved in multiple services, their prescribing patterns were situated relative to peers within the entire hospital rather than within their service. For clinicians for whom there were insufficient prescribing data to create a personalized report (e.g., clinicians who were not employed by the hospitals from 2013 to 2018), a mock report was generated using data from a randomly selected de-identified clinician who was present during the time period of interest. These clinicians were made aware when presented the report that it did not contain their actual data, and they were asked to imagine how it might feel to receive such a report. The interviewer gave the respondent as much time as they needed to review the report and then asked them a series of questions to elicit their perceptions about the report and each of the metrics.

TABLE 1 | Characteristics of interview respondents.

Respondent Characteristic (n = 34)	No. (%) Respondents
Hospital	
Small animal	22 (64.7)
Large animal	12 (35.3)
Professional role	
Faculty	11 (32.4)
Resident	23 (67.6)
Primary specialty	
Dermatology	4 (11.8)
Emergency medicine	4 (11.8)
Internal medicine	15 (44.1)
Oncology	1 (2.9)
Surgery	10 (29.4)
Years in practice	
0–3	12 (35.3)
4–10	12 (35.3)
11–20	6 (17.7)
21–30	3 (8.8)
31+	1 (2.9)

Data Analysis

All audio files were transcribed and uploaded into NVivo 12 software for coding (25). Data were independently analyzed using a flexible coding approach by two coders (26). Themes were systematically identified in a two-stage process. First, a codebook based on the interview guides and a review of the data collection memos was developed. Codes were defined clearly and discussed among the team. Second, the coders applied the codebook to the transcripts. Intercoder reliability was monitored throughout, and modifications were made to the coding procedure to ensure agreement exceeded 95%. Once line-by-line coding was complete, we utilized a framework matrix to identify variation in patterns across codes, respondent classifications, and hospitals (27).

RESULTS

Characteristics of Study Subjects

Interviews were conducted with 34 veterinarians. The majority of respondents worked in a small animal hospital setting and had been in practice 10 years or less (**Table 1**). Interviews ranged in length from 18 to 68 min, with a median of 32 min. Twenty-one (61.8%) respondents were shown their actual prescribing data while 13 (38.2%) were shown mock prescribing data.

Initial Impression of Report

Upon initial presentation, 8 (23.5%) respondents expressed negative feelings about the report, 13 (38.2%) expressed positive feelings, while 13 (38.2%) were neutral in their response. Of those respondents who were shown their actual prescribing data, 6 (28.5%) expressed negative feelings about the report while 11 (52.3%) expressed positive feelings about the report. The primary reason respondents gave for feeling negatively about the report was believing that their actual antimicrobial use performance was better than the report indicated (**Table 2**, Quote 1 [Q1]). The surprise at seeing one's poorer than expected performance coupled with comparison to colleagues led some respondents to explain that the report made them feel "judged" (Q2). Respondents who were pleased explained that their data was on par with or better than how they perceived their actual use of antimicrobials (Q3).

After considering the data in the reports carefully, all respondents expressed appreciation for the metrics. Many said they had not ever seen data like this before and felt, in general, that communicating any data about antimicrobial use could be an important technique to encourage veterinarians to think about their prescribing decisions in the aggregate, which could improve antimicrobial use (Q4). Respondents' critical feedback of the reports primarily focused on doubt that the data could account for the nuances of prescribing in diverse clinical scenarios that might cause some veterinarians to justifiably use more antimicrobials than their peers (Q5). In reflecting on how it felt to be compared to colleagues, respondents generally found this approach to be informative and motivating for behavior change. However, some expressed concern that the comparisons might not be fair based on each individual veterinarian's case mix (Q6).

Specific Suggestions for Improving Report

While some respondents ($n = 14$, 41.2%) felt that the report was satisfactory and did not need changes, most had several suggestions as to how to improve the clarity and impact of the data. The majority of respondents ($n = 22$, 64.7%) found the animal defined daily doses metric to be the least meaningful and most confusing of all the metrics despite an explanatory page at the back of the report (Q7). Respondents suggested that this metric was not intuitive or clinically relevant and would take too much time for a non-statistically savvy, busy veterinarian to understand and find it meaningful (Q8). In comparison, respondents felt more favorably toward the proportion metrics and the ranking of antimicrobial classes (Q9). Some suggested moving the explanatory page that described how the metrics were calculated to the front of the report. Other respondents felt that the amount of information provided in the reports was overwhelming and suggested delivering less information all at once or using a phased approach so people could get used to receiving a report of this length (Q10).

One of the most common reactions to the report was a desire for benchmarks that could help put the individual's performance in context (Q11). We found, as respondents looked at the reports and thought aloud, that they felt the data would be more meaningful if it could be broken down further. Specific suggestions included organizing data by case or procedure type (Q12) and comparing the following: systemic vs. regional use of antimicrobials, colleagues only within the same specialty, prescribing data by species, farm vs. inpatient large animal use of antimicrobials, and prescribing data from other universities or hospitals.

The majority ($n = 26$, 76.5%) of respondents felt that supplementary information should be provided with reports to make them more actionable. For example, some respondents suggested that the metrics would only be meaningful and likely to produce behavioral change if it was clear that there was a "gold standard" or guideline that suggested what performance on each metric was "good" (Q13). Without a goal to strive for, many respondents expressed, the numbers alone would not motivate them to change. Others felt that the reports would be more useful if they were accompanied by institution-wide discussion about the trends and education about specific classes of antimicrobials that are overused or clinical scenarios in which prescribing could be improved (Q14). Most importantly, the "ethos" behind the report would need to be clearly communicated so prescribers would know that the intent of the report was to improve the quality of care delivered and not to punish individuals (Q15).

Influence of Report on Prescribing Behavior

Respondents varied in whether they felt their prescribing behavior would change in response to receiving the reports. Some ($n = 13$, 38.2%) felt that the report would change how they prescribed antimicrobials (Q16). A smaller number ($n = 8$, 23.5%) felt that they are already making the most judicious prescribing choices possible and did not believe the report would change the way they prescribe (Q17). Others suggested that without a goal to strive for, the data were not motivating (Q13).

Other respondents ($n = 13$, 38.2%) were undecided as to whether the data would change their prescribing and offered a variety of reasons for this equivocation. They explained that prescribing choices are influenced by an individual's accumulated clinical experience and the circumstances of each case; therefore, it was difficult for them to imagine a report with such high-level, aggregate metrics prompting change in practice as a whole (Q18). These respondents found the data to be informative but felt that more detail would be needed before the reports would change how they use antimicrobials. Multiple individuals said that the impact of the reports would depend on where they found themselves on the distribution compared to their colleagues and whether they felt the comparison was fair (Q19). Other respondents were unsure if the reports would motivate them to change and admitted that they would likely think of "excuses" to justify their high-prescribing rates in comparison to their colleagues (Q20).

DISCUSSION

With increasing interest in antimicrobial stewardship in veterinary medicine (11, 28), methods to achieve stewardship goals are needed (29). In this study, we demonstrated the feasibility of providing individualized antimicrobial use reports to clinicians in veterinary hospitals, and we obtained feedback on the perceived utility of the reports in general and of the individual metrics used in the reports. The reports were generally well-received by clinicians, and all clinicians were appreciative

TABLE 2 | Interview themes and exemplar quotations.

Initial Impression of the Report	
Negative feeling about report	**Q1.** I hate to say that I don't know that this would change what I do. It's definitely food for thought, though, seeing such a high number, because I would sit here and say I'm very cognizant of antimicrobial overprescribing and stewardship, and then I look here and see mine. It's so much worse than I was expecting, but if I do think about it, pretty much every patient I cut gets—not necessarily to go home—will get an injection of antimicrobials. -*Small Animal Surgical Resident* **Q2.** I'm trying to understand those metrics. Yeah. Well, I will say on kind of first looking through it, I felt like I prescribed a lot of antimicrobials. I think I felt an initial sense of being judged. -*Small Animal Internal Medicine Resident*
Positive feeling about report	**Q3.** Initial impression of the package is I'm proud of myself. It's kind of fun to see how you compare to other people in the population. I think I'm kinda on the lower end of prescribing; I tend to not prescribe more than one antimicrobial at once, and I tend not to prescribe it for more than a week, if I'm reading this correctly. -*Small Animal Internal Medicine Faculty*
Report useful to raise awareness	**Q4.** Yeah, I think sometimes you may not realize how much we're actually prescribing or what we're doing because you're just thinking of this case, right in front of me. So to see this listed out on the chart like "oh my God, do all my cases really need these things?" -*Large Animal Internal Medicine Faculty*
Metrics in report cannot account for nuances of prescribing	**Q5.** I think a hard thing to factor into this is sometimes when we're prescribing a drug we might—if a patient, let's say, has osteomyelitis and requires a long treatment with antimicrobial, even in human medicine, I might prescribe all 6 weeks of the antimicrobial at that time, which will markedly increase some of these values. Or I might give them only a 1 or 2-week course, and then recommend they recheck, and then we'll prescribe again at that point. But it might be me prescribing again; at another point, it might be one of my colleagues, or it might be one of those primary—or it might be the patient's primary veterinarian. -*Small Animal Emergency and Critical Care Resident*
Concern about fair comparisons	**Q6.** I mean, I would feel fine about it personally. I feel like everybody can do better and so there's really no harm in that comparison. I think the only challenging thing would be how do you decide who people are being compared to. Like is it hospital-wide? Is it within a department? Is it residents only? Is it interns only? Because I think that there is going to be a pretty wide variation in some of this information, like proportion of visits where you prescribe an antimicrobial. Well, I'm a surgeon and so it's going to be a lot because I'm going to use intraoperative antimicrobials most of the time which is like its own soapbox as well as far as what's appropriate and what's not. Whereas, like our ICU clinicians, like it says critically important antimicrobial of the highest priority, I feel like our ICU clinicians are probably going to have a higher number of that than I am. And so should they necessarily be compared to me? I don't know. I mean, I don't know if it's right or wrong. I just legitimately don't. But I feel like that might be a little bit problematic just because it's probably not a fair comparison. But I feel like someone who specializes in micro infectious diseases would probably have to chime in on that to say if it truly is fair or not. -*Small Animal Surgery Resident*
Suggestions for Improving the Report	
ADD metric confusing	**Q7.** I think the ADDs of antimicrobial use per 1,000 animal days is probably not as helpful as the percentage of visits prescribed and breaking out what we might consider critically important drugs out of the field as defined by WHO maybe. I think—so I think that's probably a good starting point. I think—I just think the ADDs per 1,000 animal days I don't know. That's a tough one I think for people to get their head around potentially. Yeah. I mean I think these without benchmarks are not going to mean a lot to our docs. -*Small Animal Dermatology Faculty* **Q8.** The animal daily dose doesn't make a ton of sense to me, like I feel like I need to like really stop and read the sentences and think through them very slowly to actually understand what they're saying. But again, I am not a statistician. So, I'm sure to a much smarter person, this makes perfect sense. I am not one of those people. As far as calculating the animal daily dose, I don't know how that relates to clinical use. It seems complicated, but if this helps the researcher defining usage, great. I think I would need someone to—I can see the math, and if you gave me the numbers I could plug in the formulas and probably get the same numbers, but I'm not exactly sure what that tells us. -*Small Animal Surgery Resident*
Favorable perception of proportion and ranking metrics	**Q9.** Well, I think this is really interesting, just to see what classes we're prescribing the most, even though I figured sulfas would be—I thought penicillins would be more. This one's just more interesting than anything else. -*Large Animal Internal Medicine Resident*
Report contains too much information	**Q10.** I definitely think you can overwhelm people with data and I don't know that I would be wanting to give everybody each of these report types every month because their eyes are going to gloss over, they're going to open the email and go, "Oh that," minimize, forget about it. But you know I think quarterly or biannually would probably be more palatable and then I think it's important at least once a year or so to have a grand rounds or a morbidity and mortality rounds to discuss how as a hospital things are looking, but how do you benchmark that is the question. -*Small Animal Dermatology Faculty*
Desire for benchmarks	**Q11.** There would have to also be, I think, an effort to standardize some guidelines or something. So just data and how you compare without any kind of gold standard or evidence-based recommendation is challenging to implement any changes. -*Large Animal Internal Medicine Faculty*
Desire for breakdown of data by case type	**Q12.** Have it broken down by the case type. So like the ten doctors here, for every laceration, you have the breakdown of what the prescribing doctors are using, or how long they're using them for this particular injury. And then that's where you can—that's how you potentially change the minds of someone that's overusing or misusing the antimicrobials. They're like, "Oh, shoot. For a simple laceration, either people are using only 3 days of antimicrobials, or nobody's using any. So why am I using 14 days of TMS, whereas everyone else is only using 5 days?" And that's where they're like, "Oh, geez. Maybe I'm not using it correctly." -*Large Animal Surgery Resident*
Need comparison to standard of care for report to be behaviorally motivating	**Q13.** I think kind of like how are you measuring up vs. standard of care, that kind of information would be very helpful. I don't know that by itself, like just having this data here, don't know that it would necessarily—like this packet for me right at this minute won't necessarily change we I do in terms how I'm prescribing but, you know, if there was a little bit more information about like, you know, within the surgery department this is how many orthopedic cases you've cuts, this is how many that have gotten infected, this is how many that have gotten perioperative, plus or minus post-operative antimicrobials but, you know, I think that's just a lot of work for anybody to do. It's basically like a whole retrospective study. -*Small Animal Surgery Resident*

(Continued)

TABLE 2 | Continued

Initial Impression of the Report	
Accompany report with education and institutional clarity about goals	**Q14.** It would maybe just have it be a chance for Microbiology to sort of reflect on any new guidelines that they're recommending, especially as we sort of have some more. Because I think, over the next couple of years, there will be more formal guidelines, and there will be more evidence based medicine. So, to have both reflection and education about what we want people to change and focus on. Like— "hey, the hospital as a whole is using an awful lot of fluoroquinolones. Here are situations where maybe we should stop using that or switch to something else." *-Small Animal Oncology Resident*
Clearly communicate non-punitive rationale behind report	**Q15.** And certainly, this would have to be preceded by explanations about the ethos and the—why this is being done and the remit behind it so that everyone's on board with the fact that, even if they find illustration of their metrics in this way a little bit aggressive, at least they know it's motivated by good. *-Small Animal Internal Medicine Faculty*
Impact of Report on Prescribing Behavior	
Report would change prescribing behavior	**Q16.** Yeah, absolutely, this would change how I use antimicrobials. I do think that—you know, we all learn in different ways, and I think this—giving us a visual representation of how we compare, I think that really does impact people a lot. Especially for people who are stuck in their ways, for sure. And I think that it does allow me to think of, "Does this patient really need an antimicrobial?" and will lead me to be a little bit more judicious when I'm choosing my antimicrobial therapy in the future. *-Small Animal Internal Medicine Faculty*
Report would not change prescribing behavior	**Q17.** I don't think this would change my prescribing. I hate to say it. I think I am actually somebody that is cognizant of antimicrobial resistance; it's something I do think about, and I know that we use a lot of antimicrobials, so this is not surprising to me. *-Small Animal Surgery Resident*
More granular data needed to change behavior	**Q18.** I don't know if it would impact things. I mean, even something more specific like orthopedics vs. airways, urogenital surgery; that's really, really detailed. It would probably be like a ton of work. But surgery is just such a broad title for what we do. Sometimes we're doing surgery in very contaminated places that the animal would be dead if you didn't put it on antimicrobials. And sometimes you're doing surgery, you just don't need it. *-Large Animal Surgery Resident*
Behavior change depends on performance and comparator	**Q19.** I think it would depend on the distribution maybe. So, like, finding myself on the 60 or 70th percentile as an intern probably wouldn't bother me vs. if I was like, "Oh, I'm on the 95th percentile compared to other internists on the East Coast." Then yeah, that would definitely make me be like, "Oh, I'm definitely overprescribing this, that, or the other." Or maybe for the duration of things, I'm going out longer than others. So, yeah, I think it could be potentially beneficial, but I think it would boil down to how it was applied and who you're comparing people to. *-Small Animal Internal Medicine Resident*
Would make excuses to justify poor performance	**Q20.** No, I would just say, for me personally. I would just say oh, it's my case population. Which might be wrong. Probably would be wrong. But that's what I would say. Unless all of my medicine friends looked very different from me. But then I would still say well, I'm a resident. I get the sickest cases. I would make excuses. *-Large Animal Internal Medicine Resident*

of being able to visualize their antimicrobial prescribing patterns using different metrics.

Antimicrobial stewardship initiatives involving the provision of periodic feedback to clinicians on their antimicrobial prescribing have been used successfully in human medicine (6, 30–34) and in animal agriculture (7, 35, 36). In veterinary hospitals, such initiatives are being proposed (37, 38). However, as made clear by the participants of our study, who expressed a desire for information with which to gauge the appropriateness of their AMU, prescribing behavior should be benchmarked against universally accepted guidelines to be useful. In veterinary medicine, a general consensus about broad tenets of judicious AMU exist (39), but defined AMU guidelines exist for only a few select clinical conditions in small animal medicine (40–43). Adherence to these guidelines have been investigated within veterinary institutions (44, 45), but, to our knowledge, no use has been made of them to provide feedback to clinicians in a veterinary hospital setting. In small animals, antimicrobial use reports targeted to the clinical conditions for which guidelines exist represent the most logical option for a feedback-related antimicrobial stewardship intervention. Such interventions in the context of acute respiratory tract infections have been performed in human medicine (6, 33). However, targeted reports evaluate only a small proportion of an individual's prescriptions and may limit who can be evaluated, as veterinarians in certain specialties may not see patients with the conditions of interest. This is particularly problematic for large animal medicine, where AMU guidelines for specific conditions are lacking. The dearth of defined AMU guidelines represents an impediment to promoting appropriate antimicrobial use in the veterinary hospital, and more research is needed to develop such guidelines.

An important theme that emerged from our interviews was that of comparability. When benchmarking AMU across different units (e.g., clinicians, services, hospitals), comparability of patient populations seen by different clinicians is critical. Many of the veterinarians interviewed in this study expressed skepticism that their results could be meaningfully compared to those of their peers, as patient populations attended to differed greatly across and even within services. Situating an individual's prescribing patterns relative to peers within the same service is necessary but does not appear sufficient. Additional methods of ensuring comparability of patient populations seen by a clinician are needed. In human medicine, scoring systems such as the Medicare Severity Diagnosis Related Group or Charlson comorbidity score have been used when benchmarking AMU (46, 47). While scoring systems exist for specific conditions [e.g., equine colic (48, 49)], to our knowledge, there are no validated methods of more generally characterizing the disease severity or comorbidities of veterinary patients. Until such scoring systems are developed, clinicians may view attempts to compare their prescribing to peers' as invalid or unfair.

The question of which metrics to use when benchmarking or evaluating the appropriateness of AMU is a critical one that remains unresolved in both human medicine (50–52) and veterinary medicine (12, 53). In human medicine, a wide variety of AMU metrics exist for purposes of antimicrobial stewardship, many of which are similar to or equivalent to those used in our study (54). In animal agriculture, different metrics are used in different countries and systems (35, 55, 56), and an expansive body of literature has described and evaluated the advantages and disadvantages of these metrics (12, 23, 57–59). However, because herds of animals are treated on farms more often than individual animals, the metrics used on the farm setting may not translate well to the hospital setting. While there is some consensus among experts about which metrics should be used in the human hospital setting (60), others have argued that certain metrics, most notably the dose-based metrics which are equivalent to the ADD-based metrics used in this study, should not be used for purposes of antimicrobial stewardship (1, 52). This was corroborated by our study, as most of the clinicians found the ADD-based metrics to be confusing, even when provided with detailed explanations. While ADD-based metrics are appealing because they can be calculated from drug volumes that are often accessible in pharmacy or billing records, they are not intuitive. Moreover, we have shown that in veterinary medicine they are not, as they should theoretically be, equivalent to more intuitive duration-based metrics such as days of therapy (61) which have been used in human medicine for stewardship purposes (34). Dose-based metrics are useful for benchmarking AMU at the farm, regional, national, and international levels (62–67) and are generally recommended in these settings to monitor trends in use over time (12). Moreover, because the ADD represents a scaling factor more than an indicator of absolute AMU (23), it is well-suited for comparing a prescriber or user to his/her peers. However, at the level of the individual clinician working in a hospital setting, the ADD-based metrics are not immediately intuitive. It is unknown if prolonged exposure to these metrics will enhance a clinician's ease with these metrics, or if, as one clinician noted, they are just "tough [...] for people to get their head around." It has been suggested that duration-based metrics (e.g., individual days treated or number of individuals daily treated) may be more appropriate for hospital settings (12, 68). Unfortunately, these metrics were not easily accessible from our database and could not be extracted to present to clinicians.

In contrast, the proportion metrics (e.g., percent of visits where an antimicrobial or HP-CIA was prescribed) and the ranking of antimicrobial classes were the most well-received metrics. Both of these metrics or variants thereof [e.g., antimicrobial spectrum score (34, 69)] have been used successfully to gauge appropriateness of antimicrobial prescribing by physicians (6, 70) and veterinarians (44, 45, 71). These metrics capture information about the frequency and choice of antimicrobial prescriptions and can therefore be useful in encouraging clinicians to limit unnecessary prescribing of antimicrobials and optimize empiric antimicrobial regimens (e.g., targeted therapy over broad spectrum, lower vs. higher priority antimicrobials) (71, 72). Because they are also inherently intuitive, they were likely to be more readily accepted by clinicians.

Audit and feedback is a commonly used quality improvement intervention in human medicine. It has been demonstrated, however, that the effects of these interventions vary greatly and are not improving over time (13, 73). Simply providing professionals with data is not enough to stimulate change in the way they perform their work (74). Numbers must have salience and meaning to the individuals whose behavior is targeted for change. Antimicrobial stewardship feedback interventions that are consistent with the priorities, beliefs, and concerns of prescribers and that make meaningful social comparisons may be more successful than those that do not (5). Our study generates knowledge that can be used to inform the design and implementation of stewardship interventions in veterinary medicine. To advance the science of stewardship, interventions need to account for the social and behavioral mechanisms that are particular to the professional culture of veterinary medicine (75, 76).

Our study has several limitations. First, because we adopted a qualitative approach our findings may not be generalizable beyond the settings we studied. Second, despite explicit efforts to minimize their effects, our sample may be biased. It is possible that the respondents who agreed to participate to an interview possessed systematically different characteristics that influenced their willingness to participate and shaped their perceptions compared to those not interviewed. We were unable to assess the characteristics of respondents vs. non-respondents. It is also possible that interview respondents did not honestly share their perceptions about the Personalized Antimicrobial Use Reports in order to please the interviewer. Given that respondents did express criticism of the AMU metrics and their feelings about antimicrobial stewardship interventions, we believe the impact of social desirability bias on our data to be minimal.

CONCLUSION

Providing feedback on antimicrobial prescribing to individual veterinary clinicians may be an effective antimicrobial stewardship intervention, as long as the metrics used to describe prescribing patterns are understood by clinicians. Prescribing frequency, durations of therapy, and ranking of antimicrobial classes appear to be the metrics most well-received by veterinary clinicians, while dose-based metrics associated with the ADD are less intuitive. However, more research is needed to establish antimicrobial use guidelines against which prescribing can be measured.

DATA AVAILABILITY STATEMENT

The raw data generated and analyzed during this study is not publicly available due to the sensitive nature of the data and ethics restrictions on data sharing. Respondents did not consent to have their data publicly shared. A de-identified dataset may be made available by reasonable request.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Institutional Review Board of the University of Pennsylvania. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

LR produced individual antimicrobial use reports for all clinicians, contributed to data analysis, and manuscript writing. BM interviewed participants and contributed to data coding and analysis. JS interviewed participants and contributed to data coding, data analysis, and manuscript writing. All authors contributed to the article and approved the submitted version.

FUNDING

This work was supported by funding from the University Research Foundation of the University of Pennsylvania. JS received funding from the US Centers for Disease Control and Prevention's Cooperative Agreement [FOA#CK16-004] Epicenters for the Prevention of Healthcare Associated Infections.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fvets.2020.00582/full#supplementary-material

REFERENCES

1. Society for Healthcare Epidemiology of A, Infectious Diseases Society of A, Pediatric Infectious Diseases S. Policy statement on antimicrobial stewardship by the Society for Healthcare Epidemiology of America (SHEA), the Infectious Diseases Society of America (IDSA), and the Pediatric Infectious Diseases Society (PIDS). *Infect Control Hosp Epidemiol*. (2012) 33:322–7. doi: 10.1086/665010
2. Dellit TH, Owens RC, McGowan JE Jr, Gerding DN, Weinstein RA, Burke JP, et al. Infectious diseases society of America and the society for healthcare epidemiology of America guidelines for developing an institutional program to enhance antimicrobial stewardship. *Clin Infect Dis*. (2007) 44:159–77. doi: 10.1086/510393
3. Meeker D, Linder JA, Fox CR, Friedberg MW, Persell SD, Goldstein NJ, et al. Effect of behavioral interventions on inappropriate antibiotic prescribing among primary care practices: a randomized clinical trial. *JAMA*. (2016) 315:562–70. doi: 10.1001/jama.2016.0275
4. Shively NR, Buehrle DJ, Wagener MM, Clancy CJ, Decker BK. Improved antibiotic prescribing within a veterans affairs primary care system through a multifaceted intervention centered on peer comparison of overall antibiotic prescribing rates. *Antimicrob Agents Chemother*. (2019) 64:e00928-19. doi: 10.1128/AAC.00928-19
5. Milani RV, Wilt JK, Entwisle J, Hand J, Cazabon P, Bohan JG. Reducing inappropriate outpatient antibiotic prescribing: normative comparison using unblinded provider reports. *BMJ Open Qual*. (2019) 8:e000351. doi: 10.1136/bmjoq-2018-000351
6. Gerber JS, Prasad PA, Fiks AG, Localio AR, Grundmeier RW, Bell LM, et al. Effect of an outpatient antimicrobial stewardship intervention on broad-spectrum antibiotic prescribing by primary care pediatricians: a randomized trial. *JAMA*. (2013) 309:2345–52. doi: 10.1001/jama.2013.6287
7. Speksnijder DC, Mevius DJ, Bruschke CJ, Wagenaar JA. Reduction of veterinary antimicrobial use in the Netherlands. The Dutch success model. *Zoonoses Public Health*. (2015) 62(Suppl. 1):79–87. doi: 10.1111/zph.12167
8. Agunos A, Leger DF, Carson CA, Gow SP, Bosman A, Irwin RJ, et al. Antimicrobial use surveillance in broiler chicken flocks in Canada, 2013-2015. *PLoS ONE*. (2017) 12:e0179384. doi: 10.1371/journal.pone.0179384
9. BMEL. *Report of the Federal Ministry of Food and Agriculture on the Evaluation of the Antimicrobials Minimisation Concept Introduced With the 16th Act to Amend the Medicinal Products Act (16th AMG Amendment)*. Bonn, Germany (2019).
10. Jacob ME, Hoppin JA, Steers N, Davis JL, Davidson G, Hansen B, et al. Opinions of clinical veterinarians at a US veterinary teaching hospital regarding antimicrobial use and antimicrobial-resistant infections. *J Am Vet Med Assoc*. (2015) 247:938–44. doi: 10.2460/javma.247.8.938
11. AVMA Task Force for Antimicrobial Stewardship in Companion Animal Practice. Understanding companion animal practitioners' attitudes toward antimicrobial stewardship. *J Am Vet Med Assoc*. (2015) 247:883–4. doi: 10.2460/javma.247.8.883
12. Collineau L, Belloc C, Stärk KD, Hémonic A, Postma M, Dewulf J, et al. Guidance on the selection of appropriate indicators for quantification of antimicrobial usage in humans and animals. *Zoonoses Public Health*. (2017) 64:165–84. doi: 10.1111/zph.12298
13. Brehaut JC, Colquhoun HL, Eva KW, Carroll K, Sales A, Michie S, et al. Practice feedback interventions: 15 suggestions for optimizing effectiveness. *Ann Intern Med*. (2016) 164:435–41. doi: 10.7326/M15-2248
14. Rosa RM, Bushman AM. Impact of peer comparison on carbapenem use among inpatient prescribers at a community hospital. *Infect Control Hosp Epidemiol*. (2020) 41:376–8. doi: 10.1017/ice.2019.377
15. Charani E, Castro-Sanchez E, Sevdalis N, Kyratsis Y, Drumright L, Shah N, et al. Understanding the determinants of antimicrobial prescribing within hospitals: the role of "prescribing etiquette". *Clin Infect Dis*. (2013) 57:188–96. doi: 10.1093/cid/cit212
16. Charani E, Ahmad R, Rawson TM, Castro-Sanchèz E, Tarrant C, Holmes AH. The differences in antibiotic decision-making between acute surgical and acute medical teams: an ethnographic study of culture and team dynamics. *Clin Infect Dis*. (2018) 69:12–20. doi: 10.1093/cid/ciy844
17. Szymczak JE, Feemster KA, Zaoutis TE, Gerber JS. Pediatrician perceptions of an outpatient antimicrobial stewardship intervention. *Infect Control Hosp Epidemiol*. (2014) 35(Suppl. 3):S69–78. doi: 10.1086/677826
18. Bork JT, Morgan DJ, Heil EL, Pineles L, Kleinberg M. Peer comparison of anti-MRSA agent prescription in the inpatient setting. *Infect Control Hosp Epidemiol*. (2017) 38:1506–8. doi: 10.1017/ice.2017.219
19. Landis-Lewis Z, Kononowech J, Scott WJ, Hogikyan RV, Carpenter JG, Periyakoil VS, et al. Designing clinical practice feedback reports: three steps illustrated in Veterans Health Affairs long-term care facilities and programs. *Implement Sci*. (2020) 15:7. doi: 10.1186/s13012-019-0950-y
20. Weiss RS. *Learning From Strangers: The Art and Method of Qualitative Interview Studies*. New York, NY: Free Press (1994).
21. Malterud K, Siersma VD, Guassora AD. Sample size in qualitative interview studies: guided by information power. *Qual Health Res*. (2016) 26:1753–60. doi: 10.1177/1049732315617444
22. Redding LE, Lavigne S, Aceto HW, Nolen-Walston RD. Antimicrobial prescribing patterns of clinicians and clinical services at a large animal veterinary teaching hospital. *Am J Vet Res*. (2020) 81:103–15. doi: 10.2460/ajvr.81.2.103

23. Jensen VF, Jacobsen E, Bager F. Veterinary antimicrobial-usage statistics based on standardized measures of dosage. *Prev Vet Med*. (2004) 64:201–15. doi: 10.1016/j.prevetmed.2004.04.001
24. World Health Organization. *Critically Important Antimicrobials for Human Medicine*. Geneva: WHO (2017).
25. QSR International Pty Ltd. *NVivo (Version 12)* (2019). Available online at: https://www.qsrinternational.com/nvivo-qualitative-data-analysissoftware/home
26. Deterding NM, Waters MC. Flexible coding of in-depth interviews: a twenty-first-century approach. *Sociol Methods Res*. (2018) 0049124118799377. doi: 10.1177/0049124118799377
27. Gale NK, Heath G, Cameron E, Rashid S, Redwood S. Using the framework method for the analysis of qualitative data in multi-disciplinary health research. *BMC Med Res Methodol*. (2013) 13:117. doi: 10.1186/1471-2288-13-117
28. Prescott JF, Boerlin P. Antimicrobial use in companion animals and good stewardship practice. *Vet Record*. (2016) 179:486–8. doi: 10.1136/vr.i5908
29. Guardabassi L, Prescott JF. Antimicrobial stewardship in small animal veterinary practice: from theory to practice. *Vet Clin North Am Small Anim Pract*. (2015) 45:361–76. doi: 10.1016/j.cvsm.2014.11.005
30. Arnold FW, McDonald LC, Smith RS, Newman D, Ramirez JA. Improving antimicrobial use in the hospital setting by providing usage feedback to prescribing physicians. *Infect Control Hosp Epidemiol*. (2016) 27:378–82. doi: 10.1086/503336
31. Hux JE, Melady MP, DeBoer D. Confidential prescriber feedback and education to improve antibiotic use in primary care: a controlled trial. *CMAJ*. (1999) 161:388–92.
32. Zwar N, Wolk J, Gordon J, Sanson-Fisher R, Kehoe L. Influencing antibiotic prescribing in general practice: a trial of prescriber feedback and management guidelines. *Fam Pract*. (1999) 16:495–500. doi: 10.1093/fampra/16.5.495
33. Tong I, Dean K, Park D, Thompson J, Yan L, Liu C, et al. 195. The effect of two antibiotic stewardship interventions in a telemedicine practice. *Open Forum Infect Dis*. (2018) 5(Suppl. 1):S85–S6. doi: 10.1093/ofid/ofy210.208
34. McIntyre MT, Naik L, Bell CM, Morris AM. Development and assessment of a physician-specific antimicrobial usage and spectrum feedback tool. *Open Forum Infect Dis*. (2017) 4:ofx124. doi: 10.1093/ofid/ofx124
35. Craig AL, Buijs S, Morrison S. Evaluation of veterinary antimicrobial benchmarking systems at farm- level in Europe: implications for the UK ruminant sector. *Vet Record*. (2020). doi: 10.1136/vr.105727. [Epub ahead of print].
36. Canadian Integrated Program for Antimicrobial Resistance. *Reductions in Antimicrobial Use and Resistance: Preliminary Evidence of the Effect of the Canadian Chicken Industry's Elimination of Use of Antimicrobials of Very High Importance to Human Medicine*. (2016). Available online at: https://www.canada.ca/en/public-health/services/publications/drugs-health-products/canadian-integrated-programantimicrobial-resistances-surveillance-bulletin.html (accessed August 21, 2020).
37. CAVSNET. *Companion Animal Veterinary Surveillance Network: University of Minnesota*. Available online at: https://cavsnet.umn.edu/about-cavsnet (accessed August 21, 2020).
38. SAVSNET. *Small Animal Veterinary Surveillance Network University of Liverpool*. Available online at: https://www.liverpool.ac.uk/savsnet/ (accessed August 21, 2020).
39. Weese JS, Giguere S, Guardabassi L, Morley PS, Papich M, Ricciuto DR, et al. ACVIM consensus statement on therapeutic antimicrobial use in animals and antimicrobial resistance. *J Vet Intern Med*. (2015) 29:487–98. doi: 10.1111/jvim.12562
40. Lappin MR, Blondeau J, Boothe D, Breitschwerdt EB, Guardabassi L, Lloyd DH, et al. Antimicrobial use guidelines for treatment of respiratory tract disease in dogs and cats: antimicrobial guidelines working group of the international society for companion animal infectious diseases. *J Vet Intern Med*. (2017) 31:279–94. doi: 10.1111/jvim.14627
41. Weese JS, Blondeau JM, Boothe D, Breitschwerdt EB, Guardabassi L, Hillier A, et al. Antimicrobial use guidelines for treatment of urinary tract disease in dogs and cats: antimicrobial guidelines working group of the international society for companion animal infectious diseases. *Vet Med Int*. (2011) 2011:263768. doi: 10.4061/2011/263768
42. Marks SL, Rankin SC, Byrne BA, Weese JS. Enteropathogenic bacteria in dogs and cats: diagnosis, epidemiology, treatment, and control. *J Vet Intern Med*. (2011) 25:1195–208. doi: 10.1111/j.1939-1676.2011.00821.x
43. Hillier A, Lloyd DH, Weese JS, Blondeau JM, Boothe D, Breitschwerdt E, et al. Guidelines for the diagnosis and antimicrobial therapy of canine superficial bacterial folliculitis (Antimicrobial Guidelines Working Group of the International Society for Companion Animal Infectious Diseases). *Vet Dermatol*. (2014) 25:163–e43. doi: 10.1111/vde.12118
44. Banfield Pet Hospital. *Are We Doing Our Part to Prevent Superbugs? Antimicrobial Usage Patterns Among Companion Animal Veterinarians* (2017).
45. Banfield Pet Hospital. *A Feline Focus on Antimicrobial Usage*. Vancouver, WA, USA (2018).
46. Polk RE, Hohmann SF, Medvedev S, Ibrahim O. Benchmarking risk-adjusted adult antibacterial drug use in 70 US academic medical center hospitals. *Clin Infect Dis*. (2011) 53:1100–10. doi: 10.1093/cid/cir672
47. Ibrahim OM, Polk RE. Benchmarking antimicrobial drug use in hospitals. *Expert Rev Anti Infect Ther*. (2012) 10:445–57. doi: 10.1586/eri.12.18
48. Furr MO, Lessard P, White NA II. Development of a colic severity score for predicting the outcome of equine colic. *Vet Surg*. (1995) 24:97–101. doi: 10.1111/j.1532-950X.1995.tb01302.x
49. Grulke S, Olle E, Detilleux J, Gangl M, Caudron I, Serteyn D. Determination of a gravity and shock score for prognosis in equine surgical colic. *J Vet Med Ser A*. (2001) 48:465–73. doi: 10.1046/j.1439-0442.2001.00374.x
50. van den Bosch CMA, Geerlings SE, Natsch S, Prins JM, Hulscher MEJL, Perl TM. Quality indicators to measure appropriate antibiotic use in hospitalized adults. *Clin Infect Dis*. (2014) 60:281–91. doi: 10.1093/cid/ciu747
51. Spivak ES, Cosgrove SE, Srinivasan A. Measuring appropriate antimicrobial use: attempts at opening the black box. *Clin Infect Dis*. (2016) 63:1639–44. doi: 10.1093/cid/ciw658
52. Morris AM. Antimicrobial stewardship programs: appropriate measures and metrics to study their impact. *Curr Treat Options Infect Dis*. (2014) 6:101–12. doi: 10.1007/s40506-014-0015-3
53. Mills HL, Turner A, Morgans L, Massey J, Schubert H, Rees G, et al. Evaluation of metrics for benchmarking antimicrobial use in the UK dairy industry. *Vet Record*. (2018) 182:379. doi: 10.1136/vr.104701
54. Ibrahim OM, Polk RE. Antimicrobial use metrics and benchmarking to improve stewardship outcomes: methodology, opportunities, and challenges. *Infect Dis Clin North Am*. (2014) 28:195–214. doi: 10.1016/j.idc.2014.01.006
55. Carmo LP, Schupbach-Regula G, Muntener C, Chevance A, Moulin G, Magouras I. Approaches for quantifying antimicrobial consumption per animal species based on national sales data: a Swiss example 2006 to 2013. *Euro Surveill*. (2017) 22:30458. doi: 10.2807/1560-7917.ES.2017.22.6.30458
56. Deckert A, Gow S, Rosengren L, Leger D, Avery B, Daignault D, et al. Canadian integrated program for antimicrobial resistance surveillance (CIPARS) farm program: results from finisher pig surveillance. *Zoonoses Public Health*. (2010) 57(Suppl. 1):71–84. doi: 10.1111/j.1863-2378.2010.01356.x
57. Bosman AL, Loest D, Carson CA, Agunos A, Collineau L, Leger DF. Developing Canadian defined daily doses for animals: a metric to quantify antimicrobial use. *Front Vet Sci*. (2019) 6:220. doi: 10.3389/fvets.2019.00220
58. Postma M, Sjolund M, Collineau L, Losken S, Stark KD, Dewulf J, et al. Assigning defined daily doses animal: a European multi-country experience for antimicrobial products authorized for usage in pigs. *J Antimicrob Chemother*. (2015) 70:294–302. doi: 10.1093/jac/dku347
59. Timmerman T, Dewulf J, Catry B, Feyen B, Opsomer G, de Kruif A, et al. Quantification and evaluation of antimicrobial drug use in group treatments for fattening pigs in Belgium. *Prev Vet Med*. (2006) 74:251–63. doi: 10.1016/j.prevetmed.2005.10.003
60. Morris AM, Brener S, Dresser L, Daneman N, Dellit TH, Avdic E, et al. Use of a structured panel process to define quality metrics for antimicrobial stewardship programs. *Infect Control Hosp Epidemiol*. (2015) 33:500–6. doi: 10.1086/665324
61. Redding LE, Grunwald H, Melofchik C, Meily P, Henry A, Stefanovski D. Comparison of animal daily doses and days of therapy for antimicrobials in species of veterinary importance. *Prev Vet Med*. (2020) 176:104942. doi: 10.1016/j.prevetmed.2020.104942
62. Echtermann T, Muentener C, Sidler X, Kummerlen D. Antimicrobial drug consumption on swiss pig farms: a comparison of Swiss and European

defined daily and course doses in the field. *Front Vet Sci*. (2019) 6:240. doi: 10.3389/fvets.2019.00240

63. Sjolund M, Postma M, Collineau L, Losken S, Backhans A, Belloc C, et al. Quantitative and qualitative antimicrobial usage patterns in farrow-to-finish pig herds in Belgium, France, Germany and Sweden. *Prev Vet Med*. (2016) 130:41–50. doi: 10.1016/j.prevetmed.2016.06.003
64. Grave K, Torren-Edo J, Mackay D. Comparison of the sales of veterinary antibacterial agents between 10 European countries. *J Antimicrob Chemother*. (2010) 65:2037–40. doi: 10.1093/jac/dkq247
65. Sarrazin S, Joosten P, Van Gompel L, Luiken REC, Mevius DJ, Wagenaar JA, et al. Quantitative and qualitative analysis of antimicrobial usage patterns in 180 selected farrow-to-finish pig farms from nine European countries based on single batch and purchase data. *J Antimicrob Chemother*. (2018) 74:807–16. doi: 10.1093/jac/dky503
66. DANMAP. *DANMAP (2015) - Use of Antimicrobial Agents and Occurrence of Antimicrobial Resistance in Bacteria From Food Animals, Food and Humans in Denmark*. Copenhagen (2015).
67. European Medicines Agency. *Sales of Veterinary Antimicrobial Agents in 29 European Countries in 2014*. Amsterdam, Netherlands (2016).
68. Hamilton KW, Fishman NO. Antimicrobial stewardship interventions: thinking inside and outside the box. *Infect Dis Clin North Am*. (2014) 28:301–13. doi: 10.1016/j.idc.2014.01.003
69. Madaras-Kelly K, Jones M, Remington R, Hill N, Huttner B, Samore M. Development of an antibiotic spectrum score based on veterans affairs culture and susceptibility data for the purpose of measuring antibiotic de-escalation: a modified Delphi approach. *Infect Control Hosp Epidemiol*. (2014) 35:1103–13. doi: 10.1086/677633
70. Grijalva CG, Nuorti JP, Griffin MR. Antibiotic prescription rates for acute respiratory tract infections in US ambulatory settings. *JAMA*. (2009) 302:758–66. doi: 10.1001/jama.2009.1163
71. Hopman NEM, Portengen L, Hulscher MEJL, Heederik DJJ, Verheij TJM, Wagenaar JA, et al. Implementation and evaluation of an antimicrobial stewardship programme in companion animal clinics: a stepped-wedge design intervention study. *PLoS ONE*. (2019) 14:e0225124. doi: 10.1371/journal.pone.0225124
72. McNeil V, Cruickshank M, Duguid M. Safer use of antimicrobials in hospitals: the value of antimicrobial usage data. *Med J Australia*. (2010) 193:S114–S7. doi: 10.5694/j.1326-5377.2010.tb04026.x
73. Grimshaw JM, Ivers N, Linklater S, Foy R, Francis JJ, Gude WT, et al. Reinvigorating stagnant science: implementation laboratories and a meta-laboratory to efficiently advance the science of audit and feedback. *BMJ Qual Saf*. (2019) 28:416. doi: 10.1136/bmjqs-2018-008355
74. van Braak M, Visser M, Holtrop M, Statius Muller I, Bont J, van Dijk N. What motivates general practitioners to change practice behaviour? A qualitative study of audit and feedback group sessions in Dutch general practice. *BMJ Open*. (2019) 9:e025286. doi: 10.1136/bmjopen-2018-025286
75. Gude WT, Brown B, van der Veer SN, Colquhoun HL, Ivers NM, Brehaut JC, et al. Clinical performance comparators in audit and feedback: a review of theory and evidence. *Implement Sci*. (2019) 14:39. doi: 10.1186/s13012-019-0887-1
76. Davey P, Marwick CA, Scott CL, Charani E, McNeil K, Brown E, et al. Interventions to improve antibiotic prescribing practices for hospital inpatients. *Cochrane Database Syst Rev*. (2017) 2:CD003543. doi: 10.1002/14651858.CD003543.pub4

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Veterinary Science

ORIGINAL RESEARCH
published: 09 September 2020
doi: 10.3389/fvets.2020.00638

Check for updates

Agreement of Benchmarking High Antimicrobial Usage Farms Based on Either Animal Treatment Index or Number of National Defined Daily Doses

Dolf Kuemmerlen [1]*, Thomas Echtermann [1], Cedric Muentener [2] and Xaver Sidler [1]

[1] Division of Swine Medicine, Department for Farm Animals, Vetsuisse Faculty, University of Zurich, Zurich, Switzerland,
[2] Institute of Veterinary Pharmacology and Toxicology, Vetsuisse Faculty, University of Zurich, Zurich, Switzerland

OPEN ACCESS

Edited by:
Lucie Collineau,
Agence Nationale de Sécurité Sanitaire de l'Alimentation, de l'Environnement et du Travail (ANSES), France

Reviewed by:
Yosuke Sasaki,
University of Miyazaki, Japan
Madelaine Norström,
Norwegian Veterinary Institute (NVI), Norway

***Correspondence:**
Dolf Kuemmerlen
dolf.kuemmerlen@uzh.ch

Specialty section:
This article was submitted to Veterinary Epidemiology and Economics,
a section of the journal Frontiers in Veterinary Science

Received: 02 May 2020
Accepted: 04 August 2020
Published: 09 September 2020

Citation:
Kuemmerlen D, Echtermann T, Muentener C and Sidler X (2020) Agreement of Benchmarking High Antimicrobial Usage Farms Based on Either Animal Treatment Index or Number of National Defined Daily Doses. Front. Vet. Sci. 7:638.
doi: 10.3389/fvets.2020.00638

Introduction: While treatment frequency as an indicator of antimicrobial consumption is often assessed using defined doses, it can also be calculated directly as an Animal Treatment Index (ATI). In this study, the correlation of calculating antimicrobial usage on Swiss pig farms using either national Defined Daily Doses (DDDch) or an ATI (number of treatments per animal per year) and the agreement between the different methods for the identification of high usage farms were investigated.

Material and Methods: The antimicrobial consumption of 893 Swiss pig herds was calculated separately for suckling piglets, weaned piglets, fattening pigs, lactating and gestating sows using the indicators nDDDch (number of DDDch) per animal per year and ATI. Correlations between the indicators were investigated by calculating Spearman's Rho coefficients. The 5, 10, and 25% highest usage farms were determined by applying both methods and the interrater reliability was described using Cohen's Kappa coefficients and visualized by Bland-Altman plots.

Results: The Spearman's Rho coefficients showed strong correlations ($r > 0.5$) between nDDDch/animal/year and ATI. The lowest coefficient was shown for the correlation of both indicators in gestating sows ($r = 0.657$) and the highest in weaned piglets ($r = 0.910$). Kappa coefficients identifying high usage farms were the highest in weaned piglets ($k = 0.71$, 0.85, and 0.91, respectively for 5, 10, and 25% most frequent users) and the lowest in gestating sows ($k = 0.54$, 0.58, and 0.55 for 5, 10, and 25% most frequent users).

Conclusions: In general, the investigated indicators showed strong correlations and a broad agreement in terms of the calculated levels of antimicrobial usage and the identification of high usage farms. Nevertheless, a certain proportion of the farms were defined differently depending on the indicator used. These differences varied by age category and were larger in all age categories except weaned piglets when a higher percentage benchmark was used to define high usage farms. These aspects should be considered when designing scientific studies or monitoring systems and considering which indicator to use.

Keywords: antimicrobial usage, benchmarking, defined daily dose, animal treatment index, Suissano

INTRODUCTION

Antimicrobial resistance poses a threat to both human and animal health (1). The use of antimicrobials is a key factor in the development of antimicrobial resistance in human and veterinary medicine (2, 3). Links between the use of antimicrobials and an increase or decrease in the frequency of antimicrobial resistance have already been described in many studies (4–10). Monitoring systems have been implemented in several countries as an important measure to investigate and control the use of antimicrobials on farms (11–15). In Switzerland, the Suissano Health Programme was developed and launched in 2015 to monitor antimicrobial usage on pig farms (16).

At the beginning of monitoring antimicrobial usage (AMU), only sales of antimicrobial products at the wholesale level were known, so analyses of antimicrobial usage could only be carried out based on these data. In order to be able to compare the calculated amounts of active substances between different populations of farm animals, the European Medicines Agency (EMA) introduced the so-called "Population Correction Unit (PCU)." For each animal species, an average value for the weight at the time of antibiotic treatment is assumed. In this way, all antibiotic quantities can be standardized with a value in kilograms of PCU and different animal species can be compared with each other. However, if the consumption of all antibiotics is given as a total quantity of active substance, no account is taken of the fact that the different classes of active substance, for example penicillins and fluoroquinolones, are used in different dosages (17). For this reason, other indicators were subsequently developed to describe the usage of antimicrobials (18, 19). In human medicine, Defined Daily Doses (DDD) were developed to analyze the usage of various medicines. In analogy, DDD have also been published for veterinary medicine (20). These units describe the daily amount of active ingredient required for the treatment of an animal with a standardized weight. Recently, the EMA published guidelines for the development and publication of indicators for the description of antimicrobial use in veterinary medicine, but has also made such indicators available in the form of Defined Daily Doses (DDDvet) and Defined Course Doses (DCDvet) (21). The DDDvet values based on data from nine European countries have been shown in some cases to differ considerably from the dosages specified in the respective national summaries of product characteristics (SPCs). Therefore, national DDDs and DCDs have been developed in several countries (15, 22, 23). For this reason, separate Defined Daily Doses (DDDch) and Defined Course Doses (DCDch) were developed for Switzerland, some of which consequently showed considerable deviations from the indicators published by the EMA (21, 23–26). Due to these discrepancies, some authors consider the so-called treatment incidence based on used daily doses, which describes the proportion of treated animals at a specific point in time as the method of choice to describe the usage of antimicrobials (19, 27–30). Moreover, an Animal Treatment Index (ATI) was introduced, which described the proportion of treated animals on a farm (31).

The indicators described above are not only used in various monitoring systems to describe the usage of antimicrobials, but in most cases can also be used to identify high usage farms by setting a benchmark, and to determine interventions to lower AMU (11, 32). In this way a successful reduction of antimicrobial usage in pig farms could be demonstrated (32, 33). As the calculation methods sometimes varied considerably, differences in the identification of high usage farms were also possible: a recent study by Kasabova et al. (33) presented such differences for the evaluation of antimicrobial usage in pig and poultry farms in Germany based on Defined Daily Doses or the Used Daily Doses (17, 34, 35).

The joint Suissano/Safety+ Health Programme was launched in 2018 in cooperation of Swiss pig producers, veterinary authorities, pig trading companies and retailers. The aim of the programme was to improve transparency concerning AMU. For participating farms, it is obligatory to record each antimicrobial treatment of pigs by an electronic treatment journal, which is run on personal computers or smart phone applications. All treatments are allocated to five categories (suckling piglets, weaned piglets, fattening pigs, lactating and gestating sows). Each participating farm is quarterly provided with a feedback concerning AMU including a comparison with the AMU levels of all other participating farms. Although being a voluntary programme, the number of participating farms increases every year and by the end of 2020 it is expected that around 2200 farms, or over 50% of all Swiss pig herds will be part of the programme (Service and competence center of the Swiss pig industry, SUISAG; personal communication).

In the present study, antimicrobial usage in five different age categories (suckling piglets, weaned piglets, fattening pigs, gestating and lactating sows) was calculated for 893 pig herds participating in the Suissano/Safety+ Health Programme, either as an ATI or number of DDDch (nDDDch) per animal per year. Correlations between the two indicators and differences in the definition of high usage farms were investigated and visualized.

MATERIALS AND METHODS

Data Collection

All farms involved in the study participated in the Suissano/Safety+ Health Programme in Switzerland. Farmers recorded their antimicrobial usage using electronic treatment journals which were linked to a central database from which all data used in this study were retrieved. For each individual treatment, in addition to the antimicrobial product used and the amount administered, the number of animals treated and the duration of the treatment were recorded. Each treatment was assigned to an age category (suckling piglets, weaned piglets, fattening pigs, gestating sows, and lactating sows). In addition, the numbers of suckling piglets, weaned piglets and fattening pigs produced from all the herds participating in this study once a year had to be reported by the farmer and were registered in the

Abbreviations: AMU, antimicrobial usage; AS, active substance; ATI, Animal Treatment Index; DDDch, Defined Daily Dose Switzerland; DCDch, Defined Course Dose Switzerland; DDDvet, Defined Daily Dose (EMA); DCDvet, Defined Course Dose (EMA); EMA, European Medicines Agency; Min, minimum; Max, maximum; NT, number of treatment days; nDDDch, number of DDDch; SD, standard deviation; SW, standard weight; VMP, Veterinary Medical Product.

TABLE 1 | Number of farms out of the 893 study farms providing complete datasets of AMU for each age category; minimum (min), median, maximum (max), and the total number of animals of the respective age category on these farms.

	Number of farms	Total number of animals	Animals housed or produced		
			Median	Min	Max
Lactating sows	462	12,176	22	5	140
Gestating sows	319	30,522	75	14	536
Suckling piglets	404	1,081,410	2,200	180	16,500
Weaned piglets	360	878,154	2,000	100	15,000
Fattening pigs	531	713,661	1,050	30	8,000

electronic treatment journal, as well as the number of gestating and lactating sows housed on the study farms.

A total of 893 farms provided data for our study. Three hundred and ninety-nine were fattening farms providing data concerning fattening pigs and 481 were breeding farms (housing sows, suckling piglets, and weaned piglets), of which 190 were connected to a sow pool system (housing lactating sows, suckling piglets and weaned piglets or only gestating sows). Thirteen farms kept both weaned piglets and fattening pigs. Two hundred and seventy-seven of the 481 breeding farms also kept at least 30 fattening pigs (farrow-finish farms) and thus provided data concerning all age categories (**Table 1**).

For each age category, data were only included in the dataset if they had been recorded continuously for the study period. The second inclusion criteria meant that data must be entered in the electronic treatment journal no later than 7 days after application, according to the requirements of the Suissano/Safety+ Health Programme.

The total amount of each active substance, administered during the study period (1 year) was added up and divided by the corresponding DDDch value defined by Echtermann et al. (24) multiplied by the standard weight of the corresponding animal group (suckling piglets: 4 kg; weaned piglets: 12 kg; fattening pigs: 50 kg; sows: 220 kg) (36). This calculation was performed separately for each active substance used and then the calculated nDDDch of all active substances used in each age category were summed up. The results for nDDDch were divided by the number of animals kept (sows) or produced (suckling piglets, weaned piglets, fattening pigs) during the study period (1. October 2018 to 30. September 2019). The nDDDch/animal/year was calculated according to the following formula.

$$\frac{\sum amount\ of\ active\ substance\ used\ per\ year\ (mg)}{DDDch\ \left(\frac{mg}{kg}\right) * SW\ \ (kg) * number\ of\ animals\ housed\ per\ year}$$
$$= nDDDch/animal/year$$

The ATI was calculated for each active substance and age category by adding up all treatments performed (number of treatments, NT) and dividing the sum by the number of animals kept or produced during the study period. One treatment was equivalent to one application per animal per day. If, for example, 20 animals were treated on 3 days during a therapy, this corresponded to 60 treatments. For treatments with products containing several antimicrobial agents, each agent was individually evaluated as a treatment.

For treatments with long-acting products, multiplying factors corresponding to the duration of the pharmaceutical activity were used to adjust the treatment duration. However, since these factors only served to compare the usage of antimicrobial ingredients with different pharmaceutical activity, it had no influence on the comparison of the two calculation methods and was disregarded in this study. Recorded treatments that could be clearly identified as incorrect, due to markedly differing numbers of animals, treatment duration or quantities of Veterinary Medical Products (VMPs), were removed from the analysis.

Statistical Analyses

All datasets were prepared with Microsoft Excel® Version 16.30. Statistical analysis was carried out using IBM SPSS® Version 25. All datasets were tested for normal distribution by Shapiro-Wilk test. For not normally distributed datasets, correlations between the indicators were investigated by calculating Spearman's Rho coefficients. Further, the relationship between both indicators was visualized by scatterplots and by linear regression lines using a generalized linear model for the age categories with the lowest and the highest Spearman's Rho coefficients. The interrater reliability between the tested calculation methods for identifying the 5, 10, and 25% highest usage farms was described using Cohen's Kappa coefficients and visualized by Bland-Altman plots of means and differences between ATI and nDDDch/animal/year. Values of ±1.96 multiplied with the standard deviation of the differences mentioned were defined as outliers. The percentage of farms for which agreement could be found when determining frequent users by either nDDDch/animal/year or ATI was calculated for each age category.

RESULTS

Tables 2–6 give an overview of the antimicrobial classes used in the study farms in the different age categories. A total AMU of 649,290 treatments, respectively, 557,830 DDDch was calculated for the study period. This represents a deviation of 14%, when calculating NT or nDDDch, respectively. For the different classes of active substances, strongly deviating agreement of the indicators could be observed: While the results for the usage of sulfonamides in lactating sows were almost identical when calculated with both indicators, the NT with tetracyclines in weaning piglets was almost three times higher than the nDDDch and on the other hand, the nDDDch for treatments with aminoglycosides was 2.5 times higher than the NT. **Table 7** shows the correlation between the calculations of the AMU as ATI or nDDDch/animal/year and the agreement of the definition of 5, 10, and 25% high usage farms, depending on the method chosen. The highest correlation coefficients between both indicators could be found for lactating sows and weaned piglets and the lowest for

TABLE 2 | Total, minimum (min), median, maximum (max), 10% (0.1), 25% (0.25), 75% (0.75), 90% (0.9) percentiles and standard deviation (SD) of AMU in suckling piglets of the study farms measured using the indicators NT, ATI, nDDDch, and nDDDch/animal/year (nDDDch/a/y) displayed by active substance (AS).

	Suckling piglets									
AS	**Indicator**	**Total**	**Min**	**0.10**	**0.25**	**Median**	**0.75**	**0.90**	**Max**	**SD**
Polypeptides	NT	11,095	0.00	0.00	0.00	0.00	0.00	52	2,184	140
	ATI	0.06	0.00	0.00	0.00	0.00	0.00	0.02	0.26	0.03
	nDDDch	6,508	0.00	0.00	0.00	0.00	0.00	29	1,051	82
	nDDDch/a/y	0.01	0.00	0.00	0.00	0.00	0.00	0.01	0.39	0.03
Cephalosporines	NT	38	0.00	0.00	0.00	0.00	0.00	0.00	38	1.89
	ATI	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.03	0.00
	nDDDch	15	0.00	0.00	0.00	0.00	0.00	0.00	15	0.75
	nDDDch/a/y	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.01	0.00
Penicillins	NT	85,868	0.00	0.00	6	36	150	506	5,429	524
	ATI	0.08	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
	nDDDch	69,295	0.00	0.00	1.12	19	144	488	5,263	467
	nDDDch/a/y	0.06	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Fluoroquinolones	NT	6,453	0.00	0.00	0.00	0.00	0.00	37	678	61
	ATI	0.01	0.00	0.00	0.00	0.00	0.00	0.02	0.31	0.02
	nDDDch	9,600	0.00	0.00	0.00	0.00	0.00	29	1,520	123
	nDDDch/a/y	0.01	0.00	0.00	0.00	0.00	0.00	0.01	0.65	0.05
Aminoglycosides	NT	13,524	0.00	0.00	0.00	0.00	1.00	62	1,574	142
	ATI	0.01	0.00	0.00	0.00	0.00	0.00	0.03	0.33	0.03
	nDDDch	31,598	0.00	0.00	0.00	0.00	0.72	148	3,921	343
	nDDDch/a/y	0.03	0.00	0.00	0.00	0.00	0.00	0.05	1.19	0.09
Macrolides	NT	243	0.00	0.00	0.00	0.00	0.00	0.00	120	7.09
	ATI	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.17	0.01
	nDDDch	244	0.00	0.00	0.00	0.00	0.00	0.00	104	7.31
	nDDDch/a/y	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.13	0.01
Tetracyclines	NT	11,973	0.00	0.00	0.00	0.00	0.00	60	1,760	144
	ATI	0.01	0.00	0.00	0.00	0.00	0.00	0.03	0.54	0.05
	nDDDch	8,332	0.00	0.00	0.00	0.00	0.00	39	1,329	98
	nDDDch/a/y	0.01	0.00	0.00	0.00	0.00	0.00	0.02	0.47	0.04
Trimethoprim	NT	4,202	0.00	0.00	0.00	0.00	0.00	16	490	45
	ATI	0.00	0.00	0.00	0.00	0.00	0.00	0.01	0.22	0.02
	nDDDch	6,241	0.00	0.00	0.00	0.00	0.00	15	884	76
	nDDDch/a/y	0.01	0.00	0.00	0.00	0.00	0.00	0.01	0.24	0.03
Sulfonamides	NT	4,445	0.00	0.00	0.00	0.00	0.00	20	490	45
	ATI	0.00411	0.00	0.00	0.00	0.00	0.00	0.01	0.22	0.02
	nDDDch	6,483	0.00	0.00	0.00	0.00	0.00	18	884	76
	nDDDch/a/y	0.01	0.00	0.00	0.00	0.00	0.00	0.01	0.24	0.03
Total	NT	137,841	1.00	24	45	144	352	938	5,934	677
	ATI	0.13	0.00	0.01	0.02	0.07	0.15	0.27	1.50	0.15
	nDDDch	138,316	0.24	20	32	125	378	887	6,042	722
	nDDDch/a/y	0.13	0.00	0.01	0.02	0.06	0.16	0.35	1.83	0.19

gestating sows and fattening pigs. Both agreement (a) and the interrater reliability (Kappa coefficient) of the investigated indicators were higher when identifying the 5 and 10% high usage farms, compared to the identified 25% high usage farms (**Table 7**). Exception were the weaned piglets, where Kappa coefficient became higher when larger proportions of farms were identified as high users. Generally, weaned piglets showed the best agreement (≥96%) irrespective of the percentage of high usage farms identified and the best correlation between the indicators.

The correlation between both methods is further demonstrated with the data from weaned piglets as the age category with the best correlation between both indicators and with gestating sows, where the lowest

TABLE 3 | Total, minimum (min), median, maximum (max), 10% (0.1), 25% (0.25), 75% (0.75), 90% (0.9) percentiles and standard deviation (SD) of AMU in weaned piglets of the study farms measured using the indicators NT, ATI, nDDDch, and nDDDch/animal/year (nDDDch/a/y) displayed by active substance (AS).

	Weaned piglets									
AS	**Indicator**	**Total**	**Min**	**0.10**	**0.25**	**Median**	**0.75**	**0.90**	**Max**	**SD**
Polypeptides	NT	116,729	1.00	102	270.	740.	1,800	3,060	21,340	2,986
	ATI	0.13	0.00	0.00	0.00	0.00	0.00	0.40	2.40	0.38
	nDDDch	102,472	0.10	85	192	668	1,653	2,974	14,503	2,412
	nDDDch/a/y	0.12	0.00	0.00	0.00	0.00	0.00	0.31		0.35
Cephalosporines	NT	3	3.00	3.00	3.00	3.00	3.00	3.00	3.00	–
	ATI	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
	nDDDch	6.25	6.25	6.25	6.25	6.25	6.25	6.25	6.25	–
	nDDDch/a/y	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Penicillins	NT	51,621	0.00	0.00	0.00	9.00	40	205	10,619	717
	ATI	0.06	0.00	0.00	0.00	0.00	0.02	0.07	1.76	0.17
	nDDDch	52,086	0.00	0.00	0.00	3.33	40	196	10,700	718
	nDDDch/a/y	0.06	0.00	0.00	0.00	0.00	0.02	0.08	1.89	0.17
Fluoroquinolones	NT	2,487	1.00	2.00	4.00	12	39	253	717	157
	ATI	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.42	0.02
	nDDDch	3,626	0.42	2.11	5.00	13	33	236	1,296	268
	nDDDch/a/y	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.42	0.03
Aminoglycosides	NT	2,550	1.00	3.00	4.75	11	46	81	37	6
	ATI	0.00	0.00	0.00	0.00	0.00	0.00	0.01	0.11	0.01
	nDDDch	4,250	1.25	2.72	6.67	22	77	152	534	94
	nDDDch/a/y	0.00	0.00	0.00	0.00	0.00	0.00	0.01	0.11	0.01
Macrolides	NT	28,938	10	38	85	231	460	872	12,030	1,770
	ATI	0.03	0.00	0.00	0.00	0.00	0.00	0.03	2.51	0.18
	nDDDch	24,993	23	46	11	233	497	815	8,495	1,244
	nDDDch/a/y	0.03	0.00	0.00	0.00	0.00	0.00	0.04	1.77	0.15
Tetracyclines	NT	98,860	1.00	5.00	18	71	429	1,480	21,340	2,914
	ATI	0.11	0.00	0.00	0.00	0.00	0.01	0.16	2.96	0.31
	nDDDch	40,316	0.20	4.64	11	45	320	798	8,495	928
	nDDDch/a/y	0.05	0.00	0.00	0.00	0.00	0.00	0.09	1.77	0.18
Trimethoprim	NT	11,313	1.00	2.30	8.75	30	139	359	3,652	486
	ATI	0.01	0.00	0.00	0.00	0.00	0.00	0.01	0.73	0.06
	nDDDch	23,306	1.17	3.31	8.00	332	161	371	3,347	465
	nDDDch/a/y	0.03	0.00	0.00	0.00	0.00	0.00	0.01	1.19	0.09
Sulfonnamides	NT	46,981	0.00	0.00	0.00	0.00	5.75	211	12,030	789
	ATI	0.05	0.00	0.00	0.00	0.00	0.00	0.11	2.51	0.21
	nDDDch	65,870	0.00	0.00	0.00	0.00	6.84	206	8,084	605
	nDDDch/a/y	0.08	0.00	0.00	0.00	0.00	0.00	0.11	1.96	0.21
Pleuromutilins	NT	8,104	6.00	164	400	1,269	1,671	2,869	3,667	1,429
	ATI	0.01	0.00	0.00	0.00	0.00	0.00	0.00	0.76	0.06
	nDDDch	7,014	4.00	93	225	879.00	2,136	3,770	4,860	1,991
	nDDDch/a/y	0.01	0.00	0.00	0.00	0.00	0.00	0.00	1.01	0.06
Total	NT	367,586	1.00	4.00	20	98.00	590	2,135	42,842	3,741
	ATI	0.31	0.00	0.00	0.01	0.04	0.29	1.12	7.52	0.81
	nDDDch	300,168	0.10	3.58	15	91	642	1,933	25,076	2,209
	nDDDch/a/y	0.34	0.00	0.00	0.01	0.06	0.27	0.97	17	0.67

correlation was found (**Figures 1**, **2**). The interrater reliability is visualized by Bland-Altman plots for these age categories (**Figures 3**, **4**). Bland Altman plots of weaned piglets showed five out of 360 (2%) to be outliers, while in gestating sows this was shown to be 13 out of 319 (4%).

TABLE 4 | Total, minimum (min), median, maximum (max), 10% (0.1), 25% (0.25), 75% (0.75), 90% (0.9) percentiles and standard deviation (SD) of AMU in fattening pigs of the study farms measured using the indicators NT, ATI, nDDDch and nDDDch/animal/year (nDDDch/a/y) displayed by active substance (AS).

	Fattening pigs									
AS	**Indicator**	**Total**	**Min**	**0.10**	**0.25**	**Median**	**0.75**	**0.90**	**Max**	**SD**
Cephalosporines	NT	9	2.00	2.20	2.50	3.00	3.50	3.80	4.00	1.00
	ATI	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.01	0.00
	nDDDch	16	3.75	4.00	4.38	5.00	6.00	6.60	7.00	1.64
	nDDDch/a/y	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.01	0.00
Penicillins	NT	45,976	0.00	2.00	5.00	16	48	134	7,622	416
	ATI	0.06	0.00	0.00	0.01	0.02	0.05	0.10	2.72	0.22
	nDDDch	39,141	0.00	0.08	0.98	7.20	40	120	7,965	425
	nDDDch/a/y	0.05	0.00	0.00	0.00	0.01	0.04	0.11	3.19	0.24
Fluoroquinolone	NT	144	1.00	1.20	3.00	3.50	17	36	44	15
	ATI	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.07	0.00
	nDDDch	160	0.70	1.92	3.15	7.00	21	30	39	13
	nDDDch/a/y	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.08	0.01
Aminoglycosides	NT	1,524	1.00	1.80	3.00	6.00	18	42	96	20
	ATI	0.00	0.00	0.00	0.00	0.00	0.00	0.01	0.14	0.01
	nDDDch	1,919	0.56	1.56	3.00	8.70	22	53	223	31
	nDDDch/a/y	0.00	0.00	0.00	0.00	0.00	0.00	0.01	0.15	0.01
Macrolides	NT	11,919	3.00	3.00	7.00	95	811	1,685	7,000	1,859
	ATI	0.02	0.00	0.00	0.00	0.00	0.00	0.00	2.80	0.16
	nDDDch	12,296	0.20	1.23	7.05	73	449	1,680	8,330	2,219
	nDDDch/a/y	0.02	0.00	0.00	0.00	0.00	0.00	0.00	3.33	0.16
Tetracyclines	NT	25,152	1.00	2.00	4.00	10.00	37	224	7,000	879
	ATI	0.04	0.00	0.00	0.00	0.00	0.00	0.01	2.80	0.21
	nDDDch	20,633	0.20	1.20	2.42	8.90	18	94	8,330	910
	nDDDch/a/y	0.03	0.00	0.00	0.00	0.00	0.00	0.01	3.33	0.19
Trimethoprim	NT	8,966	1.00	1.70	2.75	6.00	183	493	6,000	1,133
	ATI	0.01	0.00	0.00	0.00	0.00	0.00	0.00	4.00	0.23
	nDDDch	5,308	0.70	1.74	3.08	6.13	106	363	3,199	606
	nDDDch/a/y	0.01	0.00	0.00	0.00	0.00	0.00	0.00	2.13	0.13
Sulfonamides	NT	29,324	0.00	0.00	0.00	0.00	0.00	0.00	12,000	622.20
	ATI	0.04	0.00	0.00	0.00	0.00	0.00	0.00	8.00	0.49
	nDDDch	22,343	0.00	0.00	0.00	0.00	0.00	0.00	8,330	473
	nDDDch/a/y	0.03	0.00	0.00	0.00	0.00	0.00	0.00		0.31
Pleuromutilines	NT	2,264	1.44	3.02	4.76	15	38	388	1,333	368
	ATI	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.35	0.02
	nDDDch	2,068	2.00	3.00	6.25	18	62	723	1,000	356
	nDDDch/a/y	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.65	0.03
Total	NT	125,278	1.00	3.00	8.00	24	75	236	25,000	1,455
	ATI	0.18	0.00	0.00	0.01	0.03	0.06	0.15	12.05	0.91
	nDDDch	103,884	0.05	1.20	3.62	16	62	178	32,955	1,558
	nDDDch/a/y	0.15	0.00	0.00	0.00	0.02	0.05	0.15	13	0.75

DISCUSSION

In the present study we were able to assess the correlation of the indicators nDDDch/animal/year and ATI when measuring AMU on pig farms and the agreement in the definition of high usage farms. The number of treatment days NT and nDDDch calculated for the study farms showed marked differences for some active substances, while for others the results were similar. The degree of agreement between the two indicators was therefore most likely dependent on which antimicrobial substances were used in an age category.

The Spearman's Rho coefficients for correlations between the indicators ATI and nDDDch/animal/year observed were statistically determined as moderate (>0.6) for fattening pigs and gestating sows and as strong or very strong (>0.7) for suckling piglets, weaned piglets and lactating sows (37). The

TABLE 5 | Total, minimum (min), median, maximum (max), 10% (0.1), 25% (0.25), 75% (0.75), 90% (0.9) percentiles and standard deviation (SD) of AMU in lactating sows of the study farms measured using the indicators NT, ATI, nDDDch and nDDDch/animal/year (nDDDch/a/y) displayed by active substance (AS).

	Lactating sows									
AS	**Indicator**	**Total**	**Min**	**0.10**	**0.25**	**Median**	**0.75**	**0.90**	**Max**	**SD**
Cephalosporines	NT	21	0.00	0.00	0.00	0.00	0.00	0.00	10	0.63
	ATI	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.50	0.03
	nDDDch	17	0.00	0.00	0.00	0.00	0.00	0.00	7.91	0.50
	nDDDch/a/y	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.40	0.03
Penicillins	NT	3,212	0.00	0.00	0.00	2.00	8.00	15	244	17
	ATI	0.26	0.00	0.00	0.00	0.09	0.30	0.66	6.35	0.56
	nDDDch	2,528	0.00	0.00	0.00	0.28	4.55	12	295	19
	nDDDch/a/y	0.21	0.00	0.00	0.00	0.01	0.18	0.50	6.85	0.63
Fluoroquinolone	NT	271	0.00	0.00	0.00	0.00	0.00	1.00	31	2.44
	ATI	0.02	0.00	0.00	0.00	0.00	0.00	0.05	0.97	0.10
	nDDDch	291	0.00	0.00	0.00	0.00	0.00	1.61	32	2.63
	nDDDch/a/y	0.02	0.00	0.00	0.00	0.00	0.00	0.06	1.02	0.11
Aminoglycosides	NT	1,587	0.00	0.00	0.00	0.00	2.00	11	204	12
	ATI	0.13	0.00	0.00	0.00	0.00	0.10	0.41	10	0.55
	nDDDch	1,573	0.00	0.00	0.00	0.00	2.27	10	189	11
	nDDDch/a/y	0.13	0.00	0.00	0.00	0.00	0.10	0.42	9.46	0.53
Macrolides	NT	8	0.00	0.00	0.00	0.00	0.00	0.00	7.00	0.33
	ATI	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.26	0.01
	nDDDch	12	0.00	0.00	0.00	0.00	0.00	0.00	12	0.55
	nDDDch/a/y	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.44	0.02
Tetracyclines	NT	347	0.00	0.00	0.00	0.00	0.00	0.00	88	5.26
	ATI	0.03	0.00	0.00	0.00	0.00	0.00	0.00	1.83	0.15
	nDDDch	244	0.00	0.00	0.00	0.00	0.00	0.00	80	4.31
	nDDDch/a/y	0.02	0.00	0.00	0.00	0.00	0.00	0.00	1.67	0.12
Trimethoprim	NT	2,251	0.00	0.00	0.00	2.00	6.00	14.00	92.00	8.31
	ATI	0.18	0.00	0.00	0.00	0.08	0.29	0.56	2.92	0.32
	nDDDch	2,222	0.00	0.00	0.00	1.61	6.75	13.96	64.36	7.91
	nDDDch/a/y	0.18	0.00	0.00	0.00	0.08	0.29	0.51	2.65	0.34
Sulfonamides	NT	2,262	0.00	0.00	0.00	2.00	6.00	14.00	92.00	8.31
	ATI	0.19	0.00	0.00	0.00	0.08	0.29	0.56	2.92	0.32
	nDDDch	2,237	0.00	0.00	0.00	1.64	6.80	13.96	64.36	7.92
	nDDDch/a/y	0.18	0.00	0.00	0.00	0.08	0.30	0.51	2.65	0.34
Total	NT	9,959	1.00	3.00	6.00	13	25	44	331	32
	ATI	0.82	0.04	0.15	0.29	0.59	1.00	1.85	16.55	1.13
	nDDDch	9,124.00	0.05	2.27	4.78	11	25	41.73	390	30
	nDDDch/a/y	0.75	0.00	0.11	0.23	0.53	0.98	1.77	15	1.14

Kappa coefficient demonstrated a substantial agreement (>0.6) when defining 5% high usage farms for all age categories, except gestating sows. If defining 10 and 25% high usage farms, a moderate (>0.4) to substantial agreement was shown for all age categories except weaned piglets, where very good agreement (>0.8) could be shown (38).

The agreement of both indicators concerning the identification of high usage farms generally was the better, the smaller the percentage of farms was determined as high usage farms. If only 5% of the farms were determined as high users, even in age categories showing lower Kappa coefficient and lower correlations between both indicators, such as gestating sows or fattening pigs, more than 95% of the high usage farms were identified in agreement of both indicators. When 25% of the farms were determined as high users, the agreement between both indicators decreased to 75 and 77% in fattening pigs and gestating sows, respectively, due to the lower correlation and Kappa coefficient, while in weaned piglets with the best correlation and highest Kappa coefficient, the agreement still was 96%.

A final statement on whether the agreement between two indicators is sufficient or not cannot be made. Since only the degree of agreement can be shown, an extensive discussion is necessary to precisely evaluate which indicator is more suitable

TABLE 6 | Total, minimum (min), median, maximum (max), 10% (0.1), 25% (0.25), 75% (0.75), 90% (0.9) percentiles and standard deviation (SD) of AMU in gestating sows of the study farms measured using the indicators NT, ATI, nDDDch and nDDDch/animal/year (nDDDch/a/y) displayed by active substance (AS).

	Gestating sows									
AS	**Indicator**	**Total**	**Min**	**0.10**	**0.25**	**Median**	**0.75**	**0.90**	**Max**	**SD**
Cephalosporines	NT	74	0.00	0.00	0.00	0.00	0.00	0.00	30	2.13
	ATI	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.21	0.02
	nDDDch	76	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
	nDDDch/a/y	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Penicillins	NT	6,908	0.00	1.00	4.00	9.00	20	46	540	47
	ATI	0.23	0.00	0.02	0.05	0.11	0.28	0.50	6.02	0.50
	nDDDch	4,438	0.00	0.07	0.57	3.55	12	30	650	46
	nDDDch/a/y	0.15	0.00	0.00	0.01	0.05	0.15	0.33	6.50	0.47
Fluoroquinolones	NT	55	0.00	0.00	0.00	0.00	0.00	0.00	16	1.31
	ATI	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.27	0.02
	nDDDch	68	0.00	0.00	0.00	0.00	0.00	0.00	26	1.79
	nDDDch/a/y	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.44	0.03
Aminoglycosides	NT	724	0.00	0.00	0.00	0.00	0.00	5.00	88	8.38
	ATI	0.02	0.00	0.00	0.00	0.00	0.00	0.09	0.73	0.08
	nDDDch	634	0.00	0.00	0.00	0.00	0.00	4.53	91	7.60
	nDDDch/a/y	0.02	0.00	0.00	0.00	0.00	0.00	0.07	0.58	0.07
Macrolides	NT	29	0.00	0.00	0.00	0.00	0.00	0.00	18	1.08
	ATI	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.13	0.01
	nDDDch	32	0.00	0.00	0.00	0.00	0.00	0.00	25	1.41
	nDDDch/a/y	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.18	0.01
Tetracyclines	NT	381	0.00	0.00	0.00	0.00	0.00	0.20	93	6.62
	ATI	0.01	0.00	0.00	0.00	0.00	0.00	0.00	0.66	0.07
	nDDDch	155	0.00	0.00	0.00	0.00	0.00	0.00	27	2.62
	nDDDch/a/y	0.01	0.00	0.00	0.00	0.00	0.00	0.00	0.25	0.03
Trimethoprim	NT	221	0.00	0.00	0.00	0.00	0.00	1.00	25	2.74
	ATI	0.01	0.00	0.00	0.00	0.00	0.00	0.01	0.34	0.03
	nDDDch	228	0.00	0.00	0.00	0.00	0.00	1.39	29	2.97
	nDDDch/a/y	0.01	0.00	0.00	0.00	0.00	0.00	0.01	0.39	0.04
Sulfonamides	NT	234	0.00	0.00	0.00	0.00	0.00	1.20	25	2.90
	ATI	0.01	0.00	0.00	0.00	0.00	0.00	0.02	0.34	0.03
	nDDDch	243	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
	nDDDch/a/y	0.01	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Total	NT	8,626	1.00	3.00	6.00	12.00	27	65	548	51
	ATI	0.28	0.01	0.04	0.08	0.17	0.37	0.64	6.32	0.54
	nDDDch	5,873	0.02	0.87	2.73	6.67	18	340	660	49
	nDDDch/a/y	0.19	0.00	0.01	0.03	0.10	0.23	0.49	6.60	0.51

when planning a scientific study or when establishing and implementing a monitoring system for which a benchmark should be set (39).

Since the DDDch have been defined on the basis of SPCs in Switzerland, in order to achieve a good agreement between the indicators it is necessary that antimicrobial treatments are carried out as closely as possible to the recommendations found in the SPCs. Any change in dosage leads to a change in the number of DDD, but not in the number of treatments. According to our analyses, for some substances, significantly different levels of DDDch and ATI were calculated per age category. This result is probably due to the effect described above and is also responsible for both the outlier shown in our Bland-Altman Plots and decreased agreement when identifying high usage farms. On the other hand, the simultaneous calculation of both indicators may contribute to a mutual plausibility check of the results by, for example, identifying incorrect entries into the electronic treatment journal.

The divergent agreement between the indicators when comparing the different age categories could also be due to different indications, treatment patterns and antimicrobials used. For example, gestating sows often are suffering from lameness compared to weaned piglets which are more frequently affected by diarrhea. Further research is needed on this issue. Also, if

TABLE 7 | Agreement (*a*) in percent when defining 5, 10, and 25% high usage farms by calculating AMU with either ATI or nDDDch/animal/year for five age categories (fattening pigs, weaned piglets, suckling piglets, lactating and gestating sows), interrater reliability between both indicators expressed as Kappa coefficient (*k*) and correlation between both indicators displayed using Spearman's Rho (*r*) coefficients.

	5% High usage		10% High usage		25% High usage		Correlation
	a	k	a	k	a	k	r
Fattening pigs	98%	0.844	93%	0.671	75%	0.510	0.673
Weaned piglets	97%	0.708	97%	0.846	96%	0.911	0.910
Suckling piglets	96%	0.643	91%	0.528	77%	0.554	0.793
Lactating sows	96%	0.634	96%	0.771	88%	0.77	0.889
Gestating sows	95%	0.539	92%	0.583	77%	0.553	0.657

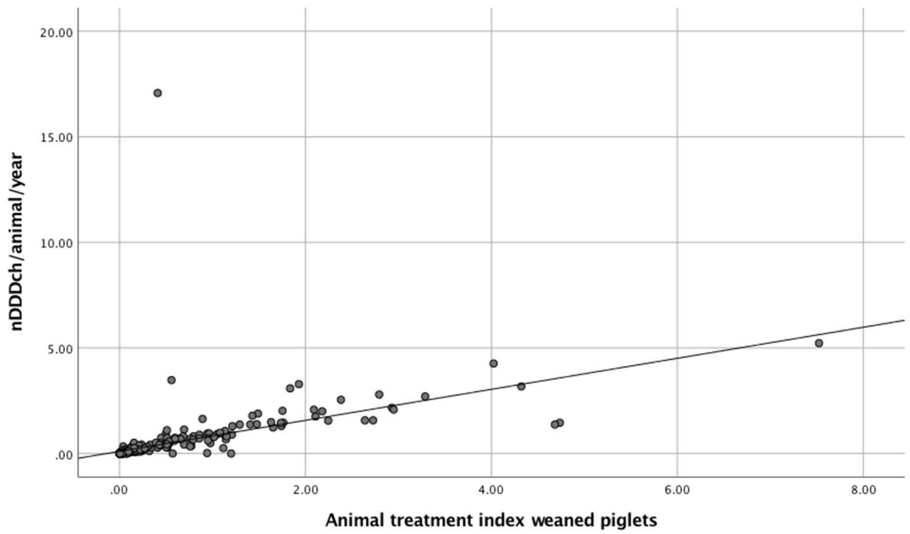


FIGURE 1 | Scatterplots and linear regression of AMU calculated either as Animal Treatment Index (ATI) or the number of DDDch/animal/year (nDDDch/animal/year) for weaned piglets from 360 study farms.

actual weights at treatment deviate from the standard weights used for the calculation of DDDch, it may contribute to differences between DDDch and ATI. While, for example, a rather uniform weight during treatment can be expected for sows particularly in the case of suckling pigs, stronger deviations can be assumed between a newly born piglet with an average weight of 1.2 kg compared to a 4-week-old piglet with a multiple of this weight.

Differences between the indicators for AMU have been shown before (25, 34, 40). An increasing number of monitoring systems are being established worldwide, however, the harmonization of the measurement of usage has so far been less advanced (17). While in some countries the evaluation of antimicrobial usage is based on DDDs, an ATI or comparable methods are also used in other countries, including Switzerland (14, 15).

Treatment frequency calculations based on DDD are only an estimate of AMU on farms because they are calculated using standardized weights and doses. This indicator may be more appropriate if it is difficult to obtain precise information concerning the AMU, especially the number of treatments, the dosage used, and the weight of the treated animals. However, if this information can be collected reliably and accurately, the calculation of an ATI or treatment frequency based on used daily doses is feasible (27). On the other hand, it must also be taken into account that development of bacterial resistance also occurs outside the animal by excreted metabolites after antimicrobial therapy. In this situation, the quantities of antimicrobials used on a farm should also be taken into account (41, 42). These can be derived more reliably from DDDs, where standard weights and dosages are used and thus standardized antimicrobial quantities. To calculate the quantities of active substances used from an ATI, further information on the weight of the treated animals and the dosage applied is necessary.

In the present study it could be shown that despite the generally good agreement between the two indicators, a considerable proportion of the farms were nevertheless rated differently as high usage farms depending on the indicator used. In Switzerland, different monitoring systems are concurrently measuring AMU on farms. The use of different indicators may cause a considerable lack of compliance by farm managers when farm rating varies depending on the monitoring system used and may adversely affect the acceptance of such programmes.

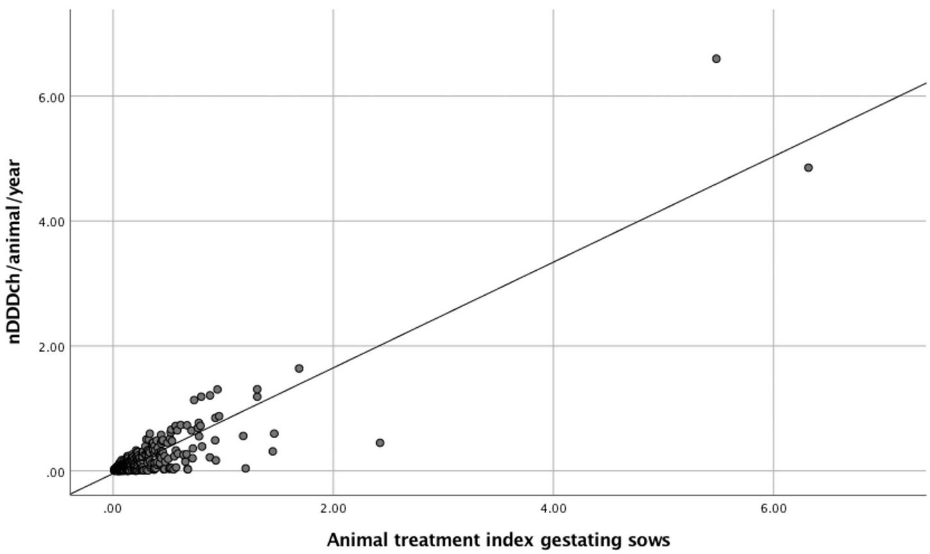


FIGURE 2 | Scatterplots and linear regression of AMU calculated either as Animal Treatment Index (ATI) or the number of DDDch/animal/year (nDDDch/animal/year) for gestating sows from 319 study farms.

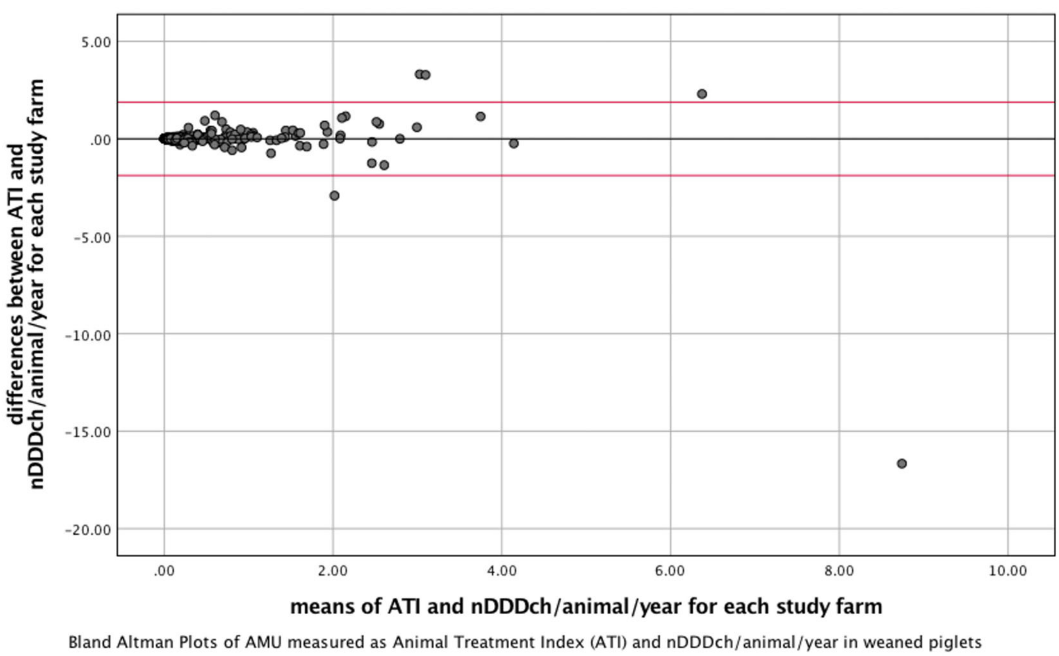


FIGURE 3 | Bland-Altman Plots visualizing interrater reliability of the indicators Animal Treatment Index (ATI) and number of DDDch (nDDDch)/animal/year for 360 farms housing weaned piglets. X-Axis: means of ATI and nDDDch/animal/year; Y-axis: differences between ATI and nDDDch/animal/year. Red lines: ±1.96 * standard deviation of the datasets calculated from the differences between ATI and nDDDch/animal/year.

Although many discussions are taking place regarding the comparability of different indicators, other factors should be taken into account which also influence the calculation of AMU: different data sources and deviating values provided, e.g., concerning the kept animals, may also result in different outcomes. In Switzerland, the numbers of animals reported to the veterinary authorities are in some cases significantly different from those used by the on-farm reproduction software, which is used as a data source for the number of animals on the farms (43).

Our earlier investigations have shown that within the Suissano/Safety+ Health Programme significant changes in the usage of antimicrobials could be achieved by only measuring and

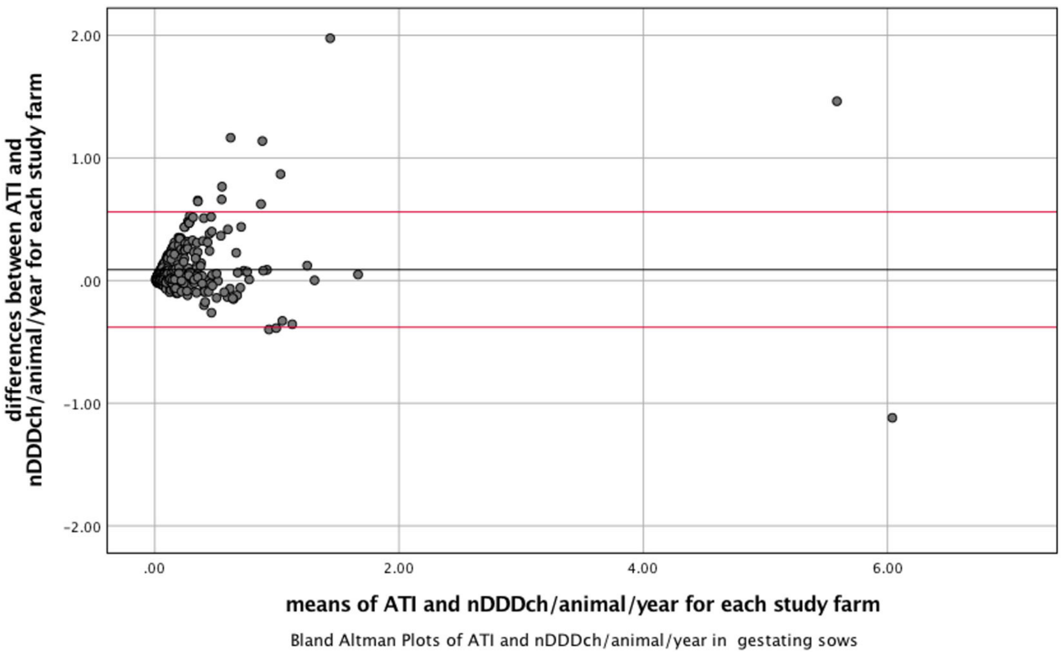


FIGURE 4 | Bland-Altman Plots visualizing interrater reliability of the indicator Animal Treatment Index (ATI) and number of DDDch (nDDDch)/animal/year for 319 farms housing gestating sows. X-Axis: mean of ATI and nDDDch/animal/year; Y-axis: differences between ATI and nDDDch/animal/year. Red lines: ±1.96 * standard deviation of the datasets calculated from the differences between ATI and nDDDch/animal/year.

communicating levels of antimicrobial usage, without defining a benchmark (44). Thus, if a benchmark is not necessarily needed and the good correlation of both indicators found in the present study is taken into consideration, it may be of secondary importance which indicator to choose for the aim of reducing AMU.

It is also important to point out that irrespective of the method of calculation, a long-term reduction in the usage of antimicrobials while respecting animal health standards can only be feasibly achieved through close collaboration with veterinary professionals. Improving biosecurity as well as animal health e.g., by introducing vaccination protocols, has a positive impact on AMU (45). Ideally, any AMU monitoring programme will intensify veterinary advice and ensure a reduced AMU without impairing animal health rather than rating farms based only on their antimicrobial usage.

CONCLUSIONS

In the present study, strong correlations and a broad agreement in identifying high usage farms could be demonstrated for the indicators nDDDch/animal/year and ATI. Nevertheless, depending on the indicator used a considerable proportion of the study farms were assessed differently. These differences varied by age category and were larger with a higher proportion of farms determined as high usage farms. These aspects have to be considered when designing scientific studies or monitoring systems and when deciding on which indicator to use.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

AUTHOR CONTRIBUTIONS

DK drafted the manuscript. DK, CM, and XS designed and directed the study design. TE prepared data processing. All authors contributed to the article and approved the submitted version.

ACKNOWLEDGMENTS

We would like to thank SUISAG and Qualiporc and all participating farmers for providing the data for this study.

REFERENCES

1. Prestinaci F, Pezzotti P, Pantosti A. Antimicrobial resistance: a global multifaceted phenomenon. *Pathog Glob Health.* (2015) 109:309–18. doi: 10.1179/2047773215Y.0000000030

2. Alali WQ, Scott HM, Harvey RB, Norby B, Lawhorn DB, Pillai SD. Longitudinal study of antimicrobial resistance among *Escherichia coli* isolates from integrated multisite cohorts of humans and swine. *Appl Environ Microbiol.* (2008) 74:3672–81. doi: 10.1128/AEM.02624-07

3. Alali WQ, Scott HM, Christian KL, Fajt VR, Harvey RB, Lawhorn DB. Relationship between level of antibiotic use and resistance among *Escherichia coli* isolates from integrated multi-site cohorts of humans and swine. *Prev Vet Med.* (2009) 90:160–7. doi: 10.1016/j.prevetmed.2009.05.018
4. Aarestrup FM. Association between the consumption of antimicrobial agents in animal husbandry and the occurrence of resistant bacteria among food animals. *Int J Antimicrob Agents.* (1999) 12:279–85. doi: 10.1016/S0924-8579(99)90059-6
5. Akwar HT, Poppe C, Wilson J, Reid-Smith RJ, Dyck M, Waddington J, et al. Associations of antimicrobial uses with antimicrobial resistance of fecal *Escherichia coli* from pigs on 47 farrow-to-finish farms in Ontario and British Columbia. *Can J Vet Res.* (2008) 72:202–10.
6. Statens Serum Institut National Veterinary Institute TUoDNFI, Technical University of Denmark. *DANMAP 2017 - Use of Antimicrobial Agents and Occurrence of Antimicrobial Resistance in Bacteria From Food Animals, Food and Humans in Denmark*. (2018). Available online at: https://www.danmap.org/-/media/arkiv/projekt-sites/danmap/danmap-reports/danmap-2017/danmap2017.pdf?la=en (accessed May 01, 2020).
7. *MARAN 2018. Monitoring of Antimicrobial Resistance and Antibiotic Usage in Animals in the Netherlands in 2017.* Available online at: https://www.wur.nl/en/show/Maran-rapport-2018.htm (accessd May 01, 2020).
8. Callens B, Cargnel M, Sarrazin S, Dewulf J, Hoet B, Vermeersch K, et al. Associations between a decreased veterinary antimicrobial use and resistance in commensal *Escherichia coli* from Belgian livestock species (2011-2015). *Prev Vet Med.* (2018) 157:50–8. doi: 10.1016/j.prevetmed.2017.10.013
9. Andersen VD, DE Knegt LV, Munk P, Jensen MS, Agersø Y, Aarestrup FM, et al. The association between measurements of antimicrobial use and resistance in the faeces microbiota of finisher batches. *Epidemiol Infect.* (2017) 145:2827–37. doi: 10.1017/S0950268817001285
10. Andersen VD, Munk P, de Knegt LV, Jensen MS, Aarestrup FM, Vigre H. Validation of the register-based lifetime antimicrobial usage measurement for finisher batches based on comparison with recorded antimicrobial usage at farm level. *Epidemiol Infect.* (2018) 146:1–9. doi: 10.1017/S0950268818000134
11. Dupont N, Diness LH, Fertner M, Kristensen CS, Stege H. Antimicrobial reduction measures applied in Danish pig herds following the introduction of the "Yellow Card" antimicrobial scheme. *Prev Vet Med.* (2017) 138:9–16. doi: 10.1016/j.prevetmed.2016.12.019
12. Stege H BF, Jacobsen E, Thougaard A. VETSTAT-the Danish system for surveillance of the veterinary use of drugs for production animals. *Prev Vet Med.* (2003) 57:105–15. doi: 10.1016/S0167-5877(02)00233-7
13. Merle R, Hajek P, Käsbohrer A, Hegger-Gravenhorst C, Mollenhauer Y, Robanus M, et al. Monitoring of antibiotic consumption in livestock: a German feasibility study. *Prev Vet Med.* (2012) 104:34–43. doi: 10.1016/j.prevetmed.2011.10.013
14. Hemme M, Ruddat I, Hartmann M, Werner N, van Rennings L, Käsbohrer A, et al. Antibiotic use on German pig farms - A longitudinal analysis for 2011, 2013 and 2014. *PLoS ONE.* (2018) 13:e0199592. doi: 10.1371/journal.pone.0199592
15. AACTING-network. *Description of Existing Monitoring Systems for Collection, Analysis, Benchmarking and Reporting of Farm-Level Veterinary Antimicrobial Usage-Version*. Available online at: https://aacting.org/monitoring-systems/ (accessed May 1, 2020).
16. Schaller C, Caspari K, Kümmerlen D. SUIS Sano – Messung, Bewertung und Steuerung des Antibiotikaverbrauchs in schweizerischen Schweinebetrieben. *Klauentierpraxis.* (2015) 23:171–5.
17. Büttner S, Müntener CR, Torriani K, Overesch G. *ARCH-Vet Bericht über den Vertrieb von Antibiotika in der Veterinärmedizin und das Antibiotikaresistenzmonitoring bei Nutztieren in der Schweiz GESAMTBERICHT 2013*. Available online at: https://www.zora.uzh.ch/id/eprint/106067/1/ARCH-Vet_2013_final.pdf (accessed May 1, 2020).
18. ESVAC. *Sales of Veterinary Antimicrobial Agents in 30 European Countries in 2017*. Available online at: https://www.ema.europa.eu/documents/report/sales-veterinary-antimicrobial-agents-31-european-countries-2017_en.pdf (accessed May 1, 2020).
19. Jensen VF, Jacobsen E, Bager F. Veterinary antimicrobial-usage statistics based on standardized measures of dosage. *Prev Vet Med.* (2004) 64:201–15. doi: 10.1016/j.prevetmed.2004.04.001
20. EMA. *Defined Daily Doses for Animals (DDDvet) and Defined Course Doses for Animals (DCDvet)*. Available online at: https://www.ema.europa.eu/en/documents/other/defined-daily-doses-animals-dddvet-defined-course-doses-animals-dcdvet-european-surveillance_en.pdf (accessed May 1, 2020).
21. Tarakdjian J, Capello K, Pasqualin D, Santini A, Cunial G, Scollo A, et al. Antimicrobial use on Italian pig farms and its relationship with husbandry practices. *Animals.* (2020) 10:417. doi: 10.3390/ani10030417
22. Bosman AL, Loest D, Carson CA, Agunos A, Collineau L, Léger DF. Developing Canadian defined daily doses for animals: a metric to quantify antimicrobial use. *Front Vet Sci.* (2019) 6:220. doi: 10.3389/fvets.2019.00220
23. Echtermann T, Müntener CR, Torgerson PR, Sidler X, Kümmerlen D. [Defining daily doses and total doses for the measurement of antibiotic usage in Swiss pig production]. *Schweiz Arch Tierheilkd.* (2018) 160:597–605. doi: 10.17236/sat00179
24. Echtermann T, Muentener C, Sidler X, Kümmerlen D. Antimicrobial drug consumption on swiss pig farms: a comparison of Swiss and European defined daily and course doses in the field. *Front Vet Sci.* (2019) 6:240. doi: 10.3389/fvets.2019.00240
25. Postma M, Sjölund M, Collineau L, Lösken S, Stärk KD, Dewulf J, et al. Assigning defined daily doses animal: a European multi-country experience for antimicrobial products authorized for usage in pigs. *J Antimicrob Chemother.* (2015) 70:294–302. doi: 10.1093/jac/dku347
26. Collineau L, Belloc C, Stärk KD, Hémonic A, Postma M, Dewulf J, et al. Guidance on the selection of appropriate indicators for quantification of antimicrobial usage in humans and animals. *Zoonoses Public Health.* (2017) 64:165–84. doi: 10.1111/zph.12298
27. van Rennings L, Merle R, von Münchhausen C, Stahl J, Honscha W, Käsbohrer A, et al. Variables describing the use of antibiotics in food-producing animals. *Berl Munch Tierarztl Wochenschr.* (2013) 126:297–309.
28. Timmerman T, Dewulf J, Catry B, Feyen B, Opsomer G, de Kruif A, et al. Quantification and evaluation of antimicrobial drug use in group treatments for fattening pigs in Belgium. *Prev Vet Med.* (2006) 74:251–63. doi: 10.1016/j.prevetmed.2005.10.003
29. Chauvin C, Madec F, Guillemot D, Sanders P. The crucial question of standardisation when measuring drug consumption. *Vet Res.* (2001) 32:533–43. doi: 10.1051/vetres:2001145
30. Qualität und Sicherheit. *Eingesetzte Antbiotikamengen Erneut Gesunken*. (2018). Available online at: https://www.q-s.de/pressemeldungen/eingesetzte-antibiotikamengen-erneut-gesunken.html (accessed August 26, 2020).
31. Blaha T., Dickhaus P., Meemken D. The "Animal Treatment Index" benchmarking pig herd health. In: *Proceedings 19TH Congress International Pig Veterinary Society*. Copenhagen, Denmark (2006). p. 189.
32. Jensen VF, de Knegt LV, Andersen VD, Wingstrand A. Temporal relationship between decrease in antimicrobial prescription for Danish pigs and the "Yellow Card" legal intervention directed at reduction of antimicrobial use. *Prev Vet Med.* (2014) 117:554–64. doi: 10.1016/j.prevetmed.2014.08.006
33. Kasabova S, Hartmann M, Werner N, Käsbohrer A, Kreienbrock L. Used daily dose vs. defined daily dose-contrasting two different methods to measure antibiotic consumption at the farm level. *Front Vet Sci.* (2019) 6:116. doi: 10.3389/fvets.2019.00116
34. Hemme M, Kaesbohrer A, von Münchhausen C, Hartmann M, Merle R, Kreienbrock L. Unterschiede in der Berechnung des betriebsbezogenen Antibiotika-Einsatzes in Monitoringsystemen in Deutschland–eine Übersicht. *Berl und Münch Tierärztl. Wochenschr.* (2017) 3:93–101.
35. Werner N, McEwen S, Kreienbrock L. Monitoring antimicrobial drug usage in animals: methods and applications. *Microbiol Spectr.* (2018) 6:569–94. doi: 10.1128/9781555819804.ch27
36. EMA. *Principles on Assignment of Defined Daily Dose for Animals (DDDvet) and Defined Course Dose for Animals (DCDvet)*. Available online at: https://www.ema.europa.eu/en/documents/scientific-guideline/principles-assignment-defined-daily-dose-animals-dddvet-defined-course-dose-animals-dcdvet_en.pdf (accessed May 1, 2020).
37. Akoglu H. User's guide to correlation coefficients. *Turk J Emerg Med.* (2018) 18:91–3. doi: 10.1016/j.tjem.2018.08.001
38. Landis JR, Koch GG. The measurement of observer agreement for categorical data. *Biometrics.* (1977) 33:159–74. doi: 10.2307/2529310

39. Giavarina D. Understanding Bland Altman analysis. *Biochem Med.* (2015) 25:141–51. doi: 10.11613/BM.2015.015
40. Taverne FJ, Jacobs JH, Heederik D, Mouton JW, Wagenaar JA, van Geijlswijk IM, et al. Influence of applying different units of measurement on reporting antimicrobial consumption data for pig farms. *BMC Vet Res.* (2015) 11:250. doi: 10.1186/s12917-015-0566-7
41. Schulz J, Kemper N, Hartung J, Janusch F, Mohring SAI, Hamscher G. Analysis of fluoroquinolones in dusts from intensive livestock farming and the co-occurrence of fluoroquinolone-resistant *Escherichia coli*. *Sci Rep.* (2019) 9:5117. doi: 10.1038/s41598-019-41528-z
42. Xie WY, Yang XP, Li Q, Wu LH, Shen QR, Zhao FJ. Changes in antibiotic concentrations and antibiotic resistome during commercial composting of animal manures. *Environ Pollut.* (2016) 219:182–90. doi: 10.1016/j.envpol.2016.10.044
43. Schnetzer P, Brügger M, Naegeli H, Müntener C. [Calculation of therapeutic intensity for pigs treated using medicated feed]. *Schweiz Arch Tierheilkd.* (2017) 159:381–6. doi: 10.17236/sat00121
44. Kümmerlen D, Echtermann T, von Gerlach F, Müntener C, Sidler X. Reduced usage of High Priority Critically Important Antimicrobial (HPCIAs) as a result of legal regulations and private initiatives in Switzerland. In: *Proceedings AACTING*. Berne (2019).
45. Lopes R, Kruse AB, Nielsen LR, Nunes TP, Alban L. Additive Bayesian Network analysis of associations between antimicrobial consumption, biosecurity, vaccination and productivity in Danish sow herds. *Prev Vet Med.* (2019) 169:104702. doi: 10.1016/j.prevetmed.2019.104702

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Veterinary Science

ORIGINAL RESEARCH
published: 13 October 2020
doi: 10.3389/fvets.2020.558793

Does the Use of Different Indicators to Benchmark Antimicrobial Use Affect Farm Ranking?

Lorcan O'Neill[1,2]*, *Maria Rodrigues da Costa*[1,2], *Finola Leonard*[2], *James Gibbons*[3], *Julia Adriana Calderón Díaz*[1], *Gerard McCutcheon*[1,4] and *Edgar García Manzanilla*[1,2]

[1] Pig Development Department, Teagasc, The Irish Food and Agriculture Authority, Moorepark, Fermoy, Ireland, [2] School of Veterinary Medicine, University College Dublin, Dublin, Ireland, [3] Irish Equine Centre, Naas, Ireland, [4] Pig Development Department, Teagasc, The Irish Food and Agriculture Authority, Oakpark, Carlow, Ireland

OPEN ACCESS

Edited by:
Miguel Ángel Moreno, Complutense University of Madrid, Spain

Reviewed by:
Peers Davies, University of Nottingham, United Kingdom
Dick Heederik, Utrecht University, Netherlands

***Correspondence:**
Lorcan O'Neill
lorcan.oneill@ucdconnect.ie

Specialty section:
This article was submitted to Veterinary Epidemiology and Economics, a section of the journal Frontiers in Veterinary Science

Received: *04 May 2020*
Accepted: *07 September 2020*
Published: *13 October 2020*

Citation:
O'Neill L, Rodrigues da Costa M, Leonard F, Gibbons J, Calderón Díaz JA, McCutcheon G and Manzanilla EG (2020) Does the Use of Different Indicators to Benchmark Antimicrobial Use Affect Farm Ranking? Front. Vet. Sci. 7:558793. doi: 10.3389/fvets.2020.558793

The need to reduce antimicrobial use (AMU) in livestock production has led to the establishment of national AMU data collection systems in several countries. However, there is currently no consensus on which AMU indicator should be used and many of the systems have defined their own indicators. This study sought to explore the effect of using different internationally recognized indicators on AMU data collected from Irish pig farms and to determine if they influenced the ranking of farms in a benchmarking system. AMU data for 2016 was collected from 67 pig farms (c. 35% of Irish pig production). Benchmarks were defined using seven AMU indicators: two based on weight of active ingredient; four based on the defined daily doses (DDD) used by the European Medicines Agency and the national monitoring systems of Denmark and the Netherlands; and one based on the treatment incidence (TI200) used in several published studies. An arbitrary "action zone," characterized by farms above an acceptable level of AMU, was set to the upper quartile (i.e., the top 25% of users, $n = 17$). Each pair of indicators was compared by calculating the Spearman rank correlation and assessing if farms above the threshold for one indicator were also above it for the comparison indicator. The action zone was broadly conserved across all indicators; even when using weight-based indicators. The lowest correlation between indicators was 0.94. Fifteen farms were above the action threshold for at least 6 of the 7 indicators while 10 farms were above the threshold for all indicators. However, there were important differences noted for individual farms between most pairs of indicators. The biggest discrepancies were seen when comparing the TI200 to the weight-based indicators and the TI200 to the $DDDA_{NED}$ (as used by Dutch AMU monitoring system). Indicators using the same numerator were the most similar. All indicators used in this study identified the majority of high users. However, the discrepancies noted highlight the fact that different methods of measuring AMU can affect a benchmarking system. Therefore, careful consideration should be given to the limitations of any indicator chosen for use in an AMU monitoring system.

Keywords: antimicrobial use, indicators, benchmark, pigs, defined daily dose

INTRODUCTION

Antimicrobial resistance (AMR) is a public health issue of global importance (1). There are concerns that antimicrobial use (AMU) in animals plays a role in the emergence and dissemination of AMR bacteria (2, 3). Antimicrobial resistance is frequently detected in zoonotic and commensal bacteria (4) and has been associated with the use of antimicrobials in animals (5, 6). This has led to a concerted effort in many countries to reduce AMU in livestock production (7, 8). Systems to measure, benchmark and monitor AMU in livestock production are considered key components of these efforts and forthcoming European Union (EU) legislation requires all Member States to collect AMU data for the pig, poultry and veal production sectors by 2024 and for all species by 2030 (9). Several AMU data collection systems have already been established in various European countries (10). The longest established and best known of these are Vetstat, which is operated by the Danish Veterinary and Food Administration in Denmark (11); and the sector specific databases overseen by the Netherlands Veterinary Medicines Institute (SDa) in the Netherlands (12). Aggregated veterinary antimicrobial sales data for all species are collected by the European Medicines Agency (EMA) for the European Surveillance of Veterinary Antimicrobial Compounds (ESVAC) project and reported annually (13). Quantification of AMU allows for a comparison of consumption between farms, veterinarians, species, types of production and even countries (14). These data can be used in a benchmarking system whereby end users can compare their performance to their peers and authorities can identify and focus on "high users" for intervention or sanction. Many of the AMU data collection systems in operation allow for benchmarking (10). Notable examples of these include the "yellow card" scheme in Denmark (15) and the "action threshold" for farms and veterinarians in the Netherlands (12, 16) where high users may be subject to increased inspection and restricted access to antimicrobials (17, 18). Quantification of AMU also allows for the monitoring of trends over time, assessment of the impact of interventions to reduce AMU (14) and can provide data to assess the relationship between consumption and the occurrence of AMR (5, 19)

One of the most important considerations when quantifying AMU is the unit of measurement, known as an indicator. Collineau et al. defined such indicators as "the number of 'technical' units of measurement (i.e., the amount of antimicrobials) consumed and normalized by the population at risk of being treated in a defined period" (14). The numerator, the amount of antimicrobials consumed, is generally expressed in terms of the weight of active ingredient or the number of Defined Daily Doses (DDD). The DDD system, developed by the World Health organization as a standardized method to measure drug consumption, assigns a specific dose to each drug or product and thus accounts for differences in potency between the various antimicrobial drugs (20). This method was first adopted for use in animals by the Vetstat system (21). Alternatively, the numerator may be expressed in terms of the number of animals treated (or equivalently, the number of treatment days). The denominator is a measure of the population of animals at risk of treatment and can be expressed in terms of the number of individuals in the population or its weight of biomass. The denominator may measure the population in terms of the numbers of animals produced, the numbers of animals present or in terms of animal time (e.g., animal days). The population's weight of biomass is determined by assigning an average weight to its constituent species and, where applicable, production categories or age groups. It is also worth noting, that when considering the particular time period under study (e.g., a calendar year), a certain proportion of the population may have been treated with antimicrobials in the preceding period and furthermore, species with more than one production cycle per year (e.g., pigs and poultry) may not have been at risk for the entire period used to calculate the denominator. Therefore, unless the population is studied batch by batch, measurement of AMU is often a proxy representation of AMU at population level rather than a measurement of actual exposure for every individual/batch.

The benchmarking systems of a selection of European countries have been reviewed by others (22). The various AMU data collection systems may differ, for example, in how they define their DDD lists and/or in the weights they assign to species or production categories (14, 22). Therefore, there are now several AMU indicators in use with none having universal acceptance (22, 23). How an indicator influences farm ranking in a benchmarking system matters because farms may be above a threshold for acceptable use with one indicator but below it if a different one is used. Some studies have shown that the use of different indicators affects the interpretation of AMU at national level (24, 25) and farm level (26–28) but did not assess how these differences would affect a benchmarking system. A few studies have shown that indicators can influence the farm classification in a benchmarking system: for cattle in the UK (29); suckling pigs, finisher pigs and poultry in Germany (30); and poultry in France (31). In pigs, the studies to date have focused on comparing national indicators to those based on ESVAC methodology (27, 30); a wider comparison of currently available indicators is lacking. Furthermore, since these comparisons were limited to specific age groups (27, 28, 30), metrics to benchmark AMU amongst farrow-to-finish farms have not yet been evaluated. The objective of this study was to determine if the use of different indicators to benchmark antimicrobial use affected farm ranking amongst a sample population of Irish farrow-to-finish pig farms. The indicators chosen for evaluation are based on those used by ESVAC for the reporting of antimicrobial sales in the EU, the Danish Integrated Antimicrobial Resistance Monitoring

Abbreviations: ADD, animal daily dose; AMR, antimicrobial resistance; AMU, antimicrobial use; AY, animal year; CIA, critically important antimicrobial; DADD, defined animal daily dose; DANMAP, Danish Integrated Antimicrobial Resistance Monitoring and Research Programme; DAPD, proportion of animal population in treatment per day; DDD, defined daily dose; DDDA, defined daily dose animal; DVFA, Danish Veterinary and Food Administration; EEA, European Economic Area; EU, European Union; EMA, European Medicines Agency; ESVAC, European Surveillance of Veterinary Antimicrobial Consumption; PCU, population correction unit; SDa- Netherlands Veterinary Medicines Institute; SPC, summary of product characteristics; TI, treatment incidence; TK, treatable kilograms.

and Research Programme (DANMAP)[1], the Monitoring of Antimicrobial Resistance and Antibiotic Usage in Animals in the Netherlands (MARAN)[2] and SDa[3] reports in the Netherlands as well as an indicator developed for use in several international studies (32–34).

METHODS

Data Collection

Antimicrobial use data for the 2016 calendar year were collected from farrow-to-finish pig farms in Ireland as part of cross-sectional study investigating AMU. Details of the data collection and descriptive results are reported elsewhere (35). Briefly, all 107 client farms of the Teagasc[4] Pig Development Department advisory service were invited to enroll in the study; 67 volunteered to participate. The sampled farms had a combined sow population of 48,000 and thus represented ∼35% of the Irish national herd in that year (36). Farm visits were conducted between September 2017 and September 2018. Farmers provided details about their antimicrobial use in medicated feed, namely, the diets and age groups treated along with the antimicrobials used. Prescription and or invoice records were consulted to determine the numbers of injectable antimicrobial preparations and oral remedies (not for premix) that were used. The farms also submit quarterly performance and production data to the e-Profit Monitor (ePM) database operated by Teagasc and this was consulted to extract population data and feed consumption data (to calculate amounts of medicated feed used) for each participating farm. Eight farms did not submit data to the ePM and provided the relevant production data directly. Further details of the data collection and quantification of antimicrobial use can be found in **Appendix A** in **Supplementary Materials**.

Calculation of Antimicrobial Use Indicators

Using the data collected, AMU for each farm was calculated using seven different indicators. The AMU indicators chosen for comparison in this study are presented in **Table 1**. This table also presents further information on the development and usage of these indicators.

In general, an indicator of AMU can be expressed as follows:

$$\text{indicator} = \frac{\text{numerator}}{\text{denominator}}$$

The numerators and denominators for each indicator were calculated using the general principles outlined below and with the appropriate DDDs and assigned weights.

The AMU indicators used at farm level in Denmark, the ADD (animal daily dose), and in the Netherlands, the $DDDA_F$ (defined daily dose animal, farm), are stage specific (11, 12). Since the aim of this study was to explore the use of indicators to measure AMU on farrow-to finish farms, the methods used to measure AMU in the pig population at national level in both countries were applied at farm level instead of using the stage specific metrics. For Denmark, this is the DAPD (proportion of animal population in treatment per day) (41) and in the Netherlands it is the $DDDA_{NAT}$ (defined daily animal dose in the Netherlands) (43). Therefore, the metric which uses the $DDDA_{NAT}$ methodology at farm level in this study is termed the $DDDA_{NED}$ in order to avoid confusion with the $DDDA_{NAT}$ and the $DDDA_F$.

Numerator

Firstly, for each farm, the amounts of active ingredient in each antimicrobial product used were calculated according the protocols outlined by the EMA (46). For the weight-based indicators, i.e., milligram per population correction unit (mg/PCU) and milligram per kilogram liveweight sold (mg/kg lwt), the numerator for an individual farm was simply the sum of the weights of each active ingredient used.

To determine the numerator for the DDD-based indicators the amount of active ingredient for each antimicrobial was converted to "treatable kilograms." In this study, treatable kilograms (TK) represents the number of kilograms of pig that can be treated with a given amount of antimicrobial if a defined dose is used. It is based on the definition outlined by the Netherlands Veterinary Medicines Institute (40).

$$TK_{DDD} = \frac{\text{weight of active ingredient}}{\text{DDD}\left(\text{mg/kg}\right)} \quad (1)$$

For the DDD_{vet}/PCU and DDD_{vet}/AY indicators, the treatable kilograms (TK_{DDDvet}) for each antimicrobial were calculated using the DDD_{vet} list for pigs (39). For the antimicrobials with no assigned DDD_{vet} (tulathromycin and tildipirosin) the consensus DDDs defined by Postma et al. were used and adjusted for duration of action using long acting factors (47). The treatable kilograms (TK_{DEN}) for the DAPD indicator used the Defined Animal Daily Doses (DADD) applied in the Danish Integrated Antimicrobial Resistance Monitoring and Research Programme (DANMAP) reports (42). Finally, for the $DDDA_{NED}$ indicator, the treatable kilograms (TK_{NED}) were calculated using the DG standard available on the SDa website (44). For each indicator, the total TK for each farm was the sum of the TKs for each antimicrobial used.

Each DDD system employs different methodologies. The DDD_{vet} is defined for each antimicrobial by species and route of administration based on the average of doses obtained from the SPC documents from nine European countries (48). The Danish equivalent, the DADD (used to calculate the DAPD), is based on approved doses for each antimicrobial, route of administration, pharmaceutical form and species (42). Dutch DDDA values are defined for each product based on the SPC document, meaning that identical antimicrobial preparations can have different DDDAs (44). The DDD systems also differ in how they treat combination products such as potentiated sulphonamides; in the Netherlands they are considered as one treatment (40) whereas the DDD_{vet} and Danish DADD treats each antimicrobial separately (39, 42).

Denominator

The denominator represents the population of animals at risk of treatment. Each denominator partitions the pig population

[1] www.danmap.org
[2] www.wur.nl/en/Research-Results/Research-Institutes/Bioveterinary-Research/In-the-spotlight/Antibiotic-resistance-2/MARAN-reports.htm
[3] www.autoriteitdiergeneesmiddelen.nl
[4] Teagasc, the Agriculture and Food Development Authority. www.teagasc.ie.

TABLE 1 | Summary explanation of the antimicrobial use indicators used in the study.

Indicator	Developed by	Numerator	Denominator	Comments
mg/kg lwt milligram per kilogram liveweight sold	Generic indicator	Weight of active ingredient	Liveweight of animals sent to slaughter or sold from farm	
mg/PCU milligram per population correction unit	EMA - ESVAC for reporting of antimicrobial sales in EU/EEA (37)	Weight of active ingredient	PCU; uses numbers of living sows and animals sold from the farm (e.g., for slaughter) Assigned weights: weaners 25 kg; finishers, 65 kg; sows, 240 kg (37)	The PCU was designed for use at national level using census, slaughter and, export/import data (37). These principles are adapted to farm level for this study.
DDD_{vet}/PCU defined daily dose per population correction unit	EMA - proposed for use when AMU data stratified by species is available (37, 38)	Treatable kilograms (TK_{DDDvet}): Defined doses based on DDD_{vet} for pigs (39)	PCU; see mg/PCU above	Not currently in use for ESVAC reports. Included in SDa national report for the AMU in the Netherlands in 2016 as a comparison to $DDDA_{NAT}$ (40)
DAPD proportion of animal population in treatment per day (expressed per 1000 animals)	DANMAP - for reporting of AMU in Denmark (41)	Treatable kilograms (TK_{DEN}): Defined doses based on DADD values (42)	Biomass days; Uses the numbers of animals produced. Assigned weights: piglets 4 kg; weaners (< 30 kg), 18.5 kg; finishers (> 30 kg), 68.5 kg; sows, 200 kg	DANMAP defines average weights and length of stay in each age group to calculate biomass days. These parameters are based on national performance data. The performance data from the sample farms was used in the same way (41).
$DDDA_{NED}$ defined daily dose animal in the Netherlands	Netherlands Veterinary Medicines Institute (SDa) - for reporting of AMU in the Netherlands (40, 43)	Treatable kilograms (TK_{NED}): Defined doses based on product level values in the DG Standard veterinary medicines database (44)	Animal year (AY); the denominator used by SDa in the Netherlands (43) Uses the average numbers of animals present (or the number of animal places) Assigned weights: piglets (< 20 kg), 10 kg; finishers, 70 kg; other pigs, 70.2 kg; sows, 220 kg	The $DDDA_{NED}$ is equivalent to the $DDDA_{NAT}$ used to report AMU at national level in the Netherlands (43). It is renamed to reflect its use in this study at farm level.
DDD_{vet}/AY defined daily dose per animal year	SDa (40)	TK_{DDDvet}	Animal year (AY); see $DDDA_{NED}$	Included in Dutch national reports since 2016 along with $DDDA_{NAT}$ (40)
TI200 treatment incidence (for 200-day lifespan)	Defined for use in pigs by Timmermann et al. (32). Adapted by Sjolund et al. (33) and Sarrazin et al. (34)	Number of animal treatment days using DDD_{vet} as defined dose and standard weights at treatment: piglets 4 kg; weaners 12 kg, finishers 50 kg (34, 45)	Number of animal days in the rearing period (birth to slaughter)	Recalculates the combined TIs for piglets, weaners and finishers into the TI200 for a standardized 200-day lifespan as per Sarrazin et al. (34)

AMU, antimicrobial use; DANMAP, Danish Integrated Antimicrobial Resistance Monitoring and Research Programme; DADD, defined animal daily doses, the DDD system used by DANMAP; DDD, Defined Daily Dose; DDD_{vet}, the DDD system developed for ESVAC; $DDDA_{NAT}$, defined daily dose animals, the indicator used to report AMU at national level in the Netherlands; EMA, European Medicines Agency; ESVAC, European Surveillance of Veterinary Antimicrobial Consumption; EU, European Union; EEA, European Economic Area; PCU, population correction unit; SDa, Netherlands Veterinary Medicines Institute; TI, treatment incidence; TK, treatable kilograms.

into age group or production categories and assigns each one a standard weight. For example, the PCU assigns finisher pigs a weight of 65 kg (see **Table 1**). The weight of biomass in each category is calculated by multiplying the numbers of animals by the assigned weight and the total denominator is simply the sum of all the weights. A detailed description of the calculation of the denominators is available in **Appendix B** in **Supplementary Materials**.

Treatment Incidence

Treatment incidence, first defined by Timmerman et al. describes the percentage of pigs in a stage of production treated with a dose of antimicrobial each day or, equivalently, the percentage time of the period at risk for which a pig was treated (32). The TI indicator, as adapted by Sarrazin et al. (34), is calculated as follows:

$$TI = \frac{\text{amount of antimicrobial used (mg)}}{\text{DDDvet (mg/kg)} \times \text{\# animals at risk} \times \text{assigned weight (kg)} \times \text{number of days at risk}} \times 100 \text{ animals at risk}$$

The TI, which is based on the DDD_{vet}, was calculated separately for piglets, weaners and finishers using respective assigned weights of 4, 12, and 50 kg (45). The number of animals and the length of stay in each section were extracted from the ePM or provided by the farmer directly. The TIs were combined and recalculated as the TI200, representing a standardized 200-day lifespan, using the formula defined by Sjölund et al. (33):

$$TI200 = \frac{TIpiglet \times \text{suckling period} + TIweaner \times \text{weaner period} + TIfinisher \times \text{finishing period}}{\text{total rearing period}} \times \frac{200\ (\text{standard life span})}{\text{total rearing period}}$$

Assigning a standard weight to each stage means that the weight at the time of treatment is accounted for (albeit based on an estimated standard) and allows for an estimation of the numbers of animals treated. Therefore, in contrast to the other dose-based indicators which consider only the numbers of kilograms treated, the numerator for the TI200 equates to the number of animal treatment days.

Data Processing and Statistical Analysis

All data were entered into a Microsoft® Excel 365 spreadsheet. Calculations of indicators and statistical analysis were carried out using Microsoft® Excel and R version 3.4.2 (49). Data visualizations was carried out in R using the ggplot2 package (50).

Spearman rank correlations were determined for each pair of indicators. An arbitrary threshold to define excessive AMU was set to the upper quartile ($n = 17$) for each indicator. Farms above this threshold were defined as being in the "action zone" whereby they could theoretically be targeted for intervention to reduce AMU. For each pair of indicators, the number of farms above the threshold for one of the indicators but below for the other was determined. Kappa coefficients were calculated for each pair of indicators to assess the overall agreement between benchmarking classifications (i.e., in action zone or not). The kappa coefficient measures the agreement between rating methods and ranges from 1 (perfect agreement) to <0 (51). Finally, for each pairwise comparison the change in rank for every farm between the two indicators was calculated.

The above pairwise analysis was repeated for injectable antimicrobials from the same AMU dataset. This was done to explore the effect of the indicators on a dataset with a different antimicrobial use profile.

The effect of selected antimicrobial use practices on farm ranking was assessed by comparing the relative rank between selected pairs of indicators between the farms that engaged in the practice and those that did not. The pairs of AMU indicators and antimicrobial use practices assessed were as follows: (1) DAPD vs. DDD_{vet}/PCU for the use of tylosin oral premix in medicated feed; DADD (used to calculate the DAPD) = 4 mg/kg (42), DDD_{vet} = 12 mg/kg (39), (2) $DDDA_{NED}$ vs. DDD_{vet}/PCU for the use of trimethoprim and sulfadiazine (TMS) oral premix; combination products such TMS are assigned a single DDD by the SDa (40, 44), separate DDD_{vet} values are assigned to each constituent antimicrobial by the EMA (39), and (3) mg/PCU vs. DDD_{vet}/PCU for the use of injectable tulathromycin; DDD_{vet}, = 0.36 mg/kg (47). For each farm, the relative rank was calculated by subtracting the farm's rank with the second named indicator from the rank with the first named indicator. The results were visualized using box and scatter plots.

RESULTS

Quantification of Antimicrobial Use

Table 2 provides a summary of AMU at farm level as measured by each of the indicators and for each route of administration. A detailed description of AMU on the sample farms is reported elsewhere (35). **Table 2** also presents the breakdown of AMU for the primary routes of administration in each indicator for the combined sample population. Medicated feed accounted for the majority of AMU and ranged from 82.5 to 89.2% of consumption depending on the indicator used whereas consumption accounted for by injectable antimicrobials ranged from 2.5 to 7.9%. **Figure 1** visualizes the breakdown of AMU in each route of administration by antimicrobial class and stage of production.

Comparison of Indicators

The frequency distributions of AMU for the 67 sample farms measured using the seven indicators is shown in **Figure 2**. **Figure 3** summarizes the pairwise comparison between each of the seven AMU indicators for the complete AMU dataset and shows the Spearman rank correlation coefficients (color code); the number of farms exchanging places between zones and the associated kappa coefficients (**Figure 3A**); and number of farms moving 10 or more places in rank between each pair (**Figure 3B**). Overall, 15 farms out of 17 were classified in the action zone for at least six of the indicators while 10 farms out of 17 were above the threshold for all seven.

The results of the pairwise comparison of indicators using the injectable AMU dataset are summarized in **Figure 4** using the same format outlined for **Figure 3** above. Twelve farms out of 17 were in the action zone for at least six of the seven indicators while eight out of 17 were there for all seven.

Effect of Selected Antimicrobial Use Practices on Farm Ranking

The effect of selected antimicrobial use practices on farm ranking is visualized in **Figure 5**. Eleven out of 15 farms using tylosin oral premix had a lower rank when measured in DDDvet/PCU compared to the DAPD (**Figure 5A**). Of the 23 farms that used trimethoprim/sulfadiazine oral premix, 16 had a lower rank when measured with the $DDDA_{NED}$ compared to the DDDvet/PCU (**Figure 5B**). Ten farms used injectable tulathromycin. Seven of those farms ranked lower when AMU was measured in mg/PCU compared to DDDvet/PCU for the injectable AMU dataset

TABLE 2 | Summary of antimicrobial use (AMU) at farm level expressed in various indicators for total AMU (overall), AMU with oral premix and AMU with injectable antimicrobials.

	Summary statistics for AMU at farm level			Breakdown of AMU by route of administration		
	Overall	Oral premix	Injectable	Oral premix	Other oral remedies	Injectable
mg/kg lwt	63.34 (18.29–153.33)	54.31 (9.72–150.61)	2.79 (1.38–4.01)	89.2%	8.3%	2.5%
mg/PCU	93.93 (25.14–214.64)	78.25 (13.82–205.20)	3.91 (2.07–5.84)	89.2%	8.3%	2.5%
DDD_{vet}/PCU	4.50 (1.50–9.97)	3.66 (0.83–8.75)	0.41 (0.25–0.70)	83.1%	10.7%	6.2%
DAPD	40.49 (14.11–92.41)	31.64 (7.16–80.63)	2.84 (1.81–5.32)	85.2%	10.4%	4.4%
$DDDA_{NED}$	11.91 (4.09–28.47)	8.44 (2.18–23.73)	1.18 (0.77–2.25)	84.0%	8.9%	7.1%
DDD_{vet}/AY	9.83 (3.49–20.95)	7.59 (1.84–18.26)	0.90 (0.58–1.56)	83.1%	10.7%	6.2%
TI200	15.37 (6.05–35.67)	12.87 (3.41–29.99)	1.17 (0.69–2.15)	82.5%	9.6%	7.9%

Median values are shown with the interquartile range in brackets. The percentage breakdown of consumption by route of administration is also shown.
mg/kg lwt, milligram per kilogram liveweight sold; mg/PCU, milligram per population correction unit; DDD_{vet}/PCU, defined daily dose per population correction unit; DAPD, proportion of animal population in treatment per day; $DDDA_{NED}$, defined daily dose animal in the Netherlands; DDD_{vet}/AY, defined daily dose per animal year; TI200, treatment incidence (TI200). Note that the mg/kg lwt and mg/PCU share the same numerator (weight of active ingredient) as do the DDD_{vet}/PCU and DDD_{vet}/AY [treatable kilograms (DDD_{vet})].

(**Figure 5D**). This effect was not apparent for the complete AMU dataset.

DISCUSSION

This study explored the effect of using different indicators on a theoretical AMU benchmarking system created for a sample population of 67 Irish pig farms. The study farms represented ∼35% of the Irish pig herd and the farrow-to-finish system, operated by all herds, accounts for virtually all pig production in the country (52). The insights gained from this study are likely to be applicable to any future efforts to benchmark AMU amongst pig farms. The indicators chosen for investigation have been used in national and international AMU reports and employ a variety of methods to calculate their respective numerators and denominators. Although each indicator measures the same event, i.e., antimicrobial use on the farm during the year, the outcome is expressed in a different way. The mg/kg lwt and mg/PCU express AMU in terms of mg of active ingredient per kg of animal produced. The DDD based systems, in contrast, express AMU in terms of the weight of biomass treated per kg of animal. Here the interpretation depends on the denominator: it is per kg of animal produced if the PCU denominator is used (DDD_{vet}/PCU); per kg animal present (or animal place) per year if the AY is used ($DDDA_{NAT}$ and DDD_{vet}/AY); and, per kg biomass day for the DAPD. Finally, the TI200 expresses the percentage of animals in treatment per day (or the percentage of their lifespan spent in treatment) by using standardized weights for each age group to estimate the numbers of animals treated. These disparate measures make comparison of the absolute values obtained from the different indicators challenging and it is further complicated by the different weightings applied to the various antimicrobials and categories of pig. Therefore, the effect on farm ranking in a benchmarking system was used to evaluate the differences between indicators and the central hypothesis of this study was that the different methodologies employed by each indicator would produce different results in terms of whether farms were classified as "high users" or not. The threshold to define an action zone, characterized by farms with unacceptably high AMU, was arbitrarily set to the upper quartile. This method has been used by others (30, 31) and is not intended to reflect what any future threshold should be. In the Netherlands, for example, these thresholds are species and production category specific, and have evolved over time in response to changing patterns of AMU (53).

When applied to the complete Irish AMU dataset, the seven indicators produced similar results. All AMU indicators showed similar right skewed distributions, as reported in other studies in pigs (54), in cattle (55) and in sheep (56), indicating a distinct subset of the population with high AMU. The action zone, which, for the purpose of this study consisted of the 17 farms with the highest AMU, was broadly conserved. For each indicator pair, no more than three farms (4.5% of sample) exchanged places between zones. Fifteen farms were in the action zone for six out of seven indicators while 10 were in all seven. Therefore, while the use of different indicators did affect farm ranking, these fluctuations did not cause widespread changes to the action zones. Echtermann et al. found high correlations between indicators based on Swiss and EMA defined doses and concluded that both systems would produce similar results in a benchmarking system (27). In the present study, relatively high levels of agreement held true even when comparing weight- and dose-based indicators. Another study which applied different indicators to AMU data from poultry had a similar finding, contrary to its authors' expectations, and proposed that low variation in patterns of AMU between farms might explain this unexpected result (31). Routine prophylactic administration of medicated feed to weaned piglets was the predominant AMU practice on Irish pig farms. Four classes of antimicrobials, tetracyclines, potentiated sulphonamides, macrolides and penicillins, accounted for almost all use. Moreover, high use was always associated with medication of older weaner pigs and or finisher pigs (35). Therefore, it seems that the overall pattern of use is a more important determinant of rank than the weighting given to the antimicrobial used. In other words, a farm which medicates large portions of the herd for extended periods will almost always rank higher than a farm which does not regardless of the choice of antimicrobial.

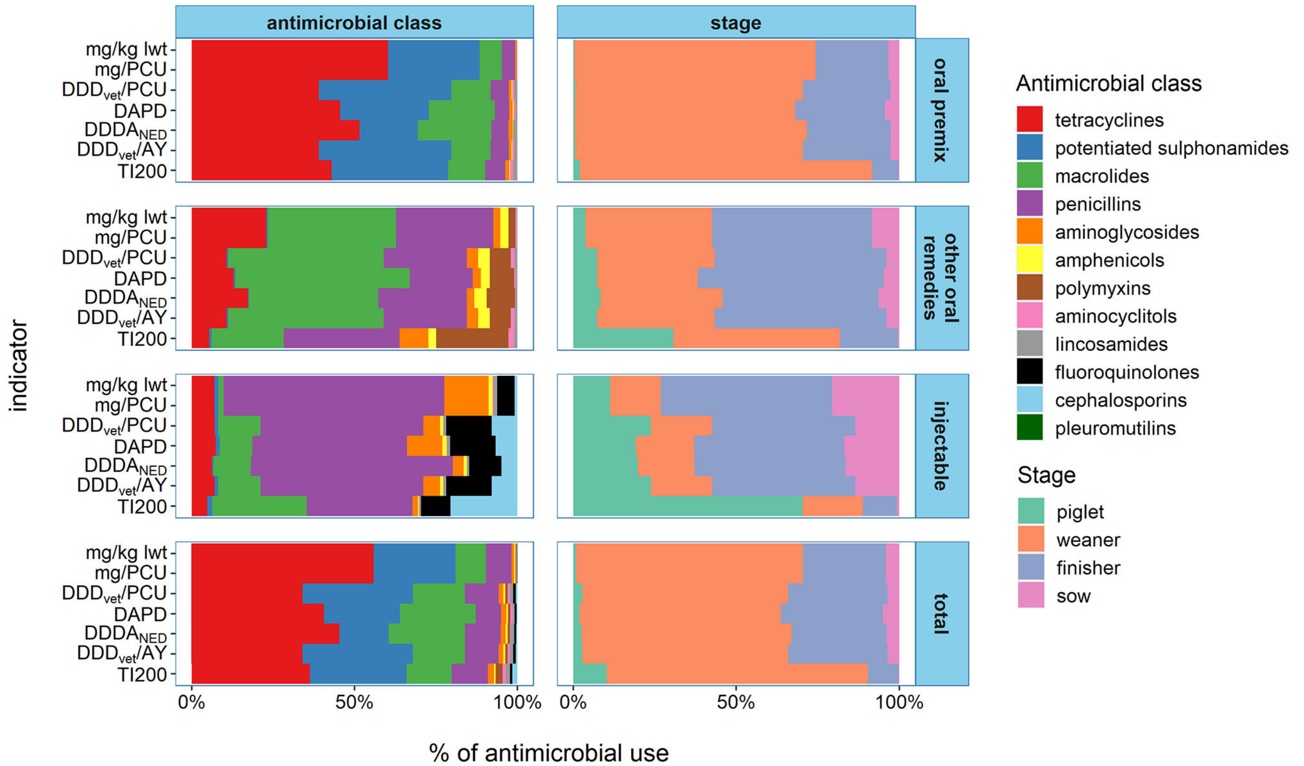


FIGURE 1 | Summary of antimicrobial use for 67 farms in 2016 by antimicrobial class and stage of production measured in the various numerators and stratified by route of administration. Legend: mg/kg lwt, milligram per kilogram liveweight sold; mg/PCU, milligram per population correction unit; DDD_{vet}/PCU, defined daily dose per population correction unit; DAPD, proportion of animal population in treatment per day; $DDDA_{NED}$, defined daily dose animal in the Netherlands; DDD_{vet}/AY, defined daily dose per animal year; TI200, treatment incidence (TI200). Note that the mg/kg lwt and mg/PCU share the same numerator (weight of active ingredient) as do the DDD_{vet}/PCU and DDD_{vet}/AY [treatable kilograms (DDD_{vet})].

The injectable AMU dataset differed from the complete AMU dataset in terms of the antimicrobial class profile with increased relative importance of the macrolide, fluoroquinolone and cephalosporin classes. Members of these three classes are typically more potent than older classes of antimicrobials such as penicillins or tetracyclines. Therefore, AMU could be underestimated on farms using these antimicrobial classes if weight-based indicators are used. This would be problematic since these classes contain the highest priority critically important antimicrobials (CIA) which are considered as the most important to human health (57). In fact, compared to the analysis for the complete AMU dataset, relatively modest reductions in agreement between benchmarking classifications were apparent if the TI200 was excluded from the analysis of the injectable AMU dataset with at most one extra farm exchanging places between zones for each pair. However, there was marked disagreement between indicators pairs involving the TI200. For these comparisons, Spearman rank correlation coefficients ranged from 0.48 to 0.74 ($p < 0.001$) and the kappa coefficients ranged from 0.37 to 0.53 with between six and eight farms exchanging places between zones. There were also larger fluctuations in rank with up to 62.1% of farms moving 10 or more places (for mg/PCU vs. TI200, see **Figure 4**). The discrepancies between the TI200 and the other indicators can be explained by differences in the method of calculation. Since the TI200 uses the estimated number of treatment days as the numerator, treatments to piglets, weaners and finishers are treated equally. Therefore, farms with high AMU in piglets ranked higher with the TI200 than they did with the other indicators because of the large number of piglets that can be treated with a relatively small amount of antimicrobial. Conversely, farms with high AMU in finishers would rank lower with the TI200 despite the large amounts of antimicrobials needed to medicate heavier animals. This was important for the injectable AMU dataset because in terms of treatment incidence, piglets were the highest consumers (see **Figure 1**). A similar indicator, the Treatment Frequency (TF), uses the actual weight at treatment and the actual dose administered to measure AMU in Germany (58). Kasabova et al. also found that body weight at treatment influenced the benchmarking system when comparing TF to the DDD_{vet} based indicator (30). This was not an important consideration for TI200 with the complete AMU dataset as medicated feed in the weaners was still the dominant AMU practice. The observation that highest priority CIAs did not have an impact on overall consumption suggests that consideration should be given to benchmarking these separately.

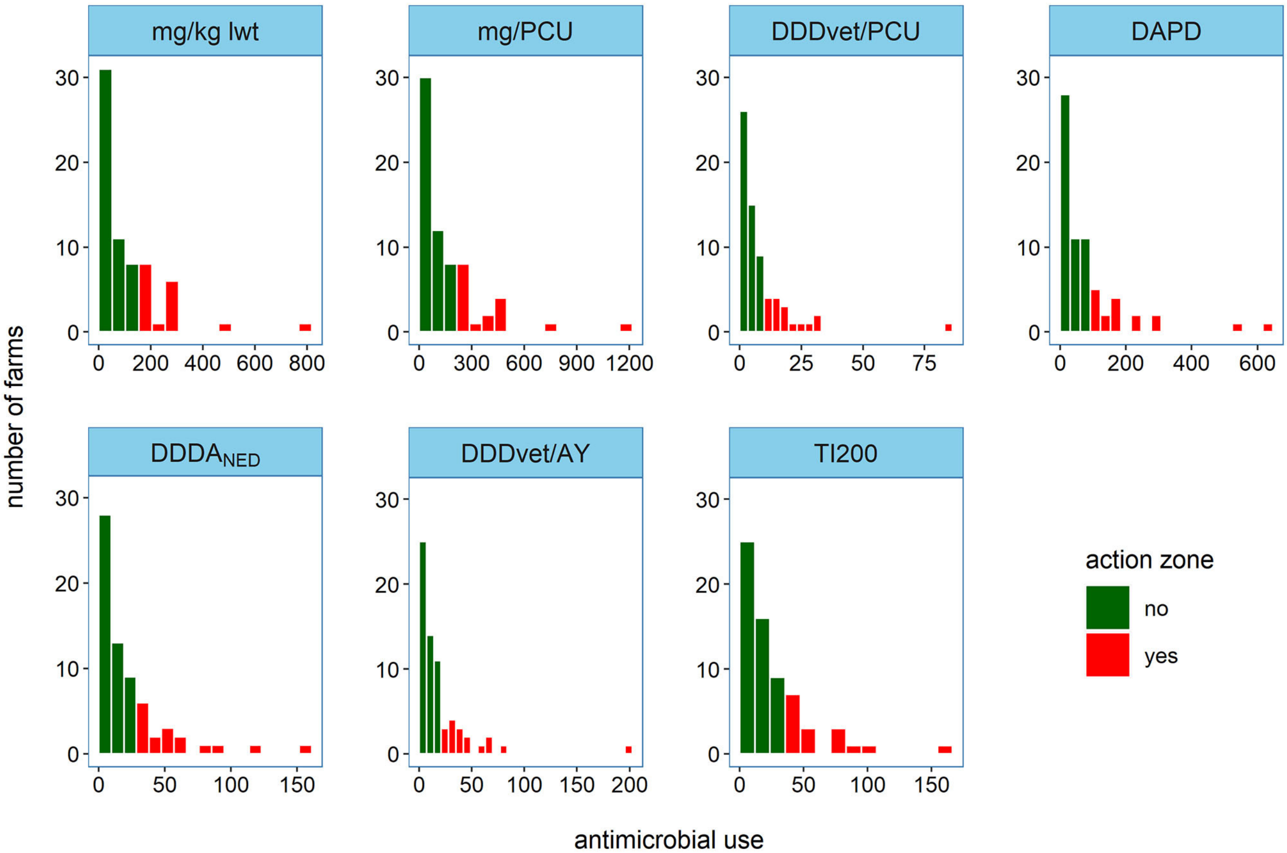


FIGURE 2 | Frequency distribution of antimicrobial use from 67 farms in 2016 measured by each indicator. The action zone was defined as the upper quartile of AMU ($n = 17$). Legend: mg/kg lwt, milligram per kilogram liveweight sold; mg/PCU, milligram per population correction unit; DDD_{vet}/PCU, defined daily dose per population correction unit; DAPD, proportion of animal population in treatment per day; $DDDA_{NED}$, defined daily dose animal in the Netherlands; DDD_{vet}/AY, defined daily dose per animal year; TI200, treatment incidence (TI200).

While it did not affect the benchmarking system as much as expected, using different indicators did affect farm rank. Two pairs of indicators [mg/PCU vs. mg/kg lwt and DDD_{vet}/PCU vs. DDD_{vet} per animal year (AY)] shared identical numerators and thus differed only in their denominator. These pairs had the highest correlations, the least fluctuation in rank and generally high agreement in the benchmark classification in both analyses While the different denominators produce different absolute values, they are all related to the underlying structure of the pig population. For example, the DDD_{vet}/PCU and DDD_{vet}/AY differ roughly by a factor of 2.2 which is close to the number of production cycles per sow per year on a farrow-to-finish farm. In other words, each animal place (AY) produces 2.2 pigs (PCU) per year. Similarly, if the kg biomass days denominator (used by the DAPD) and the AY denominator used the same assigned weights, they would differ by a factor of 365 since the former measures treatment per day and the latter treatment per year. Therefore, the denominator has less influence on ranking than the numerator when applied to a specific animal production sector. This does not hold true if one wants to compare AMU between different sectors with different life cycles. In its comparison of the EMA's methodology to its own, the SDa found that AMU in broiler production was lower than for pigs when measured in DDD_{vet}/PCU but higher when measured in DDD_{vet}/AY (40). This is because there are more production cycles per year in poultry. In terms of the numerator, the biggest discrepancies are between weight-based and dose-based metrics. For instance, the DDD_{vet} value for chlortetracycline is 30 mg/kg while for ceftiofur it is 0.8 mg/kg (39) which raises concerns that a weight-based metric could encourage the use of some of the highest priority critical antimicrobials. The example of tulathromycin illustrated in **Figures 5C,D** shows that seven of the ten farms that used it had a more favorable rank when mg/PCU was used to measure their injectable AMU compared to the DDD_{vet}/PCU. This effect was not apparent for the complete AMU dataset because of its low relative importance compared to oral antimicrobials. However, discrepancies were also apparent between the indicators using different DDD systems. **Figure 1** shows that the different DDD systems produce different consumption patterns even though the underlying data for each is identical. This is in agreement with Taverne et al. who found that AMU in the Dutch pig population appeared lower

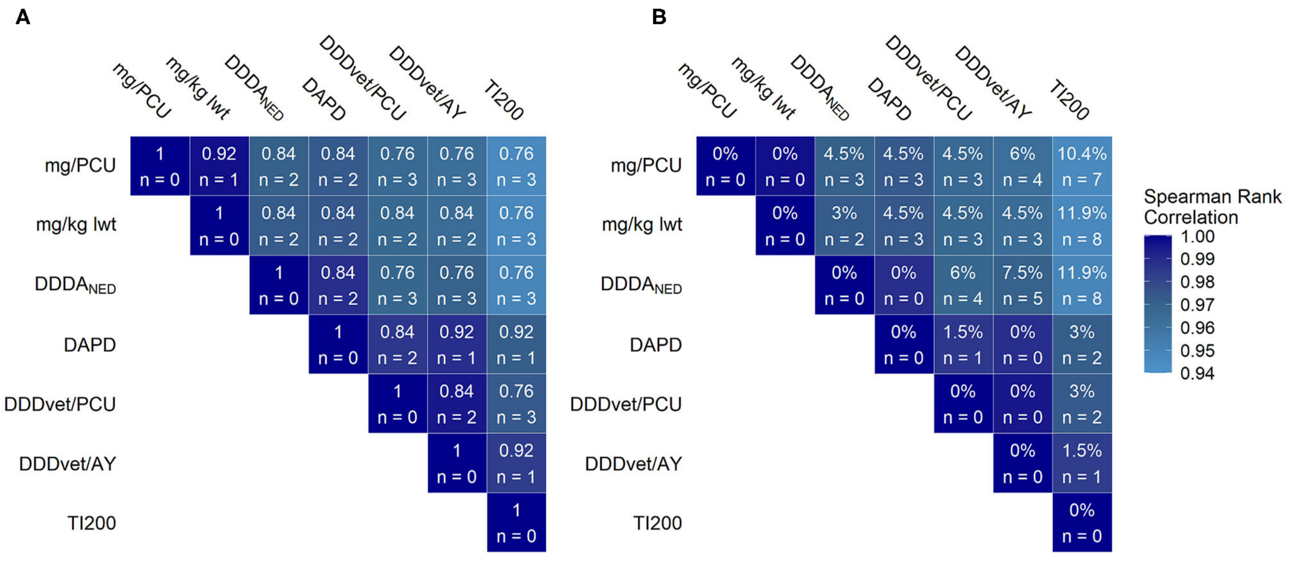


FIGURE 3 | Pairwise comparison of antimicrobial use (AMU) benchmarking systems using the various AMU indicators for all antimicrobial use; 67 farms, 2016. The color of the tile indicates the Spearman's rank correlation coefficient of each pair of indicators. **(A)** The values within the tiles indicate the kappa coefficient and the number of farms ranked in the AMU "action zone" (threshold = upper quartile of AMU) with one indicator but below the threshold in the comparison indicator. **(B)** The values within the tiles indicate the percentage of farms who's rank changed 10 or more places when comparing a given pair of indicators. Legend: mg/PCU, milligram per population correction unit; mg/kg lwt, milligram per kilogram liveweight sold; $DDDA_{NED}$, defined daily dose animal in the Netherlands; DAPD, proportion of animal population in treatment per day; DDD_{vet}/PCU, defined daily dose per population correction unit; DDD_{vet}/AY, defined daily dose per animal year; TI200, treatment incidence (TI200).

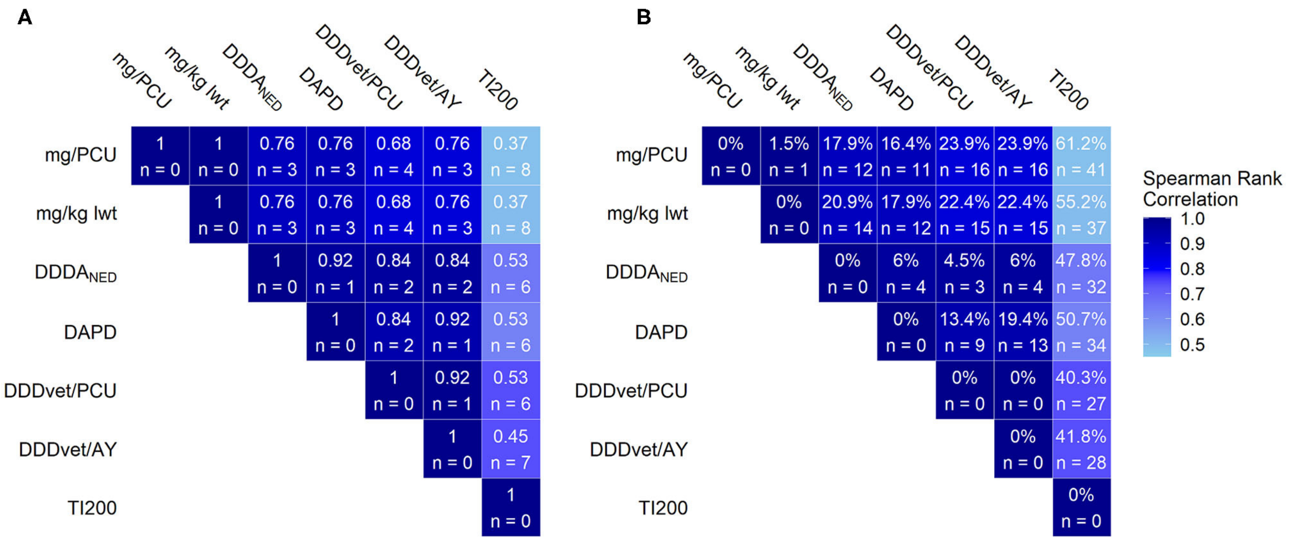


FIGURE 4 | Pairwise comparison of antimicrobial use AMU benchmarking systems using the various AMU indicators for injectable antimicrobial use; 67 farms, 2016. The color of the tile indicates the Spearman's rank correlation coefficient of each pair of indicators. **(A)** The values within the tiles indicate the kappa coefficient and the number of farms ranked in the AMU "action zone" (threshold = upper quartile of AMU) with one indicator but below the threshold in the comparison indicator. **(B)** The values within the tiles indicate the percentage of farms who's rank changed 10 or more places when comparing a given pair of indicators. Legend: mg/PCU, milligram per population correction unit; mg/kg lwt, milligram per kilogram liveweight sold; $DDDA_{NED}$, defined daily dose animal in the Netherlands; DAPD, proportion of animal population in treatment per day; DDD_{vet}/PCU, defined daily dose per population correction unit; DDD_{vet}/AY, defined daily dose per animal year; TI200, treatment incidence (TI200).

if measured with the Danish metrics (24) and highlights that international AMU comparisons should be made with caution. At farm level, the example of tylosin, noted by Echtermann et al. was also apparent in this study (27). The DDD_{vet} for oral tylosin is 12 mg/kg (39) whereas the DADD for tylosin oral premix used by DANMAP to calculate DAPD is 4 mg/kg (42).

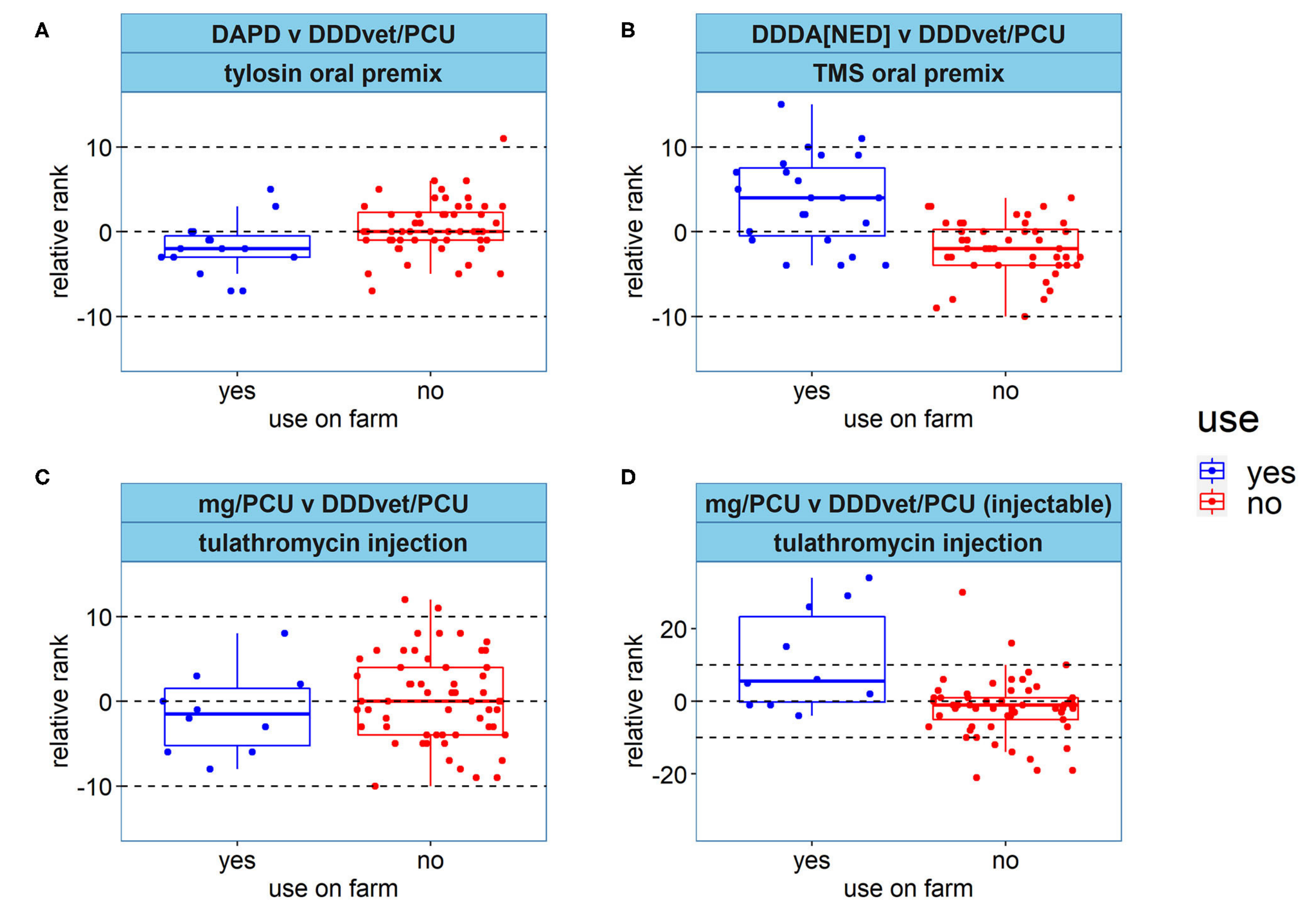


FIGURE 5 | Comparison of farm rank between indicators for selected antimicrobial use (AMU) practices. Positive relative rank values mean the farm ranked higher for the first named indicator; negative relative rank means the farm ranked higher for the second named indicator. **(A–C)** show the comparisons for the complete AMU dataset. **(D)** shows the comparison for the injectable AMU dataset. **(A)** Comparison of relative rank between DAPD and DDD_{vet}/PCU for tylosin oral premix. DADD oral premix = 4 mg/kg; the DDD_{vet} = 12 mg/kg. **(B)** Comparison of relative rank between $DDDA_{NED}$ and DDD_{vet}/PCU for farms using potentiated sulphonamides in medicated feed. The $DDDA_{NED}$ treats combination products as a single treatment, the DDD_{vet} assigns a DDD to each component separately. **(C,D)** Comparison of relative rank between mg/PCU and DDDvet/PCU for farms using injectable tulathromycin; DDD_{vet} = 0.36 mg/kg. Legend: DAPD, proportion of animal population in treatment per day; DDD_{vet}/PCU, defined daily dose per population correction unit; $DDDA_{NED}$, defined daily dose animal in the Netherlands; TMS, trimethoprim and sulfadiazine; mg/PCU, milligram per population correction unit.

In this instance, using a DDD higher than the dose typically used could encourage its use (see **Figure 5A**). Similarly, assigning separate DDDs to the constituents of combination products might discourage their use, as seen in **Figure 5B**. The values assigned to DDD have been shown to influence the choice of antimicrobial. In Denmark, Animal Daily Doses (ADD) were defined at product level until it became apparent that products containing the same antimicrobial but with higher labeled doses than their competitors were being used to manipulate AMU reporting (25). Thereafter, the animal daily doses (ADD) - for use with Vetstat - and the DADD (for use in the DANMAP) were defined at the level of active ingredient (42). More recently, the DVFA modified the "yellow card" system by introducing weighting factors for certain antimicrobials (e.g., 1.2 for tetracycline and 10 for colistin, 3rd and 4th generation cephalosporins and fluoroquinolones) and DANMAP has since reported declines in use of both tetracycline and colistin as a result (59).

The appropriate indicator for use in a surveillance system should be as fair as possible to all participants and should not inadvertently promote one AMU practice over another. To this end it may be preferable if the indicator reflects local conditions regarding the DDD system and assigned weights (27, 29). Accounting for the numbers of individual animals treated produced the most divergent results in the benchmarking classification and, as such, the question of whether to use indicators such as the TI or treatment frequency which focus on the number of animals treated or, indicators that focus on the weight of biomass treated, ultimately depends on which is more important in development of AMR; this requires further study. The TI200 and age group specific indicators require accurate attribution of AMU to the correct age group. This can be challenging when collecting AMU data from pig farms with more than one age group, even for well-established data collection systems (53). It is also important that animals are allocated to the correct age group, an issue that may be complicated by variations in terminology used by different farmers as noted by Kasabova et al. (30). These factors meant that the TI200 indicator was the most challenging to determine as its calculation required more detailed knowledge of the population structure on the farm and the length of stay in each section as well as accurate attribution of antimicrobials. The other indicators, on the other hand, required only the amounts of antimicrobials used and basic population data for their calculation. While it is no doubt preferable for an AMU database to collect as much data as possible, AMU data collection in the field can be challenging (34) and comprehensive AMU data collection systems take considerable time and resources to set up (14). Some data collection systems rely on data input by the farmer (10, 60) and in this scenario, the need for a user friendly and easily understandable system should be evident. It should also be remembered that benchmarking is a communication tool whose aim is to increase understanding of antimicrobial stewardship amongst its end users, farmers and veterinarians, and ultimately to promote engagement with efforts to reduce AMU. In this regard, it is preferable that the chosen indicator has meaning to the end users, although, which indicator is most understandable to the lay person has yet to be established. This study, rather than demonstrate the ideal indicator, showed that none were perfect and that even those that are considered less than ideal (i.e., weight-based indicators and/or production-based indicators) had an acceptable performance in identifying high users. Further study is needed to confirm that these findings apply to AMU data in other settings. However, they may be applicable in settings where the time and resources needed to set up a comprehensive data collection system are not yet in place and thus encourage the implementation of a basic system which can be refined later.

CONCLUSION

This study demonstrated that the use of different indicators to benchmark AMU produced broadly similar results when applied to AMU data collected from Irish pig farms. Overall patterns of use in terms of treatment duration and age groups treated were more important than the combination of numerator and denominator in determining the benchmarking classification. Careful consideration should be given to the choice of indicator to ensure it gives a fair and accurate comparison of AMU amongst participants and does not unintentionally promote unwanted shifts in AMU practices. Indicators based on weight of active ingredient, which are used by some data collection systems, can be used to give a meaningful benchmarking classification provided their limitations are accounted for.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

AUTHOR CONTRIBUTIONS

LO'N designed the study, performed the analysis, and drafted the manuscript. EM, JG, and FL were responsible for the conceptualisation and design of, and funding acquisition for the cross-sectional study on which this investigation is based. LO'N, MR, JCD, GM, and EM performed the data collection in the field. LO'N, MR, FL, and EM reviewed and edited the manuscript. All authors contributed to the article and approved the submitted version.

FUNDING

The current study was conducted within the AMURAP project (Antimicrobial Use and Resistance in Animal Production) which investigates AMU and AMR in the Irish pig and poultry industries. This project was funded by the Irish Department of Agriculture Food and the Marine (grant reference number 15 S 676). The funders had no role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript.

ACKNOWLEDGMENTS

The authors would like to thank the participating farmers and their private veterinary practitioners for their cooperation with this study. The authors would also like to thank the advisors in the Teagasc Pig Development Department for their advice and assistance with farm visits and data collection.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fvets.2020.558793/full#supplementary-material

REFERENCES

1. United Nations. *Political Declaration of the High-Level Meeting of the General Assembly on Antimicrobial Resistance.* (2016). Available online at: https://digitallibrary.un.org/record/842813/ (accessed April 27, 2020).
2. Marshall B, Levy S. Food animals and antimicrobials: impacts on human health. *Clin Microbiol Rev.* (2011) 24:718–33. doi: 10.1128/CMR.00002-11
3. Vieira AR, Collignon P, Aarestrup FM, McEwen SA, Hendriksen RS, Hald T, et al. Association between antimicrobial resistance in *Escherichia coli* isolates from food animals and blood stream isolates from humans in Europe: an ecological study. *Foodborne Pathog Dis.* (2011) 8:1295–301. doi: 10.1089/fpd.2011.0950
4. EFSA (European Food Safety Authority) and ECDC (European Centre for Disease Prevention and Control). 2019 The European Union summary report on antimicrobial resistance in zoonotic and indicator bacteria from humans, animals and food in 2017. *EFSA J.* (2019) 17:5598. doi: 10.2903/j.efsa.2019.5598

5. Chantziaras I, Boyen F, Callens B, Dewulf J. Correlation between veterinary antimicrobial use and antimicrobial resistance in food-producing animals: a report on seven countries. *J Antimicrob Chemother.* (2014) 69:827–34. doi: 10.1093/jac/dkt443
6. Munk P, Knudsen BE, Lukjacenko O, Duarte ASR, Gompel LV, Luiken REC, et al. Abundance and diversity of the faecal resistome in slaughter pigs and broilers in nine European countries. *Nat Microbiol.* (2018) 1:194647. doi: 10.1101/194647
7. Department of Health. *Ireland's National Action Plan on Antimicrobial Resistance 2017–2020.* (iNAP). (2017). Available online at: https://www.agriculture.gov.ie/media/migration/animalhealthwelfare/amr/inap/IrelandNationalActionPlanAntimicrobialResistance030818.pdf (accessed December 2, 2019).
8. HM Government. *Tackling Antimicrobial Resistance 2019-2024 – The UK's Five-Year National Action Plan.* (2019). Available online at: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/773130/uk-amr-5-year-national-action-plan.pdf (accessed March 22, 2020).
9. Regulation (EU). 2019/6 of the European Parliament and of the Council of 11 December 2018 on veterinary medicinal products and repealing Directive 2001/82/EC (Text with EEA relevance). *Off J Eur Union.* (2019) L4:43–167. Available online at: http://data.europa.eu/eli/reg/2019/6/oj (accessed April 4, 2020).
10. AACTING-network. *Systems for Quantification of Antimicrobial Usage.* (2020). Available online at: http://www.aacting.org/monitoring-systems/ (accessed March 27, 2020).
11. Stege H, Bager F, Jacobsen E, Thougaard A. VETSTAT—the Danish system for surveillance of the veterinary use of drugs for production animals. *Prev Vet Med.* (2003) 57:105–15. doi: 10.1016/S0167-5877(02)00233-7
12. Bos ME, Taverne FJ, Geijlswijk IM van, Mouton JW, Mevius DJ, Heederik DJ, et al. Consumption of antimicrobials in pigs, veal calves, and broilers in the Netherlands: quantitative results of nationwide collection of data in 2011. *PLoS One.* (2013) 8:e77525. doi: 10.1371/journal.pone.0077525
13. European Medicines Agency, European Surveillance of Veterinary Antimicrobial Consumption. *'Sales of Veterinary Antimicrobial Agents in 31 European Countries in 2017'.* (2019). Available online at: https://www.ema.europa.eu/en/documents/report/sales-veterinary-antimicrobial-agents-31-european-countries-2017_en.pdf (accessed December 2, 2019).
14. Collineau L, Belloc C, Stärk KDC, Hémonic A, Postma M, Dewulf J, et al. Guidance on the selection of appropriate indicators for quantification of antimicrobial usage in humans and animals. *Zoonoses Public Health.* (2017) 64:165–84. doi: 10.1111/zph.12298
15. Ministry of Environment and Food of Denmark. *Special Provisions for the Reduction of the Consumption of Antibiotics in Pig Holdings (The Yellow Card Initiative).* (2015). Available online at: https://www.foedevarestyrelsen.dk/english/SiteCollectionDocuments/Dyrevelfaerd%20og%20veterinaermedicin/Veterin%C3%A6rmedicin/Yellow%20Card,%20English%20version,%20180517.pdf (accessed March 27, 2020).
16. Bos ME, Mevius DJ, Wagenaar JA, Geijlswijk IM van, Mouton JW, Heederik DJ. Antimicrobial prescription patterns of veterinarians: introduction of a benchmarking approach. *J Antimicrob Chemother.* (2015) 70:2423–5. doi: 10.1093/jac/dkv104
17. Jensen VF, Knegt LV de, Andersen VD, Wingstrand A. Temporal relationship between decrease in antimicrobial prescription for Danish pigs and the "Yellow Card" legal intervention directed at reduction of antimicrobial use. *Prev Vet Med.* (2014) 117:554–64. doi: 10.1016/j.prevetmed.2014.08.006
18. Speksnijder D, Mevius D, Bruschke C, Wagenaar J. Reduction of veterinary antimicrobial use in the Netherlands. The dutch success model. *Zoonoses Public Health.* (2015) 62:79–87. doi: 10.1111/zph.12167
19. ECDC (European Centre for Disease Prevention and Control), EFSA (European Food Safety Authority), and EMA (European Medicines Agency). 2017 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) 15:4872–135. doi: 10.2903/j.efsa.2017.4872
20. World Health Organization. *WHO Collaborating Centre for Drug Statistics Methodology. DDD: Definition and General Considerations.* (2018). Available online at: https://www.whocc.no/ddd/definition_and_general_considera/ (accessed March 12, 2020).
21. Jensen VF, Jacobsen E, Bager F. Veterinary antimicrobial-usage statistics based on standardized measures of dosage. *Prev Vet Med.* (2004) 64:201–15. doi: 10.1016/j.prevetmed.2004.04.001
22. Craig A-L, Buijs S, Morrison S. Evaluation of veterinary antimicrobial benchmarking systems at farm- level in Europe: implications for the UK ruminant sector. *Vet Record.* (2020). doi: 10.1136/vr.105727
23. Lekagul A, Tangcharoensathien V, Yeung S. The use of antimicrobials in global pig production: a systematic review of methods for quantification. *Prev Vet Med.* (2018) 160:85–98. doi: 10.1016/j.prevetmed.2018.09.016
24. Taverne F, Jacobs J, Heederik D, Mouton J, Wagenaar J, Geijlswijk I van, et al. Influence of applying different units of measurement on reporting antimicrobial consumption data for pig farms. *BMC Vet Res.* (2015) 11:7. doi: 10.1186/s12917-015-0566-7
25. Dupont N, Fertner M, Kristensen C, Toft N, Stege H. Reporting the national antimicrobial consumption in Danish pigs: influence of assigned daily dosage values and population measurement. *Acta Veterinaria Scandinavica.* (2016) 58:27. doi: 10.1186/s13028-016-0208-5
26. Brault SA, Hannon SJ, Gow SP, Otto SJ, Booker CW, Morley PS. Calculation of antimicrobial use indicators in beef feedlots—effects of choice of metric and standardized values. *Front Vet Sci.* (2019) 6:330. doi: 10.3389/fvets.2019.00330
27. Echtermann T, Muentener C, Sidler X, Kümmerlen D. Antimicrobial drug consumption on swiss pig farms: a comparison of swiss and european defined daily and course doses in the field. *Front Vet Sci.* (2019) 6:240. doi: 10.3389/fvets.2019.00240
28. Waret-Szkuta A, Coelho V, Collineau L, Hémonic A, Buy C, Treff M, et al. How input parameters and calculation rules influence on-farm antimicrobial use indicators in animals. *Front Vet Sci.* (2019) 6:438. doi: 10.3389/fvets.2019.00438
29. Mills HL, Turner A, Morgans L, Massey J, Schubert H, Rees G, et al. Evaluation of metrics for benchmarking antimicrobial use in the UK dairy industry. *Vet Rec.* (2018) 182:379. doi: 10.1136/vr.104701
30. Kasabova S, Hartmann M, Werner N, Käsbohrer A, Kreienbrock L. Used daily dose vs. defined daily dose-contrasting two different methods to measure antibiotic consumption at the farm level. *Front Vet Sci.* (2019) 6:116. doi: 10.3389/fvets.2019.00116
31. Chauvin C, Querrec M, Perot A, Guillemot D, Sanders P. Impact of antimicrobial drug usage measures on the identification of heavy users, patterns of usage of the different antimicrobial classes and time-trends evolution. *J Vet Pharmacol Ther.* (2008) 31:301–11. doi: 10.1111/j.1365-2885.2008.00960.x
32. Timmerman T, Dewulf J, Catry B, Feyen B, Opsomer G, Kruif A de, et al. Quantification and evaluation of antimicrobial drug use in group treatments for fattening pigs in Belgium. *Prev Vet Med.* (2006) 74:251–63. doi: 10.1016/j.prevetmed.2005.10.003
33. Sjölund M, Postma M, Collineau L, Lösken S, Backhans A, Belloc C, et al. Quantitative and qualitative antimicrobial usage patterns in farrow-to-finish pig herds in Belgium, France, Germany and Sweden. *Prev Vet Med.* (2016) 130:41–50. doi: 10.1016/j.prevetmed.2016.06.003
34. Sarrazin S, Joosten P, Gompel LV, Luiken RECE, Mevius DJ, Wagenaar JA, et al. Quantitative and qualitative analysis of antimicrobial usage patterns in 180 selected farrow-to-finish pig farms from nine European countries based on single batch and purchase data. *J Antimicrob Chemother.* (2019) 74:807–16. doi: 10.1093/jac/dky503
35. O'Neill L, Rodrigues da Costa M, Leonard FC, Gibbons J, Calderón Díaz JA, McCutcheon G et al. Quantification, description and international comparison of antimicrobial use on Irish pig farms. *Porc Health Manage.* (2020) 6:30. doi: 10.1186/s40813-020-00166-y
36. Central Statistics Office (CSO). *Pig Survey June 2016.* (2016). Available online at https://www.cso.ie/en/releasesandpublications/er/ps/pigsurveyjune2016/ (accessed on April 1, 2020).
37. European Medicines Agency. *Trends in the Sales of Veterinary Antimicrobial Agents in Nine European Countries.* (2011). Available online at: https://www.ema.europa.eu/documents/report/trends-sales-veterinary-antimicrobial-agents-nine-european-countries_en.pdf (accessed on December 2, 2019).

38. European Medicines Agency. *Guidance on Collection and Provision of National Data on Antimicrobial use by Animal Species/Categories.* (2018) Available online at: https://www.ema.europa.eu/en/documents/scientific-guideline/guidance-collection-provision-national-data-antimicrobial-use-animal-species/categories_en.pdf (accessed March 20, 2020).
39. European Medicines Agency. *Defined Daily Doses for Animals (DDDvet) and Defined Course Doses for Animals (DCDvet) European Surveillance of Veterinary Antimicrobial Consumption (ESVAC).* (2016). Available online at: https://www.ema.europa.eu/en/documents/other/defined-daily-doses-animals-dddvet-defined-course-doses-animals-dcdvet-european-surveillance_en.pdf (accessed March 20, 2020).
40. The Netherlands Veterinary Medicines Institute. *Usage of Antibiotics in Agricultural Livestock in the Netherlands in 2016 Trends and Benchmarking of Livestock Farms and Veterinarians.* (2017). Available online at: https://cdn.i-pulse.nl/autoriteitdiergeneesmiddelen/userfiles/Publications/engels-def-rapportage-2016-deel-1-en-2-22-09-2017.pdf (accessed August 19, 2019).
41. DANMAP (Danish Integrated Antimicrobial Resistance Monitoring and Research Programme). *DANMAP 2012 Use of Antimicrobial Agents and Occurrence of Antimicrobial Resistance in Bacteria from Food Animals, Food and Humans in Denmark.* (2013). Available online at: https://www.danmap.org/-/media/arkiv/projekt-sites/danmap/danmap-reports/danmap-2012/danmap_2012.pdf?la=en (accessed March 3, 2020).
42. DANMAP (Danish Integrated Antimicrobial Resistance Monitoring and Research Programme). DADD description. *DANMAP 2018 Use of Antimicrobial Agents and Occurrence of Antimicrobial Resistance in Bacteria from Food Animals, Food and Humans in Denmark.* (2019). Available online at: https://www.danmap.org/-/media/arkiv/projekt-sites/danmap/danmap-reports/danmap-2018/dadd-beskrivelse_250919.pdf?la=en (accessed December 2, 2019).
43. The Netherlands Veterinary Institute. *Standard Operating Procedure. Calculation of the DDDA for Antimicrobials by the SDa for the Cattle, Veal, Pig, Broiler, Turkey and Rabbit Farming Sectors.* (2020). Available online at: http://cdn.i-pulse.nl/autoriteitdiergeneesmiddelen/userfiles/overige%20rapporten/sop-rekensystematiek-website-03032020.pdf (accessed April 2, 2020).
44. The Netherlands Veterinary Institute. *DG Standard.* (2019). Available online at: https://cdn.i-pulse.nl/autoriteitdiergeneesmiddelen/userfiles/doseringstabel/dg-standaard-30jul2019-tbv-website.pdf (accessed August 2, 2019).
45. European Medicine Agency. *Revised ESVAC Reflection Paper on Collecting Data on Consumption of Antimicrobial Agents per Animal Species, on Technical Units of Measurement and Indicators for Reporting Consumption of Antimicrobial Agents in Animals.* (2013). Available online at: https://www.ema.europa.eu/documents/scientific-guideline/revised-european-surveillance-veterinary-antimicrobial-consumption-esvac-reflection-paper-collecting_en.pdf (accessed August 2, 2019).
46. European Medicines Agency. *European Surveillance of Veterinary Antimicrobial Consumption (ESVAC) Sales Data and Animal Population Data Collection Protocol.* (2019) Available online at: https://www.ema.europa.eu/en/documents/other/european-surveillance-veterinary-antimicrobial-consumption-esvac-web-based-sales-animal-population_en.pdf (accessed August 19, 2019).
47. Postma M, Sjölund M, Collineau L, Lösken S, Stärk KD, Dewulf J, et al. Assigning defined daily doses animal: a European multi-country experience for antimicrobial products authorized for usage in pigs. *J Antimicrob Chemother.* (2015) 70:294–302. doi: 10.1093/jac/dku347
48. European Medicines Agency. *Principles on Assignment of Defined Daily Dose for Animals (DDDvet) and Defined Course Dose for Animals (DCDvet).* (2015). Available online at: https://www.ema.europa.eu/en/documents/scientific-guideline/principles-assignment-defined-daily-dose-animals-dddvet-defined-course-dose-animals-dcdvet_en.pdf (accessed April 1, 2020).
49. R Core Team. *R: A language and environment for statistical computing.* R Foundation for Statistical Computing, Vienna, Austria (2017).
50. Wickham H. *ggplot2: Elegant Graphics for Data Analysis.* New York, NY: Springer-Verlag. (2016).
51. Cohen J. A coefficient of agreement for nominal scales. *Educ Psychol Measure.* (1960) 20:37–46. doi: 10.1177/001316446002000104
52. Marquer P, Rabade T, Forti, R. Pig farming in the European Union: considerable variations from one member state to another. *Eurostat: Statis Focus.* (2014). 15:1–13. Available online at: https://ec.europa.eu/eurostat/statistics-explained/pdfscache/3688.pdf (accessed March 30, 2020).
53. The Netherlands Veterinary Medicines Institute, 2019. *Usage of Antibiotics in Agricultural Livestock in the Netherlands in 2018 Trends and Benchmarking of Livestock Farms and Veterinarians*. Available online at: https://cdn.i-pulse.nl/autoriteitdiergeneesmiddelen/userfiles/Publications/2018-def-rapport1.pdf (accessed March 30, 2020).
54. Callens B, Persoons D, Maes D, Laanen M, Postma M, Boyen F, et al. Prophylactic and metaphylactic antimicrobial use in Belgian fattening pig herds. *Prev Vet Med.* (2012) 106:53–62. doi: 10.1016/j.prevetmed.2012.03.001
55. Hyde RM, Remnant JG, Bradley AJ, Breen JE, Hudson CD, Davies PL, et al. Quantitative analysis of antimicrobial use on British dairy farms. *Vet Record.* (2017) 181:vetrec-2017-104614. doi: 10.1136/vr.104614
56. Davies P, Remnant JG, Green MJ, Gascoigne E, Gibbon N, Hyde R, et al. Quantitative analysis of antibiotic usage in British sheep flocks. *Vet Rec.* (2017) 181:511. doi: 10.1136/vr.104501
57. World Health Organization (WHO). *Critically Important Antimicrobials for Human Medicine-—6th Revision 2018.* (2019). Available online at: https://apps.who.int/iris/bitstream/handle/10665/312266/9789241515528-eng.pdf?ua=1 (accessed April 1, 2020).
58. Hemme M, Ruddat I, Hartmann M, Werner N, Rennings L van, Käsbohrer A, et al. Antibiotic use on German pig farms - a longitudinal analysis for 2011, 2013 and 2014. *PLoS ONE.* (2018) 13:e0199592. doi: 10.1371/journal.pone.0199592
59. DANMAP (Danish Integrated Antimicrobial Resistance Monitoring and Research Programme). *DANMAP 2018 Use of Antimicrobial Agents and Occurrence of Antimicrobial Resistance in Bacteria from Food Animals, Food and Humans in Denmark.* (2019). Available online at: https://www.danmap.org/-/media/arkiv/projekt-sites/danmap/danmap-reports/danmap-2018/danmap_2018.pdf?la=en (accessed April 1, 2020).
60. UK-VARSS. *UK Veterinary Antibiotic Resistance and Sales Surveillance Report (UK-VARSS 2018).* Veterinary Medicines Directorate. (2019). Available online at: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/842678/PCDOCS-_1705145-v1-UK-VARSS_2018_Report__2019__FINAL_v2.pdf (accessed November 20, 2019).

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Veterinary Science

ORIGINAL RESEARCH
published: 19 October 2020
doi: 10.3389/fvets.2020.567872

Antimicrobial Use Indices—The Value of Reporting Antimicrobial Use in Multiple Ways Using Data From Canadian Broiler Chicken and Turkey Farms

Agnes Agunos, Sheryl P. Gow, David F. Léger, Anne E. Deckert, Carolee A. Carson, Angelina L. Bosman, Stefanie Kadykalo and Richard J. Reid-Smith*

Public Health Agency of Canada, Center for Foodborne, Environmental and Zoonotic Infectious Diseases, Guelph, ON, Canada

OPEN ACCESS

Edited by:
Ioannis Magouras,
City University of Hong Kong,
Hong Kong

Reviewed by:
Cedric Muentener,
University of Zurich, Switzerland
Annemarie Kaesbohrer,
University of Veterinary Medicine
Vienna, Austria

****Correspondence:***
Agnes Agunos
agnes.agunos@canada.ca

Specialty section:
This article was submitted to
Veterinary Epidemiology and
Economics,
a section of the journal
Frontiers in Veterinary Science

Received: *30 May 2020*
Accepted: *15 September 2020*
Published: *19 October 2020*

Citation:
Agunos A, Gow SP, Léger DF, Deckert AE, Carson CA, Bosman AL, Kadykalo S and Reid-Smith RJ (2020) Antimicrobial Use Indices—The Value of Reporting Antimicrobial Use in Multiple Ways Using Data From Canadian Broiler Chicken and Turkey Farms. Front. Vet. Sci. 7:567872. doi: 10.3389/fvets.2020.567872

We have previously described the importance of using multiple indicators for reporting national farm-level antimicrobial use (AMU) information, but the distribution of flock-level AMU and how these indicators relate to each other has not yet been fully explored. Using farm-level surveillance data (2013–2019), for broiler chickens (n = 947 flocks) and turkeys (n = 427), this study aims to (1) characterize flock-level AMU and identify high users, (2) identify appropriate AMU indicators and biomass denominator [population correction unit (PCU) vs. kg weight at pre-slaughter], and (3) make recommendations on the application to veterinarian-producer and national-level reporting. Diverse AMU patterns were identified in broiler chickens (156 patterns) and turkeys (68 patterns); of these, bacitracin, reported by 25% of broiler chicken and 19% of turkey producers, was the most frequently occurring pattern. Depending on the indicator chosen, variations in reported quantity of use, temporal trends and relative ranking of the antimicrobials changed. Quantitative AMU analysis yielded the following results for broiler chickens: mean 134 mg/PCU; 507 number (n) of Canadian (CA) defined daily doses (DDDvet) per 1,000 chicken-days and 18 nDDDvetCA/PCU. Analysis in turkey flocks yielded the following: mean 64 mg/PCU, 99 nDDDvetCA/1,000 turkey-days at risk and 9 nDDDvetCA/PCU. Flocks were categorized based on the percentiles of the mg/PCU distribution: "medium" to "low" users (≤75th percentile) and "high" users (>75th percentile). The odds of being a high user in both broiler chickens and turkeys were significantly increased: if water medications were used, and if trimethoprim-sulfonamides, bacitracins, and tetracyclines were used. Pairwise correlation analysis showed moderate correlation between mg/PCU and the nDDDvetCA/1,000 animal days at risk and between mg/PCU and nDDDvetCA/PCU. Significantly high correlation between nDDDvetCA/1,000 animal days at risk and nDDDvetCA/PCU was observed, suggestive that either of these could be used for routine monitoring of trends in AMU. One source of discrepancy between the indicators was the antimicrobial. Understanding the choice of parameter input and effects on reporting trends in AMU will inform surveillance reporting best practices to help industry understand the impacts of their AMU reduction strategies and to best communicate the information to veterinarians, their producers, and other stakeholders.

Keywords: antimicrobial use, indicators, turkeys, broiler chickens, surveillance, Canada

INTRODUCTION

In recent years, methodologies for monitoring antimicrobials intended for use in animals have advanced and improved, which complements national and global priorities for mitigating the impact of antimicrobial resistance (AMR) using a One Health approach (1). The OIE has provided guidelines for data collection and reporting (2, 3) and published its 4th annual report with the global data on quantities of antimicrobials intended for use in animals expressed in milligrams per kilogram of animal biomass (mg/kg) (2). Recently (August 2019), the European Surveillance for Veterinary Antimicrobial Consumption (ESVAC) project under the European Medicines Agency has also published the reporting requirements for veterinary medicinal products (VMP) used in animals (4). The ESVAC implementing measures cite the use of milligrams of active substance adjusted by species population correction unit (mg/PCU), number of Defined Daily Doses (DDDvet) adjusted by species PCU (DDDvet/PCU) and Defined Course Dose for animals adjusted by species PCU (DCDvet/PCU) for reporting (4).

The use of multiple antimicrobial use (AMU) metrics (technical units of measurements such as frequency of use, number of medicated rations, days medicated, milligrams, number of DDDs) and indicators (an AMU metric in relation to a denominator such as the animal biomass and animal-time units) for AMU surveillance reporting has been previously described (5, 6). Multiple metrics and indicators are routinely used by the Canadian Integrated Program for Antimicrobial Resistance Surveillance (CIPARS) to better understand the temporal shifts in AMU and AMR in relation to poultry industry-wide AMU reduction strategies (7). The use of multiple AMU indicators is valuable, as interpretation of the surveillance data is highly influenced depending on the indicator chosen, thus multiple indicators provide a more complete picture of AMU. In the context of poultry production, when making comparisons across AMU indicators, there are several factors which can influence the resulting estimates, such as dose of the antimicrobial active ingredient (AAI), mortality levels (suggestive of a disease condition) and timing of administration of the antimicrobial (8). A change in an input parameter, such as the contextualizing denominator (animal biomass), can thus impact the overall interpretation of the AMU findings (9).

In Canada, recent changes in AMU regulations require a veterinary prescription and a valid veterinarian-client-patient relationship for the administration of medically important antimicrobials in animals (10). Recommended levels of drug or feed inclusion rates are indicated in the Compendium of Medicating Ingredients Brochure (11) and Compendium of Veterinary Products (12). All medically-important antimicrobials according to Health Canada's Veterinary Drugs Directorate's List A: List of certain antimicrobial active pharmaceutical ingredients (13) requires veterinary prescription.

In Canada, broiler chickens and turkeys are sold under a quota system, through which they are supply managed by national and provincial marketing boards. Food-borne pathogens resistant to antimicrobials deemed as high priority critically-important antimicrobials such as the 3rd generation cephalosporins and fluoroquinolones (14) and isolates with multiclass resistance are routinely detected from poultry products in Canada (7). Because of the food safety implications of these organisms, the larger poultry industry and allied industries (feed sector) developed "Responsible antimicrobial use in the Canadian chicken and turkey sector" guidelines in 2016 (15). Building on this strategy, sector-specific AMU policies were implemented to progressively eliminate the preventive use of medically important antimicrobials. The Chicken Farmers of Canada's AMU policy aimed to eliminate the preventive use of certain antimicrobial classes: 3rd generation cephalosporins and fluoroquinolones (Step 1—May 2014); aminoglycosides, macrolides, lincosamides, penicillins, trimethoprim and sulfonamides, and streptogramins (Step 2—end of 2018), and; bacitracins (Step 3—contingent upon reassessment of the impact of Step 2 by the end of 2020 (16). The turkey sector has also implemented a similar strategy) (17).

The Public Health Agency of Canada (PHAC) operates the Canadian Integrated Program for Antimicrobial Resistance Surveillance (CIPARS). CIPARS, which has been collecting AMU at the farm-level since 2013 in broiler chickens and turkeys. In the turkey sector, farm surveillance was initially implemented in one Canadian province (British Columbia) and progressively expanded to other provinces in collaboration with the establishment of FoodNet Canada (FNC) sentinel sites. FNC is another surveillance program also within PHAC, with a food safety and One Health theme. We have previously highlighted the early indications of the impact of Step 1 of the broiler chicken sector's AMU strategy (18) and the value of using multiple AMU indicators and integration of data to track the impact of this strategy (19). It is envisaged that the CIPARS farm component will enable informed decision-making by the industry, veterinarians and producers, in order to optimize AMU stewardship and preserve the effectiveness of antimicrobials currently available for use in the poultry sector in Canada. Using flock-level data collected across Canada (2013–2019), this study aimed to: (1) identify high users of antimicrobials using routine AMU analysis, (2) identify appropriate AMU indicators for reporting and compare AMU indicators with biomass denominators derived from two time points, average weight at treatment (PCU) vs. average weight at pre-slaughter (kg), and (3) make recommendations on the application to national-level data. The results will inform surveillance reporting best practices to help industry understand the impacts of their AMU reduction strategies and to best communicate this information to veterinarians and their producers.

MATERIALS AND METHODS

Data Source

Farm data, collected by broiler chicken and turkey producers via their veterinarians using CIPARS species-specific questionnaires (**Supplementary Material 1**), between 2013 and 2019 were entered into the CIPARS AMU PostGresSQL database and extracted into Microsoft Excel (Office). Detailed farm-level methodology has been previously described (7, 19). Although other farm-level data on management and flock characteristics were available, for the purposes of this analysis we utilized the basic farm characteristics data such as flock inventory (birds at risk), pre-harvest live weight (defined as pre-slaughter weight in this paper; the weight ∼1 week before shipment to slaughter plants), age of the birds at pre-harvest sampling (pertains to days at risk of being treated; from chick placement to pre-harvest sampling), stocking density in birds per square meter of floor space, the province and region where the flocks were raised and the frequency and quantity of antimicrobials used by all routes of administration. As previously, described (7, 19) a flock is defined as a group of birds originating from the same hatchery and placed approximately the same day in the sampling unit (e.g., barn, floor or pen).

Data Analysis

All analyses were performed using Stata SE 15 (College Station, Texas).

Descriptive Statistics, Quantitative AMU Estimation, and Identification of High Users of AMU for Farm-level Reporting

Flock characteristics and frequency and quantity of AMU

Farm and flock-level characteristics which included conventional, antibiotic-free (ABF), raised without antibiotics (RWA), organic and other flock classifications were descriptively summarized**.** Ten broiler chicken flocks with partial or missing data were excluded from the analysis. Further analysis (pairwise correlation, comparison and identification of high users) included only the conventional flocks, regardless of their AMU exposures during the grow-out period. Excluded were flocks raised as ABF, RWA, and organic intended for the mainstream market because the decision not to use antimicrobials was market-driven and not based on flock health or production efficiency goals.

The first step involved routine CIPARS AMU data summaries and analyses (**Table 1**) and such as frequency of use by route of administration (number of flocks treated divided by the total flocks surveyed), patterns of AMU, duration of treatment, weight at treatment, days exposed, and level of drug/inclusion rates. For the purposes of our analysis, a flock AMU pattern was determined by combining all the AAI exposures via any route of administration during the life span of the bird. Flock-level estimates of antimicrobials administered via feed, water and injection were calculated using equations based on previously described methodology (7, 19). Briefly, within the CIPARS AMU database, the AAIs administered via feed (e.g., pre-starter, starter, grower, finisher, roaster or developer rations) were calculated using simple regression and integral calculus based on ration information (age at start of the ration and days the ration was fed) and using feed consumption charts for the breeds commonly used in Canada to obtain feed consumption for each ration per bird. This amount was then multiplied by the number of birds exposed, converted to tons and then multiplied by the reported level of drug per AAI. The level of drug pertains to the AAI inclusion rates in grams per ton of feed (11). For AAI administered via the drinking water, the quantity of use was estimated either by: (1) mg AAI per liter of drinking water multiplied by the estimated (calculated as described above for feed) water consumed during the course of treatment, or, (2) the total number of VMPs used during the course of treatment multiplied by the concentration of the AAI/s. For AAIs administered at the hatchery via *in ovo* or subcutaneous injections, the mg per hatching egg/broiler chick (or poult) was multiplied by the total number of broiler chicks or poults placed in the sampled barn. All values were converted to mg AAI for further AMU quantification.

The second step categorized flocks based on the percentiles of the resulting mg/PCU distribution as "medium" to "low" users (≤75th percentile) and "high" users (>75th percentile). Differences between high and medium- to-low users were examined more closely using logistic regression and exact logistic regression where appropriate. Independent variables investigated included route of administration and antimicrobial class used. Milligrams per PCU differed significantly between provinces for chickens and between turkey weight categories for turkeys and therefore these variables were included as fixed effects in the respective analyses. Due to the industry AMU reduction strategy that was implemented during the period of this study, year was also forced into the analyses.

Comparison of AMU Indicators and Exploration of Alternate Weights Used in the Denominators

Pairwise Comparisons of AMU Indicators

The purpose of pairwise comparisons of indicators was to inform the selection of the most appropriate indicator (s) for communicating AMU surveillance results to the poultry industry and for providing feedback to veterinarians and their producers. The three different flock-level AMU indicators were assessed for correlation using Pearson's correlation coefficient (PCC). A *P*-value of 0.0001 was considered significant for each of the correlation pairs shown in **Tables 6**, **7** and **Supplementary Material 2**.

TABLE 1 | Methods used to calculate antimicrobial use for surveillance data collected from sentinel broiler chicken and turkey farms, 2013–2019.

Measurements	Numerator	Denominator
1. Frequency	No. of flocks using antimicrobials	Total no. of flocks surveyed
2. Days exposed per AAI	No. of days exposed	N/A
3. mg AAI	*Feed:* Ton fed × level of drug in the feed in grams × 1,000 *Water:* g AAI per liter of water × 1,000 *Injections:* mg AAI injected per bird or hatching egg	
Routine CIPARS AMU estimation methodology		
4. mg/PCU^{a}_{Br} and mg/PCU^{a}_{Tk}	By class: mg of all AAIs (#3) Total flock: mg of all classes	Broilers: Birds at risk × 1 kg ESVAC average weight at treatment Turkeys: Birds at risk × 6.5 kg ESVAC average weight at treatment
5. nDDDvetCA/1,000 broiler chicken-days at risk[a] and nDDDvetCA/1,000 turkey-days at risk [a]	mg adjusted by the DDDvetCA standard By class: nDDDvetCA[c]'s of all AAIs Total flock: nDDDvetCA's of all classes	Broilers: Birds at risk × 1 kg ESVAC average weight at treatment × days at risk Turkeys: Birds at risk × 6.5 kg ESVAC average weight at treatment × days at risk
6. nDDDvetCA/PCU^{a}_{Br} and nDDDvetCA/PCU^{a}_{Tk}	As above in #5	As above in #4
Alternate AMU estimation methodology		
7. mg/kg^{b}_{Br} and mg/kg^{b}_{Tk}	By class: mg of all AAIs, all routes (as in #4) Total flock: mg of all classes, as in #4	Broilers: Birds at risk × kg broiler biomass[1] Turkeys: Birds at risk × kg turkey biomass[1]
8. nDDDvetCA/1,000 broiler chicken days at risk[b] and nDDDvetCA/1,000 turkey-days at risk [b]	By class: nDDDvetCAs of all AAIs (as in #5) Total flock: nDDDvetCA's of all classes (as in #5)	Broilers: Birds at risk × kg broiler biomass × days at risk Turkeys: Birds at risk × kg turkey biomass × days at risk
9. nDDDvetCA/kg^{b}_{Br} and nDDDveCA/kg^{b}_{Tk}	As above in #8	(As in #7)

[1] *Broiler chicken and turkey average pre-slaughter live weights in kg (the animal biomass).*
[a] *Based on routine CIPARS formula (7, 19).*
[b] *kg broiler chicken and turkey live pre-slaughter weights.*
[c] *DDDvetCA—defined daily doses for animals using Canadian standards. DDDvetCA standards described elsewhere (20).*
AAI, antimicrobial active ingredient.
nDDDvetCA, number of defined daily doses for animals using Canadian standards.
ESVAC, European Surveillance for Veterinary Antimicrobial Consumption.
PCU, population correction unit.
N/A, not applicable.
Br, broilers.
Tk, turkeys.

Exploration of alternate weights in the denominators

The purpose was to explore the impact of different choices of weights of the animals on the reported AMU indicator. For these analyses, the same equations were used but the actual recorded pre-slaughter live weight was applied to the denominator, replacing the PCU or average weight at treatment of 1 kg and 6.5 kg for broiler chickens and turkeys, respectively. In brief, flock-level AMU was estimated based on numerator and denominator input parameters described in **Table 1**. The Canadian defined daily doses for animals (DDDvetCA) standards developed for broiler chickens and turkeys (20) were used to estimate the total number (*n*) of defined daily doses in animals using Canadian standards (nDDDvetCA). Route-specific DDDvetCA standards were applied. The pre-slaughter weight was used as a surrogate for slaughter weight (actual weight at slaughter) and actual days at risk (as per routine CIPARS analysis) were used. For the dose-based indicator, nDDDvetCA/1,000 broiler chicken (or turkey)-days at risk, or the proportion of animals treated daily with an average dose, was based on previously described methodologies (21, 22).

Overall National AMU Estimation and Temporal Trends

This section aimed to update the previous AMU results reported by CIPARS for national farm-level data, applying routine methods and those used above (exploration of alternate weights in the denominators) (7, 23). National data were estimated as previously described using the sum of milligrams of AAI used, total nDDDvetCA's and the total bird population at risk. The national estimates using both routine and the alternative weight (pre-slaughter weight) AMU indicator were plotted in Microsoft Excel (Office).

TABLE 2 | Characteristics of the studied broiler chicken flocks (*n* = 934), 2013–2019.

Characteristics	Units	Mean of flocks (standard error of the mean)
Age sampled/days at risk	Days	35 (0.1)
Pre-slaughter live weights[a]	kg	2 (0.01)
Birds at risk	n birds	23,735 (441)
Total pre-slaughter live weight	kg, total	47,873 (916)
Stocking density	birds/m^2	11 (0.01)
Farm capacity	*n* birds	62, 311 (1,936)
Mortality	%	4 (0.1)

[a]*Used interchangeably with pre-harvest throughout the manuscript (farm visit and data collection before shipment for slaughter).*

RESULTS

Broiler Chickens

General Description of AMU and Flock/Farm Characteristics

Flock and farm characteristics

A cumulative total of 934 broiler chicken flocks across 5 Canadian provinces participated in the CIPARS broiler chicken farm surveillance between 2013 and 2019 (British Columbia: 204 flocks, Alberta: 195 flocks, Saskatchewan: 59 flocks, Ontario: 279 flocks and Québec: 197 flocks). Overall, the flocks sampled during the 7 years encompassed 22 million birds (∼3 million birds/year) or the equivalent of 48 million kg of broiler chicken biomass (∼6 million kg/year). Descriptive statistics for flock-level characteristics are summarized in **Table 2**.

Antimicrobial active ingredients and routes of administration

There were 23 AAIs used in broiler chickens (**Table 3**). Seven AAIs were administered via feed (tylosin, procaine penicillin, virginiamycin, trimethoprim and sulfadiazine, bacitracin, oxytetracycline, and avilamycin). Thirteen AAIs were administered via water (enrofloxacin, apramycin, amoxicillin, lincomycin, penicillin, penicillin and streptomycin, oxytetracycline and neomycin, tetracycline, tetracycline and neomycin, sulfadimethoxine, sulfaquinoxaline, and sulfaquinoxaline and pyrimethamine). Three AAIs were administered via subcutaneous and *in ovo* injections (ceftiofur, gentamicin and lincomycin and spectinomycin).

Frequency

The vast majority of the flocks (83%) were medicated via feed (i.e., represented the greatest route of AAI exposures), 27% of flocks were medicated via injections, and a small percentage were medicated via water (10%). More than half of the producers used one (34%) or two (30%) AAIs during the grow-out period by all routes combined; the remaining flocks used three (16%), four (5%), and 5 or more AAIs (<1%). One hundred and three flocks (11%, excluded in subsequent AMU analysis as these flocks did not contribute to multiple units of comparisons) were intended for the mainstream market including RWA, ABF and organic without any exposures to medically-important antimicrobials, ionophores, or chemical coccidiostats. There were 3,239 treatment frequencies recorded (252 injections, 2,875 feed, 110 water).

AMU patterns

The data indicated that there were diverse AMU patterns (156 patterns) utilized by the broiler chicken producers (**Supplementary Material 3**). The most frequently occurring patterns were treatment of the flock with bacitracin (25%, $n = 197$ flocks), avilamycin-bacitracin (6%, $n = 50$ flocks), bacitracin-lincomycin and spectinomycin combination (5%, $n = 42$), avilamycin (5%, $n = 38$), and virginiamycin (5%, $n = 36$) during the broiler growing period. The diversity of AMU patterns decreased over time from 54 AMU patterns (highest in 2014) to 19 AMU patterns (2019).

Total birds exposed to AAIs

More than half of the total population sampled were medicated with bacitracin (57%, 12.6 million birds). Other notable bird exposures were avilamycin (23%, 5.2 million birds) and virginiamycin (21%, 4.6 million birds).

Duration of exposure to AAIs

In treated flocks, the mean number of medicated rations was 4 rations per flock and the mean days medicated was 30 days. Therefore conventional flocks, on average, were commonly exposed to medicated feed ∼86% of the time during the growing period. For days of exposure to specific in-feed AAI's, the longest days of exposure were for bacitracin (mean: 26 days, range 25–27), followed by tylosin (mean 21 days, 19–23), and virginiamycin (mean 22 days, 21–24). The AAIs reportedly used for treatment, oxytetracycline and trimethoprim-sulfadiazine, had a mean of 10 and 7 days, respectively. For water administered AAIs, largely intended for treatment, the mean duration of treatment was relatively shorter and varied by AAIs from 2 days (lincomycin) to 6 days (amoxicillin) but the recommended duration of treatment (3–5 days) was used for the remaining AAIs (12). Injections were provided once at either day 18 of incubation (*in ovo*) or at day of hatch (subcutaneous) at the hatchery.

Age at treatment

The mean age at treatment varied by route of administration and AAI (**Figure 1**, **Table 3**), but combined data from all routes yielded a mean of 17 days.

Weight at treatment

The mean weight at treatment also varied by route of administration and AAI (**Figure 1**, **Table 3**), but combined data from all routes yielded a mean of 0.84 kg, slightly lower than ESVAC's 1 kg.

Inclusion rates or level of drug

The quantity of AAIs (**Table 3**) administered via feed (grams/ton), water (g/liter of drinking water or mg/bird), and injection (mg/hatching egg or chick) were largely according to the approved claims indicated in the Compendium of

TABLE 3 | Reported antimicrobial use by route of administration by antimicrobial active ingredient in broiler chicken flocks, 2013–2019.

							Indicators mean (standard error of the mean)		
	***n* (%) flocks treated[a]**	**Total birds treated ('000)**	**Days exposed, mean (min-max)**	**No. (%) of treatments[b]**	**kg weight at treatment, mean (min–max)**	**Level of drug or inclusion rates, mean (min–max)**	**mg/PCU**	**nDDDvetCA/1,000 broiler-chicken days**	**$nDDDvet/PCU_{Br}$**
Injection (*in ovo* or subcutaneous)				**No. (%) injections**		**ml/chick**			
Ceftiofur	39 (4%)	1,022	1	39 (1%)	0.04	0.1	0.1 (0.01)	1 (0.1)	0.05 (0.004)
Gentamicin	36 (4%)	867	1	37 (1%)	0.04	0.2	0.2 (0.01)	1 (<0.01)	0.02 (<0.01)
Lincomycin-spectinomycin	177 (19%)	4,014	1	177 (5%)	0.04	0.75	1 (0.02)	4 (0.1)	0.13 (<0.01)
Feed				**No. (%) medicated rations**		**Grams/ton**			
Avilamycin	213 (23%)	5,160	18 (17–19)	434 (15%)	0.87 (0.07–2.32)	15 (15–30)	31 (1)	307 (12)	11 (0.43)
Bacitracin	509 (54%)	12,564	26 (25–27)	1,482 (52%)	0.95 (0.05–3.35)	55 (11–110)	144 (3)	406 (8)	14 (0.32)
Oxytetracycline	7 (1%)	143	10 (7–13)	7 (0.2%)	0.87 (0.41–1.22)	440 (97–440)	448 (106)	656 (131)	27 (6.34)
Penicillin procaine	83 (9%)	2,370	16 (15–17)	150 (5%)	0.61 (0.11–1.65)	55 (20–110)	56 (3)	318 (18)	10 (0.60)
Trimethoprim-sulfadiazine	81 (9%)	1,995	7 (6–8)	84 (3%)	0.93 (0.11–2.44)	300 (200–300)	175 (13)	768 (52)	27 (2)
Tylosin	91 (10%)	2,392	21 (19–23)	232 (8%)	0.82 (0.07–2.46)	22 (22–44)	43 (3)	48 (3)	2 (0.1)
Virginiamycin	192 (21%)	4,557	22 (21–24)	487 (17%)	0.99 (0.06–3.28)	22 (11–44)	48 (2)	481 (20)	17 (0.8)
Water				**No. (%) water treatments**		**Total mg/bird[c]**			
Amoxicillin	15 (2%)	398	6 (5–6)	16 (0.5%)	0.85 (0.11–1.59)	53 (14–443)	63 (14)	158 (37)	5 (1.2)
Apramycin	1 (0.1%)	40	4	1 (0.03%)	0.12	30	30	34	1
Enrofloxacin	3 (0.2%)	79	5 (3–6)	3 (0.1%)	0.12 (0.09–0.13)	0.5 (0.3–0.5)	0.4 (0.1)	2 (0.2)	0.1 (0.01)
Lincomycin	1 (0.1%)	10	2	1 (0.03%)	1.34	63	63	502	17
Penicillin	29 (2%)	675	5 (5–6)	31 (1%)	0.88 (0.07–2.04)	153 (8–432)	166 (21)	114 (14)	4 (0.5)
Penicillin-streptomycin	13 (1%)	569	4 (5–6)	19 (0.6%)	0.21 (0.07–1.09)	13 (7–321)	41 (18)	150 (77)	5 (3)
Sulfamethazine	9 (1%)	293	4 (3–5)	9 (0.3%)	0.25 (0.11–0.74)	136 (34–311)	137 (28)	19 (4)	1 (0.1)
Sulfaquinoxaline	12 (1%)	358	3 (3–4)	11 (0.3%)	0.55 (0.12–1.86)	66 (13–208)	80 (15)	32 (6)	1 (0.2)
Sulfaquinoxaline (*pyr*)[d]	7 (1%)	207	3 (2–4)	7 (0.0%)	1.22 (0.09–1.86)	12 (4–39)	15 (4)	37 (9)	1 (0.4)
Oxytetracycline-neomycin	1 (0.1%)	19	4	1 (0.03%)	0.2	66	66	78	3
Tetracycline	3 (0.3%)	64	4 (3–6)	3 (0.1%)	0.68	19 (16–113)	49 (32)	63 (40)	2 (1)
Tetracycline-neomycin	8 (1%)	326	4 (4–5)	8 (0.2%)	0.25 (0.18–0.49)	44 (24–233)	73 (26)	102 (37)	3 (1)

[a] *Number of flocks treated/total flocks surveyed.*
[b] *Number of treatments/ total treatments from all routes of administration.*
[c] *The estimated total milligrams administered per bird during the course of water treatment. This was reported as grams per liter of drinking water (2013–2018) or total grams of active ingredient administered during the course of treatment per bird in the flock treated.*
[d] *This is in combination with pyrimethamine (a coccidiostat); only the sulfaquinoxaline component was included in the estimates.*

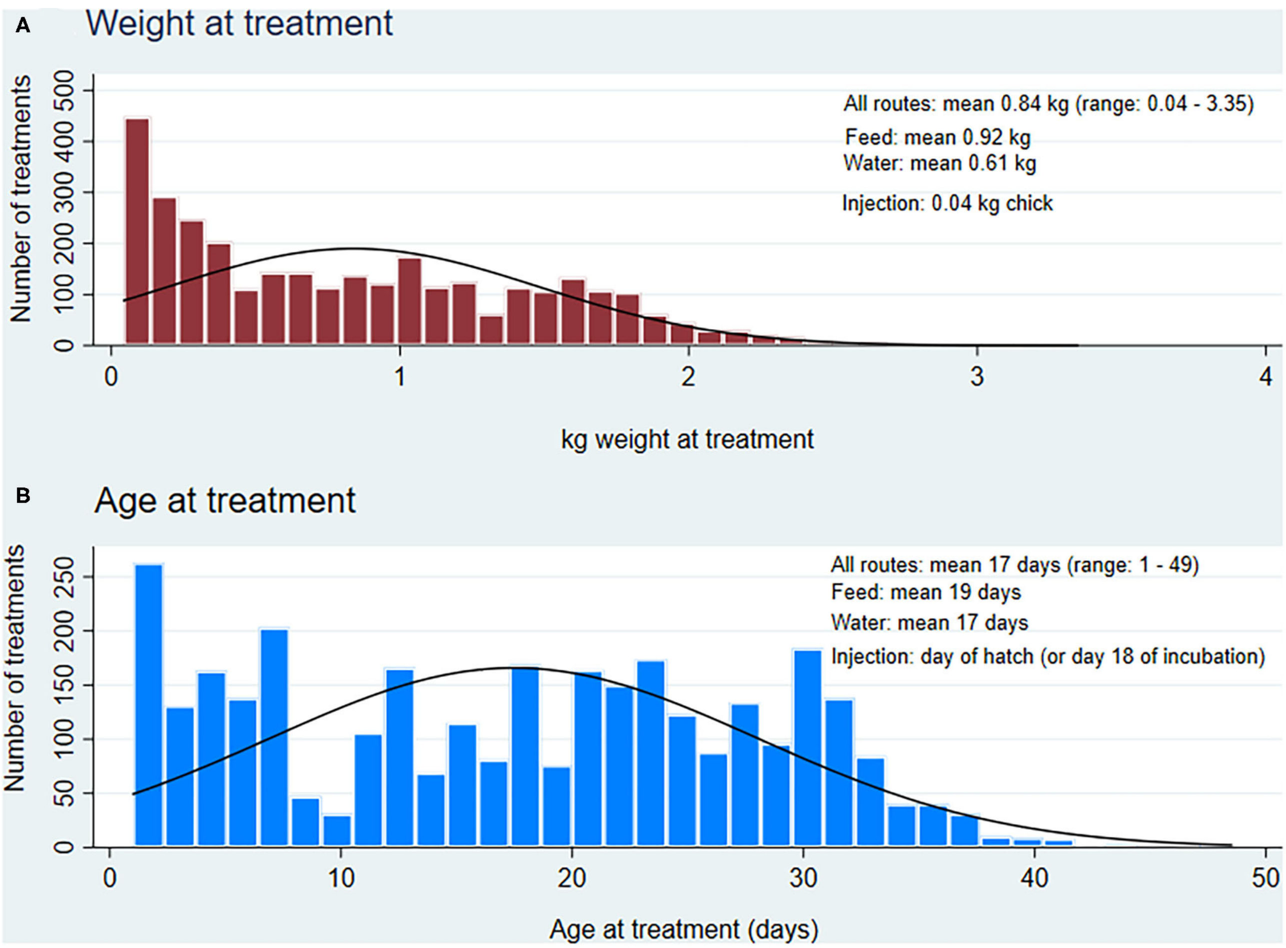


FIGURE 1 | Distribution of weight and age at treatment ($n = 3,876$ treatments via feed, water and injection) for broiler chickens, 2013 to 2019. **(A)** Weight at treatment combines all the estimated weights for each treatment via injection, water and feed routes of administration, **(B)** Age at treatment combines all the reported age for each treatment via injection (default at day 1), water and feed routes of administration.

Medicating Ingredients Brochure (11). For medicated rations, the inclusion rates of AAI in feed were consistent throughout the growing period (if used in multiple rations), except in cases where a stepwise approach for the drug administration with a changing inclusion rate during the growing period was used. For example, 110 g/ton of bacitracin in the pre-starter ration for "reduction of early mortality due to diminished feed consumption and chilling" was reduced to 55 g/ton in subsequent rations for the prevention of necrotic enteritis. Similarly, avilamycin was added at 15–30 g/ton as per product label and approved level of drug in the feed (11, 12).

Quantity of antimicrobials reported to be used

The flock-level AMU data showed a skewed distribution where the mean values were higher than the median in the three AMU indicators; zeros represented flocks that were raised as ABF, RWA, organic or other production types not exposed to any AAI [(24); **Figure 2**]. Across the participating flocks, the mean AMU at the flock-level in mg/PCU_{Br} was 134 (median: 123; minimum: 57 and maximum: 1,268). When adjusted for dose and animal-time parameters, nDDDvetCA/1,000 broiler chicken-days at risk and nDDDvetCA/PCU_{Br}, the mean was 507 (median: 494; 305–2, 713) and 18 (median: 17; 10–125), respectively (**Figure 2**).

Descriptive statistics by AAI for the weight-based and dose-based AMU indicators are shown in **Table 3**. Data aggregated by antimicrobial class and the distribution of the flock-level mg/PCU_{Br} are also presented in **Supplementary Material 1**. The three highest means in mg/PCU_{Br} were flocks that were medicated with the following classes: tetracyclines ($n = 19$ flocks, 190 mg/PCU_{Br}), trimethoprim-sulfonamides ($n = 106$ flocks; 157 mg/PCU_{Br}), and bacitracins ($n = 509$; 144 mg/PCU_{Br}). For nDDDvetCA/1,000 broiler-chicken days at risk, the relative ranking of the antimicrobial classes changed and the highest means were flocks that consumed trimethoprim-sulfonamides, streptogramins, and bacitracins at 594, 481, and 406 nDDDvetCA/1,000 broiler chicken-days at risk, respectively. For nDDDvetCA/PCU, the highest means paralleled the previous

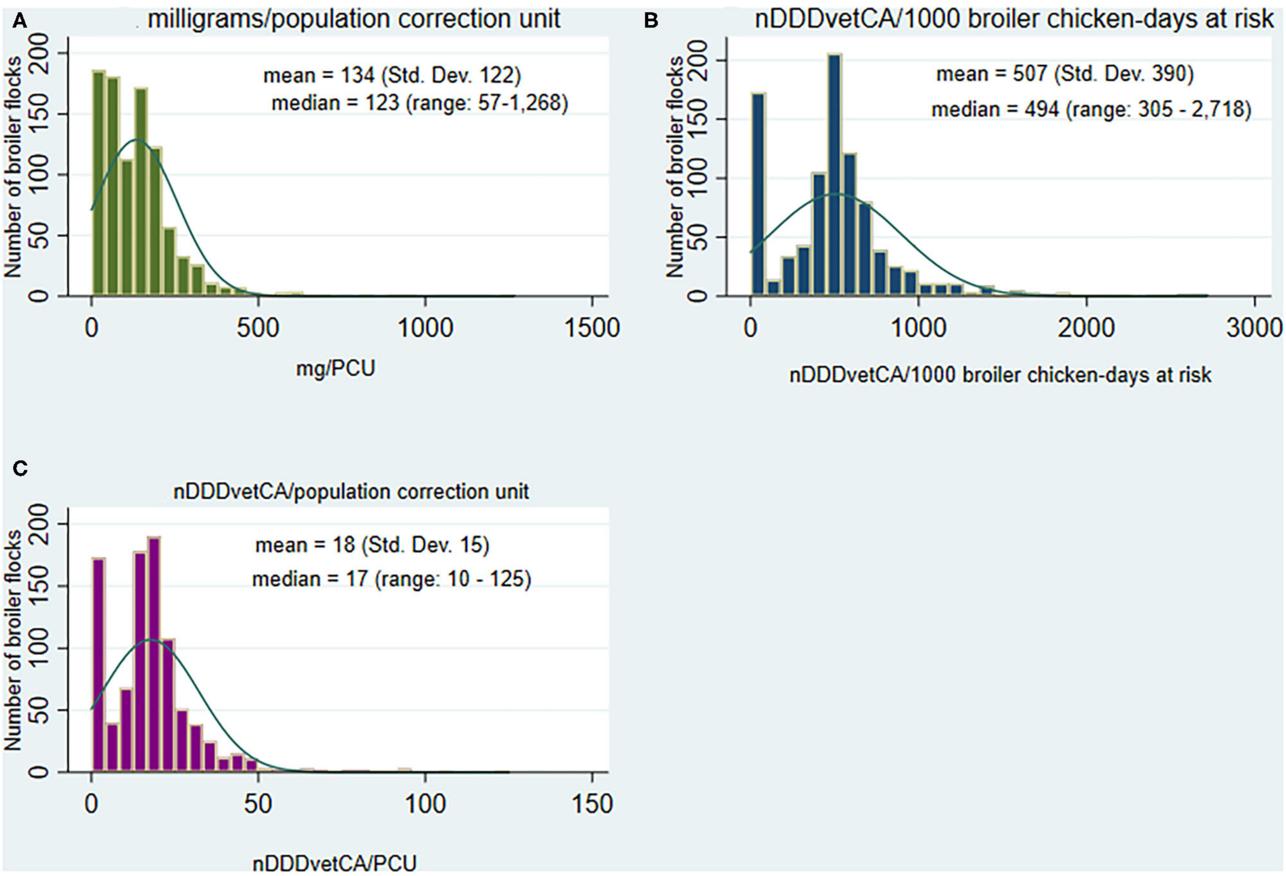


FIGURE 2 | Distribution of the quantities of antimicrobials reported to be used, by antimicrobial use indicators, in broiler chicken flocks (n = 934 flocks), 2013 to 2019. **(A)** Broiler flock-level milligrams adjusted by population and weight (population correction unit), **(B)** Broiler flock-level number of defined daily doses for animals using Canadian standards adjusted by population, weight at treatment and days at risk, and **(C)**. Broiler flock-level number of defined daily doses for animals using Canadian standards adjusted by population and broiler weight (population correction unit).

indicator at 21, 17, and 14 nDDDvetCA/PCU for trimethoprim and sulfonamides, streptogramins, and bacitracins, respectively.

Identification of High Users of AMU in Broiler Chickens

Flocks defined as high users based on mg/PCU_{Br} were significantly ($P \leq 0.05$) more likely to have used antimicrobials in water [Odds ratio (OR) = 6.49]. These were conventional flocks that were treated with antimicrobials via feed for routine necrotic enteritis prevention, plus medicated via water for treatment of diseases other than necrotic enteritis. For example, when diagnosed with any of the lesions associated with avian pathogenic *E. coli* (APEC) including yolksacculitis, septicemia or airsacculitis, and occasionally vertebral osteomyelitis (*Enterococcus cecorum*) or *Staphylococcus aureus* (osteomyelitis) infections. These flocks were also significantly more likely to have used aminoglycosides (OR = 3.41), bacitracins (OR = 4.27), penicillins (OR = 2.47), tetracyclines (OR = 9.17), and trimethoprim-sulfonamides (OR = 13.34). As well, these flocks were significantly ($P \leq 0.05$) more likely to be in the top 25th percentile of aminoglycosides (OR = 3.42), bacitracins (OR = 74.48), and penicillins (OR = 5.95) users based on mg/PCU_{Br}. Flocks using macrolides (OR = 0.36), streptogramins (OR = 0.41), and orthosomycins (OR = 0.43) were significantly ($P \leq 0.05$) less likely to be classified as high users based on mg/PCU_{Br}. It should be noted that all of the antimicrobial classes listed above were administered through multiple routes.

Turkeys

General Description of AMU and Flock/Farm Characteristics

Flock and farm characteristics

A cumulative total of 427 turkey flocks across four Canadian provinces participated in the CIPARS turkey farm surveillance between 2013 and 2019 (British Columbia: 206 flocks, Alberta: 20 flocks, Ontario: 121 flocks and Québec: 80 flocks). The total birds sampled were 3.2 million birds (∼0.25–0.68 million birds/year) equivalent to 29 million kg turkey biomass (∼2–6 million kg/year). Descriptive statistics for farm and flock characteristics by marketing weight categories are summarized in **Table 4**.

The mean pre-harvest sampling age or days at risk across the turkey flocks sampled was 89 days and varied by marketing

TABLE 4 | Characteristics of the studied turkey flocks (n = 427) by marketing weight categories, 2013–2019.

Characteristics	Units	Mean of flocks (Standard error of the mean)					
		Broiler turkeys (n = 84)	**Light hens (n = 105)**	**Heavy hens (n = 67)**	**Light tom (n = 48)**	**Heavy tom (n = 123)**	**Overall (n = 427)**
Age sampled	Days	64 (1)	78 (1)	96 (1)	96 (1)	107 (1)	89 (1)
Preslaughter live weight[a]	kg bird	5 (0.1)	7 (0.1)	9 (0.2)	12 (0.2)	15 (0.2)	10 (0.2)
Birds at risk	n birds	8, 624 (478)	8,215 (453)	7,596 (562)	7,131 (464)	6,171 (279)	7,488 (198)
Total preslaughter live weights	kg, total	42, 457 (2,552)	55,122 (3,159)	68,277 (4,626)	87,546 (6,009)	89,773 (4,121)	68,321 (2,009)
Stocking density	birds/m^2	6 (0.2)	6 (0.2)	5 (0.2)	3 (0.2)	3 (0.1)	5 (0.1)
Farm capacity	n birds	23, 704 (3, 844)	27,528 (2,190)	31,259 (2,865)	26,726 (3,061)	25,642 (2,095)	26,924 (1,242)
Mortality	%	4 (0.3)	5 (0.4)	6 (0.4)	6 (0.4)	8 (0.4)	6 (0.2)

[a]*Used interchangeably with pre-harvest throughout the manuscript (i.e., farm visit and data collection before shipment for slaughter).*

weight categories, and was shortest in broiler turkeys (64 days) and longest in heavy toms (107 days). Fifty-six percent of the producers raised birds in the heavier weight categories (combined heavy hens, light toms and heavy toms).

Antimicrobial active ingredients and routes of administration

There were 20 different AAIs used in turkeys (**Table 5**) and 8 AAIs were administered via feed (tylosin, procaine penicillin, virginiamycin, trimethoprim-sulfadiazine, bacitracin, chlortetracycline, oxytetracycline, and avilamycin), 10 in water (enrofloxacin, neomycin, amoxicillin, penicillin G potassium, oxytetracycline-neomycin, tetracycline-neomycin, sulfaquinoxaline, and sulfaquinoxaline-pyrimethamine), and 2 via injections (ceftiofur, gentamicin).

Frequency

Most flocks (72%) were treated via the feed (i.e., represented the greatest route of AAI exposures as with broilers), nearly half of the flocks were medicated via injections (45%) and a small percentage were medicated via water (11%). Fifty-seven flocks (13%, excluded in subsequent AMU analysis as these flocks did not contribute to multiple units of comparisons) were intended for the mainstream market including RWA, ABF, and organic without any exposures to medically-important antimicrobials, ionophores, and chemical coccidiostats. As with the broiler chickens, more than half of the turkey producers used one (31%) or two (33%) AAIs during the grow-out period by all routes combined; the remaining flocks used three (10%), four (4%), and more than five AAIs (<1%). There were 1,721 total treatment frequencies recorded (191 injections, 1,469 feed, and 61 water). It is important to note that a single flock could have been exposed to AAIs via multiple routes of administration.

AMU patterns

Combined data from all routes indicated that there were different AMU patterns utilized by the turkey producers during the grow-out period, though less diverse compared to broilers (68 patterns). The most frequently occurring patterns were treatment of the flock with bacitracin (19%, $n = 65$), gentamicin-virginiamycin (17%, $n = 57$), bacitracin-gentamicin (15%, $n = 50$), virginiamycin (10%, $n = 35$), and gentamicin (28%, $n = 268$). Over time, the number of patterns decreased from 24 AMU patterns (2016, national program commenced) to 20 AMU patterns (2019) (**Supplementary Material 3**).

Total birds exposed to AAIs

Almost half of the total population sampled were medicated with gentamicin (49%, 1.6 million birds). Other notable antimicrobial exposures were bacitracin (35%, 1.4 million birds) and virginiamycin (33%, 1.05 million birds).

Duration of exposure to AAIs

In treated flocks, the mean number of medicated rations was 4 per flock (up to 8 rations in heavier weight categories). The mean exposure days in feed-administered AAIs were longest for bacitracin (66 days; 6–110), followed by virginiamycin (64; 7–112) and tylosin (59; 14–84). For AAIs administered via water, the mean days of exposure varied depending on the AAI but were relatively shorter than feed exposures from 3 days (oxytetracycline-neomycin) to 7 days (penicillin). The maximum durations for AAIs administered via water were documented for tetracycline-neomycin (21 days) and penicillin (28 days) reportedly used for the treatment of secondary bacterial infection and clostridial dermatitis, respectively.

Age at treatment

The mean age at treatment varied by route of administration and AAI (**Figure 3**, **Table 5**), but combined data from all routes yielded a mean age of 35 days.

Weight at treatment

Similarly, the weight at treatment varied by route of administration and AAI, but combined data from all routes yielded a mean treatment weight of 3 kg (**Figure 3**, **Table 5**), relatively lower than ESVAC's 6.5 kg.

TABLE 5 | Reported antimicrobial use by route of administration and by antimicrobial active ingredient in turkey flocks, 2013–2019.

	n (%) flocks treated[a]	Total birds treated ('000)	Days exposed, mean (min-max)	No (%) of treatments[b]	kg weight at treatment mean (min-max)	Level of drug mean (min-max)	Indicators, mean (standard error of the mean)		
							mg/PCU_{Tk}	nDDDvet/1,000 turkey-days at risk	$nDDDvet/PCU_{Tk}$
Injection				**No. (%) injections**		**mg/poult**			
Ceftiofur	1 (0.2%)	14	1	1 (0.1%)	0.06	0.2	0.03	< 0.1	< 0.1
Gentamicin	190 (44%)	1,563	1	190 (11%)	0.06	1	0.2	0.16	0.2
Feed				**No. (%) medicated rations**		**Grams/ton**			
Avilamycin	10 (2%)	74	40 (11–70)	24 (1%)	3.80 (0.26–11.76)	18 (15–25)	19 (5)	69 (13)	6 (2)
Bacitracin	181 (42%)	1,442	66 (6–110)	799 (46%)	3.08 (0.15–16.08)	55 (55–110)	96 (5)	103 (4)	9 (0.5)
Chlortetracycline	10 (2%)	102	16 (4–42)	12 (1%)	2.64 (0.26–6.83)	330 (220–440)	114 (30)	68 (15)	7 (2)
Oxytetracycline	2 (0.5%)	81	49	4 (0.2%)	1.36 (0.45–2.27)	440 (220–660)	182	99	11
Penicillin procaine	15 (4%)	4	26 (14–42)	25 (1%)	1.17 (0.26–3.02)	33 (33–110)	16 (3)	32 (6)	3 (0.5)
Trimethoprim-sulfadiazine	21 (5%)	139	13 (4–28)	22 (1%)	4.33 (0.55–11.76)	300 (200–300)	113 (22)	181 (32)	17 (3)
Tylosin	9 (2%)	61	59 (14–84)	35 (2%)	4.43 (0.26–11.76)	22 (22–22)	44 (10)	17 (4)	2 (0.4)
Virginiamycin	130 (30%)	1,054	64 (7–112)	548 (32%)	2.80 (0.26–13.95)	22 (16.5–44)	33 (2)	131 (5)	12 (1)
Water				**No. (%) water treatments**		**Total mg/bird[c]**			
Amoxicillin	5 (1%)	27	5 (4–6)	5 (0.3%)	2.99 (0.15–5.22)	63 (0.5–413)	20 (11)	17 (9)	2 (10)
Enrofloxacin	4 (1%)	40	4 (4–5)	4 (0.2%)	2.46 (0.37–6.16)	9 (5–13)	1 (0.27)	3 (1)	0.2 (0.1)
Neomycin	3 (1%)	25	5	3 (0.2%)	2.42 (1.97–3.31)	26 (25–401)	23 (19)	11 (9)	1 (1)
Penicillin	21 (5%)	156	7 (3–28)	23 (1.3%)	4.78 (0.26–13.95)	63 (4–1786)	38 (14)	10 (4)	1 (0.3)
Penicillin-streptomycin	7 (2%)	50	5 (1–8)	8 (0.5%)	1.36 (0.15–3.88)	4	1 (1)	2 (1)	1 (1)
Sulfaquinoxaline	2 (0.5%)	9	5 (3–6)	1 (0.1%)	5.07 (3.31–6.83)	85 (75–95)	13 (2)	2 (0.10)	0.2
Sulfaquinoxaline (pyr)[d]	1 (0.2%)	79	4	2 (0.1%)	4.37 (4.37–4.37)	12	2	2	0.2
Oxytetracycline-neomycin	1 (0.2%)	44	3	1 (0.1%)	4.37 (4.37–4.37)	55	9	4	9
Tetracycline	7 (2%)	7	6 (4–10)	5 (0.3%)	2.50 (0.52–4.98)	11 (0.03–227)	8 (5)	5 (3)	0.4 (0.2)
Tetracycline-neomycin	6 (1%)	3	9 (5–21)	9 (0.5%)	2.70 (0.15–11.75)	54 (24–186)	17 (5)	8 (3)	17 (5)

[a] *Number of flocks treated/total flocks surveyed.*
[b] *Number of treatments/total treatments from all routes of administration.*
[c] *The estimated total milligrams administered per bird during the course of water treatment. This was reported as grams per liter of drinking water (2013–2018) or total grams of active ingredient administered during the course of treatment per bird in the flock treated.*
[d] *This is in combination with pyrimethamine (a coccidiostat). Only the sulfaquinoxaline component was included in the estimates.*

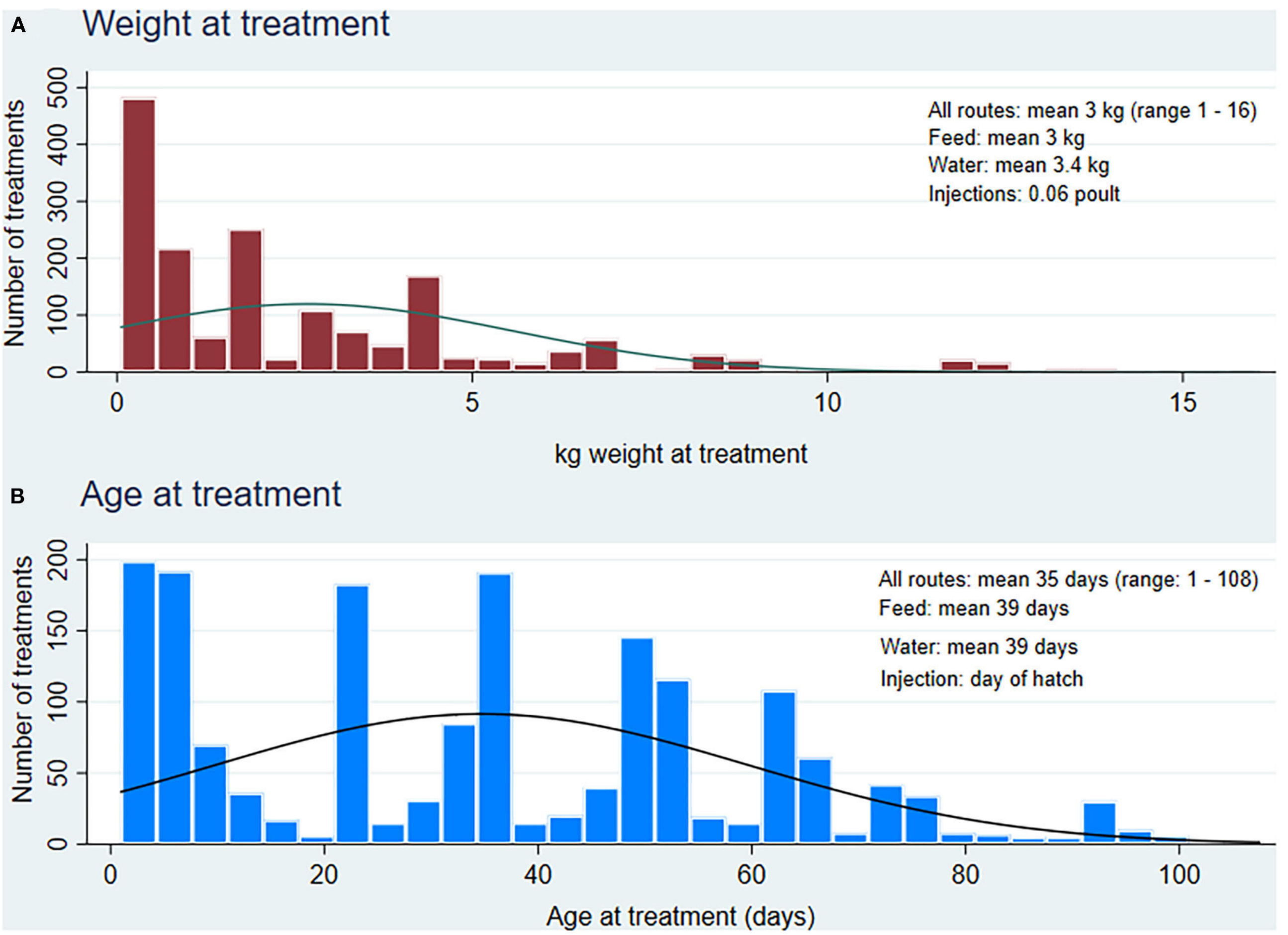


FIGURE 3 | Distribution of weight and age at treatment in treated turkey flocks ($n = 1,721$ treatments via feed, water and injection), 2013 to 2019. **(A)** Weight at treatment combines all the estimated weights for each treatment via injection, water and feed routes of administration, **(B)** Age at treatment combines all the reported age for each treatment via injection (default at day 1), water and feed routes of administration.

Inclusion rates or level of drug in feed, water, and injection

As with the broiler chickens, the amount of AAIs added through feed, drinking water and injections were largely according to the Compendium of Medicating Ingredients Brochure (11) and the Compendium of Veterinary Products (12).

Quantity of antimicrobial use reported

The flock-level AMU indicators data showed a skewed distribution (**Figure 4**) as with the broiler chickens. The mean value was higher than the median for mg/PCU_{Tk} but similar for the dose-based indicators. There were also zero values, as with the broiler chickens, for flocks raised as ABF, RWA, organic, or other production types not exposed to antimicrobials (24). Across the studied flocks, the mean antimicrobials reported was 64 mg/PCU_{Tk} (median: 39; minimum:0.15, and maximum: 528). The dose-based indicators also showed between flock variations in nDDDvetCA/1,000 turkey-days at risk and nDDDvetCA/PCU_{Tk} at a mean of 102 (median: 99; 0.19–557) and mean of 9 (median: 8; 0.01–57), respectively.

Descriptive statistics aggregated by AAIs for the weight-based and dose-based AMU indicators are shown in **Table 5**. Data aggregated by antimicrobial class and the distribution of mg/PCU_{Tk} by antimicrobial class are presented in **Supplementary Material 2**. The three highest means in mg/PCU_{Tk} were flocks that were medicated with trimethoprim-sulfonamides ($n = 24$ flocks, 109 mg/PCU_{Tk}), bacitracins ($n = 181$ flocks; 96 mg/PCU_{Tk}), and tetracyclines ($n = 26$ flocks; 62 mg/PCU_{Tk}). For the dose based indicators, the relative ranking changed and the three highest means for nDDDvetCA/1,000 turkey-days at risk were noted in flocks that were medicated with trimethoprim and sulfonamides, streptogramins, and bacitracins at 174, 131, and 103, respectively. For nDDDvetCA/PCU_{Tk}, the highest means paralleled the previous indicator at 17, 12, and 9 for trimethoprim and sulfonamides, streptogramins, and bacitracins.

Identification of High Users of AMU in Turkey Flocks

Flocks defined as high users based on mg/PCU_{Tk} were significantly ($P \leq 0.05$) more likely to have used antimicrobials in water ($OR = 3.5$) and feed ($OR = 37.65$). These flocks were also significantly ($P \leq 0.05$) more likely to have used trimethoprim and sulfonamides ($OR = 7.17$), bacitracins ($OR = 12.31$), and

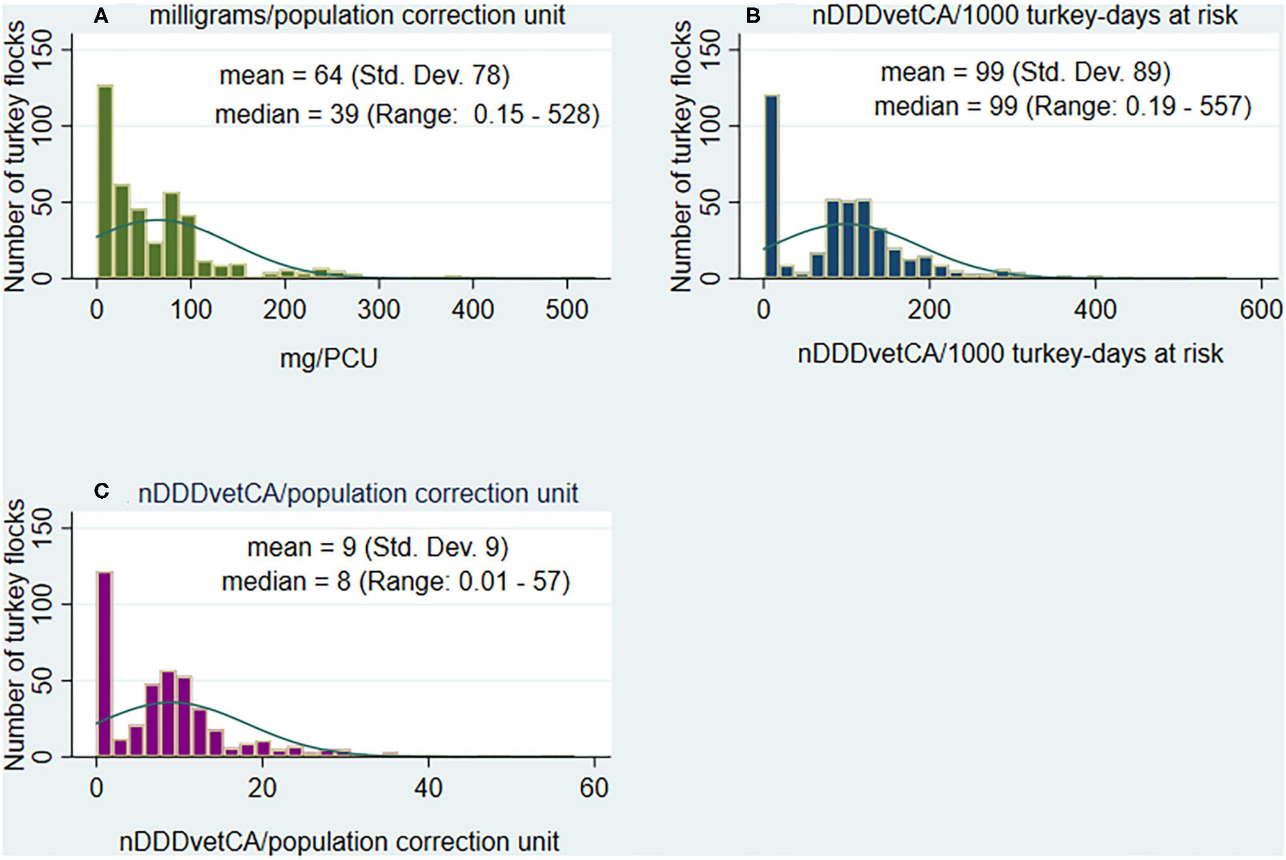


FIGURE 4 | Distribution of the quantities of antimicrobials reported to be used, by antimicrobial use indicators in turkey flocks (n = 427 flocks), 2013 to 2019. **(A)** Turkey flock-level milligrams adjusted by population and turkey weight (population correction unit), **(B)** Turkey flock-level number of defined daily doses for animals using Canadian standards adjusted by population, turkey weight at treatment and days at risk, and **(C)** Turkey flock-level number of defined daily doses for animals using Canadian standards adjusted by population and turkey weight (population correction unit).

tetracyclines ($OR = 9.96$). As well, these flocks were significantly more likely to be in the top 25th percentile of penicillins ($OR = 5.01$) users based on mg/PCU_{Tk}. Flocks using streptogramins ($OR = 0.24$) were significantly ($P \leq 0.05$) less likely to be classified as high users based on mg/PCU_{Tk}. It should be noted that all of the antimicrobial classes listed above were administered through multiple routes. It should also be noted that differences were observed between the different marketing weight categories, which may be further explored in future years when data from a larger number of turkey flocks are available.

Selection of AMU Indicator and Exploration of Alternative Weight in Denominator for Reporting and Communication

Pairwise Correlations Between AMU Indicators

Broiler chickens

Pairwise correlation analysis (data from conventional or medicated flocks, $n = 831$) indicated moderate correlations between mg/PCU_{Br} and nDDDvetCA/1,000 broiler-chicken days at risk [Pearson correlation coefficient (PCC) = 0.7039, $P < 0.001$] and between mg/PCU_{Br} and $nDDDvetCA/PCU_{Br}$ (PCC = 0.7503, $P < 0.001$). A significantly high PCC was observed between nDDDvetCA/1,000 broiler-chicken days at risk and $nDDDvetCA/PCU_{Br}$ (PCC = 0.9667, $P < 0.001$).

Turkeys

As with broiler chickens, PCC using (data from conventional flocks, $n = 370$) indicated moderate correlations between mg/PCU_{Tk} and nDDDvetCA/1,000 turkey-days at risk (PCC = 0.7062, $P < 0.001$) and between mg/PCU_{Tk} and $nDDDvetCA/PCU_{Tk}$ (PCC = 0.7062, $P < 0.001$). A significantly high correlation was observed between nDDDvetCA/1,000 turkey-days at risk and $nDDDvetCA/PCU_{Tk}$ (PCC = 0.9631, $P < 0.001$).

Tables 6, **7** summarizes the pairwise correlation matrix of the AMU indicators comparing routine CIPARS AMU estimation and using alternate weights in the denominator in broiler chickens and turkeys, respectively. The three pairwise correlation pairs (routine estimations) are also shown in **Supplementary Material 2** depicting the highly positive correlation between the two dose-based indicators.

TABLE 6 | Pairwise correlation matrix, antimicrobial use indicators in broiler chicken flocks (n =831).

ROUTINE CIPARS AMU ANALYSIS			
	Mean	**Standard error of the mean**	**95% Confidence intervals**
$mg/PCU_{Br}^{(CIPARS)}$	150	4	142–159
nDDDvetCA/1,000 broiler chicken-days at risk $^{(CIPARS)}$	570	13	545–595
$nDDDvetCA/PCU_{Br}^{(CIPARS)}$	20	0.5	19–21
PAIRWISE CORRELATION MATRIX			
	$mg/PCU_{Br}^{(CIPARS)}$	nDDDvetCA/1,000 broiler chicken-days at risk $^{(CIPARS)}$	$nDDDvetCA/PCU_{Br}^{(CIPARS)}$
$mg/PCU_{Br}^{(CIPARS)}$	1		
nDDDvetCA/1,000 broiler chicken-days at risk $^{(CIPARS)}$	**0.7039***	1	
$nDDDvetCA/PCU_{Br}^{(CIPARS)}$	**0.7503***	**0.9667***	1
ALTERNATE AMU ANALYSIS			
	Mean	Standard error of the mean	95% Confidence intervals
$mg/kg_{Br}^{(ALT)}$	73	2	70
nDDDvetCA/1,000 broiler chicken-days at risk $^{(ALT)}$	284	6	271
$nDDDvetCA/kg_{Br}^{(ALT)}$	10	0.2	9
PAIRWISE CORRELATION MATRIX			
	$mg/kg_{Br}^{(ALT)}$	nDDDvetCA/1,000 broiler chicken-days at risk $^{(ALT)}$	$nDDDvetCA/kg_{Br}^{(ALT)}$
$mg/kg_{Br}^{(ALT)}$	1		
nDDDvetCA/1,000 broiler chicken-days at risk $^{(ALT)}$	**0.6878***	1	
$nDDDvetCA/kg_{Br}^{(ALT)}$	**0.7000***	**0.9638***	1

Analysis excluded flocks which were intentionally raised without antibiotics under designated programs for mainstream market such as "Raised without Antibiotics," "Antibiotic-Free," and organic.
CIPARS—Canadian Integrated Program for Antimicrobial Resistance Surveillance.
$^{(CIPARS)}$Based on routine formula used by CIPARS.
$^{(ALT)}$kg broiler chicken live pre-slaughter weights, alternate estimation methods.
nDDDvetCA—number of defined daily doses for animals using Canadian standards.
PCU—population correction unit (based on the European Surveillance for Veterinary Antimicrobial Consumption average weight at treatment for broiler chickens at 1 kg).
Br—broilers.
$^{*}P < 0.0001$, Pearson correlation coefficient.

Exploration of Alternate Weights in the Denominators

Broiler chickens

When the input parameter in the denominator was changed to the actual kg broiler chicken biomass recorded at the time of the pre-harvest visit or the pre-slaughter live weight (mean of 2 kg; 1.2–4.4) instead of the ESVAC's average weight at treatment of 1 kg, the estimates of use decreased by ∼50% (**Table 6**).

It is important to note (**Table 6**) that the change in denominator to kg live broiler chicken biomass resulted in a slight decrease in PCC, though it remained moderate between the weight-based mg/kg vs. the two dose-based indicators nDDDvetCA/1,000 broiler chicken-days at risk (PCC = 0.6951, $P < 0.0001$) and nDDDvetCA/PCU (PCC = 0.7058, $P < 0.0001$). Correlation between the two dose-based indicators remained significantly high (PCC = 0.9648, $P < 0.0001$).

Turkeys

Using actual kg live turkey biomass (mean weights: all categories [10 kg], broiler turkeys [5 kg], light hens [7 kg], heavy hens [9 kg], light toms [12 kg], heavy tom [15 kg]) at the time of the pre-harvest visit instead of the ESVAC's average weight at treatment of 6.5 kg (**Table 3**), decreased the estimates by ∼33% unlike the broiler chickens data where reduction was by 50% (**Table 7**).

Unlike the broiler chickens, the change in denominator to kg live turkey biomass had a greater impact on the PCC values (**Table 7**). Pearson correlation coefficients decreased between the weight-based mg/kg vs. the two dose-based indicators nDDDvetCA/1,000 turkey-days at risk (PCC = 0.5376, $P < 0.0001$) and nDDDvetCA/PCU (PCC = 0.5727, $P < 0.0001$). Correlation between the two dose-based indicators slightly decreased but remained significantly high (PCC = 0.8662, $P < 0.0001$; **Table 7**).

Overall AMU by Route of Administration and National Temporal Trends

For broiler chickens, when the quantitative data from all years were combined, the highest proportion of antimicrobials reported were those administered via the feed (92%) and smaller proportion was administered via water (8%) and injections (<1%). Similar proportions of antimicrobials reported were noticed for turkeys for feed (96%), water (8%), and injections (1%). Over time, the proportion of use by route of administration remained consistent until 2018 (**Supplementary Material 2**) where the proportion of antimicrobials administered via water increased from 5 to 14% in broiler chickens and from 3 to 11% in turkeys. Antimicrobials administered via injection constituted <1% of the total AMU and frequency of this use

TABLE 7 | Pairwise correlation matrix, antimicrobial use indicators in turkey flocks ($n = 370$).

ROUTINE CIPARS AMU ANALYSIS			
Indicator	Mean	Standard error of the mean	95% Confidence interval
$mg/PCU_{Tk}^{(CIPARS)}$	75	4	66–83
nDDDvetCA/1,000 turkey-days at risk $^{(CIPARS)}$	114	4	105–122
$nDDDvetCA/PCU_{Tk}^{(CIPARS)}$	10	0.5	9–11
PAIRWISE CORRELATION MATRIX			
	mg/PCU_{Tk}	nDDDvetCA/1,000 turkey-days at risk $^{(CIPARS)}$	$nDDDvetCA/PCU_{Tk}^{(CIPARS)}$
$mg/PCU_{Tk}^{(CIPARS)}$	**1**		
nDDDvetCA/1,000 turkey-days at risk $^{(CIPARS)}$	**0.7062***	**1**	
$nDDDvetCA/PCU_{Tk}^{(CIPARS)}$	**0.7604***	**0.9631***	**1**
ALTERNATE AMU ANALYSIS			
	Mean	Standard error of the mean	95% Confidence interval
$mg/kg_{Tk}^{(ALT)}$	50	2	45–54
nDDDvetCA/1,000 turkey-days at risk $^{(ALT)}$	86	3	79–92
$nDDDvetCA/kg_{Tk}^{(ALT)}$	7	0	7–8
PAIRWISE CORRELATION MATRIX			
	$mg/kg_{Tk}^{(ALT)}$	nDDDvetCA/1,000 turkey-days at risk $^{(ALT)}$	$nDDDvetCA/kg_{Tk}^{(ALT)}$
$mg/kg_{Tk}^{(ALT)}$	**1**		
nDDDvetCA/1,000 turkey-days at risk $^{(ALT)}$	**0.5376***	**1**	
$nDDDvetCA/kg_{Tk}^{(ALT)}$	**0.5727***	**0.8662***	**1**

Analysis excluded flocks which were intentionally raised without antibiotics under designated programs for mainstream market such as "Raised without Antibiotics," "Antibiotic-Free," and organic.

CIPARS—Canadian Integrated Program for Antimicrobial Resistance Surveillance.

$^{(CIPARS)}$Based on routine CIPARS formula.

$^{(ALT)}$kg turkey live pre-slaughter weights, alternate estimation methods.

nDDDvetCA—number of defined daily doses for animals using Canadian standards.

PCU—population correction unit (based on the European Surveillance for Veterinary Antimicrobial Consumption average weight at treatment for turkeys at 6.5 kg).

Tk—turkeys.

**$P < 0.0001$, Pearson correlation coefficient.*

decreased over time; a small quantity of injectable antimicrobial, lincomycin-spectinomycin, was administered in broiler chicks and gentamicin in turkey poults at the hatchery via injections in 2019. One turkey flock in 2013 was treated with ceftiofur *in ovo* at the hatchery.

For trends over time, estimates using routine CIPARS methodology and using alternate weights in the denominator showed relatively similar trends but as anticipated, a lower magnitude using the pre-harvest weights for both broilers and turkeys (**Figure 5**). Similar trends were observed in the dose-based indicators (nDDDvetCA/1,000 broiler-chicken or turkey-days at risk). It is important to note that this latter indicator, which corrects for dose showed a decrease in 2019 unlike the weight based indicator (**Figure 6**) due to the shift in the AAIs that constituted overall use for that year in both species (i.e., shift from AAIs with low DDDvetCA's to AAIs with relatively higher DDDvetCA's).

DISCUSSION

Building on our methodology for estimating farm-level national AMU data (7, 19) this study further explored AMU characteristics and the utility of different AMU indicators at the flock-level with the intent of informing best practices for surveillance analysis and reporting. We demonstrated how the application of quantitative AMU indicator (mg/PCU) and qualitative AMU metrics (frequency of use, route of administration) complement each other in characterizing high users of antimicrobials. We envisaged that this approach will enhance the methodology for producer and veterinarian reporting and for providing feedback to the poultry industry. Our data indicated that high users were those that used antimicrobials via water and certain classes indicated for the therapy of systemic diseases in poultry; these are in addition to a routine necrotic enteritis program.

We determined that the three AMU indicators currently used by CIPARS were moderately or closely related, suggestive of the necessity of using at least two indicators, one weight-based and one dose-based, to better characterize the evolving AMU patterns associated with current AMU reduction initiatives in broilers and turkeys in Canada (16, 17). Finally, we have shown that a change to the input parameter in the denominator did not impact reported AMU distribution and AMU trends. Thus, alternate choices for weight of the birds could be considered for their utility for national surveillance reporting, evaluated for relevance in the Canadian

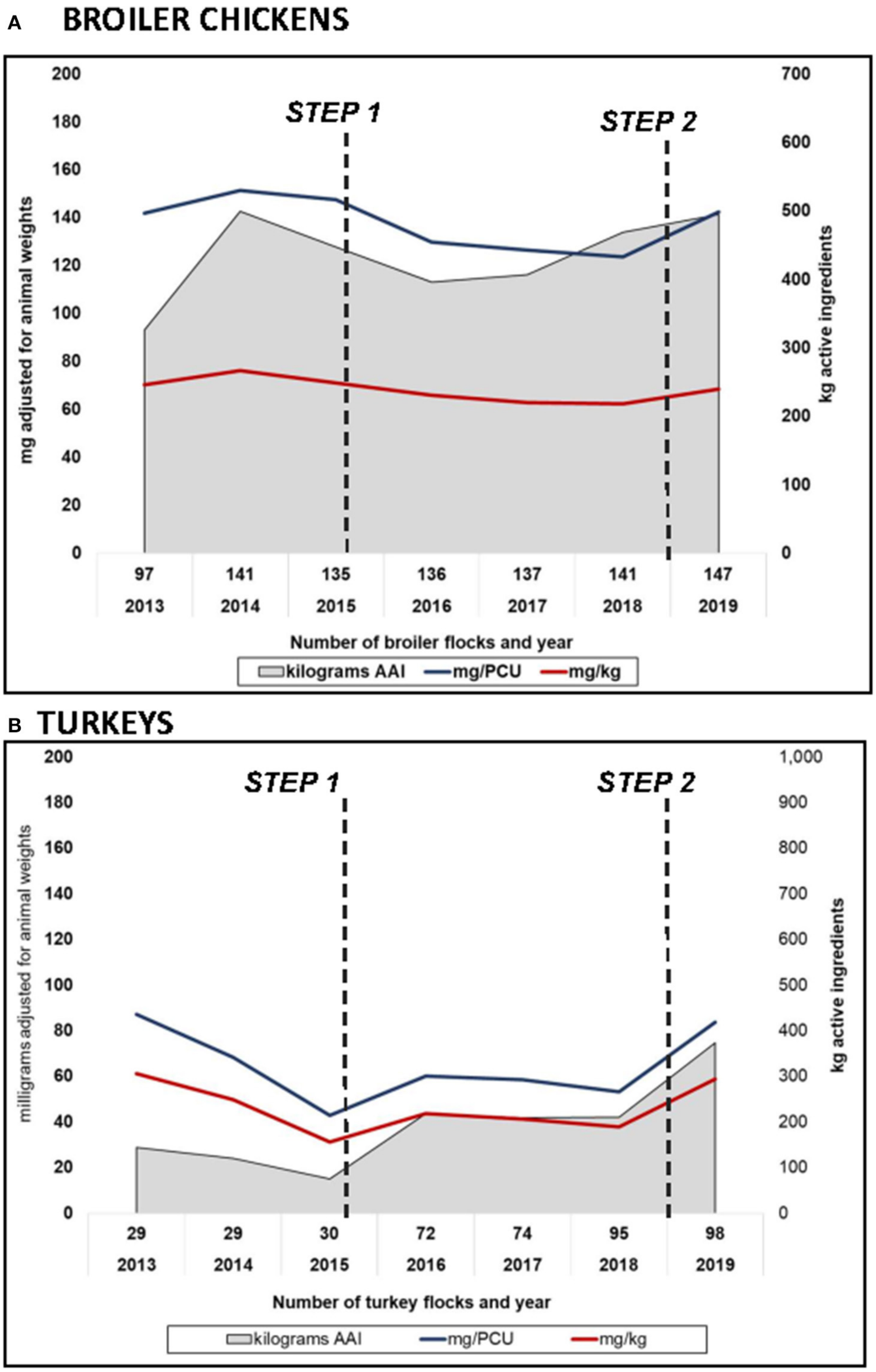


FIGURE 5 | Temporal trends in reported antimicrobial use in **(A)** broiler chickens and **(B)** turkey flocks using routine CIPARS estimation methodology and alternative biomass calculations, milligrams per population correction unit (mg/PCU) using ESVAC's average weight at treatment (mg/PCU), and alternate biomass estimation using milligrams per kg live pre-slaughter weight or animal biomass. *2013 to 2015 data in turkeys pertain to British Columbia (initial surveillance site). Steps 1 and 2 correspond to the industry antimicrobial use reduction strategy*.

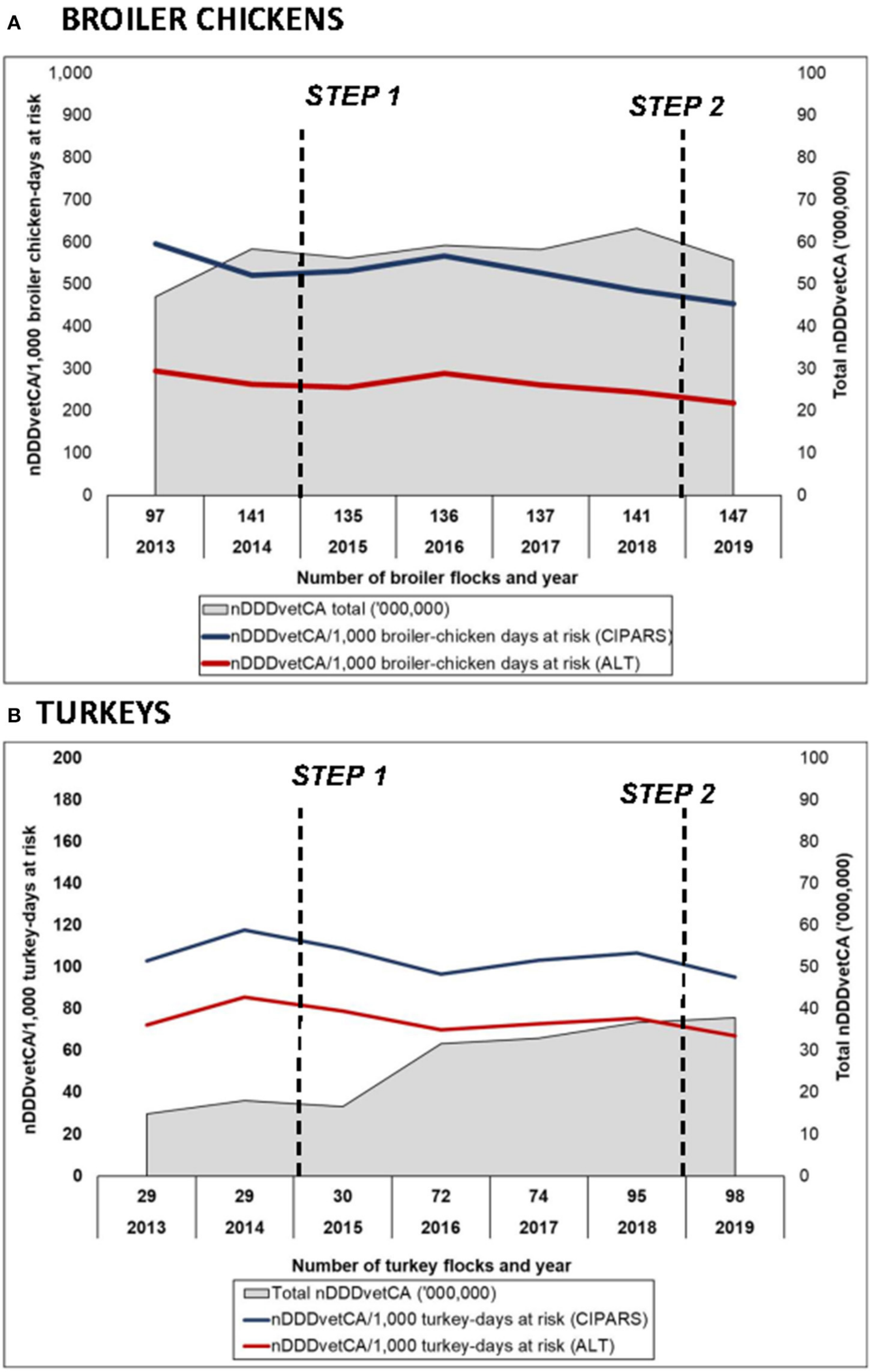


FIGURE 6 | Temporal trends in reported antimicrobial use in **(A)** broiler chickens and **(B)** turkey flocks using routine CIPARS estimation methodology and alternate estimation, number of defined daily doses in animals using Canadian standards per 1,000 animal-days at risk. *2013–2015 data in turkeys were British Columbia (initial surveillance site). Steps 1 and 2 correspond to the industry antimicrobial use reduction strategy*.

industry context and well as their uptake by veterinarians and producers.

This study provided new and detailed information about AMU in Canadian broiler chickens and turkeys by exploring data at the flock level. We previously described the use of the weight-based (mg/PCU) and dose-based (nDDDvetCA/1,000 animal-days at risk and nDDDvet/PCU) indicators in the aggregated farm AMU data and concluded that the interpretation of the results could change depending on the indicator chosen (19, 23). In particular, the relative ranking of the antimicrobial classes changed, depending on the indicator chosen, similar to another poultry AMU study in France (25). Our data also showed variations in temporal trends between the dose-based and weight-based indicators. However, in terms of flock distribution, the 3 AMU indicators showed similar patterns (i.e., all skewed distribution), indicative of the overall range of production practices and evolving AMU patterns of use in Canadian poultry.

The flocks raised as RWA, ABF, and organic flocks (i.e., no exposures to any antimicrobials) were excluded from the analysis evaluating the correlation between the AMU indicators. The decision not to use antimicrobials in these flocks was not based on flock-level parameters such as mortality, health status, or chick source, but instead on program-level requirements (i.e., market-driven). Differences in flock-level parameters between conventional flocks and flocks participating in these programs have been explored in other research (26).

CIPARS currently does not conduct benchmarking of AMU, but provides feedback on AMU to the industry and to participating producers and veterinarians, in addition to generating national AMR and AMU estimates. It is acknowledged that dose-based AMU indicators are utilized in other countries for benchmarking purposes (22, 27, 28). For comparability with other animal species (i.e., where DDDvetCA standards are yet to be developed) and other sources of AMU data (e.g., national sales and distribution data for terrestrial and aquatic animals) within Canada, we utilized the weight-based indicator, mg/PCU to identify high users, and complemented this with other qualitative data collected through our questionnaire. In our present study, there were diverse AMU patterns utilized by broiler chicken and turkey producers. Our analysis indicated that high users were significantly more likely to have used antimicrobials in water and specific classes including bacitracins, penicillins, tetracyclines, and trimethoprim-sulfonamides. Analysis in turkeys yielded similar results with the exception of aminoglycosides. As we have previously described (29), conventional flocks were typically fed with AAIs efficacious against Gram positive organisms, primarily *Clostridium perfringens,* the causative agent of necrotic enteritis. It can be inferred that the high users administered other antimicrobials in addition to their preventive necrotic enteritis program in the face of a clinical condition or bacterial disease outbreak (and may be explained by the flock AMU profiles with $\geq$3 AAIs). The classes associated with high use were those that have broad-spectrum of activity and are indicated for the treatment of systemic bacterial infections (30). Bacitracin was also associated with high use and could be due to the following reasons: (1) higher inclusion rate in feed for "reduction of early mortality due to diminished feed consumption and chilling" (11), and (2) evolving patterns of use in the poultry industry as a result of the AMU reduction strategy (increased use of VDD's medium important antimicrobial classes such as bacitracins). The prophylactic use of antimicrobials and other farm-level factors (e.g., AMU decisions by the producer or farm staff) have been identified as a risk factor for high use in turkeys (31).

It is important to note that the other classes used for the prevention of necrotic enteritis such as, macrolides, streptogramins, and orthosomycins were found to be associated with low users of antimicrobials. The approved level of drug or inclusion rates in g/ton of feed for these classes are relatively lower (11). Except avilamycin, the preventive use of these antimicrobial classes was eliminated at the end of 2018. Hence, AMU patterns may continue to evolve and the reported quantity of use could further change over time.

Taken together, the complementarity of a quantitative AMU indicator and qualitative AMU metrics in identifying high users are essential variables in understanding the dynamics of AMU practices. For providing feedback to veterinarians and producers, it may be useful to identify and highlight those flocks that used treatment via water and classes other than those that are indicated for necrotic enteritis. Our future analysis will investigate the factors associated with high and medium-to-low users of antimicrobials based on DDDvetCA/1,000 chicken-days at risk. This will address the effect of the type of antimicrobial reported to be used on the results. As in another poultry study (31), additional flock health (e.g., vaccinations and non-antimicrobial alternatives), biosecurity, and farm-level demographic factors will also be included in these future analyses in order to better understand the drivers of higher use in broiler chicken and turkey flocks in Canada. Using input parameters already collected by CIPARS (e.g., treatment frequency, duration of treatment/days of exposure, weight at actual treatment), future work could explore other potential dose-based AMU indicators to use for identifying high users of antimicrobials.

For the purposes of surveillance reporting at both the national and veterinarian-producer level, we explored how the AMU indicators are correlated in order to facilitate the selection of indicator(s). By investigating the degree of correlation between the multiple metrics, we have shown that using different numerators is quite informative. Due to the use of the same input parameters (i.e., formulaically the same), data reported using the weight-based and dose-based indicators will be necessarily correlated. One source of variation between results reported by different AMU indicators is the AAI, which could vary by dose, duration of exposure, weight at treatment and reasons for use. The dose-based indicator, nDDDvetCA/1,000 animal days at risk accounts for both population and days at risk of being exposed to antimicrobials. The days at risk depends on production type and life span of the bird, for example, it is shorter in broiler chickens [our study and a similar broiler AMU study (21)] and longer in small holder chicken flocks (8) or turkeys (our study). The CIPARS farm-level AMU data is based on one grow-out cycle from sentinel farms unlike some other farm-level AMU monitoring programs where continuous full-year (i.e., the data collection period at risk) data are collected (5). This could limit the ability to compare our data with that from other surveillance programs or poultry studies that do not have a similar design or the same period at risk. However, our analysis indicated that the two dose-based indicators, nDDDvetCA/1,000 animal-days at risk and nDDDvetCA/PCU showed high correlation indicating that either of these could be used for characterizing temporal trends and facilitate comparability with other surveillance programs. This is particularly important, since sampling from one grow-out period vs. the entire year may require fewer resources and be more attainable for some countries. The choice of which indicator to use should consider stakeholder understanding, relevance to stakeholders, or preference and availability of the input parameters required, such as days at risk. The nDDDvetCA/PCU (4) could be used in datasets or data collection points where the time component is unavailable or constant (e.g., annual aggregated sales data), or in smaller scale targeted studies (32).

For characterizing national temporal trends, we explored the use of different weights in the denominator, as the reported antimicrobial use estimates for a specific indicator could also change depending on the input parameters (9). In the present study, the mg/PCU and analysis using alternate biomass using the broiler chicken and turkey live pre-slaughter weight, showed similar temporal trends, indicative that the choice of which weight in the denominator to use is a preference, which affects the magnitude of the measure, but will not alter the reported trends; provided that a consistent weight is applied over time.

The 2 kg average weight for broiler chickens at slaughter was within the industry standards for the commonly raised breeds in Canada at 34–35 days. This weight is double the ESVAC average weight at treatment of 1 kg. Using the 2 kg weight in the denominator consequently reduced the magnitude of the AMU estimates by 50%. Whereas for turkeys, because of the different marketing weight categories and higher proportion of heavy bird categories, the average kg at slaughter was closer to the ESVAC average weight at treatment of 6.5 kg, yielding smaller differences between mg/PCU and mg/kg. In a similar study in pigs, changing an input parameter in the denominator (9) did not impact the distribution of AMU, as the choice of weight is simply a different scaler variable in the denominator applied equally to the numerator for each antimicrobial.

For communication with producers, veterinarians and the industry in general, the mg/kg live pre-slaughter weight might be preferable because it might be easier to understand. For example, "results pertain to mg of AAIs used for every kg of chicken or turkey live-weight shipped for slaughter during growing cycle A" or nDDDvet/kg could be expressed as "results pertain to the total number of doses used for every kg of chicken or turkey live weight shipped for slaughter during the growing cycle B." However, the kg pre-slaughter weight, driven by specific market weight preferences, potential disease conditions, and change in genetics or nutrition requirements could also vary over time. The stability of this measurement needs to be considered. The mean weights at treatment were also characterized in this study; it is important to note that the mean weights at treatment in our dataset were 0.84 and 3.0 kg for broiler chickens and turkeys, respectively. The mean treatment weights varied over time and also related to the evolving AMU practices in the industry, specifically, the removal of the preventive use of certain AAIs belonging to higher VDD categories and typically used in younger birds (i.e., injection of ceftiofur, lincomycin-spectinomycin, and gentamicin at day of hatch). With the full implementation of the AMU reduction strategy, it is conceivable that AMU practices could further change. In particular the practice of continuous administration of AAI via feed for prevention beginning at day 1 (chick or poult placement) is expected to shift toward targeted treatment when birds are most likely to be susceptible to enteric and respiratory diseases or only when deemed necessary. From an AMU stewardship standpoint, in our circumstance, the average actual weight at treatment may not also be a stable denominator to use for characterizing temporal trends as it potentially influence the accuracy of reflecting true use changes over time, which are critical for monitoring the impact of an AMU intervention.

Overall, our analysis indicated that the quantity of antimicrobials used in broiler chickens and turkeys in Canada was relatively higher compared to poultry in Europe, for example, Sweden (33) and the United Kingdom (34) in terms of mg/kg, and Belgium (21) in terms of nDDDvetCA/1,000 animal-days at risk (or treatment incidence). Water treatment and the use of certain classes (trimethoprim-sulfonamides, tetracyclines) were associated with high use of antimicrobials, thus underlying factors (e.g., coinfection with emerging viral diseases, barn-level factors) contributing to the diseases targeted by the classes implicated with high use warrants further research. The decreasing diversity of AAIs in more recent years (2018–2019) is indicative of evolving AMU patterns of use related to voluntary decisions by the poultry industry. The industry AMU strategy called for the elimination of the preventive use of at least 5 antimicrobial classes. However, the effect of the shift from prevention to treatment uses needs to be monitored; as these would still contribute to the overall quantity of AMU. At the national level, the interpretation of overall AMU could change depending on the indicator chosen, particularly, the change in the relative ranking of the classes and temporal trends. The dose-based indicator corrects for differences in AMU classes and/or practices, thus enabling between-farm comparisons and better detection of temporal shifts in AMU. This further emphasizes the need for more than one AMU indicator in characterizing the flock-level and national level AMU dynamics in the poultry industry. Finally, we have shown that a change in the denominator (animal biomass) will impact the magnitude of the measure but will not alter the trends provided that a consistent weight is applied. The choice of the weight should reflect the surveillance system objectives; which could be to facilitate reporting back to farmers/veterinarians (i.e., reflective of their preference for understanding and uptake) or for international reporting (creating an appropriate comparison), or both. Stakeholder consultations to explore reporting preferences and the development of an algorithm for identifying high users for farm-level reporting are necessary next steps.

DATA AVAILABILITY STATEMENT

All datasets presented in this study are included in the article/**Supplementary Material**.

ETHICS STATEMENT

No animal studies/experiments included in the manuscript. Data were extracted from the CIPARS database. No personal identifiers linking the producers, farm location, or veterinarian were collected. Data pertains to the animals and obtained from farm records and actual farm visit. An informed consent form was administered by the veterinarian to the producer prior to the farm visit.

AUTHOR CONTRIBUTIONS

AA, AD, SG, DL, and CC conceived the study. AA and AD conducted the formal analysis. AB, DL, and CC developed the DDDvetCA methodology/assignment. SG, SK, and AA contributed to the ongoing refinements to the AMU database, data curation, and data validation. RR-S, AA, SG, DL, and AD acquired partial funding. RR-S provided overall technical supervision and farm program operation. CC, DL, SG, AD, AB, SK, and AA contributed to the writing, editing, and review of the manuscript. All authors contributed to the article and approved the submitted version.

FUNDING

CIPARS and FoodNet Canada are surveillance programs operated and funded by the Public Health Agency of Canada. Partial funding for the CIPARS/FoodNet Canada farm components was provided by the Ontario Ministry of Agriculture, Food and Rural Affairs (FS2015-2639/ARIO Project SF6116), Alberta Agriculture, Saskatchewan Agriculture and the Canadian Poultry Research Council (AMN 092 2016-2018).

ACKNOWLEDGMENTS

The authors acknowledge the producers and veterinarians who enabled sample and data collection. We are grateful for the support of the poultry industry (national and provincial marketing boards) for ongoing discussions and for providing industry context to our findings. We thank Matt Hurst (statistical advice), Dr. Rebecca Irwin, and Lisa Landry for their guidance. Finally, we thank Ron Templeman for the development and ongoing refinements of the AMU database.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fvets.2020.567872/full#supplementary-material

Supplementary Material 1 | Antimicrobial use patterns in broiler chickens and turkeys during the study timeframe (2013–2019).

Supplementary Material 2 | Example, farm-level antimicrobial use questionnaire (2019 version).

Supplementary Material 3 | Other findings. Other antimicrobial use descriptive statistics and correlation matrices.

REFERENCES

1. World Health Organization. *WHO Global Action Plan on Antimicrobial Resistance.* (2015). Available online at: http://apps.who.int/iris/bitstream/10665/193736/1/9789241509763_eng.pdf?ua=1 (accessed August 14, 2020).
2. World Organization for Animal Health (OIE). *OIE Annual Report on Antimicrobial Agents Intended for use in Animals. Better Understanding of the Global Situation. Fourth Report*. (2020). Available online at: https://www.oie.int/fileadmin/Home/eng/Our_scientific_expertise/docs/pdf/A_Fourth_Annual_Report_AMU.pdf(accessed August 14, 2020).
3. World Organization for Animal Health (OIE). *Guidance for Completing the OIE Template for the Collection of Data on Antimicrobial Agents Intended for Use in Animals.* (2019). Available online at: https://www.oie.int/fileadmin/Home/eng/Our_scientific_expertise/docs/pdf/AMR/ENG_AMUse_Guidance_Final_2019.pdf (accessed August 14, 2020).
4. European Medicines Agency. *Advice on Implementing Measures Under Article 57(3) of Regulation (EU) 2019/6 on Veterinary Medicinal Products - Report on Specific Requirements for the Collection of Data on Antimicrobial Medicinal Products used in Animals.* (2019). Available online at: https://www.ema.europa.eu/en/documents/report/advice-implementing-measures-under-article-573-regulation-eu-2019/6-veterinary-medicinal-products-report-specific-requirements-collection-data-antimicrobial-medicinal_en.pdf (accessed August 14, 2020).
5. AACTING network on quantification, benchmarking and reporting of veterinary antimicrobial usage at farm level. *Guidelines for Collection, Analysis and Reporting of Farm-Level Antimicrobial use, in the Scope of Antimicrobial Stewardship.* (2018). Available online at: https://aacting.org/aacting-guidelines/ (accessed August 14, 2020).
6. Collineau L, Belloc C, Stark KD, Hemonic A, Postma M, Dewulf J, et al. Guidance on the selection of appropriate indicators for quantification of antimicrobial usage in humans and animals. *Zoonoses Public Health*. (2016) 64:165–84. doi: 10.1111/zph.12298
7. Government of Canada. *Canadian Integrated Program for Antimicrobial Resistance Surveillance* 2016. Annual Report (2019). Available online at: http://publications.gc.ca/collections/collection_2018/aspc-phac/HP2-4-2016-eng.pdf (accessed August 14, 2020).
8. Cuong NV, Phu DH, Van NTB, Dinh Truong B, Kiet BT, Hien BV, et al. High-resolution monitoring of antimicrobial consumption in Vietnamese small-scale chicken farms highlights discrepancies between study metrics. *Front Vet Sci.* (2019) 6:174 doi: 10.3389/fvets.2019.00174
9. Waret-Szkuta A, Coelho V, Collineau L, Hemonic A, Buy C, Treff M, et al. How input parameters and calculation rules influence on-farm antimicrobial use indicators in animals. *Front Vet Sci.* (2019) 6:438. doi: 10.3389/fvets.2019.00438
10. Government of Canada. *Food and Drugs Act. Regulations Amending the Food and Drug Regulations (Veterinary Drugs — Antimicrobial Resistance),* 15. (2017). Available online at: http://www.gazette.gc.ca/rp-pr/p2/2017/2017-05-17/html/sor-dors76-eng.php (accessed August 14, 2020).
11. Government of Canada. *Canadian Food Inspection Agency Compendium of Medicating Ingredient Brochure*. (2020). Available online at: http://www.inspection.gc.ca/animals/feeds/medicating-ingredients/eng/1300212600464/1320602461227 (accessed August 14, 2020).
12. Animalytix LLC. *Compendium of Veterinary Products 2020.* Available online at: https://bam.cvpservice.com/ (accessed August 14, 2020).
13. Government of Canada. *Health Canada, Veterinary Drugs Directorate. List A: List of Certain Antimicrobial Active Pharmaceutical Ingredients.* (2018). Available online at: https://www.canada.ca/en/public-health/services/antibiotic-antimicrobial-resistance/animals/veterinary-antimicrobial-sales-reporting/list-a.html (accessed August 14, 2020).
14. World Health Organization. *Critically Important Antimicrobials for Human Medicine 6th Revision*. (2019). Available online at: https://www.who.int/foodsafety/publications/antimicrobials-sixth/en/(accessed June 6, 2020).
15. Chicken Farmers of Canada. *Responsible antimicrobial use in the Canadian chicken and turkey sectors, Version 2.0*. (2016). Available online at: http://www.chickenfarmers.ca/wp-content/uploads/2015/12/AMU-Booklet-June-2015-EN.pdf (accessed August 14, 2020).
16. Chicken Farmers of Canada. *AMU Strategy, a Prescription for Change.* (2018). Available: online at: http://www.chickenfarmers.ca/wp-content/

uploads/2018/01/AMU-Magazine_ENG_web-2.pdf (accessed August 14, 2020).

17. Turkey Farmers of Canada. *Guidelines for Antimicrobial use in the Turkey Industry*. (2019). Available online at: https://www.amstewardship.ca/guidelines-for-antimicrobial-use-in-the-turkey-industry-published-by-the-turkey-farmers-of-canada/ (accessed August 14, 2020).
18. Government of Canada. Public Health Agency of Canada, Canadian Integrated Program for Antimicrobial Resistance Surveillance (CIPARS), Surveillance Bulletin. *Reductions in Antimicrobial Use and Resistance: Preliminary Evidence of the Effect of the Canadian Chicken Industry's Elimination of Use of Antimicrobials of Very High Importance to Human Medicine*. (2016). Available online at: https://www.canada.ca/en/public-health/services/publications/drugs-health-products/canadian-integrated-program-antimicrobial-resistances-surveillance-bulletin.html (accessed August 14, 2020).
19. Agunos A, Gow SP, Leger DF, Carson CA, Deckert AE, Bosman AL, et al. Antimicrobial use and antimicrobial resistance indicators-integration of farm-level surveillance data from broiler chickens and turkeys in British Columbia, Canada. *Front Vet Sci*. (2019) 6:131. doi: 10.3389/fvets.2019.00131
20. Bosman AL, Loest D, Carson CA, Agunos A, Collineau L, Leger DF. Developing Canadian defined daily doses for animals: a metric to quantify antimicrobial use. *Front Vet Sci*. (2019) 6:220. doi: 10.3389/fvets.2019.00220
21. Persoons D, Dewulf J, Smet A, Herman L, Heyndrickx M, Martel A, et al. Antimicrobial use in Belgian broiler production. *Prev Vet Med*. (2012) 105:320–5. doi: 10.1016/j.prevetmed.2012.02.020
22. DANMAP. *DANMAP 2018 - Use of Antimicrobial Agents and Occurrence of Antimicrobial Resistance in Bacteria from Food Animals, Food and Humans in Denmark*. (2018). Available online at: https://www.danmap.org/-/media/arkiv/projekt-sites/danmap/danmap-reports/danmap-2018/danmap_2018.pdf?la=en (accessed August 14, 2020).
23. Agunos A, Leger DF, Carson CA, Gow SP, Bosman A, Irwin RJ, et al. Antimicrobial use surveillance in broiler chicken flocks in Canada, 2013-2015. *PLoS ONE*. (2017) 12:e0179384 doi: 10.1371/journal.pone.0179384
24. Government of Canada. *Canadian Food Inspection Agency*. *Manual of Procedures*. *Chapter 19-Poultry Inspection Programs*. (2018). Available online at: http://www.inspection.gc.ca/food/meat-and-poultry-products/manual-of-procedures/chapter-19/eng/1360962146879/1360962607138?chap=3 (accessed August 14, 2020).
25. Chauvin C, Querrec M, Perot A, Guillemot D, Sanders P. Impact of antimicrobial drug usage measures on the identification of heavy users, patterns of usage of the different antimicrobial classes and time-trends evolution. *J Vet Pharmacol Ther*. (2008) 31:301–11. doi: 10.1111/j.1365-2885.2008.00960.x
26. Roberts T, McEwen S, Reid-Smith R, Sargeant J, Agunos A, Léger D, et al. Prevalence, risk factors and profiles of resistant *Salmonella* isolates obtained from Ontario broiler chicken farms at chick placement and pre-harvest. In: *Proceedings of the 64th Western Poultry Disease Conference*. Sacramento, CA. WPDC (2015).
27. Kasabova S, Hartmann M, Werner N, Kasbohrer A, Kreienbrock L. Used daily dose vs. defined daily dose-contrasting two different methods to measure antibiotic consumption at the farm level. *Front Vet Sci*. (2019) 6:116. doi: 10.3389/fvets.2019.00116
28. National Institute for Public Health and the Environment, Ministry of Health, Welfare and Sports. MARAN 2019. *Monitoring of Antimicrobial Resistance and Antibiotic Usage in Animals in the Netherlands in* 2018. (2019). Available online at: https://rivm.openrepository.com/handle/10029/623134 (accessed August 8, 2020).
29. Agunos A, Deckert A, Leger D, Gow S, Carson C. Antimicrobials used for the therapy of necrotic enteritis and coccidiosis in broiler chickens and Turkeys in Canada, farm surveillance results (2013-2017). *Avian Dis*. (2019) 63:433–45. doi: 10.1637/11971-091718-Reg.1
30. Hofacre CL, Fricke JA, Inglis T. Antimicrobial drug use in poultry. In: *Antimicrobial Therapy in Veterinary Medicine*. Ames, IA: John Wiley & Sons, Inc. (2013). p. 569–87. doi: 10.1002/9781118675014.ch34
31. Chauvin C, Bouvarel I, Beloeil PA, Orand JP, Guillemot D, Sanders P. A pharmaco-epidemiological analysis of factors associated with antimicrobial consumption level in turkey broiler flocks. *Vet Res*. (2005) 36:199–211. doi: 10.1051/vetres:2004064
32. Tarakdjian J, Capello K, Pasqualin D, Santini A, Cunial G, Scollo A, et al. Antimicrobial use on Italian Pig Farms and its Relationship with Husbandry Practices. *Animals*. (2020) 10:417. doi: 10.3390/ani10030417
33. Public Health Agency of Sweden and National Veterinary Institute. SWEDRES-SVARM 2019. *Sales of Antibiotics and Occurrence of Antibiotic Resistance in Sweden*. (2019) Available online at: https://www.sva.se/en/our-topics/antibiotics/svarm-resistance-monitoring/swedres-svarm-reports/ (accessed August 14, 2020).
34. Veterinary Medicines Directorate, United Kingdom. *UK VARSS Veterinary Antimicrobial Resistance and Sales Surveillance 2018*. (2019). Available online at: https://www.gov.uk/government/publications/veterinary-antimicrobial-resistance-and-sales-surveillance-2018 (accessed August 14, 2020).

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Veterinary Science

ORIGINAL RESEARCH
published: 30 October 2020
doi: 10.3389/fvets.2020.568881

Antibiotic Use in Organic and Non-organic Swedish Dairy Farms: A Comparison of Three Recording Methods

Gabriela Olmos Antillón[1]*, *Karin Sjöström*[1], *Nils Fall*[1], *Susanna Sternberg Lewerin*[2] and *Ulf Emanuelson*[1]

[1] Department of Clinical Sciences, Faculty of Veterinary Medicine and Animal Science, Swedish University of Agricultural Sciences, Uppsala, Sweden, [2] Department of Biomedical Sciences and Veterinary Public Health, Faculty of Veterinary Medicine and Animal Science, Swedish University of Agricultural Sciences, Uppsala, Sweden

Biases of antimicrobial use (AMU) reporting systems pose a challenge to monitoring of AMU. Our study aimed to cross-compare three data sources of AMU in Swedish dairy herds to provide an account of the validity of AMU reports. We studied AMU differences between two production systems, to investigate how the reporting system affected this comparison. On-farm quantification of AMU via a manual collection of empty drug containers (BIN) took place in organic (n = 30) and conventional (n = 30) dairy herds during two periods between February 2016 and March 2017. A data extract mirroring these periods was obtained from two linked datasets that contain AMU data as reported by the prescribing veterinarians. These included data from the Swedish Board of Agriculture system (SBA) and Växa milk recording system (VXA). Using the European Medicines Agency technical units, the total number of defined daily doses (DDD_{vet}), and defined course doses (DCD_{vet}) per animal/year were calculated for each herd/period/dataset. Descriptive statistics and Bland–Altman plots were used to evaluate the agreement and systematic bias between the datasets. Mixed models for repeated measures were used to assess AMU differences between production systems. We found consistent numerical differences for the calculated AMU metrics, with BIN presenting higher usage compared to the SBA and VXA. This was driven by a disparity in intramammary tubes (IMt) which appear to be underreported in the national datasets. A statistically significant interaction (BIN dataset) between the production system and drug administration form was found, where AMU for injectable and lactating cow IMt drug forms differed by the production system, but no difference was found for dry-cow IMt. We conclude that calculating AMU using DDD_{vet} and DCD_{vet} metrics at a herd level based on Swedish national datasets is useful, with the caveat of IMt potentially being misrepresented. The BIN method offers an alternative to monitoring AMU, but scaling up requires considerations. The lower disease caseload in organic herds partly explains the lower AMU in particular drug forms. The fact that organic and conventional herds' had equally low AMU for dry-cow IMt, coupled with mismatches in IMt report across herds indicated an area of further research.

Keywords: BIN method, national surveillance systems, farm level, DDD_{vet} metric, DCD_{vet} metric, AMU

OPEN ACCESS

Edited by:
Carolee Anne Carson,
Public Health Agency of Canada (PHAC), Canada

Reviewed by:
Cedric Muentener,
University of Zurich, Switzerland
Preben William Willeberg,
Technical University of Denmark, Denmark
Simon More,
University College Dublin, Ireland

****Correspondence:***
Gabriela Olmos Antillón
gabriela.olmos.antillon@slu.se

Specialty section:
This article was submitted to Veterinary Epidemiology and Economics,
a section of the journal Frontiers in Veterinary Science

Received: *02 June 2020*
Accepted: *24 September 2020*
Published: *30 October 2020*

Citation:
Olmos Antillón G, Sjöström K, Fall N, Sternberg Lewerin S and Emanuelson U (2020) Antibiotic Use in Organic and Non-organic Swedish Dairy Farms: A Comparison of Three Recording Methods.
Front. Vet. Sci. 7:568881.
doi: 10.3389/fvets.2020.568881

INTRODUCTION

Antimicrobial resistance (AMR) is a global issue, and the current pattern and reduction in its harmful consequences to the biosphere's health (1, 2) require concerted actions from the human, animal, agricultural, and environmental sectors (3). A key measure for AMR mitigation is reducing antimicrobial use (AMU), especially "Critically Important Antimicrobials" (CIAs) for human health (4–6). The livestock industry is predicted to be responsible for 70% of the global AMU by 2030 (2, 7) and the possible relationship between AMU in animal production, and the development of AMR has been highlighted (8). Despite the association between AMR in livestock and humans, there is uncertainty about its magnitude (9–11).

Measuring AMU is fundamental for monitoring and reduction of AMU. Key indicators for understanding the patterns include (a) monitoring trends over time; (b) comparisons between different populations (e.g., types of production, species, or countries); (c) benchmarking; and (d) study of associations between AMU and AMR (12). To date, no standardised AMU measurement fulfils all these objectives. Thus, suitable measurement(s) must be determined based on a trade-off between the set goals and data at hand. Data resolution, comprehensiveness, and stability over time are important for the assessment of exposure and comparison of AMU within and between populations (12, 13).

All the practicalities around collection and reporting, regardless of the chosen resolution (e.g., animal, herd, or country level), have a high impact on AMU measurements. In turn, this affects the transparency and comparability of figures obtained. Despite this, only a few studies have addressed the qualitative and quantitative biases of AMU reporting systems (12, 14–16).

In Sweden, AMU in animals is only allowed on veterinary prescription, and veterinary drugs are sold exclusively through registered pharmacies. Sweden has had a leading role in the reduction of AMU, as well as the quantification and reporting of AMU statistics in animals and humans via the Swedres-Svarm reports (17). These reports are based on national sales data, which are not always the same as the amount prescribed or used in a country.

Although no recent effort has been made to evaluate AMU at herd level in Swedish dairy herds (18), the tools to do so are available through official records of veterinary treatments. The "Djursjukdata DAWA" is owned by the Swedish Board of Agriculture (in Swedish: Jordbruksverket). This is the oldest data collection system for veterinary treatments in Sweden, including antimicrobial use at herd level, initially compiled via paper records and launched at a national level in 1984. Currently, a computerised system covers all food-producing animals and horses, although 30% of the data is still fed to the system in paper format. Moreover, this system provides health information to Växa, the biggest dairy Levy group in Sweden that aims to monitor and improve the productivity, health and welfare of Swedish dairy cows (19). Växa's national database thus opens the window to understanding AMU in the context of detailed herd characteristics not available in the DAWA system.

Based on the EU rules for organic farming, dairy herds are expected to maintain a restrictive AMU (20). In practice, these rules limit the number of treatments per animal/year, and depending on the member state, might include the extension of drug withdrawal periods or the promotion of alternative medicines. Since conventional herds do not have to abide by such rules, it is often assumed that AMU would be higher in these herds. Although some studies have confirmed that organic herds have a lower AMU than conventional herds (5, 21–25), this research area remains unexplored in Sweden. The requirements may also impact the role of prescribing veterinarians under the two systems and, thus, also the AMU recordings. Hence, a comparison between AMU in organic and conventional dairy herds provides a case for AMU data evaluation.

This study aimed to provide a qualitative and quantitative assessment of how data source affects AMU reports, including treatment characteristics and characteristics of the population treated and at risk within a herd. Additionally, we wanted to quantify, describe, and compare the AMU in organic and conventional Swedish dairy herds and explore if AMU recording differs between the systems.

METHODOLOGY

Herd Enrolment

The study design adhered to the good scientific practice guidelines set out by Swedish legislation and did not include direct animal testing. Thus, no ethical evaluation or permit was required for its execution. Suitable farms were invited to participate through veterinarians, farmer's organisations and advisors. The farms were chosen to reflect the size and distribution of dairy herds in Sweden. Each organic and conventional farm was geographically matched. The overall aims of the study were explained to the farmers who, when they agreed to join, signed a form that approved the use of data from their herds for research purposes within the context of this study. A total of 60 farmers were enrolled in the project, 30 organic and 30 conventional dairy farms.

Data Collection

The AMU was assessed during two periods: February to May 2016 and November 2016 to March 2017 using three data sources (see **Figure 1**). Two data sources are based on antimicrobial prescription data [Växa Sverige (VXA) and Swedish Border of Agriculture (SBA)] while the third one [empty drug containers (BIN)] compiled data on actual AMU on farm.

On-Farm Collection of Empty Drug Containers (BIN)

The second author (KS) met with the owners and farm staff 1 day before the start of the observation period. The methodology was explained/reinforced, and labelled plastic bags were provided. Staff were instructed to place discarded packaging (empty or partially full: bottles, boxes of pills/boluses, empty infusion tubes or other) of any drug used on-farm (administered by them or a visiting veterinarian) into the plastic bags throughout the observation period. The farm staff decided where to place the bags to facilitate the collection on their respective farms. Bags

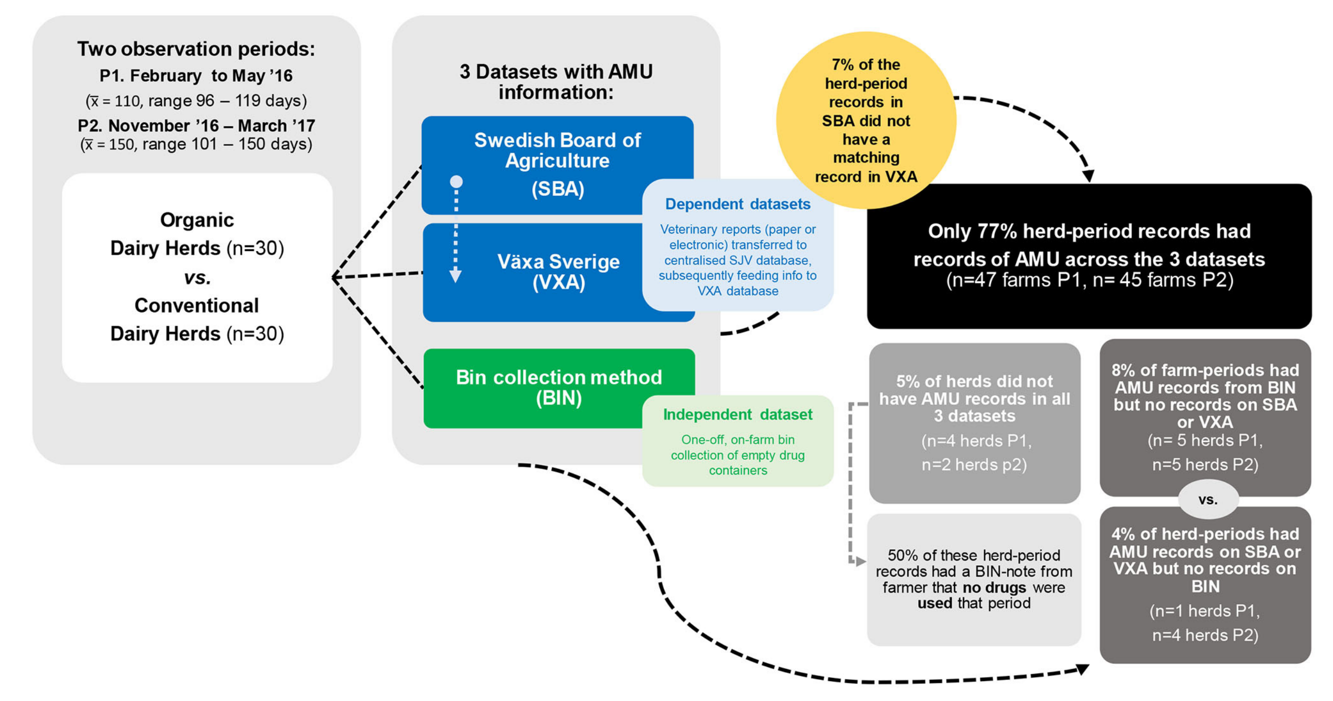


FIGURE 1 | Flow diagram of methodology, dataset relationship, and data availability for antimicrobial use collection for a sample of 30 organic and 30 conventional Swedish dairy herds across two observation periods and as reported by three different datasets.

were collected 1 day after the end of each observation period. Due to travel logistics, not all farms were visited on the same day or had the same length of the collection period.

Only herd owners who stated "having used drugs" and had items in the bags/bins ($n = 55$ and $n = 54$ herds in sample period 1 and 2, respectively) or those who stated "not having used drugs" and had no items in the bins ($n = 3$ and $n = 5$ herds in sample period 1 and 2, respectively) were considered for each observation period. The contents of the bags from each herd were tallied, and (1) anonymised herd code and collection period, (2) drug commercial name, (3) drug amount and unit, (4) drug concentration (e.g., mg/ml or gr/unit), and (5) name of related active ingredients were recorded into a Microsoft® Excel (Microsoft Corporation, Redmond, WA, USA) spreadsheet for further analysis. If drug packages were not empty, only the amount used was noted. The commercial names were linked to the corresponding code of the Anatomical, Therapeutic, and Chemical Veterinary (ATC_{vet}) classification registered under the Swedish Pharmaceutical Industry Association Service (Läkemedelsindustriföreningens Service AB). This is publicly available in the online compendium known as Pharmaceutical specialties in Sweden (www.fass.se). If the commercial name/active ingredients were not found/registered under this system, the ATC_{vet} code was assigned based on information retrieved from the European Head of Medicines Agency (www.hma.eu).

Swedish Board of Agriculture Antimicrobial Use Data Extract (SBA)

A data extract of the drugs used by the participating herds comprising the two observation periods was requested from the Swedish Board of Agriculture. Such information is contained in one of the three main DAWA report sections. The reports are submitted by state-employed veterinarians in the form of text files from their computer program LINK, via the DAWA e-service. Most private veterinarians also use a similar format with <30% of them sending in physical practice journal forms.

The original extract had the following information: (1) anonymised herd code, (2) diagnostic code, (3) drug commercial name, (4) ATC_{vet} code, (5) drug unit and amount used, (6) type of treatment (single, group, or all animals), (7) number of animals involved, and (8) treatment date.

The received data extract was screened for usability. The following problems were found, and data records were corrected or discarded as follows. Records with non-existent, incomplete, or incoherent drug name or ATC_{vet} codes were identified. If such records had a recognisable drug name or a partial ATC_{vet} code, a complete code was assigned following the same procedure as for the BIN dataset. Some records had no name or ATC_{vet} code, but instead, a note indicating "error of data transfer," "drug under license," or "unknown product" was found. As no valid assumptions could be made about the data entries (i.e., unknown relation), such records were eliminated from further analysis. Lastly, only records/events that took place during the individual herd's observation periods were kept for further investigation.

Växa Sverige Data Extract (VXA)

The second data extract of drug use came from Växa Sverige (VXA), the Swedish dairy cattle association that provides on-farm advice and milk recording services to their members. VXA registers 2,003 herds (76% of all Swedish herds) comprising 220,131 animals (78% of all Swedish dairy cows) in their data control system (19, 26). The system captures animal-level events based on their unique national animal identifier. Such events include pedigree, birth/death, cow movements, calving events, milk quantity and quality records, and disease events. An extract of the pedigree, cattle movement, and sickness events was obtained covering the two observation periods of all animals related to the participating herds. Besides, summary statistics per participating herd for the fiscal year October 2016 to September 2017 were also obtained from Växa Sverige.

The pedigree and cattle movement reports are actively updated by on-farm staff, providing information about the actual herd size and composition at the time of the two observation periods. Moreover, the disease reports contained information about drug use at the animal level. Such reports are generated by pulling data from the SBA system, including the drug use, through an active back-end communication interface between the two systems. Additional but minimal input by farm staff can happen, but without affecting drug usage information.

Data extracts were screened for usability and, when necessary, edited. There were no errors found with the pedigree or cow movement data. The animal age and number of days each animal was active in the participating herds at each observation period were calculated. Based on cow age, a new variable was created that classifies animals as either (a) cows/bulls (adult animals >730 days old), (b) heifer/steers (animals >365 ≤730 days old), and(c) young/calves (<365 days old). The common information allowed calculating the individual herds' population at risk of receiving antimicrobial treatment during each observation period so that AMU estimates could be adjusted for herd size and age differences.

Disease data provided the following information at animal level: drug/treatment product as a code, treatment date, diagnosis code, and amount used. The treatment code was cross-matched with a translation code list that provides information about the commercial drug name, and ATC_{vet} code comparable to the SBA dataset. Some data entries matched no name or ATC_{vet} code but had notes indicating "drug under license" or "unknown product." Such entries (i.e., unknown relation) were removed from further analysis. Lastly, only records/events that mirrored the individual on-farm BIN observation periods were kept for further investigation.

Estimation of Herd-Level AMU

A full list of commercial drug names and linked ATC_{vet} codes identified across the three datasets was compiled. The list contained only ATC_{vet} codes mentioned in the European Medicines Agency (EMA) protocol (27) for AMU quantification. These ATC_{vet} code groups include (A) Intestinal/oral (O) use: QA07AA, QA07AB; (B) Intrauterine (IU) use: QG01AA, QG01AE, QG01BA, QG01BE, QG51AA, QG51AQ; (C) Systemic/Injectable (IN) use: QJ01; (D) Intramammary tubes (IMt): QJ51; and (E) Antiparasitic agents: QP51AG. The final list had 16 individual ATC_{vet} codes, representing 26 commercial products, of which 38% were products with a combination of drugs (i.e., products had two or more active ingredients in its composition). We used this list to select records relevant for AMU calculations from each dataset and the herd/dataset/period AMU metric calculations.

Animals of all ages were included in the AMU calculations. The standardised live weight used in the EMA protocol is lower than the national average in Swedish national statistics (19, 28). Instead, it was decided to use the following standard weights. Cows/bulls (i.e., adults animals) = 600 kg; heifers/steers (i.e., pubescent animals) = 300 kg; and calves (i.e., young animals) = 100 kg, as these figures represent the Swedish national herd. Production days were defined as the actual number of days an animal was kept in the herd during the observation periods, according to livestock movement data in the VXA dataset extract. The number of cow-years per herd was calculated using the total number of cows' production days per herd divided by 365.

Amounts of active antimicrobial substance were calculated by multiplying the volume administered to the animals (usually in ml) by the concentration of the active antimicrobial substance (e.g., mg/ml) to give the total mass of active antimicrobial substance in mg for each dataset. Then, the number of defined daily doses (DDD_{vet}) and defined course doses (DCD_{vet}) administered was calculated using the DDD_{vet} and DCD_{vet} values assigned to the individual antimicrobial substances (based on ATC_{vet} code) and animal species by the European Medicines Agency (29, 30). The number of defined daily doses per animal and year ($nDDD_{vet}$/animal/year), the number of defined course doses per animal and year ($nDCD_{vet}$/animal/year) for the individual ATC_{vet} code, and the summation of all codes by herd were calculated following the formula as advised by the network on quantification, benchmarking and reporting of AMU at farm level (AACTING) (13) as follows:

$$\sum_{i=1}^{n} \frac{\text{amount } AI_i \text{ in period P (mg)}}{DDDvet_i \left(\frac{mg}{kg/day}\right) \times \#\text{ animal days in period P } (\text{days}) \times \text{standard weight (kg)}} (365\text{ days}) \quad (1)$$

where:

$\boldsymbol{AI_i}$ = amount (in mg) of active ingredient i used in period P

$\boldsymbol{i} = 1, 2, \ldots, n$

 # animal days in period P = # animals present daily during P (days).

Standard weight = standard cow weight at treatment (in kg)

$\boldsymbol{DDDvet_i}$ = Defined Daily Dose of active ingredient i (in mg/kg/day); to calculate the number of days under treatment over the defined period. If $\boldsymbol{DDDvet_i}$ is replaced by $\boldsymbol{DCDvet_i}$ (Defined Course Doses), then the average number of courses per animal will be calculated.

$\boldsymbol{DDDvet_i}$ & $\boldsymbol{DCDvet_i}$ can also be expressed in terms of the number of items (e.g., IMt, bolus or pills), in which case the number of items used in period P will be used in the formula instead of the amount of active ingredient. Lactating intra-mammary tubes are dosed at the number of tubes/cow/day, while dry cow tubes are dosed as "4/cow" as a single treatment, and intrauterine products are one unit per cow. Thus, $\boldsymbol{DCDvet_i}$ figures can be calculated for dry-cow intra-mammary tubes and intrauterine products.

Similar calculations were done according to the administration route for each drug formulation (i.e., IN, O, lactation IMt, dry-cow IMt, and IU) and by the classification of critically important antimicrobials (CIAs) set by EMA/AMEG/2016 (5, 25, 31) at the time when data was collected. The classification set by EMA is a categorisation of the list of highest-priority CIAs (HP-CIAs) for humans set by the World Health Organization (WHO) (6). The EMA classification aims to consider and advise on the public health risk from the use of antimicrobials in animals expressed by WHO (6, 32), but balancing against the need to protect animal health—providing a One Health context considering the needs of humans, animals, and environment and at the same time these sectors as sources of AMR (5, 31). The EMA/AMEG/2016 classification (5, 25) includes three categories: (1) antimicrobials used in veterinary medicine, where the risk for public health is estimated as low or limited; (2) antimicrobials used in veterinary medicine where the risk for public health is estimated higher; and (3) antimicrobials not approved for use in veterinary medicine.

Statistical Analyses

All analyses were conducted in SAS/STAT 14.3 (SAS Institute Inc., Cary NC, USA).

Descriptive Presentation of Herd Characteristics and AMU Metrics

A descriptive analysis of the key herd characteristics (VXA dataset) and AMU metrics as DDD_{vet} and DCD_{vet}/animal/year (all datasets) by active ingredient was done by calculating the mean, median, standard deviation, and interquartile range. Similar descriptive analyses were done for the summation of all ATC_{vet} codes within the herd (i.e., total DDD_{vet}/animal/year and total DCD_{vet}/animal/year) and the total split by drug administration form or by CIAs.

AMU Dataset Agreement and Biases Analyses

Bland–Altman plots consisting of the mean between two datasets [(Dataset A + Dataset B)/2] of the herd total DCD_{vet}/animal/year plotted against the difference between the two datasets (Dataset B–Dataset A) were constructed. The mean difference *d* between dataset A and B represents the bias or lack of agreement between datasets. The standard deviation of the difference *d* represents the variability of the differences and is used to calculate 95% limits of agreement between the datasets. The 95% limits of agreement represent the range within which 95% of the observations (i.e., differences between dataset A and B) fall. They are not confidence limits but function instead as a reference interval (33). If the values of the differences within the range are considered "clinically acceptable," then the two methods could be used interchangeably. The mean bias of the methods and the SD of the bias were calculated, across the three datasets for the herd total $nDCD_{vet}$/animal/year and also split according to the drug administration form. Ninety-five % limits of agreement, calculated as the mean difference in dataset measures $\pm 1.96^{*}$SD, were calculated and labelled on the Bland–Altman plots. A horizontal line at $y = 0$ was added to the plot to indicate the line of equality upon which all points would lie if both methods yielded the same results. Plots were then examined visually to identify any patterns in the data. A second plot line was investigated. This corresponded to the potential for bias that is not constant across the range of values (proportional bias). For that, a linear regression model was fitted for each dataset, with the VXA or SBA (Dataset A) dataset as the outcome variable and BIN (Dataset B) dataset as the independent variable. The slope of the regression line was used to evaluate the extent of systematic bias between two particular datasets.

Analysis of AMU Differences Between Conventional and Organic Dairy Herds

The association between the production system (conventional vs. organic) and AMU was assessed using linear mixed models (PROC MIXED), with the total number of DCD_{vet}/animal/year as the dependent variable and sampling period included as a repeated effect within herd. This procedure was done for BIN and VXA datasets separately. The residuals were tested for normality both visually and analytically; when a variable was not normally distributed, the Box–Cox methodology was used to identify the most appropriate transformation. The analyses were undertaken on the transformed, normally distributed data, and back-transformed results are presented. Fixed effects tested in the model were production system, observation period, drug administration type (IN, lactating IMt, dry-cow IMt, O, and IU), and the interaction between production type and drug administration type. Compound symmetry was the selected covariance structure used for all models. Factors significantly ($P < 0.05$) associated with the dependent variable were retained in the model.

RESULTS

Herd Characteristics and the Number of Farms With Evidence of AMU

A summary of participating herds' characteristics according to their production system is presented in **Table 1**. Organic and conventional farms had a similar herd size. However, organic farms had lower milk production, mortality, lameness, and clinical mastitis caseload, but higher bulk milk somatic cell count than conventional farms.

The ratio of available data entries in SBA— "related" (i.e., ATC_{vet} code linked to an antimicrobial formulation), "Not related" (i.e., ATC_{vet} code not linked to an antimicrobial formulation), and with "Unknown relation" to AMU were 352 (27%): 839 (65%): 104 (8%) and 386 (24%): 1,130 (70%): 104 (6%) for periods one and two, respectively. As for the VXA dataset, the ratio of available data entries "related," "Not related," and with "Unknown relation" to AMU were 385 (27%): 903 (62%): 159 (11%) and 399 (20%): 1,274 (65%): 289 (15%) for periods one and two, respectively.

Corresponding records of AMU across datasets (i.e., at least one entry of AMU per farm/period across all dataset) were found in 77% of the farm/period entries ($n = 47$ farms P1, $n = 45$ farms P2). Only 2.5% of the farm/period entries had a note in the BIN stating no AMU for the given period and no AMU entry in the SBA and VXA datasets. This left 20.5% of the farm/period entries with mismatching records of AMU across datasets (**Figure 1**).

TABLE 1 | Yearly herd characteristics in a sample of 26 organic and 25 conventional Swedish dairy herds.

Yearly herd characteristics (Reporting period Oct. 2016–Sep. 2017)	Production system	Mean	Lower quartile	Median	Upper quartile
Average number cows/year	Organic	103.8	66.3	73.1	133.2
	Conventional	107.7	66.7	101.5	138.2
Energy corrected milk production *(kg/cow/year)*	Organic	9,464	8,763	9,261	10,057
	Conventional	10,545	10,132	10,743	11,055
*Bulk milk somatic cell count *(1,000 cells/ml)*	Organic	282.8	234.0	300.5	327.0
	Conventional	226.6	185.0	216.0	267.0
Mastitis *(cases/100 cows/year)*	Organic	6.8	1.5	4.7	9.2
	Conventional	10.1	3.7	9.0	10.6
On-farm mortality *(cases/100 cows/year)*	Organic	4.1	2.8	4.1	5.2
	Conventional	5.3	3.7	5.1	7.4
Lameness *(cases/100 cows/year)*	Organic	2.6	0.0	1.0	4.1
	Conventional	5.2	0.0	2.0	5.2

**An average estimate derived from the somatic cell count and milk yield of the individual cows at each monthly test-day.*
At the time of data extraction; full data was available only for 51/60 herds involved in the study.

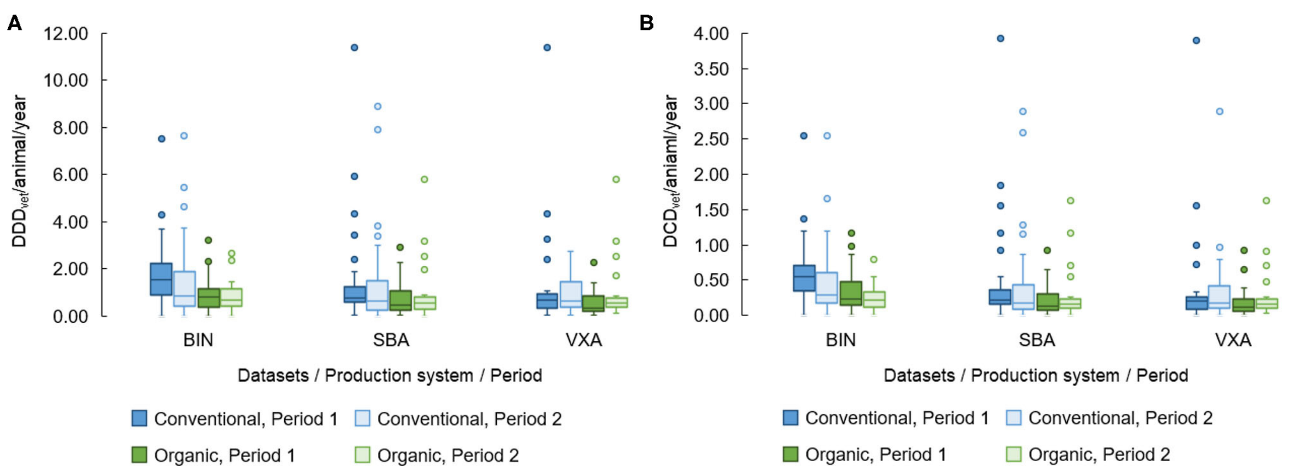


FIGURE 2 | Distribution of **(A)** herd total number of defined daily doses per animal/year (DDD_{vet}/animal/year) and **(B)** herd total number of defined course doses (DCD_{vet}/animal/year) per animal/year in a sample of organic ($n = 30$) and conventional ($n = 30$) Swedish dairy herds reported across two periods and three datasets. Box = the range between the 1st and 3rd quartiles; horizontal line = median; lower and upper whisker = interquartile range; dots = outliers. BIN, Bin collection method records, $n = 57$ and $n = 55$ herds had reported use in P1 and P2, respectively. SBA, Swedish Board of Agriculture database, $n = 51$ and $n = 53$ herds had reported use in P1 and P2, respectively. VXA, Växa Sverige database; $n = 48$ and $n = 48$ had reported use in P1 and P2, respectively.

Overall AMU Descriptive Statistics by Dataset, Production Type, and Period

The DDD_{vet}/animal/year and DCD_{vet}/animal/year are presented in **Figure 2**. At the same time, descriptive statistics are given in the **Supplementary Material** along with details of AMU concerning ATCvet codes. More herds with confirmed AMU and higher within-herd AMU were observed in the BIN dataset compared to the SBA and VXA datasets. Regardless of dataset, organic herds had a numerically lower total AMU compared to conventional farms.

Across datasets, injectable procaine benzylpenicillin (QJ01CE09) was the main antibiotic prescribed of a list of 16 drug formulations found. For all the drugs used, there was a variation between prescription and the related number of DCDvet/animal/year across datasets for each period/production system. Further details can be found in the **Supplementary Material** section of this paper.

Agreement and Biases Between Datasets: Bland–Altman Plots and Regression Analysis Results

The number of herd observations per dataset and the number of corresponding observations between the datasets are shown in **Table 2**. The number of herds reporting AMU for the primary drug forms (IN and IMt) was higher for the BIN dataset than SBA and VXA. The number of corresponding reports between

TABLE 2 | Slope of the regression line comparing antimicrobial use (AMU) DCD_{vet}/animal/year metric of three datasets, and bias, variability of the bias, and limits of agreement for AMU across three datasets in a sample of 60 Swedish dairy herds (30 conventional and 30 organic).

Drug administration form	Comparison *A* vs. B *dataset		[a]Mean bias	SD	[b]LL and UL of agreement		Slope of regression line (Dataset A vs. B)	*P*-value indicating a significant difference from 1 for the slope	Herd × period with at least one record of AMU in Dataset A vs. B, (*n* = concurrent records found, % of total herd observations within category)
All forms	*BIN*	VXA	−0.15	0.315	−0.766	0.469	0.16	**0.011**	108/96 (92, 77%)
		SBA	−0.08	0.337	−0.738	0.583	0.30	**<0 0.0001**	108/104 (98, 82%)
	SBA	VXA	−0.07	0.258	−0.577	0.435	−0.13	**0.003**	104/96 (96, 81%)
Injectables/Parenteral	*BIN*	VXA	−0.11	0.248	−0.598	0.374	0.18	**<0.0001**	107/96 (92, 81%)
		SBA	−0.08	0.239	−0.545	0.394	0.25	**<0.0001**	107/102 (96, 85%)
	SBA	VXA	−0.04	0.128	−0.287	0.214	−0.08	**0.017**	102/96 (96, 85%)
Intramammary lactation tubes	*BIN*	VXA	−0.01	0.092	−0.190	0.171	0.12	0.194	38/31 (23, 47%)
		SBA	0.05	0.219	−0.379	0.479	0.73	**<0.0001**	38/38 (27, 55%)
	SBA	VXA	−0.06	0.215	−0.481	0.362	−0.60	**<0.0001**	38/31 (31, 63%)
Intramammary dry–cow tubes	*BIN*	VXA	−0.07	0.123	−0.315	0.169	0.06	0.759	54/12 (9, 15%)
		SBA	−0.05	0.137	−0.321	0.215	0.19	0.358	54/21 (14, 23%)
	SBA	VXA	−0.02	0.058	−0.134	0.094	−0.08	0.227	21/12 (12, 20%)

[a]*The mean bias represents the difference between datasets as defined course doses/animal/year "B" —defined course doses/animal/year "A".* [b]*The LL (lower agreement limit) and UL (upper agreement limit) represents the mean "bias" −1.96 × SD and the mean "bias" + 1.96 × SD, respectively.*
**BIN, Bin collection method records; SBA, Swedish Board of Agriculture database; VXA, Växa Sverige database. Bold values indicate the P-value <0.05.*

BIN and the other two datasets was low while between SBA and VXA it was high. The number of corresponding reports between datasets was high for IN formulations but low for IMt formulations, especially for dry-cow IMt. Usage of O drugs was found for two herds. The herds involved and time of observation differed between BIN and the matching reports in the VXA and SBA datasets. No usage of IU drugs was found in the BIN dataset for any herd at any period, but records were found in SBA and VXA for four herds in the first period.

The mean differences in the herd total DCD_{vet}/animal/year metric between datasets for the different drug forms, i.e., the mean bias, the standard deviations of these differences, and the limits of agreement, are shown in **Table 2**. Again, a greater AMU was reported in the BIN than in the SBA and VXA datasets (mean bias < 0). However, when comparing BIN and SBA datasets for lactating IMt, higher AMU was reported in the SBA dataset than in the BIN (mean bias > 0).

Figures 3A–C present a selected example (all drug types) of AMU metric comparisons between BIN vs. SBA, BIN vs. VXA, and SBA vs. VXA, respectively. Very few data points were found in the line of equality ($y = 0$), thus confirming discrepancies between datasets. A great variability but no clear pattern was observed between the datasets. The presence and extent of potential systematic bias between compared datasets were evaluated with a regression line (red dotted line in **Figure 3**) and related agreement limits. If two dataset metrics are similar, then the regression line should be coincident with the line of equality ($x = y$), i.e., the slope of the regression line should be equal to one. For most of the comparisons made, the slopes were significantly different from one, indicating no real agreement between the methods (**Table 3**). However, for dry-cow IMt (all comparisons) and lactating IMt (BIN vs. SBA), the slopes of the regression lines were not significantly different from one (**Table 2**), indicating agreement between the dataset for those farms where IMt was recorded.

Associations Between Production Type, Administration Form, and AMU

The associations between total DCD_{vet}/animal/year and production type (conventional vs. organic production), observation period, and drug administration form, as estimated in the linear models, in the VXA dataset are given in **Table 3** and the BIN dataset in **Table 4**.

VXA Dataset

No difference in AMU was found between production systems and observation period had no association with AMU. However, drug administration form did have an impact on the metric in that injectable drug had the highest AMU metric compared to the other drug presentations, where intrauterine drugs had the lowest AMU metric.

BIN Dataset

Numerical but non-statistical differences were found between organic and conventional herds, and no difference in AMU was seen between observation periods. However, drug administration form affected the AMU metric. Injectable drugs had the highest metric while lactating IMt the lowest. An interaction between the production system and drug administration form was found. Injectable drugs and IMt for lactating cows differed by the production system, where organic herds had a lower AMU metric

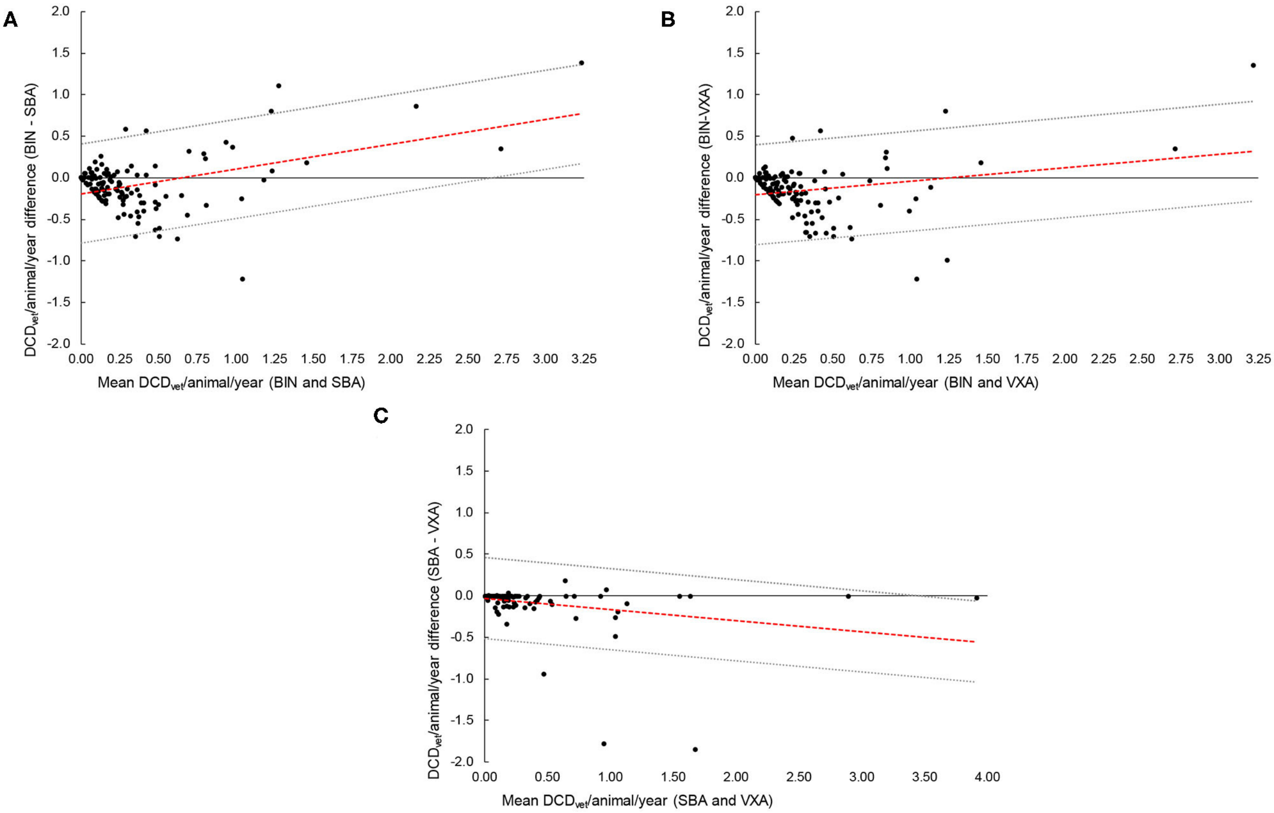


FIGURE 3 | Bland–Altman plots of **(A)** BIN vs. SBA dataset **(B)** BIN vs. VXA dataset and **(C)** SBA vs. VXA datasets on a sample of 60 farms in Sweden. (−−−) Regression line between the measures; (….) Limits of agreement for the regression line; (____) Line of equality (y = 0).

than the conventional herds. However, organic and conventional herds had similar AMU metrics for dry-cow IMt.

DISCUSSION

To effectively address the situation of AMU and AMR, herd-level data are needed. To our knowledge, this is the first study to provide a full description of AMU regardless of medical indication and split by production type (i.e., organic and conventional herds) in a Swedish dairy context.

The BIN method captured more drug use than SBA and VXA. The first type of discrepancy found was in the number of herds with corresponding reports of AMU across all datasets. The lowest percentage of discrepancies was found between SBA and VXA reports, especially for the injectable forms. Yet, the highest percentage of discrepancies was found between BIN and VXA datasets, especially for intramammary tubes for dry-cow treatments. The second type of discrepancy was in the amount of AMU reported among datasets. Here, Bland–Altman analyses indicated an overall trend of AMU underreporting in the SBA and VXA datasets compared to the reports from the BIN dataset. In most cases, the limits of agreement were large but not beyond what would be considered "clinically acceptable" (33), as in most cases, the disagreement represented <1 treatment course per animal. Consequently, datasets could be used interchangeably. However, as large discrepancies were found for intramammary drug forms, any metrics should take this into account.

A major strength of the BIN dataset is that "overreporting" of AMU is unlikely. This could occur if farm staff discarded outdated or unused drugs, or if half-empty packages/bottles/tubes were reported as fully used. We reduced that risk by making sure that all recorded packages were either empty or reported as the amount used if a half-empty package/bottle was found. In Sweden, the amount of the drug prescribed and dispensed to a farm or individual should match the volume/amount necessary to cover the treatment. Any leftovers must be safely discarded, preventing antimicrobial hoarding or imprudent handling of waste (34). Adherence to this could not be confirmed on the visiting farms. Yet, finding partially used bottles/packages in the BIN might suggest that staff on-farm indeed discard leftovers as required.

However, when SBA or VXA report higher AMU than in the BIN, we have little room to know if actual "underreporting" in the BIN occurred, i.e., if farm staff forgot (intentionally or not) to put the empty packaging in the BIN. In our study, we could establish real, yet probably unintentional, underreporting in the BIN for intrauterine drugs. We found no intrauterine drug packages in the BIN; however, a few such reports were found in the other datasets. Upon discussion with veterinary practitioners, it was

TABLE 3 | Associations between production type and drug administration form [least-square (LS) means, 95% confidence intervals (CI)] on antimicrobial use (obtained from VXA data) measured as the number of defined courses animal/year (DCD_{vet}/animal/year) and as estimated in a linear mixed model, in a sample of 56 (27 Organic and 29 Conventional) Swedish dairy herds.

	Factor	*DCD_{vet}/animal/year			
		LS mean	**Low 95% CI**	**High 95% CI**	***P*-value**
Production type	Organic	0.02	0.007	0.040	0.408
	Conventional	0.02	0.011	0.051	
Drug administration form	Intramammary tube (lactating cow)	0.05	0.032	0.087	**<0.001**
	Intramammary tube (dry-cow)	0.06	0.030	0.123	
	Intrauterine	0.02	0.003	0.058	
	Parenteral/injectable	0.14	0.106	0.184	

**DCDvet/animal/year (i.e., dependent variable) required a Box–Cox transformation for analysis; back-transformed data are presented. Besides production type, only factors significantly (P < 0.05) associated with the dependent variable were retained in the model and are presented in the table. Bold values indicate the P-value <0.05.*

TABLE 4 | Associations between production type and drug administration form [least-square (LS) means, 95% confidence interval (CI)] and antimicrobial use (obtained from BIN data) measured as the number of defined courses animal/year (DCD_{vet}/animal/year) and as estimated in a linear mixed model, in a sample of 60 (30 organic and 30 conventional) Swedish dairy herds.

Factor			*DCD_{vet}/animal/year			***P*-value**
			LS mean	**Low 95% CI**	**High 95% CI**	
Production type	Organic		0.08	0.059	0.118	***0.067***
	Conventional		0.13	0.096	0.171	
Drug administration form	Intramammary tube (lactating cow)		0.04	0.030	0.066	**<0.001**
	Intramammary tube (dry-cow)		0.09	0.065	0.119	
	Parenteral/injectable		0.25	0.206	0.304	
**Interaction: (Production type) × (Drug administration form)	Intramammary (lactating cow)	Organic	0.03	0.013	0.054	**0.033**
		Conventional	0.07	0.043	0.106	
	Intramammary (dry cow)	Organic	0.09	0.055	0.138	0.970
		Conventional	0.09	0.058	0.129	
	Parenteral/injectable	Organic	0.20	0.148	0.264	**0.026**
		Conventional	0.31	0.240	0.404	

**DCDvet/animal/year (i.e., dependent variable) required a Box–Cox transformation for analysis; back-transformed data are presented. Besides production type, only factors significantly (P < 0.05) associated with the dependent variable were retained in the model and are presented in the table.*
***For the interaction, P-values of the pairwise comparison between production systems for each drug administration form are presented. Bold and italic values indicate the P-value <0.05.*

understood that the few intrauterine treatments that take place on a farm are performed by the veterinarian on the spot. Hence, the veterinarian routinely discards the gloves, and drug packaging used together without the involvement of the staff on-farm, and the packaging does not reach the bin. This behaviour may also partially explain the overall trend of BIN underreporting AMU for intramammary tubes for lactating cows. These treatments can also be carried out on the spot by the veterinarian, and again, the discarded containers would not necessarily reach the bin.

Several studies have compared AMU based on drug packaging collections (i.e., BIN method) against other data sources, mainly farmers' reports (14, 16, 35). Similar to our study, the authors found that the BIN method/dataset outperforms other data sources. These studies attributed the success of the method to the convenience for staff in reporting AMU with the simple act of discarding packages, saving them from the burden of collating information. In our study, the prescribing veterinarians provided the data for the compared datasets. So, in essence, SBA and VXA reflect prescriptions, while BIN captures actual use. Veterinarians in the research team (KS, NF, and SSL) recognise that AMU reporting is an administrative burden. Depending on the tools available, records can be either collated manually (i.e., pen and paper), scanned and sent to SBA to be uploaded electronically, or transferred manually into a web portal. Alternatively, records could be transferred electronically directly to the SBA database. Transferal could be done on the spot as an individual record or as a bulk of prescriptions later on. Thus, the ability to correctly collate the information is highly depending on the clinical record-keeping. Indeed, upon revision of working datasets ahead of calculations, many treatment records had to be removed as not enough details were present to determine if they were AMU. Poor quality in reporting could explain why some herds failed to present records in SBA or VXA datasets when treatment was performed based on what was found in the BIN dataset. Another explanation could be that the full veterinary prescription was issued before the study period and hence did not appear in the databases. However, the actual use of the drug occurred during the study period, as shown in the BIN.

Nevertheless, the observed discrepancies are consistently larger for intramammary forms, primarily when related to dry-cow treatments (77 to 85% of missing records in either SBA or VXA datasets compared to BIN). Thus, contrary to what is expected, some prescriptions do not get reported as required. In Sweden, current recommendations condemn the storage of antimicrobials (e.g., hoarding of antimicrobial leftovers). Moreover, blanket treatments or preventive AMU is not allowed; selective dry cow therapy is permitted only in individual animals, and cows will only get treated after a diagnosis is made (36, 37). Thus, the lack of reports in SBA and VXA datasets compared to the BIN might be an indication of some practice deviations. If so, further understanding of the quality, magnitude, and drivers of this are needed.

Based on our results, it could be said that BIN provided more information on AMU at herd level for short observation periods. Yet, it is unsustainable for long periods and challenging to scale up on a national basis. On the other hand, our study confirms that SBA and VXA could be used interchangeably. Yet, VXA offers the advantage of being the only standalone dataset for obtaining herd-level AMU metrics in the recommended unit, since time-at-risk can be calculated, over a long time, and scaled to a national level. Nonetheless, underreporting of intramammary drug forms needs to be adequately addressed for SBA and consequently for VXA. Here, we suggest the application of a biannual screening of a random selection of herds using the BIN methodology. This exercise would allow formalizing the monitoring and validation of results captured by SBA and the VXA dataset.

With a focus on BIN reports, we found that the studied farms had an average treatment incidence and average course treatment of 0.43 DDD_{vet}/animal/year and 0.22 DCD_{vet}/animal/year, respectively. Procaine benzylpenicillin (QJ01CE09) was the preferred (92%) antimicrobial to be used in the reported treatment entries, where more than half (56%) were related to udder problems. This is only the second time in more than 20 years that AMU at herd level is published for dairy cattle in Sweden (38, 39). Direct comparison with these and work in other countries where treatment incidences are reported (23, 40, 41) are constrained mainly by variations in sources of data, calculation methodology, and study design (12).

Despite the challenge of direct comparisons between studies, current AMU in Swedish dairy herds is much lower compared to previous reports for Sweden (6.4 DDDcow/1,000 cow-days for injectable; 3.45 DDDcow/1,000 cow-days intramammary drugs) (38). Equally, it is also low in an international comparison of the median number of doses reported (interquartile range 5.5–13.6 DDDcow/1,000 cow-days) (40). Moreover, results agree with latest reports by EMA (42, 43). Such reports use the "population correction unit" (PCU) based on livestock demographics to estimate the total weight of the livestock population in each country to then compare AMU across the EU in mg/PCU. The report indicates that Sweden is the EU member state with the lowest AMU and after Iceland and Norway the third lowest within all European countries (43).

Only 16 ATC_{vet} codes, representing six antimicrobial classes, were found across the datasets. The list is smaller than that previously reported in Sweden (39, 44) or found in other international reports (40). For example, our study found no reports of macrolides. This use was common 20 years ago and continues to be so in some countries (40). We found no ATC_{vet} codes representing antimicrobial groups like cephalosporins, amphenicols, lincosamides, or pleuromutilins. Injectable (QJ01CE09, 92% farms) and intramammary penicillins (QJ51CE09, 32% farms) were the most used antimicrobials followed by tetracyclines (QJ01AA06, 17% farms), albeit with a low DDD_{vet}/animal/year value compared to that of penicillins. Internationally, the most reported antimicrobial groups in dairy cattle are penicillins, and third-generation cephalosporins (40) and highest-priority critically important antibiotic (HPCIA) treatments of mastitis could range from 10 to 80% depending on the veterinary practice (44). In our study, udder health was also the main reason behind the observed AMU. Yet, the HPCIA treatments were low, and cephalosporin use was not recorded at all. HPCIA category 1 includes macrolides, certain penicillins, and tetracyclines, while category 2 includes ampicillins, aminoglycosides, quinolones, 3rd- and 4th-generation cephalosporins, and polymyxins (e.g., colistin).

Moreover, our study also found large variations of HPCIA treatment percentages across farms. Yet, that includes many herds with no HPCIA treatments for category 2. Furthermore, the HPCIA reports for category 2 were mainly due to the use of aminoglycosides or quinolones but not to cephalosporins as in other countries. Sweden has a long-standing history of strengthening its policy recommendations across the human and veterinary sectors to reduce the AMR burden (43, 45). The efforts made have had a definite impact on the reduction as well as the pattern of AMU (17).

Previous studies comparing organic and conventional dairy herds under Swedish conditions found a marginal difference in udder health and reproductive performance, implying equally good animal health in both systems (46–48). Our study presented marginal differences between organic and conventional farms. It should be noted, however, that the small differences are due to an equally low AMU in conventional Swedish farms. Organic herds had a small advantage in that they had a lower mortality and less lameness and mastitis cases. Yet, the bulk milk somatic cell counts were higher for organic farms. Differences had been reported elsewhere between organic and conventional herds (23, 24), indicating that organic herds had a substantially lower level of AMU, but the difference in management between organic and conventional herds is typically larger outside Sweden (49, 50).

Organic herds had numerically lower treatment incidence and a lower number of treatment courses regardless of dataset or treatment form. Yet, at a closer look on the BIN dataset and DCD_{vet}/animal/year metric, an interaction between the production system and drug administration form was found. Organic herds had a significant lower AMU for injectables and intramammary lactating cow treatment forms. Yet, organic and conventional farms had a similar AMU for intramammary dry-cow treatment forms.

A potential explanation for the AMU difference between organic and conventional herds for particular drug forms, as suggested by others (23, 24), could be the underlying marginal difference in udder health between production systems in Sweden. Yet, evidence also exists that multiple factors beyond production type characteristics drive the choice of therapy and related management practices, such as farmers' and veterinarians' beliefs and social pressure (51, 52). A qualitative enquiry in the study herds could not relate any particular AMU perception to production type. Still, the authors highlight some behavioural discord among the farmers and veterinarians around udder treatments (53). This, in combination with our findings of underreporting of dry-cow intramammary tubes, suggests that these behaviours are a product of a different set of beliefs around the treatment of cows at dry-off and the practicalities of prescription and administration across herds, but this requires further investigation.

CONCLUSION

We conclude that herd-level assessment of AMU is possible using reported prescriptions in combination with herd data, such as in the VXA database, with the caveat that intramammary drugs may be misrepresented. The BIN methodology offered a more comprehensive alternative to gain an account of AMU at herd level. However, as this method is labour- and resource-demanding, it is difficult to apply routinely at a national scale. Thus, for Sweden, we suggest the application of the BIN methodology on a random selection of herds to monitor and validate results captured by SBA and VXA. We also suggest improving the understanding and reduction of underreporting of intramammary drug forms.

This study provides a detailed contemporary account of AMU in Swedish dairy herds. It confirms the reported low AMU based on sales data. Moreover, we conclude that AMU differs between organic and conventional farms for particular drug forms that may partly be driven by the marginal difference in disease prevalence. The use and reporting of dry-cow intramammary drug forms requires further investigation.

DATA AVAILABILITY STATEMENT

The datasets for this article are not publicly available because of privacy and confidentiality reasons. Requests to access the datasets should be directed to the corresponding author, Jordbruksverket (jordbruksverket@jordbruksverket.se) and Växa Sverige (info@vxa.se), respectively.

ETHICS STATEMENT

Ethical review and approval was not required for the animal study because the study design adhered to the good scientific practice guidelines set out by Swedish legislation and did not include direct animal testing. Thus, no further ethical evaluation or permit was required for its execution. Written informed consent was obtained from the owners for the participation of their animals in this study.

AUTHOR CONTRIBUTIONS

GO was in charge of the analysis and wrote the manuscript. KS was in charge of the data acquisition and made a substantial contribution to the conception and revision of the document. SS and NF provided valuable expertise in the conceptualisation of the idea and writing process. UE assisted in the conceptualisation of the idea, analytical process, and revision of the manuscript. All the authors have read and approved the manuscript.

FUNDING

The funding for this project was provided by Formas—The Swedish Research Council for Environment, Agricultural Sciences, and Spatial Planning Grant No. 2014-281 (Stockholm, Sweden).

ACKNOWLEDGMENTS

We are grateful to all the farmers that kindly accepted to take part in this study and for taking time to collect all the empty drug containers for us so willingly and judiciously.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fvets.2020.568881/full#supplementary-material

REFERENCES

1. Woolhouse M, Ward M, van Bunnik B, Farrar J. Antimicrobial resistance in humans, livestock and the wider environment. *Philos Trans Roy Soc B Biol Sci.* (2015) 370:1–7. doi: 10.1098/rstb.2014.0083
2. OECD. *Steeming the Superbug Tide: Just a Few Dollars More.* Paris: OECD Publishing (2018)
3. Woolhouse M, Farrar J. An intergovernmental panel on antimicrobial resistance. *Nature.* (2014) 509:555–7. doi: 10.1038/509555a
4. OIE. *List of Antimicrobial Agents of Veterinary Importance.* Paris: (2015) Available online at: http://www.oie.int/fileadmin/Home/eng/Our_scientific_expertise/docs/pdf/Eng_OIE_List_antimicrobials_May2015.pdf
5. EMA/AMEG. *Updated Advice on the use of Colistin Products in Animals within the European Union: Development of Resistance and Possible Impact on Human and Animal Health.* (2016) Available online at: https://www.ema.europa.eu/en/documents/scientific-guideline/updated-advice-use-colistin-products-animals-within-european-union-development-resistance-possible_en-0.pdf: European Medicines Agency, Contract No.: EMA/CVMP/CHMP/231573/2016

6. WHO. *WHO Critically Important Antimicrobials for Human Medicine 5th revision Raleigh*, USA: World Health Organization (2016). Available online at: http://www.who.int/foodsafety/publications/cia2017.pdf?ua=1 (accessed January, 2018).
7. Van Boeckel TP, Brower C, Gilbert M, Grenfell BT, Levin SA, Robinson TP, et al. Global trends in antimicrobial use in food animals. *Proc Natl Acad Sci USA*. (2015) 112:5649–54. doi: 10.1073/pnas.1503141112
8. Scott AM, Beller E, Glasziou P, Clark J, Ranakusuma RW, Byambasuren O, et al. Is antimicrobial administration to food animals a direct threat to human health? A rapid systematic review. *Int J Antimicrob Agents*. (2018) 52:316–23. doi: 10.1016/j.ijantimicag.2018.04.005
9. Burke CR, Meier S, McDougall S, Compton C, Mitchell M, Roche JR. Relationships between endometritis and metabolic state during the transition period in pasture-grazed dairy cows. *J Dairy Sci*. (2010) 93:5363–73. doi: 10.3168/jds.2010-3356
10. Chang QZ, Wang WK, Regev-Yochay G, Lipsitch M, Hanage WP. Antibiotics in agriculture and the risk to human health: how worried should we be? *Evol Appl*. (2015) 8:240–7. doi: 10.1111/eva.12185
11. Barber DA, Miller GY, McNamara PE. Models of antimicrobial resistance and foodborne illness: examining assumptions and practical applications. *J Food Prot*. (2003) 66:700–9. doi: 10.4315/0362-028X-66.4.700
12. Collineau L, Belloc C, Stark KDC, Hemonic A, Postma M, Dewulf J, et al. Guidance on the selection of appropriate indicators for quantification of antimicrobial usage in humans and animals. *Zoon Public Health*. (2017) 64:165–84. doi: 10.1111/zph.12298
13. AACTING-network. *Guidelines for Collection, Analysis and Reporting of Farm-Level Antimicrobial Use, in the Scope of Antimicrobial Stewardship*. Contract No.: VERSION 1.1_2018-03-23. Ghent: AACTING-network (2018).
14. Redding LE, Cubas-Delgado F, Sammel MD, Smith G, Galligan DT, Levy MZ, et al. Comparison of two methods for collecting antibiotic use data on small dairy farms. *Prev Vet Med*. (2014) 114:213–22. doi: 10.1016/j.prevetmed.2014.02.006
15. Mills HL, Turner A, Morgans L, Massey J, Schubert H, Rees G, et al. Evaluation of metrics for benchmarking antimicrobial use in the UK dairy industry. *Vet Record*. (2018) 182:379. doi: 10.1136/vr.104701
16. Nobrega DB, De Buck J, Naqvi SA, Liu G, Naushad S, Saini V, et al. Comparison of treatment records and inventory of empty drug containers to quantify antimicrobial usage in dairy herds. *J Dairy Sci*. (2017) 100:9736–45. doi: 10.3168/jds.2017-13116
17. Swedres-Svarm. *Consumption of Antibiotics and Occurrence of Resistance in Sweden*. (2016). Solna/Uppsala Available online at: https://www.sva.se/media/1xocwfe3/swedres_svarm2016.pdf: ISSN 1650-6332, Article No. 16124
18. Duse A. *Antimicrobial resistant Escherichia coli in faeces from preweaned dairy calves* [Doctoral Thesis]. Uppsala, Sweden: Swedish University of Agricultural Sciences. (2015)
19. VÄXA. *Husdjursstatistik/Cattle statistics* 2017. Sweden: VÄXA SVERIGE (2017).
20. EC. Council Regulation (EC) No 834/2007 On organic production and labelling of organic products and repealing Regulation (EEC) No 2092/91. *Eur Union Law*. (2007) 8:139–61. Available online at: https://eur-lex.europa.eu/legal-content/EN/TXT/HTML/?uri=LEGISSUM:f86000&from=EN
21. Pol M, Ruegg PL. Treatment practices and quantification of antimicrobial drug usage in conventional and organic dairy farms in Wisconsin. *J Dairy Sci*. (2007) 90:249–61. doi: 10.3168/jds.S0022-0302(07)72626-7
22. Osterberg J, Wingstrand A, Jensen AN, Kerouanton A, Cibin V, Barco L, et al. Antibiotic resistance in escherichia coli from pigs in organic and conventional farming in four european countries. *PLoS ONE*. (2016) 11:12. doi: 10.1371/journal.pone.0157049
23. Krogh MA, Nielsen CL, Sørensen JT. Antimicrobial use in organic and conventional dairy herds. *Animal*. (2020) 14:2187–93. doi: 10.1017/S1751731120000920
24. Bennedsgaard TW, Klaas IC, Vaarst M. Reducing use of antimicrobials - experiences from an intervention study in organic dairy herds in Denmark. *Livestock Sci*. (2010) 131:183–92. doi: 10.1016/j.livsci.2010.03.018
25. EMA/AMEG. *Answers to the Request for Scientific Advice on the Impact on Public Health and Animal Health of the Use of Antibiotics in Animals - Answer to the Second Request From the EC (Ranking of Antibiotics); ANSWER to the Third From the EC (New Antibiotics); Answer to the Fourth Request From the EC (Risk Mitigation Options)*. Contract No.: EMA/381884/2014. London: EMA/AMEG (2014).
26. VÄXA. *Växa Fakta Sweden: VÄXA*. (2020). Available online at: https://www.vxa.se/fakta/styrning-och-rutiner/mer-om-mjolk/ (accessed May 29, 2020).
27. ESVAC. *Revised ESVAC Reflection Paper on Collecting Data on Consumption of Antimicrobial Agents Per Animal Species, on Technical Units of Measurement and Indicators for Reporting Consumption of Antimicrobial Agents in Animals*. Report No.: EMA/286416/2012-Rev.1 Contract No.: EMA/286416/2012-Rev.1. London: European Medicines Agency, Division VM (2013).
28. Jordbrukeverket. *Report: JO 48 SM 1712. Table 3a: Slakt av större husdjur vid slakteri*. (2017). Available from: http://www.jordbruksverket.se/webdav/files/SJV/Amnesomraden/Statistik,%20fakta/Animalieproduktion/JO48SM1712/JO48SM1712_tabeller3.htm (accessed January 19, 2018).
29. EMA. *Principles on Assignment of Defined Daily Dose for Animals (DDDA) and Defined Course Dose for animals (DCDA)*. (2015). Available online at: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2015/06/WC500188890.pdf: European Medicines Agency, EMA/710019/2014
30. EMA. *Defined Daily Doses for Animals (DDDvet) and Defined Course Doses for Animals (DCDvet): European Surveillance of Veterinary Antimicrobial Consumption (ESVAC)*. (2016). Available online at: http://www.ema.europa.eu/docs/en_GB/document_library/Other/2016/04/WC500205410.pdf: European Medicines Agency, EMA/224954/2016.
31. EMA. *CVMP Strategy on Antimicrobials 2016-2020*. London: European Medicines Agency (2015). EMA/CVMP/209189/2015 Contract No.: EMA/CVMP/209189/2015.
32. WHO. *WHO Guidelines on use of Medically Important Antimicrobials in Food-Producing Animals*. Geneva: World Health Organization; (2017). Available online at: : https://creativecommons.org/licenses/by-nc-sa/3.0/igo.
33. Bland JM, Altman DG. Measuring agreement in method comparison studies. *Stat Methods Med Res*. (1999) 8:135–60. doi: 10.1191/096228099673819272
34. Sweden GOo. *Swedish Strategy to Combat Antibiotic Resistance*. Goverment Offices of Sweden; (2020). p. 24
35. Carson CA, Reid-Smith R, Irwin RJ, Martin WS, McEwen SA. Antimicrobial use on 24 beef farms in Ontario. *Can J Vet Res*. (2008) 72:109–18. PubMed PMID: WOS:000255703200005.
36. Koops W, Ekström J, Armstrong D. 5.8: *Report on Practical Strategies to Reduce Antimicrobial Use in Dairy Farming*. Amersfoort (2018).
37. Swedres-Svarm. *Consumption of Antibiotics and Occurrence of Antibiotic Resistance in Sweden*. Solna/Uppsala (2019). Available online at: https://www.sva.se/media/0hihej1c/swedres-svarm-2019.pdf: ISSN1650-6332, Article No. 18092.
38. Grave K, Greko C, Nilsson L, Odensvik K, Mork T, Ronning M. The usage of veterinary antibacterial drugs for mastitis in cattle in Norway and Sweden during 1990-1997. *Prev Vet Med*. (1999) 42:45–55. doi: 10.1016/S0167-5877(99)00057-4
39. Ortman K, Svensson C. Use of antimicrobial drugs in Swedish dairy calves and replacement heifers. *Vet Rec*. (2004) 154:136–40. doi: 10.1136/vr.154.5.136
40. Cuong NV, Padungtod P, Thwaites G, Carrique-Mas JJ. Antimicrobial usage in animal production: a review of the literature with a focus on low- and middle-income countries. *Antibiotics*. (2018) 7:75. doi: 10.3390/antibiotics7030075
41. Hommerich K, Ruddat I, Hartmann M, Werner N, Käsbohrer A, Kreienbrock L. Monitoring antibiotic usage in german dairy and beef cattle farms—a longitudinal analysis. *Front Vet Sci*. (2019) 6:244. doi: 10.3389/fvets.2019.00244
42. ESVAC. *Seventh ESVAC Report: Sales of Veterinary Antimicrobial Agents in 30 European Countries in 2015. Trends from 2010 to 2015*. Contract No.: EMA/184855/2017. London: European Medicines Agency (2017).
43. ESVAC. *Sales of Veterinary Antimicrobial Agents in 31 European Countries in 2017*. EMA/294674/2019. Amsterdam: European Medicines Agency (2019).
44. Firth CL, Kasbohrer A, Schleicher C, Fuchs K, Egger-Danner C, Mayerhofer M, et al. Antimicrobial consumption on Austrian dairy farms: an observational study of udder disease treatments based on veterinary medication records. *PeerJ*. (2017) 5:e4072. doi: 10.7717/peerj.4072
45. Mölstad S, Lofmark S, Carlin K, Erntell M, Aspevall O, Blad L, et al. Lessons learnt during 20 years of the Swedish strategic programme

against antibiotic resistance. *Bull World Health Org.* (2017) 95:764–73. doi: 10.2471/BLT.16.184374

46. Fall N, Emanuelson U. Milk yield, udder health and reproductive performance in Swedish organic and conventional dairy herds. *J Dairy Res.* (2009) 76:402–10. doi: 10.1017/S0022029909990045
47. Fall N, Emanuelson U, Martinsson K, Jonsson S. Udder health at a Swedish research farm with both organic and conventional dairy cow management. *Prev Vet Med.* (2008) 83:186–95. doi: 10.1016/j.prevetmed.2007.07.003
48. Fall N, Forslund K, Emanuelson U. Reproductive performance, general health, and longevity of dairy cows at a Swedish research farm with both organic and conventional production. *Livestock Sci.* (2008) 118:11–9. doi: 10.1016/j.livsci.2008.01.017
49. Andreasen SN, Sandoe P, Forkman B. Can animal-based welfare assessment be simplified? A comparison of the welfare quality (R) protocol for dairy cattle and the simpler and less time-consuming protocol developed by the Danish Cattle Federation. *Anim Welfare.* (2014) 23:81–94. doi: 10.7120/09627286.23.1.081
50. Emanuelson U, Sjostrom K, Fall N. Biosecurity and animal disease management in organic and conventional Swedish dairy herds: a questionnaire study. *Acta Veterinaria Scandinavica.* (2018) 60:23. doi: 10.1186/s13028-018-0376-6
51. Lam T, Jansen J, Wessels RJ. The reset mindset model applied on decreasing antibiotic usage in dairy cattle in the Netherlands. *Irish Vet J.* (2017) 70:1–9. doi: 10.1186/s13620-017-0085-x
52. Lam T, van den Borne BHP, Jansen J, Huijps K, van Veersen JCL, van Schaik G, et al. Improving bovine udder health: a national mastitis control program in the Netherlands. *J Dairy Sci.* (2013) 96:1301–11. doi: 10.3168/jds.2012-5958
53. Fischer K, Sjostrom K, Stiernstrom A, Emanuelson U. Dairy farmers' perspectives on antibiotic use: A qualitative study. *J Dairy Sci.* (2019) 102:2724–37. doi: 10.3168/jds.2018-15015

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Veterinary Science

ORIGINAL RESEARCH
published: 30 October 2020
doi: 10.3389/fvets.2020.558455

Comparing Farm Biosecurity and Antimicrobial Use in High-Antimicrobial-Consuming Broiler and Pig Farms in the Belgian–Dutch Border Region

Nele Caekebeke[1], Franca J. Jonquiere[2], Moniek Ringenier[1], Tijs J. Tobias[2], Merel Postma[1], Angelique van den Hoogen[2], Manon A. M. Houben[3], Francisca C. Velkers[2], Nathalie Sleeckx[4], J. Arjan Stegeman[2] and Jeroen Dewulf[1] on behalf of the i-4-1-Health Study Group[1]*

[1] Veterinary Epidemiology Unit, Department of Reproduction, Obstetrics and Herd Health, Faculty of Veterinary Medicine, Ghent University, Merelbeke, Belgium, [2] Farm Animal Health Unit, Department of Population Health Sciences, Faculty of Veterinary Medicine, Utrecht University, Utrecht, Netherlands, [3] GD Animal Health, Deventer, Netherlands, [4] Experimental Poultry Centre, Geel, Belgium

OPEN ACCESS

Edited by:
Miguel Ángel Moreno,
Complutense University of Madrid, Spain

Reviewed by:
Agnes Agunos,
Public Health Agency of Canada, Canada
Håkan Vigre,
Technical University of Denmark, Denmark

***Correspondence:**
Nele Caekebeke
nele.caekebeke@ugent.be

Specialty section:
This article was submitted to Veterinary Epidemiology and Economics,
a section of the journal Frontiers in Veterinary Science

Received: 02 May 2020
Accepted: 23 September 2020
Published: 30 October 2020

Citation:
Caekebeke N, Jonquiere FJ, Ringenier M, Tobias TJ, Postma M, van den Hoogen A, Houben MAM, Velkers FC, Sleeckx N, Stegeman JA and Dewulf J (2020) Comparing Farm Biosecurity and Antimicrobial Use in High-Antimicrobial-Consuming Broiler and Pig Farms in the Belgian–Dutch Border Region. Front. Vet. Sci. 7:558455. doi: 10.3389/fvets.2020.558455

As antimicrobial resistance is a worldwide problem, threatening both livestock and public health, understanding the drivers for resistance in different settings and countries is essential. Therefore, 30 pig and 30 poultry farms with country-specific high antimicrobial use (AMU) were recruited in the Belgian–Dutch border region. Information regarding production parameters, farm characteristics, biosecurity, and AMU was collected. On average, more biosecurity measures were implemented on Dutch farms, compared to Belgian farms in both animal species. In addition, more opportunities were found to increase the level of internal biosecurity compared to external biosecurity in both countries. AMU, quantified as treatment incidence (TI), differed marginally significant between broiler farms in Belgium and the Netherlands (median BE: 8; NL: 3), whereas in weaned piglets (median BE: 45 and NL: 14) and finishing pigs (median BE: 5 and NL: 1), there was a substantial difference in AMU between farms from both countries. Overall, Dutch farms showed less between-farm variation in TI than did Belgian farms. In both poultry and pig production, the majority of antimicrobials used were extended-spectrum penicillins (BE: 32 and 40%; NL: 40 and 24% for poultry and pigs, respectively). Compared to Belgian farms, Dutch poultry farms used high amounts of (fluoro)quinolones (1 and 15% of total AMU, respectively). None of the production parameters between broiler farms differed significantly, but in pig production, weaning age in Belgian farms (median: 23) was lower than in Dutch farms (median: 27). These results indicate considerable room for improvement in both countries and animal species. Farm-specific preventive strategies can contribute to lowering the risk for animal disease and hence the need for AMU.

Keywords: antimicrobial use (AMU), farm biosecurity, preventive measures, intensive livestock, alternatives to antimicrobials

INTRODUCTION

It is estimated that, by 2050, antimicrobial resistance (AMR) could contribute to 10 million human fatalities per year worldwide if no actions are taken (1). The selection of AMR is largely driven by the (incorrect) use of antimicrobials (AM). As the development of new AM is limited (1, 2), treatment options are diminishing, endangering both human and animal healthcare.

The cross-border region of Belgium (Flanders) and the Netherlands is one with abundant movements of both humans and animals, due to high population numbers and intensive pig and poultry production, consequently posing a risk for dissemination of resistant bacteria and resistance genes, as AMR is not bound by country borders. Therefore, a multidisciplinary (One Health) approach needs to be complemented with cross-border cooperation to help understand and control the AMR problem (3).

AM in pig and poultry production are frequently administered orally, for group treatment of diseases of predominantly the respiratory and digestive tract (4–6). This method of treatment has a higher probability of improper dosing of the AM and contributes to the (over)exposure of healthy or non-infected animals to AM (7, 8). Therefore, these animal production systems need extra attention regarding their antimicrobial use (AMU).

Already in 2010, the Secretary of Agriculture of the Netherlands announced compulsory reductions of AMU in production animals (9, 10). This was quickly followed by a public–private program to reduce AMU in the Netherlands. In Belgium, AMU reduction plans were organized by the livestock sector (bottom-up approach) in 2012 and invigorated by the national government since 2016 to achieve the predetermined reduction goals. Substantial reductions in AMU have already been established in livestock in Belgium and the Netherlands (11, 12). Nevertheless, further reductions remain necessary, as high levels of AMR are still found (12–14).

By working together, both countries can learn from each other and harmonize methods of infection prevention, as it is believed that the latter will reduce the necessity for AMU, improving the safety of human and animal healthcare (15–17).

The objective of this manuscript is to describe and compare 30 pig and 30 poultry farms, selected for high AMU and located in the border region of Belgium and the Netherlands, with regard to production parameters, farm characteristics, biosecurity, and AMU. This inventory and comparison increase knowledge on potential associations between countries, species- or farm-specific parameters, and AMU, which can help identify where improvements should be made in order to reduce the problem of AMR.

MATERIALS AND METHODS

Study Design and Data Collection

A cross-sectional survey was performed on 15 pig and 15 poultry farms in each country (60 farms in total). During a farm visit, farm characteristics and biosecurity levels were determined. In addition, data on technical performance and AMU were obtained, going back 1 year preceding the visit. The farm visits during which data were collected took place between September 2017 and April 2018.

To minimize observer bias, the execution of farm visits was restricted to two researchers/veterinarians (one for Belgium and one for the Netherlands), who were trained simultaneously and conducted 10 mutual farm visits to align methodologies.

Before enrolling, all participating farmers were informed on the aim and methodology of the study. All farmers signed an informed consent form for the collection, exchange, and publication of data. The Animal Welfare Body from Utrecht University was consulted and concluded that the study was exempt for an ethical evaluation, as the project did not include experimental procedures with animals according to EC/2010/63.

Farm Selection

In each country, farms were recruited by sending out public announcements via different channels (newsletters, agricultural magazines, and professional contacts of the authors). The inclusion of farms was based on a "first come, first served" principle and the following criteria in order to obtain comparable farms in both countries: (1) for farm type, poultry farms needed to be conventional broiler farms (i.e., no organic production or slow-growing breeds), as conventional farms represent the majority of the farm systems in both countries, and pig farms needed to be a sow farm with weaned piglets present on the premises; (2) for farm location, all farms needed to be located within the Belgian–Dutch border region, comprising Flanders (northern region of Belgium) and the southern provinces of the Netherlands (Zeeland, Noord-Brabant, and Limburg); (3) for AMU, in the year preceding the farm visit, AMU needed to be above the national benchmark value, selecting for country-specific high users of AM. At the start of the project, no benchmark system was yet available for broilers in Belgium. Therefore, information provided by the farmer or herd veterinarian was considered. The latter criterion was included in view of further coaching the farmers toward a reduced AMU. To verify the inclusion of high-antimicrobial-consuming farms in this study, the AMU data retrieved from these farms were compared to national reference values (**Supplementary Table 1**).

Before or during the farm visits, one pig farm in Belgium and two broilers farms in the Netherlands withdrew from the project and were not replaced. Data of these farms are not presented.

Farm Characteristics, Management, and Technical Performance

Farm characteristics and technical performance data were collected from the farmers in an interview and from farm management programs. The performance data were collected for 1 year preceding the farm visit for collection of the data. For all poultry farms, the number of houses with the total amount of broilers on the farm and the parameters mortality (during the 1st week and round total) and feed conversion ratio (FCR) were obtained for seven production rounds (about 1 year in total). At the pig farms, information regarding animal capacity (maximum amount of animals), weaning age, pre-weaning mortality, and the number of piglets per sow per year was collected.

Biosecurity

The level of biosecurity was determined by completing the Biocheck.UGent™ questionnaire on-site in collaboration with the farmers and after visual appraisal of the farm. The questionnaire is a risk-based scoring system, evaluating the on-farm biosecurity in an objective manner (18, 19), resulting in a farm-specific report that scores external (all measures preventing the introduction of pathogens in the farm) and internal (all measures taken to prevent spread within the farm) biosecurity. The total biosecurity level on a farm is the weighted average of the external and internal biosecurity scores. Scores range from 0 to 100, with the latter being the implementation of all biosecurity measures, indicating the farmers' compliance to high biosecurity standards. Detailed information on the different subcategories within external and internal biosecurity can be found on the website of Biocheck.UGent™ (https://www.biocheck.ugent.be) or in Gelaude et al. (19) and Laanen et al. (18).

To prevent interviewer bias, the Biocheck.UGent™ questionnaire was filled-in while or after doing a farm visit. This way, part of the answers to the questionnaire could be visually evaluated by the researcher.

AMU Data

Data on AMU were obtained from the country-specific poultry or pork quality assurance organizations, the farmer, or the herd veterinarian. The data retrieved from either source are equal. However, collecting the data from the farmer or the veterinarian is much faster, as the reports provided by the quality organizations are only delivered a couple of times a year. To have data as soon as possible, the researchers got it directly from the farmer/veterinarian whenever possible.

The AMU was quantified in a standardized manner using the treatment incidence (TI) per 100 days as described by Persoons et al. (20) as the analysis of AMU data between Belgium and the Netherland differs in some aspects and as comparison is difficult without conversion. An overview of the different national monitoring systems is available on the AACTING website (https://www.aacting.org/monitoring-systems/).

The total amount of active substance prescribed equals the nominator, and the denominator represents the multiplication of (1) the defined daily dose (DDDvet, defined doses of an antimicrobial in mg per kg of animal), (2) the observation period (the number of days an animal is possibly exposed to a treatment), and (3) the amount of kg animals at risk. The ratio was then multiplied by 100 animal-days at risk to obtain the TI.

$$\mathrm{TI} = \frac{\text{Total amount of active substance prescribed (mg)}}{\text{DDDvet}\ (\text{mg/kg/day}) \ast \text{observation period} \ast \text{kg animals at risk}} \ast 100$$

The TI represents the percentage of time an animal was treated with AM during its life cycle.

For broilers, the observation period was the length of the production period. The kg animals at risk was determined by the standard weight for broilers of 1 kg corresponding with ESVAC guidelines (21), multiplied by the number of broilers on the farm. For weaners and finishers, the same formula was used, the standard weights of which, according to ESVAC, are 12 and 50 kg, respectively. However, the formula needed modification for sows and suckling piglets, as in Belgium, AMU in both categories is registered separately, whereas in the Netherlands, AMU in sows and suckling piglets are registered as one animal category. As disentanglement of the latter was not possible for data of the Dutch farms, an adjusted formula for AMU in sows and suckling piglets in both countries was determined:

$$\mathrm{TI} = \frac{\text{Total amount of active substance prescribed (mg)}}{\text{DDDvet}\ (\text{mg/kg/day}) \ast ((\text{observation period} \ast \text{kg sow at risk}) + (\text{farrowing period} \ast \text{kg sucklers at risk}))} \ast 100$$

The kg sow at risk is the multiplication of the standard weight of 220 kg for sows, according to ESVAC, with the number of sows present at the farm. Standard farrowing period was set at 28 days, the minimum weaning age according to EU legislation (EU Directive 2008/120/EEC). The value of kg sucklers at risk was calculated as the multiplication of the standard weight of suckling piglets (4 kg according to ESVAC), with a standard number of weaned piglets per sow per year of 28 (17), adjusted to the observation period and the number of sows: number of sows * (28/365 * observation period). An average number of piglets per sow per year was chosen to enable comparison between farms and countries.

The frequency of use of each antimicrobial class was determined and visualized by the number of prescriptions/total prescriptions. The antimicrobial classes were defined according to the ATCvet code (22).

Data Analysis

Descriptive statistics were performed using IBM SPSS Statistics 25.0 (IBM, New York, United States). For comparison between countries and animal categories, the data are described by the mean value and the minimum-to-maximum range. Normality of the data was tested by visual inspection of the Q–Q plots. When data were not normally distributed, a logarithmic transformation of the data was performed. The equality of variances was tested by means of a Levene's test. An independent-samples t-test was used on all continuous variables whenever normality was demonstrated. Significance level was set at a $p < 0.05$. The 95% confidence interval (CI) for the difference in the mean was provided when

TABLE 1 | Median and the minimum-to-maximum range of the most important characteristics of the participating broiler farms (Belgium $n = 15$, the Netherlands $n = 13$).

	Belgium	Reference Belgium	the Netherlands	Reference the Netherlands
Houses	3 [1–4]	NA	3 [1–10]	NA
Total broilers/farm	85,000 [50,000–180,000]	74,648[a] (Flanders)	77,700 [23,400–490,000]	83,143[c]
Age of depopulation	41 [38–45]	42.4[a] (Flanders)	41 [38–45]	41 [36–48][d]
Mortality week 1 (%)	1.0 [0.3–2.9]	NA	1.0 [0.3–2.1]	NA
Mortality total (%)	2.9 [1.4–7.1]	3.3[a] (Flanders)	3.0 [1.2–5.4]	3.5 [2.5–4.5][c,d]
FCR total	1.6 [1.5–2.0]	1.61 [1.54–1.65][a,b]	1.6 [1.5–1.7]	1.60 [1.33–1.65][d]

Data are from seven production rounds (± 1 year) preceding the farm visit. Median reference values for both countries were added.
FCR, feed conversion ratio.
[a]Department of Agriculture and Fisheries in Flanders (23); [b]Pluimveeloket (24); [c]Ago and food portal (25); [d]Blanken et al. (26).

TABLE 2 | Scores of the Biocheck.UGent™ questionnaire for broilers in the participating farms in Belgium ($n = 15$) and the Netherlands ($n = 13$).

		Median score	Min–max score
Belgium	External biosecurity	61	51–75
	Internal biosecurity	54	41–74
the Netherlands	External biosecurity	71	60–79
	Internal biosecurity	66	51–75

The questionnaire was filled in during the farm visit, jointly by the external researcher and the farmer.

significant differences were found. Results were rounded to whole numbers.

RESULTS

Broiler Production

Farm Characteristics, Management, and Technical Performance

The main farm characteristics from the participating broiler farms are presented in **Table 1**. Most farms in Belgium had three ($n = 6$) to a maximum of four houses. In the Netherlands, most farms had two houses ($n = 5$), except for one farm with 10 houses. The total number of broilers per farm was higher in the Netherlands, with almost 117,000 broilers on average (median: 77,700) compared to just over 90,000 on average (median: 85,000) in Belgian farms. None of the production parameters differed significantly between both countries.

Biosecurity

Scores for biosecurity are represented in **Table 2**. Scores were on average significantly lower in the Belgian farms in comparison to those in the Dutch farms, for both internal and external biosecurity. From the different subcategories of external biosecurity, the best scoring subcategory in both Belgium and the Netherlands was infrastructure and biological vectors with, respectively, a median score of 78 and 93. This includes proper rodent control and prevention of direct contact between production animals and wild birds. One of the subcategories of the poultry questionnaire scoring low in both countries was feed and water supply, with 44 and 48 as median scores on Belgian and Dutch farms, respectively. All participating farmers yearly submitted water samples for quality analyses. However, 50% of the Dutch farmers took samples at the source, and the other half took samples both at the source and at the end of the line, with the latter being the ideal biosecurity measure. In Belgium, most farmers took only samples at the end of the waterline.

Concerning internal biosecurity, house-specific and recognizable materials and farm clothing (subcategory materials and measures between compartments) were largely absent on farms in both countries. In four of the participating Belgian farms, there was an age difference between the flocks in different houses on the farm, with a maximum of 3 days, whereas broilers on participating Dutch farms were always of the same age across the houses. Detailed results per broiler farm are provided in **Supplementary Table 2**.

AMU

All of the AM applied on the poultry farms were administered via the drinking water. The median TI per production round per farm in Belgium, in the year before the farm visit took place, was 8 (range: 0–47, mean: 10). This equals treatment durations around 4 days on a standard production round of 42 days. On the Dutch farms, TI had a median value of 3 (range: 0–45, mean: 6). There was a marginally significant (p: 0.049) difference between the TI values in both countries, with a lot of variation between the different rounds within one farm and between farms per country (**Figure 1**). The AMU on farm level in each country is presented in the supplementary materials (**Supplementary Figures 1**, **2**).

The majority of AM prescribed in broiler production were extended-spectrum (ES) penicillins (amoxicillin), with 32 and 40% of total registrations, respectively, for participating farms from Belgium and the Netherlands (**Figure 2**). In Belgian farms, just over 30% of AMU constituted a combination of lincomycin and spectinomycin, which was used on all farms. In the Dutch participating farms, 25% of total prescriptions constituted a combination of trimethoprim and a sulfonamide. However, this percentage is the result of the frequent use of the combination of trimethoprim and a sulfonamide on three Dutch farms.

(Fluoro)quinolones were used in $< 1\%$ of the prescriptions in Belgium. However, in the Dutch farms, this accounted for 15% of the total use. Colistin (antibiotic class of the polymyxins) was used on two Dutch farms, accounting for 3% of all prescriptions on the farms.

Pig Production

Farm Characteristics, Management, and Technical Performance

The main production parameters from the participating pig farms are presented in **Table 3**. The average capacity on the

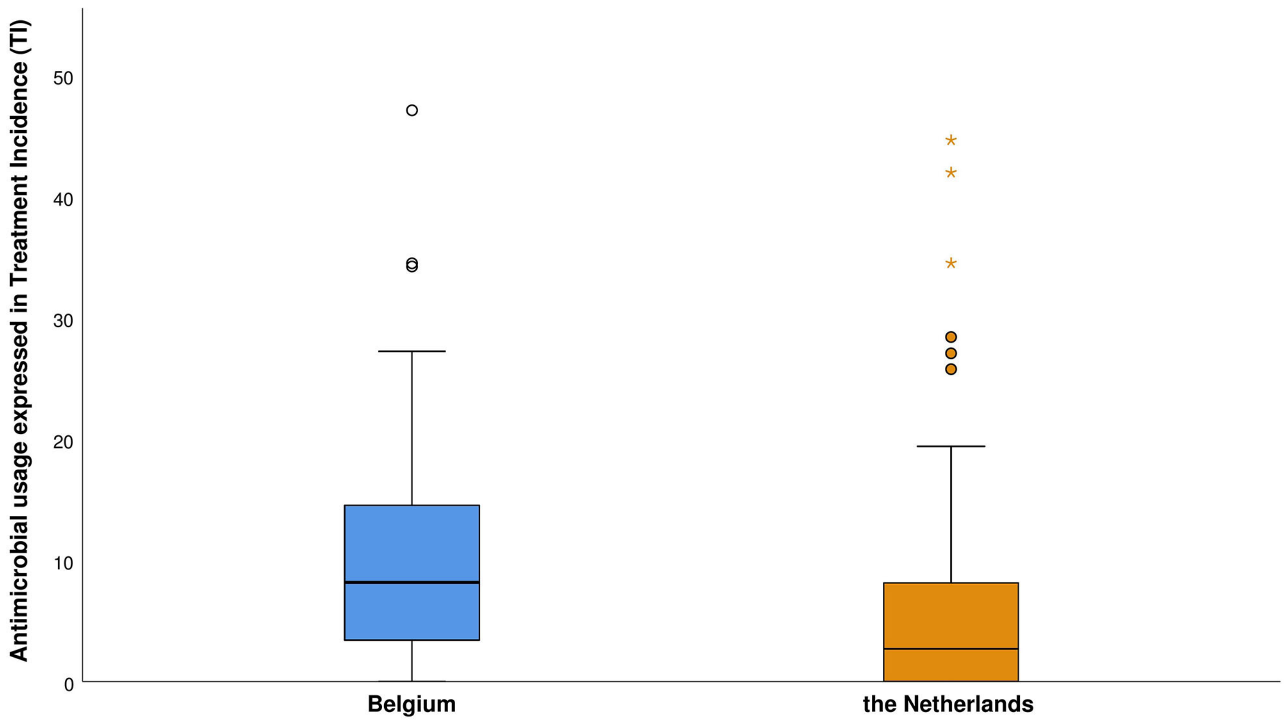


FIGURE 1 | The antimicrobial use per production round of the participating broiler farms per country, based on seven rounds (± 1 year) preceding the farm visit. Antimicrobial use is expressed in treatment incidence (TI) on 100 days, i.e., the number of days an animal was treated with antimicrobials out of 100 days.

Belgian farms was lower than on the Dutch participating farms for the different animal groups. Production in Belgium was organized in a 3- or 4-week batch farrowing system. In participating farms from the Netherlands, 1-week production systems were seen on the majority of farms ($n = 10$).

The weaning age on farms from Belgium was significantly lower than on farms from the Netherlands (−3 days, 95% CI: [−5; −1]). Pre-weaning mortality was slightly higher on average (not significant) on Belgian farms, and the number of weaned piglets per sow per year was similar in farms from both countries.

Biosecurity

The participating Dutch farms scored on average higher for external and internal biosecurity in comparison with the Belgian farms (**Table 4**). Detailed information per farm is provided in **Supplementary Table 3**.

The subcategory with the lowest scores on average for both countries was feed, water, and equipment supply (median scores of 27 and 53 for Belgian and Dutch farms, respectively). The best scoring subcategory in Belgium was purchase of pigs and semen (median score of 88), as more than half of the farms did not purchase any animals. The best scoring subcategory in the Dutch farms was vermin and bird control (median score of 100); all Dutch farms stated to have little to no problems with vermin and control programs were established on all farms. Above that, no companion animals were allowed into the stables.

Concerning internal biosecurity, the subcategory measures between compartments, working lines, and equipment had a median score of only 32 (64 in the Netherlands) on participating Belgian farms. On farms from both countries, the farrowing and suckling period had low median scores of 36 and 50 in Belgium and the Netherlands, respectively, as many farmers from both countries transferred piglets between different sows later than 4 days post-farrowing. Also, during castration, only one blade was used, and/or the blades were not disinfected after each piglet.

AMU

Variation was observed between different farms (**Supplementary Figures 3–8**), both within and between animal categories (**Figure 3**) and with respect to antimicrobial compounds used. For both countries, the majority of AMU was within the animal category of the weaners. In Belgium, AMU in the weaners ranged from a TI of 6 to over 80 (median: 45, mean: 46). In the finishers, AMU ranged from 0 to 20 (median: 5, mean: 6). AMU in the farrowing unit (sows + suckling piglets) was the lowest, ranging from 0 to 5 (median: 2, mean: 2). In the Dutch farms, overall AMU was lower and showed less variation in comparison to the Belgian participating farms. The AMU within the weaners ranged from 2 to 38 (median: 14, mean: 16) in the Dutch farms. The finishers showed the lowest average use with 0 to 3 (median: 1, mean: 1). Sows and their piglets had a TI of 0 to 6 (median: 2, mean: 2). There was a significant difference in TI of 30 within the weaners of each country [95% CI: (15; 45)]

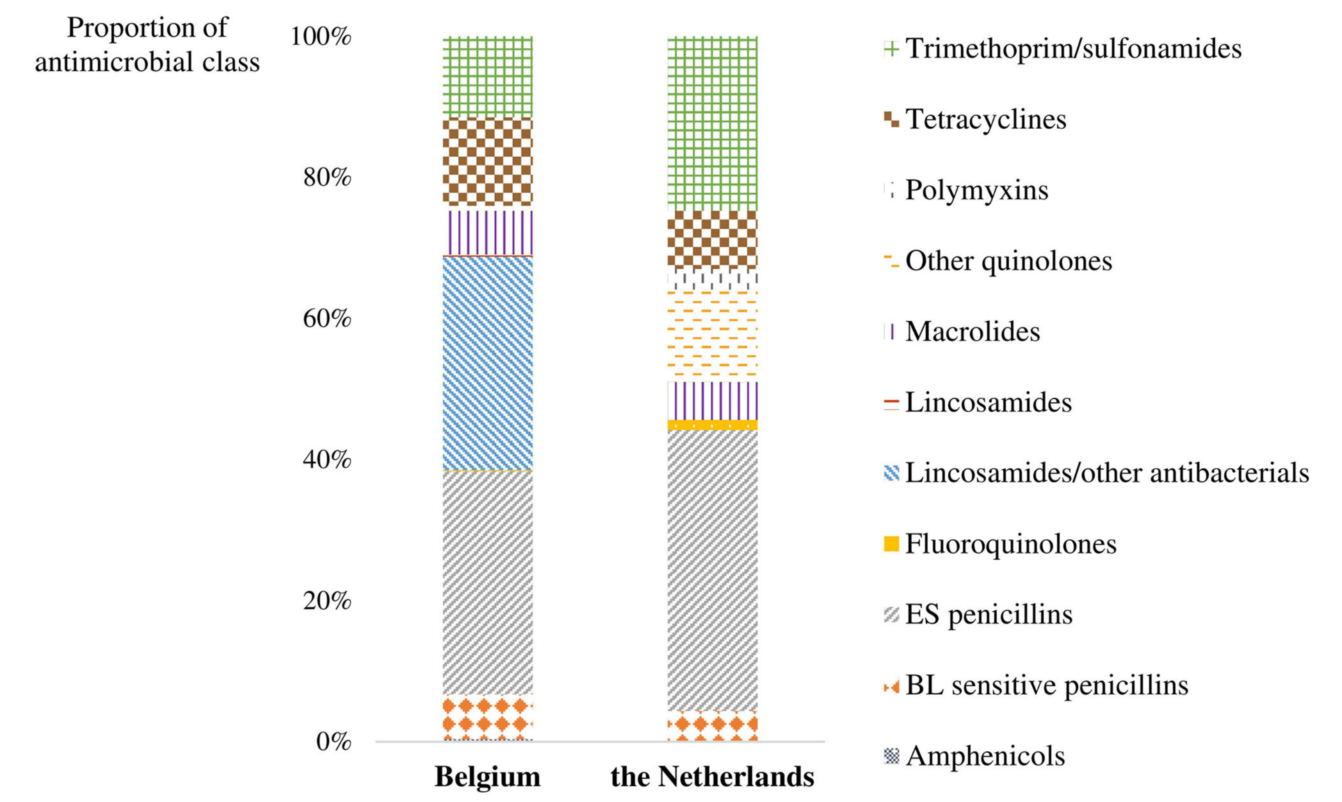


FIGURE 2 | The proportion of each antimicrobial class prescribed on participating farms in Belgium and the Netherlands for broilers in the seven rounds preceding the farm visit. BL sensitive penicillins, β-lactamase sensitive penicillins; ES penicillins, extended-spectrum penicillins.

and a significant difference of 5 within the finishers of each country [95% CI: (1; 8)], where Belgian farms on average had a higher use.

Figure 4 represents the proportion of the different antimicrobial compounds prescribed in all participating farms, per country. In Belgium, ES penicillin (amoxicillin and ampicillin) was the largest group of antimicrobial prescriptions in all animal categories, but especially in the weaners, where ES penicillins accounted for more than 50% of all prescriptions. In finishers, tetracyclines accounted for a large proportion of the prescriptions (19%) as well. The antimicrobial classes prescribed differed in the Dutch farms between different animal groups. In the weaners and the sows and suckling piglets, again the ES penicillins were prescribed the most (35 and 23%, respectively), whereas in the finishers, more than 42% of all prescriptions consisted of tetracyclines. Fluoro(quinolones) were used on two Belgian farms in the animal group of the sows and suckling piglets. One of those farms was also solely responsible for the proportion of third-generation cephalosporins in the Belgian weaners (1%). Polymyxins (colistin) were used in both countries in all animal categories, although the proportion was clearly larger in the Belgian compared to Dutch farms. The variety in antimicrobial classes prescribed was higher in the Belgian participating farms (15 vs. 9 classes in the Netherland).

DISCUSSION

This study has provided an inventory and comparison of poultry and pig farms with high AMU in Belgium and the Netherlands with regard to farm-specific performance, management, biosecurity, and AMU in order to identify opportunities for improvements. Overall, Dutch farms scored better on biosecurity, but internal biosecurity needs more attention in both countries. The Dutch farms had a lower AMU in broiler farms in comparison to Belgian farms; however, a higher amount of critically important AM for use in human medicine was used. In pig production, the AMU was significantly higher within the weaners and finishers of the Belgian farms.

Production parameters from the participating farms were similar in both Belgium and the Netherlands, except for weaning age in pig production. As 3- to 4-week batch farrowing systems occurred more frequently in the Belgian farms, the average weaning age was expected to be lower in comparison to the Dutch participating farms, where most farms worked with a 1-week production system. However, the higher weaning age in Dutch farms and a significantly lower AMU within the weaners are supporting previous findings that weaning at an earlier age may have a negative effect on AMU (15, 29).

TABLE 3 | Median and the minimum-to-maximum range of the most important production parameters of the participating pig farms (Belgium $n = 14$, the Netherlands $n = 15$).

	Belgium	Reference Belgium	the Netherlands	Reference the Netherlands
Capacity sows	326 [95–1,494]	233[a]	480 [315–1,600]	463[b]
Capacity weaners	1,238 [200–6,000]	NA	1,824 [800–8,000]	NA
Capacity finishers	2,143 [136–4,342]	1,465[a]	2,633 [300–14,350]	1,349[b]
Weaning age (days)	22.7 [19.3–30.8]	23.2[a]	26.7 [22.9–31.3]	23.4[d]
Mortality sucklers (%)	14.4 [2.4–24.7]	17[a]	13.0 [10.5–20.6]	14.2[d]
Weaned piglets/sow/year	30.9 [19.4–38.9]	25.6[a]	30.7 [26.7–33.5]	29.3[c]

Data are from 1 year preceding the farm visit. Median reference values for both countries were added.
Capacity, maximum amount of animals that can be housed on the farm.
[a]Department of Agriculture and Fisheries in Flanders (23); [b]CBS (27); [c]Ago and food portal (25); [d]Agrovision (28).

TABLE 4 | Scores of the Biocheck.UGent™ questionnaire for pigs in the participating farms from Belgium ($n = 14$) and the Netherlands ($n = 15$).

		Median score	Min–max score
Belgium	External biosecurity	59	47–74
	Internal biosecurity	46	24–72
the Netherlands	External biosecurity	74	61–84
	Internal biosecurity	73	45–92

The questionnaire was filled in during the farm visit, jointly by the external researcher and the farmer.

With regard to biosecurity, the low scores for the subcategory feed and water supply for both countries and animal species were remarkable. These low scores were mainly linked to questions with regard to water quality, emphasizing the need for more attention to the importance of good-quality drinking water for animal health. The results from this study also suggest that there is more room for improvement in the measures linked to internal biosecurity compared to external biosecurity measures. Both findings are in line with the national biosecurity data as presented on the Biocheck.UGent™ website (30). The lower scores for internal biosecurity could be explained by a bigger awareness of the farmers for the risk of introduction of disease coming from other farms (31) or the belief that it is easier to impose guidelines upon external visitors than to change habits on the farm (18).

In both broiler and pig production, the average biosecurity levels from the Dutch participating farms were higher than those on the Belgian farms. This is in accordance with previous studies, where Belgian farms did not score very high on their biosecurity level (19, 31–34). The establishment of reduction goals for AMU already in 2010 (6 years earlier than government-supported goals in Belgium) could have encouraged the Netherlands to increase biosecurity on animal farms sooner in order to keep their animals safe.

The earlier initiation of reduction goals by the Dutch government also shows its positive effects in AMU reduction numbers in comparison to Belgium on a national level (4). This earlier adaptation of reduction goals in the Netherlands may be linked to high public pressure on AMU reduction in the Netherlands as a result of the discovery at that time that production animals could be reservoirs for antimicrobial resistant bacteria (e.g., methicillin-resistant *Staphylococcus aureus*) (10). The effect of these measures can explain the overall lower AMU in the Dutch participating farms in comparison to the Belgian farms.

The lower level of AMU in the Dutch broiler farms was partially the result of multiple production rounds where no AM were used. This illustrates that it is possible to raise animals without the use of AM. Therefore, there is still a lot of room for reducing AMU in high-consuming farms.

There was a big difference in AMU in pig production between both countries. However, we did not find significant differences in production parameters, except for weaning age, suggesting that room for improvement is possible in Belgium, without risking negative effects on technical performances (16, 17, 35, 36). The overall lower AMU in the Netherlands could also be a consequence of the overall higher biosecurity levels, as biosecurity as an alternative to AMU was already described in previous studies (15, 37, 38).

Due to the selection criteria, it should be noted that the farms included in this study cannot be considered representative for the full pig and broiler production in Belgium and the Netherlands. For this study, only farms within certain geographical borders were selected, and the selected farms had an AMU above the national benchmark value. In addition, the selection on a first come, first served basis may have led to a sample of farmers with a preexisting interest in AMU/AMR reduction. Moreover, as 30 farms per animal species were enrolled in this study, we only included a small part of the entire production in both countries. However, due to this limited number, detailed information per farm could be obtained.

Calculation and expression of AMU in both countries differed, which made recalculations necessary before comparison between countries was possible. As two different formulas were required for AMU calculation in pig production, no TI covering the entire lifetime of a pig could be calculated. Therefore, no total AMU in pig production could be measured and consequently compared to broiler production. These differences highlight the need for European harmonization in calculating AMU if a valid comparison between countries is aimed for.

The differences in policy regarding AMU between Belgium and the Netherlands might explain the different uses of antimicrobial classes between both countries in this study. For instance, the definitions of first- and second-choice compounds differ sometimes per country; e.g., in Belgium, macrolides are always considered second choice in pigs and poultry (39),

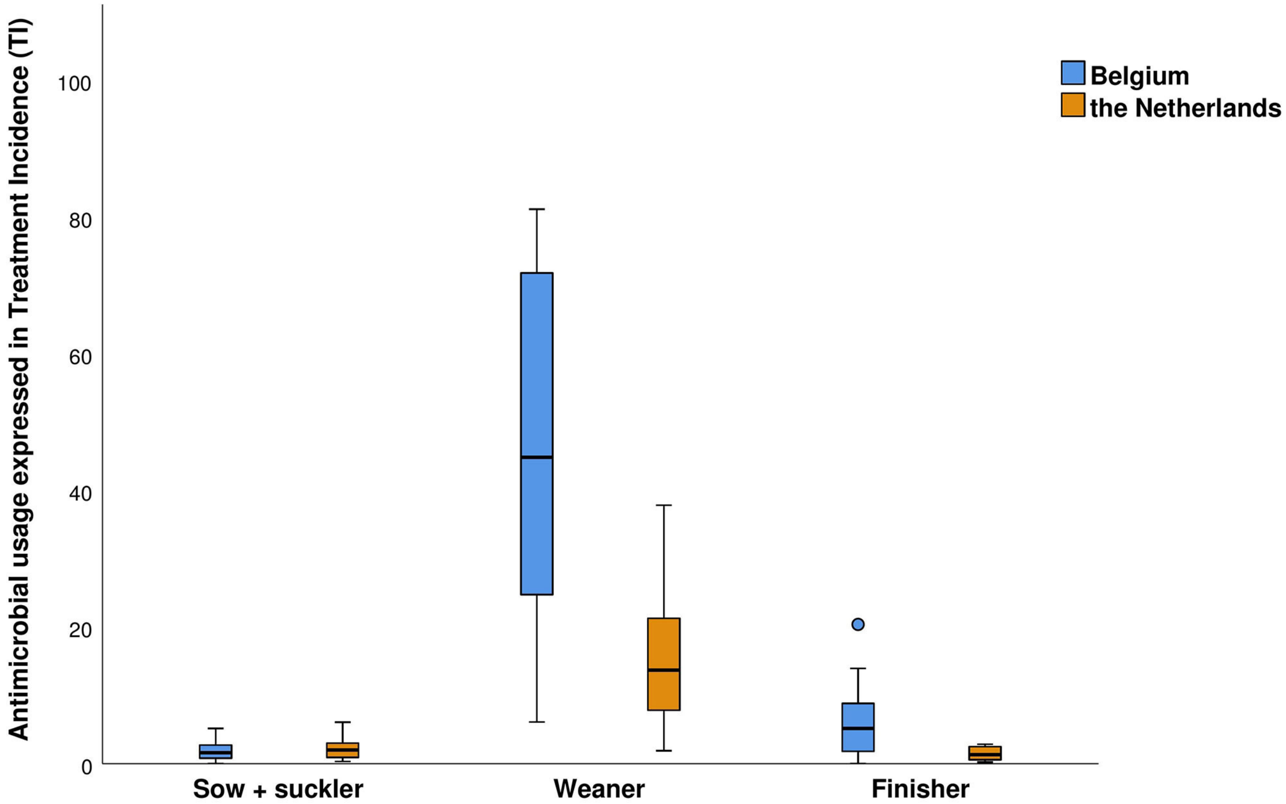


FIGURE 3 | The antimicrobial use on the participating pig farms per country, 1 year preceding the farm visit. Antimicrobial use is expressed in treatment incidence (TI) on 100 days, which is the number of days an animal was treated with antimicrobials out of 100 days.

whereas in the Netherlands, depending on the active compound and animal species, macrolides can be first or second choice (40). The same applies to quinolones, which are second-choice compounds in the Netherlands and third choice in Belgium. These differences raise questions, as the effect of AM on the bacteria is the same, regardless of the country. Especially concerning the critically important AM used in human medicine (41), again, some harmonization would be welcomed here as these different classifications often cause confusion among farmers and veterinarians working in a border region.

In both the Netherlands and Belgium, there is a ban on the preventive use of AM, and the combination product lincomycin with spectinomycin is classified as second choice in broiler production. Broiler farmers have used this product often in the 1st days post-hatch to reduce the risk of bacterial chondronecrosis and osteomyelitis of the femoral head due to *Enterococcus cecorum* later in the production period, which is associated with severe locomotion problems and high therapeutic use of AM with limited success (42). The absence of use of this combination product in the Dutch farms, in comparison to its high use in the Belgian farms, can be explained by the strict repercussions for farmers or veterinarians in the Netherlands due to not following legislation, which is not yet present in Belgium.

No cephalosporins or (fluoro)quinolones, belonging to the critically important AM for use in human medicine, were applied in pig production in the Netherlands in the year preceding the farm visit. This shows that it is possible to rear animals without using these AM.

CONCLUSION

In this paper, we used a standardized methodology for collection and analysis of the data in two countries and animal species, making it possible to compare participating farms with respect to farm characteristics, biosecurity, and AMU.

Important differences in AMU between both countries were found. The higher weaning age in Dutch pig production, associated with a lower AMU, could indicate the benefits of higher weaning age on AMU, especially as most AM were used within the weaners. The use of critically important AM for human medicine in livestock production should be further investigated to limit this use as much as possible.

Reduction targets for AMU on a national level can drive the reduction of AMU on farm level supported by many different management, housing, and feeding measures, among which improved biosecurity is certainly an important component.

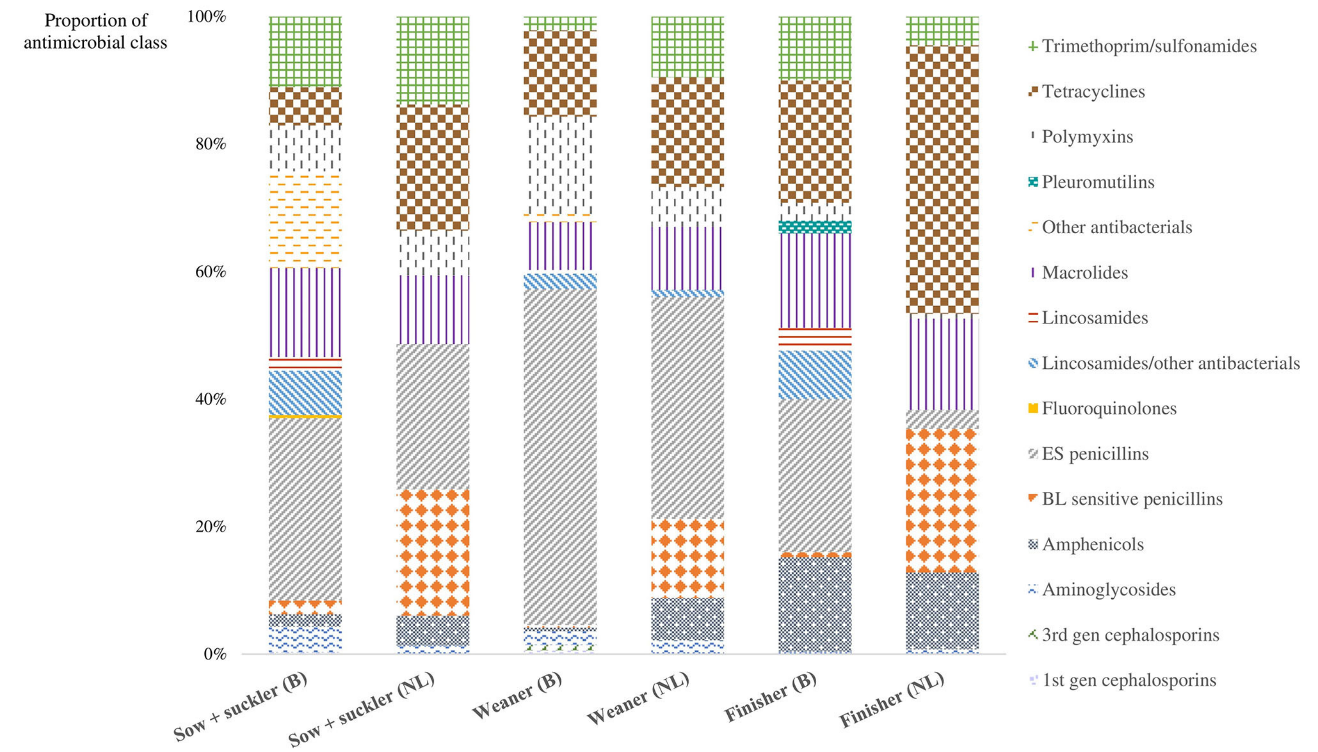


FIGURE 4 | The proportion of each prescribed antimicrobial class in the Belgian and the Dutch farms for the different animal categories in pig production in the year preceding the farm visit. BL sensitive penicillins, β-lactamase sensitive penicillins; ES penicillins, extended-spectrum penicillins.

Further investigation into the specific preventive measures that could offer the biggest benefits for AMU reduction is needed. To improve sustainability and compliance of these measures, change management techniques may prove useful (43). The farms in this study will be followed up for 1 year, where improvement in biosecurity will be the main target in combination with the coaching of the farmers toward increased animal health.

DATA AVAILABILITY STATEMENT

The datasets presented in this article are not readily available because the project management needs to give it's approval whether databases can be shared. Requests to access the datasets should be directed to i41health@amphia.nl.

ETHICS STATEMENT

Before enrolling, all participating farmers were informed on the aim and methodology of the study. All farmers signed an informed consent form for the collection, exchange and publication of data. The Animal Welfare Body from Utrecht University was consulted, and concluded that the study was exempt for an ethical evaluation, as the project did not include experimental procedures with animals according to EC/2010/63.

AUTHOR CONTRIBUTIONS

NC, MR, TT, MP, AH, MH, FV, NS, JS, and JD contributed to conception and design of the study. NC, MR, and AH (afterwards replaced by FJ) performed the farm visits and collected all data. NC, MR, and FJ organized the database. NC performed the statistical analysis and the writing of the manuscript. NC, MR, TT, MP, FV, NS, JS, and JD contributed to manuscript revision, read, and adjustments. All authors approved the submitted version.

FUNDING

Data from this manuscript were collected within the context of the i-4-1-Health project, financed by the Interreg V program Flanders-the Netherlands. Financial support was provided by the European Regional Development Fund (ERDF). Additional financial support was received from the Dutch Ministry of Health, Welfare and Sport, the Dutch Ministry of Economic Affairs, the Province of Noord-Brabant, the Belgian Department of Agriculture and Fisheries, the Province of Antwerp and the Province of East-Flanders. More information can be found on https://www.grensregio.eu/en.

ACKNOWLEDGMENTS

The authors would like to thank all participating farmers and their herd veterinarians. Furthermore, we would like to show our appreciation for the help of PJ in determining the AMU formulas.

Partial results from this study (only pig production) were orally presented at the European Symposium of Porcine Health Management (ESPHM) in May 2019, Utrecht, the Netherlands. The abstract from this presentation was published in the ESPHM abstract book.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fvets.2020.558455/full#supplementary-material

REFERENCES

1. Roope LS, Smith RD, Pouwels KB, Buchanan J, Abel L, Eibich P, et al. The challenge of antimicrobial resistance: what economics can contribute. *Science.* (2019) 364:eaau4679. doi: 10.1126/science.aau4679
2. Roca I, Akova M, Baquero F, Carlet J, Cavaleri M, Coenen S, et al. The global threat of antimicrobial resistance: science for intervention. *New Microbes New Infect.* (2015) 6:22–9. doi: 10.1016/j.nmni.2015.02.007
3. World Health Organisation. *Global Action Plan on Antimicrobial Resistance.* (2015). Available online at: https://www.who.int/antimicrobial-resistance/global-action-plan/en/ (accessed April 30, 2020).
4. European Medicines Agency. *Sales of Veterinary Antimicrobial Agents in 31 European Countries in 2017 (Ninth ESVAC Report).* (2019). Available online at: https://www.ema.europa.eu/en/veterinary-regulatory/overview/antimicrobial-resistance/european-surveillance-veterinary-antimicrobial-consumption-esvac (accessed April 23, 2020).
5. Joosten P, Sarrazin S, Van Gompel L, Luiken RE, Mevius DJ, Wagenaar JA, et al. Quantitative and qualitative analysis of antimicrobial usage at farm and flock level on 181 broiler farms in nine European countries. *J Antimicrob Chemother.* (2019) 74:798–806. doi: 10.1093/jac/dky498
6. Sarrazin S, Joosten P, Van Gompel L, Luiken RE, Mevius DJ, Wagenaar JA, et al. Quantitative and qualitative analysis of antimicrobial usage patterns in 180 selected farrow-to-finish pig farms from nine European countries based on single batch and purchase data. *J Antimicrob Chemother.* (2019) 74:807–16. doi: 10.1093/jac/dky503
7. Toutain PL, Ferran A, Bousquet-Mélou A. Species differences in pharmacokinetics and pharmacodynamics. In: Cunningham F, Elliott J, Lees P, editors. *Comparative and Veterinary Pharmacology. Handbook of Experimental Pharmacology*, Berlin; Heidelberg: Springer (2010). p. 19–48. doi: 10.1007/978-3-642-10324-7_2
8. Landoni MF, Albarellos G. The use of antimicrobial agents in broiler chickens. *Vet J.* (2015) 205:21–7. doi: 10.1016/j.tvjl.2015.04.016
9. Anonymous. *Deskundigenberaad RIVM en Reductie Antibioticumgebruik.* Letter to the Parliament. VDC 10 117 (2010).
10. Speksnijder DC, Mevius DJ, Bruschke CJ, Wagenaar JA. Reduction of veterinary antimicrobial use in the Netherlands. The Dutch success model. *Zoo Public Health.* (2015) 62:79–87. doi: 10.1111/zph.12167
11. *Belgian Veterinary Surveillance of Antimicrobial Consumption (BelVetSAC) - National Consumption Report 2018.* (2019). Available online at: https://belvetsac.ugent.be/ (accessed March 16, 2020).
12. Veldman K, Mevius D, Wit B, Van Pelt W, Franz E, Heederik DJ. *MARAN 2019: Consumption of Antimicrobial Agents and Antimicrobial Resistance Among Medically Important Bacteria in the Netherlands.* (2019). Available online at: https://www.wur.nl/upload_mm/a/7/9/89640bbc-53a2-40f0-ba4a-a9a34a7bf416_Nethmap%20Maran%202019.pdf (accessed March 16, 2020).
13. Cargnel M, Catry B. *Antimicrobial Resistance in Commensal Escherichia coli from Livestock in Belgium.* (2018). Available online at: https://www.amcra.be/swfiles/files/Rapport%20AMR%202011-2017_180601_12.07.2018_finaal_223.pdf (accessed March 17, 2020).
14. AMCRA. *Activiteiten en Realisaties Met Betrekking tot de Reductie van Antibioticagebruik en -Resistentie bij Dieren in België in 2018.* (2019). Available online at: https://www.amcra.be/swfiles/files/Publiek%20rapport%2019_06_2019_versie%20finaal_NL_303.pdf (accessed March 17, 2020).
15. Postma M, Backhans A, Collineau L, Loesken S, Sjölund M, Belloc C, et al. Evaluation of the relationship between the biosecurity status, production parameters, herd characteristics and antimicrobial usage in farrow-to-finish pig production in four EU countries. *Porc Heal Manag.* (2016) 2:9. doi: 10.1186/s40813-016-0028-z
16. Rojo-Gimeno C, Postma M, Dewulf J, Hogeveen H, Lauwers L, Wauters E. Farm-economic analysis of reducing antimicrobial use whilst adopting improved management strategies on farrow-to-finish pig farms. *Prev Vet Med.* (2016) 129:74–87. doi: 10.1016/j.prevetmed.2016.05.001
17. Collineau L, Rojo-Gimeno C, Léger A, Backhans A, Loesken S, Okholm Nielsen E, et al. Herd-specific interventions to reduce antimicrobial usage in pig production without jeopardising technical and economic performance. *Prev Vet Med.* (2017) 144:167–78. doi: 10.1016/j.prevetmed.2017.05.023
18. Laanen M, Beek J, Ribbens S, Vangroenweghe F, Maes D, Dewulf J. Bioveiligheid op varkensbedrijven: ontwikkeling van een online scoresysteem en de resultaten van de eerste 99 deelnemende bedrijven. *Vlaams Diergeneeskd Tijdschr.* (2010) 79:302–6. Available online at: https://lib.ugent.be/catalog/pug01:1055534
19. Gelaude P, Schlepers M, Verlinden M, Laanen M, Dewulf J. Biocheck.UGent: a quantitative tool to measure biosecurity at broiler farms and the relationship with technical performances and antimicrobial use. *Poult Sci.* (2014) 93:2740–51. doi: 10.3382/ps.2014-04002
20. Persoons D, Dewulf J, Smet A, Herman L, Heyndrickx M, Martel A, et al. Antimicrobial use in Belgian broiler production. *Prev Vet Med.* (2012) 105:320–5. doi: 10.1016/j.prevetmed.2012.02.020
21. European Medicines Agency. *Revised ESVAC Reflection Paper on Collecting Data on Consumption of Antimicrobial Agents per Animal Species, on Technical Units of Measurement and Indicators for Reporting Consumption Of Antimicrobial Agents in Animals.* (2013). Available online at: https://www.ema.europa.eu/en/veterinary-regulatory/overview/antimicrobial-resistance/european-surveillance-veterinary-antimicrobial-consumption-esvac (accessed November 12, 2019).
22. WHO Collaborating Centre for Drug Statistics Methodology (WHOCC). *WHOCC - ATCvet Index.* (2020). Available online at: https://www.whocc.no/atcvet/atcvet_index/ (accessed May 1, 2020).
23. Department of Agriculture and Fisheries in Flanders. *Landbouwcijfers.* (2017). Available online at: https://lv.vlaanderen.be/nl/voorlichting-info/publicaties-cijfers/landbouwcijfers# (accessed August 14, 2020).
24. Pluimveeloket. *Voederconversie Vleeskuikens.* (2019). Available online at: https://www.pluimveeloket.be/Voeder/Vraag-VC-vleeskuikens (accessed August 14, 2020).
25. *Agro and Food Portal, Wageningen University.* (2017). Available online at: https://www.agrimatie.nl/Default.aspx (accessed August 14, 2020).
26. Blanken K, de Buisonje F, Evers A, Ouweltjes W, Verkaik J, Vermeij I, et al. *Kwalitatieve Informatie Veehouderij (KWIN) 2017-2018.* Netherlands: Wageningen University (2017). p. 384.
27. Statistics Netherlands (CBS). *Landbouwtelling.* (2014). Available online at: https://www.cbs.nl/nl-nl (accessed August 14, 2020).
28. *Agrovision Mean Production Parameters.* (2016). Available online at: https://www.agrovision.com/nl/ (accessed August 14, 2020).
29. Sjölund M, Postma M, Collineau L, Lösken S, Backhans A, Belloc C, et al. Quantitative and qualitative antimicrobial usage patterns in farrow-to-finish pig herds in Belgium, France, Germany and Sweden. *Prev Vet Med.* (2016) 130:41–50. doi: 10.1016/j.prevetmed.2016.06.003
30. Biocheck.UGent. *Worldwide Page.* (2020). Available online at: https://biocheck.ugent.be/en (accessed April 27, 2020).
31. Postma M, Backhans A, Collineau L, Loesken S, Sjölund M, Belloc C, et al. The biosecurity status and its associations with production and management characteristics in farrow-to-finish pig herds. *Animal.* (2016) 10:478–89. doi: 10.1017/S1751731115002487

32. Filippitzi ME, Brinch Kruse A, Postma M, Sarrazin S, Maes D, Alban L, et al. Review of transmission routes of 24 infectious diseases preventable by biosecurity measures and comparison of the implementation of these measures in pig herds in six European countries. *Transbound Emerg Dis*. (2018) 65:381–98. doi: 10.1111/tbed.12758
33. Ssematimba A, Hagenaars TJ, de Wit JJ, Ruiterkamp F, Fabri TH, Stegeman JA, et al. Avian influenza transmission risks: analysis of biosecurity measures and contact structure in Dutch poultry farming. *Prev Vet Med.* (2013) 109:106–15. doi: 10.1016/j.prevetmed.2012.09.001
34. Van Limbergen T, Dewulf J, Klinkenberg M, Ducatelle R, Gelaude P, Méndez J, et al. Scoring biosecurity in European conventional broiler production. *Poult Sci.* (2018) 97:74–83. doi: 10.3382/ps/pex296
35. Postma M, Vanderhaeghen W, Sarrazin S, Maes D, Dewulf J. Reducing antimicrobial usage in pig production without jeopardizing production parameters. *Zoonoses Public Health.* (2017) 64:63–74. doi: 10.1111/zph.12283
36. Rodrigues da Costa M, Gasa J, Calderón Díaz JA, Postma M, Dewulf J, Mccutcheon G, et al. Using the Biocheck. UGent scoring tool in Irish farrow-to-finish pig farms: assessing biosecurity and its relation to productive performance. *Porc Heal Manag.* (2019) 5:4 doi: 10.1186/s40813-018-0113-6
37. Laanen M, Persoons D, Ribbens S, de Jong E, Callens B, Strubbe M, et al. Relationship between biosecurity and production/antimicrobial treatment characteristics in pig herds. *Vet J.* (2013) 198:508–12. doi: 10.1016/j.tvjl.2013.08.029
38. Raasch S, Postma M, Dewulf J, Stärk KD, grosse Beilage E. Association between antimicrobial usage, biosecurity measures as well as farm performance in German farrow-to-finish farms. *Porc Heal Manag.* (2018) 4:30. doi: 10.1186/s40813-018-0106-5
39. AMCRA. *AMCRA Formularium*. (2018) Available online at: https://formularium.amcra.be/classification.php (accessed April 23, 2020).
40. Werkgroep Veterinair Antibiotica Beleid (WVAB). *WVAB-Richtlijn Classificatie van Veterinaire Antimicrobiële Middelen*. (2015). Available online at: https://www.wvab.nl/richtlijnen/ (accessed March 15, 2020).
41. WHO. *Highest Priority Critically Important Antimicrobials*. (2020). Available online at: https://www.who.int/foodsafety/cia/en/ (accessed June 10, 2020).
42. Koninklijke Nederlandse Maatschappij voor Diergeneeskunde (KNMvD). *Richtlijn Veterinair Handelen bij Vleeskuikens Rondom de Opzet en in de Eerste Levensweek op Het Vleeskuikenbedrijf*. (2017). Available online at: https://www.knmvd.nl/ (accessed March 9,2020).
43. Shepherd ML, Harris ML, Chung H, Himes EM. Using the awareness, desire, knowledge, ability, reinforcement model to build a shared governance culture. *J Nurs Educ Pract.* (2014) 4:6. doi: 10.5430/jnep.v4n6p90
44. The Netherlands Veterinary Medicines Institute (SDa). *Usage of Antibiotics in Agricultural Livestock in the Netherlands in 2018*. (2019). Available online at: https://cdn.i-pulse.nl/autoriteitdiergeneesmiddelen/userfiles/Publications/2018-def-rapport1.pdf (accessed August 14, 2020).
45. AMCRA. *Antibioticagebruik op Bedrijfsniveau: Resultaten SANITEL-MED en AB Register*. (2019). Available online at: https://www.amcra.be/swfiles/files/3_Wannes%20Vanderhaeghen%20-%20AMCRA_NL_289.pdf (accessed August 14, 2020).

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Veterinary Science

ORIGINAL RESEARCH
published: 13 November 2020
doi: 10.3389/fvets.2020.00545

Quantifying Antimicrobial Exposure in Dogs From a Longitudinal Study

María Méndez[1] *and Miguel A. Moreno*[1,2]*

[1] *Department of Animal Health, Veterinary Faculty, Complutense University, Madrid, Spain,* [2] *VISAVET Center, Complutense University, Madrid, Spain*

Bacterial resistance to antimicrobials (AMR) is a growing public health threat, and exposure to antimicrobials (AMs) is, on the whole, a major risk factor for the occurrence of AMR. During the past decade, a limited number of studies about AM exposure in dogs have been published, showing a noticeable diversity regarding numerators (AMU), denominators (population at risk), and indicators. The aim of this study is to show that metrics based on the most easily recorded data about treatments and a follow-up design are a promising method for a preliminary assessment of AM exposure in companion animals when more detailed data are not available. To quantify AM exposure, two simple indicators were used: the number of treatments (Ts) per 100 dogs and the number of treatments per 10 dog-years. Overall figures of AM exposure were 194 Ts/100_dogs (480 treatments and 248 dogs) and 18.4 Ts/10_dog-years (480 treatments and 95,171 dog-days), respectively. According to the administration route, AM exposure figures were 126 Ts/100 dogs (305 treatments and 242 dogs) and 12.1 Ts/10_dog-years (305 treatments and 92,059 dog-days) for systemic use and 66 Ts/100 dogs (160 treatments and 242 dogs) and 6.3 Ts/10_dog-years (160 treatments in 92,059 dog-days) for topical use. Since there is no current agreement regarding an indicator for quantifying AM exposure in dogs, in addition to other measures, the simplest indicators based on the most frequently available information should also be reported as a preliminary compromise for permitting a comparative analysis of the different scenarios.

Keywords: pets, antibiotics, exposure, metrics, follow-up, Spain

OPEN ACCESS

Edited by:
Ioannis Magouras,
City University of Hong Kong,
Hong Kong

Reviewed by:
Roswitha Merle,
Freie Universität Berlin, Germany
Philip Joosten,
Ghent University, Belgium

Correspondence:
Miguel A. Moreno
mamoreno@ucm.es

Specialty section:
This article was submitted to Veterinary Epidemiology and Economics, a section of the journal Frontiers in Veterinary Science

Received: *02 April 2020*
Accepted: *13 July 2020*
Published: *13 November 2020*

Citation:
Méndez M and Moreno MA (2020) Quantifying Antimicrobial Exposure in Dogs From a Longitudinal Study. Front. Vet. Sci. 7:545. doi: 10.3389/fvets.2020.00545

INTRODUCTION

Bacterial resistance to antimicrobials (AMR) is a growing public health threat, and exposure to antimicrobials (AMs) is, on the whole, a major risk factor for the occurrence of AMR; but demonstrating their causal link is challenging (1).

Seminal international conferences in the twentieth century [such as the 1998 Copenhagen recommendations (2)] highlighted the need for an accurate measurement of antimicrobial use (AMU) in humans and animals due to the role of AMU as a key driver of AMR. Shortly afterwards, several influential papers were published in the veterinary field (3–5) stressing both approaches and weaknesses when dealing with this topic. More recently, Collineau et al. (6) summarized this subject focusing on the expected use of AMU metrics.

In the veterinary field, AMU is the most common approach for measuring exposure to AMs, and consequently, numerous AMU metrics have been proposed (7). Most of them are based on the amount of AMs (sold, prescribed, or administered), delivered as raw data (weight of AMs) or standardized for correcting differences in posology (dosage and treatment duration) among both AMs and animal species [for instance, defined daily dose for animals [DDDA] and defined course dose for animals [DCDA], among others].

Curiously, the number of DDDAs indicates the number of days of AM usage, and the number of DCDAs expresses the number of individuals treated; nevertheless, metrics directly computing the days of treatment or treated animals are seldom reported.

These diverse AMU metrics are employed as the numerator for elaborating indicators using a measurement of the population at risk as the denominator. A summary of numerators, denominators, and indicators has been produced (7).

Regarding the design of the studies aimed to assess AMU, the ecological approach is used for international organizations delivering supranational or country-level data [like those reported by the European Medicines Agency in the ESVAC reports (8)]. In this case, different data sources for numerators and denominators are used.

The research studies designed for gathering data for specific animal species are usually retrospective longitudinal studies since data comprise AMU for a study period belonging to an animal population. For food-producing animals, where a closed population model can be used, farms are the natural study units providing records of both AM treatments and a number of animals at risk (including movements). Nevertheless, in the case of companion animals, we do not have groups of animals (except breeding kennels, boarding kennels, and animal shelters), and veterinary practices are the best data source, although the population at risk is not as accurately defined.

During the past decade, a limited number of studies about AM exposure in dogs have been published, showing a noticeable diversity regarding numerators (AMU), denominators (population at risk), and indicators (**Table 1**).

The aim of this study is to show that metrics based on the most easily recorded data are a promising method for a preliminary assessment of AM exposure in companion animals.

MATERIALS AND METHODS

Sampling Design

Two web-based calls for veterinary practitioners attending dogs in the Autonomous Community of Madrid were launched with the collaboration of the Association of Companion Animals Veterinarians of Madrid (AMVAC) during November and December 2017.

In addition, veterinary practices previously collaborating in a prior study (18) were invited to participate in the study.

In all cases, veterinarians were left blind regarding the main subject of the study (AMU quantification) and were asked by letter if they could provide the full 2016 case history of 10 dogs regularly attending their veterinary practices, as well as the last record of 2015 (a non-illness visit) and the first record of 2017.

Data Collection and Storage

Data were collected and sent by the veterinarians (usually as a file submitted electronically) or collected at the veterinary practice by the first author.

Data were stored in two spreadsheets (Microsoft Excel). The first contained animal data (date of birth, name, sex, breed) and a summary of the visits. Each visit to a veterinary practice was classified as a non-illness visit (healthy animal going for vaccinations, health checks, or other procedures) or an illness visit (sick animals for any condition including postsurgical visits). The total number of visits, both non-illness and illness, were compiled. In addition, illness visits where an AM was used or prescribed were also accumulated. This spreadsheet also contained data regarding the date and health status of the last visit in 2015 and the date and health status of the first visit in 2017.

The second spreadsheet contained data of AMs, including dog, date, commercial name, active substance, administration route, dosage, duration, and treated condition. Administration routes were grouped as systemic (oral and parenteral routes) and topical (administrations on skin, ears, eyes, etc.).

No personal data from owners or veterinary practitioners (except postal code for veterinary practices) were recorded.

Quantification of Antimicrobial Exposure

To quantify AM exposure in dogs, two metrics were used: the number of treatments (Ts) per 100 dogs (d) and the number of treatments per 10 dog-years (d-y).

Treatments were used for both numerators and count both AM administration at the veterinary practice and AM prescriptions for at-home use. Treatments starting at the veterinary practice followed by home administration were considered two events.

We used the same numerator for both indicators, including all the AM treatments recorded, irrespective of the number of treatments per dog and of their duration.

Denominators were dog at risk to be AM-treated and dog-year at risk to be AM-treated (sum of the follow-up periods computed as days and then transformed to years).

For the denominator of the second indicator, and assuming that dogs under an AM treatment remain at risk for another AM treatment, the risk period for each dog was the entire follow-up period.

RESULTS

A retrospective follow-up study was conducted with a convenience sample of 28 veterinary practices. The timeframe of the data set ranged from February 2015 to November 2017.

Study Population

From the 28 veterinary practices participating in the study, case histories from 279 dogs were obtained. Thirty-one of them were removed; 3 were duplicates from the same dog, 12 were case histories where a non-illness visit for entering the study was not provided, 15 were case histories without visits in 2016, and 1 was a case history with a follow-up period shorter than 3 months.

TABLE 1 | Published data of antimicrobial (AM) exposure in dogs.

References and country	Data source	Design/period	Numerator	Denominator (available study size)	Indicator
Radford et al. (9) UK	SAVSNET, clinical data, Sick animals	Three months	Consults with AM	Consults (15,727)	% of consults involving systemic AMs
Mateus et al. (10), UK	Veterinary practices data	January 1, December 31, 2007	A/P[a] of AMs	Dogs (34,928)	% of dogs with A/P of AMs
Escher et al. (11), Italy	Clinical paper forms	Cross-sectional-−2000–2007	AM prescriptions	Clinical forms (688)	Prevalence of prescriptions
Buckland et al. (12), UK	VetCompass, electronic patient records (EPR)	Two years	AM event	Dogs (963,463)	• % of AM events • Overall quantity of AMs used
Singleton et al. (13), UK	SAVSNET, electronic health records (HER)	1 April 2014 /31 March 2016 (2 years)	• Consultations with AM • Dogs with an AM prescription	• HER (918,333) • Dogs (413,870)	• % of consultations where at least one AM agent was prescribed. • % of dogs prescribed with an AM agent
Hardefeldt et al. (14), Australia	Pet insurance files	2013 to 2017 (4 years)	A/P of a systemic AM and of a systemic AM with a high-importance rating	• Dogs (222,069) • Dog-years (813,172)	• Average proportion of animals exposed to AMs (n° per 1000 dogs) • Incidence rate of exposure to AMs (prescription by 10 dog-year)
Hopman et al. (15), the Netherlands	Veterinary practices data	2012, 2013, 2014	AVMP[b] procurement data used for calculation of DDDAs[c]	228,000 dogs (110 clinics)	• No. of DDDA clinic/year. Theoretical number of days per year an animal (dog, cat, or rabbit) was treated with AVMPs in the clinic concerned
Joosten et al. (16), Belgium, Italy, and the Netherlands	Veterinary practitioners	Cross-sectional—January 2015–February 2016	Treatment duration X long-acting factor × 100 animals at risk	No. of days at risk (151 dogs)	Treatment incidence (TI) (No. of DDDca[d]/100 days at risk/animal
Hurd et al. (17), Australia	Electronic patient records	2013–2017	Consultations with AM	Total consultations (3,263,615)	AMs dispensed per 1000 consultations

[a] *Administration/Prescription.*
[b] *Antimicrobial Veterinary Medicinal Products.*
[c] *Defined Daily Doses Animal.*
[d] *Defined Daily Dose for companion animals.*

Finally, 248 dogs were included in the study. One hundred thirty (52.4%) of them were male, and 118 (47.6%) were female.

Breed was recorded for 231 dogs. About 48 different breeds were documented, including crossbreeds. The most recorded breed was crossbred (48 dogs), followed by Yorkshire terrier (20 dogs).

Date of birth was included in 223 case histories and was used for establishing the age (age was calculated by subtracting the reported date of birth from the date of the first appointment). Mean and median age were 5.4 ±3.6 and 4.8 years of age, respectively, ranging from 0.3 to 15.9 years of age (interquartile range 2.3–8.5).

A total of 95,171 days of follow-up were computed from these 248 dogs. The mean and median follow-up times were 384 ±90 and 382 days, respectively, ranging from 121 to 731 days (interquartile range 345–427).

Visits

A total of 2,148 visits from case histories of 248 dogs were included in the study. The mean number of visits per dog was 8.7 ±6.5 (range, 1 to 49 visits per dog); 1,079 (50.3%) of these were non-illness visits, and 1,069 (49.7%) were illness visits.

Seventeen of the 248 dogs have no records of non-illness visits. The mean number of non-illness visits per dog was 4.4 ±3.4 (range, 0–23). Regarding illness visits, 45 dogs had no records. The mean number of illness visits per dog was 4.3 ±5.0 (range, 0–39 visits).

In addition, the number of illness visits when an AM was prescribed or used was recorded as 423 visits from 157 dogs. The mean number of illness visits with AM per dog was 1.7 ±2.2 (range, 0–14).

Antimicrobial Exposure

As explained before, to quantify AM exposure, two simple and easily calculable indicators were used: the number of treatments (Ts) per 100 dogs (d) and the number of treatments per 10 dog-years (d-y).

Overall figures of AM exposure were 194 Ts/100_dogs (95% C.I., 177/100–212/100_dogs) (480 treatments and 248 dogs) and

18.4 Ts/10_d-y (95% C.I., 16.7/10–20/10_d-y) (480 treatments and 95,171 dog-days), respectively.

The administration route was explicit on 385 records, and for an additional 80, it was extracted based on the commercial name of the medical product. Thus, this information was available for 465 treatments corresponding to 151 dogs. According to the administration route, AM exposure figures were 126 Ts/100_dogs (95% C.I., 112/100–141/100_dogs) (305 treatments and 242 dogs) and 12.1 Ts/10_d-y (95% C.I., 10.8/10–13.5/10_d-y (305 treatments and 92,059 dog-days) for systemic and 66 Ts/100_dogs (95% C.I., 56/100–77/100_dogs) (160 treatments and 242 dogs) and 6.3 Ts/10_d-y (95% C.I., 5.4/10–7.4/10_d-y) (160 treatments and 92,059 dog-days) for topical use.

AM exposure figures per administration route and most frequently used active substances are presented in **Table 2**. For producing these figures, data were provided from 464 treatments corresponding to 150 dogs. Figures are lower when both administration route and active substance are included because in two records for one dog, only data about administration route were available.

Among AMs for systemic use, beta-lactams, metronidazole, and fluoroquinolones were the families most recorded, whereas by the topical route, they were aminoglycosides, fluoroquinolones, polymyxins, and phenicols.

TABLE 2 | Antimicrobial exposure from a 1-year follow-up study of 248 dogs (95,171 dog-day) in Madrid, Spain.

Antimicrobials and administration route	ATCvet codes	No. of treatments	No. of treated dogs	Treatments per 100 dogs	Treatments per 10 dog-year
All		480	157	194	18.4
Systemic*:		305	115	126	12.1
· Amoxicillin clavulanate**	QJ01CR02	69	42	29	2.8
· Amoxicillin / ampicillin**	QJ01CA04 QJ01CA01	68	40	28	2.7
· Cefalexin**	QJ01DB01	17	11	7	0.7
· Cefovecin**	QJ01DD91	13	11	5	0.5
· Metronidazole**	QJ01FA99 QJ01XD01	52	34	22	2.1
· Enrofloxacin**	QJ01MA90	14	9	6	0.6
· Marbofloxacin**	QJ01MA93	9	8	4	0.4
· Sulphonamides**	QJ01EW13 QJ01EQ30	15	8	6	0.6
Topical*		160	82	66	6.3
· Neomycin**	QS01AA30 QS01AA03 QS02AA07 QS02AA57 QD06AX04	40	28	17	1.6
· Tobramycin**	QS01AA12	25	19	10	1
· Polymyxin B**	QS02AA11 QS02AA57	22	19	9	0.9
· Marbofloxacin**	QS02AA	22	11	9	0.9
· Florfenicol**	QS02AA	15	8	6	0.6

*Denominators for indicators were 242 dogs and 92,059 dog-day, respectively.
**Denominators for indicators were 241 dogs and 91,249 dog-day, respectively.*

DISCUSSION

Scope

The analysis of the most frequently used AMs in dogs, including administration routes or other related features, has been addressed in several papers (10–13, 18–20), showing that amoxicillin-clavulanate was, by far, the most frequently used by the systemic routes (10–13, 18, 19). For performing these studies, a population of clinical histories recording AM treatments or AM-treated animals is sufficient as the denominator. Although this information is valuable, this approach does not account for a population at risk, precluding the assessment of AM exposure.

Data

Although the data used for constructing the above explained indicators for AM exposure have been showed, some decisions must be detailed.

For computing the numerator, we chose the number of treatments since this information was always recorded. Special cases were sequential treatments (starting at the veterinary practice and followed at home) and simultaneous treatments (use of AM combinations). As explained before, we computed two events for sequential treatments since many times the AM prescribed for administration at home was different from the one used at the veterinary practice. Simultaneous treatments were computed as a single treatment for calculating the overall exposure indicators, although active substances, except amoxicillin plus clavulanic acid, were segregated for presenting the exposure data per active substance (**Table 2**). Long-acting products were computed as one event since the duration of the treatment was not considered for constructing the numerator.

In the case of the denominator counting animal time at risk of AM treatment, it was built by adding the duration of the whole observation time of each enrolled dog. Because treatment duration was not always recorded, it was not subtracted from the denominator. Besides, longer observation times usually belong to healthy dogs attending veterinary services once a year for health checks. Consequently, this denominator probably was overestimated.

Taking together the convenience sampling, the low sampling size, and the above-mentioned circumstances, the extrapolation of our figures to the entire country is not easy to assess. Nevertheless, our feeling is that the veterinary prescription of AMs for dogs is very similar among the Spanish practitioners, irrespective of the geographical area, but we do not know published studies to support this statement.

Data Sources and Metrics for AM Exposure Assessment

In food animals, where animals are raised by groups and information regarding medication is systematically recorded (mandatory for farmers in many countries), the quantification of both AM exposure and population at risk is easier than in the case of companion animals, where these data are scarce or are not recorded at all.

Since pet owners have no obligation to record this information, records of veterinary practices (case histories) are the only putative source for AM data; but many differences exist between companion animal veterinarians regarding mandatory recording of data for prescriptions or data storage procedures (paper or electronic databases). For instance, in Spain, all the prescriptions of AMs must be issued electronically as from January 2019, but only in the case of farm animals. As stated by Joosten et al. (16), "Currently there is no binding European policy that requires countries to report their veterinary AMU for companion animals. Yet, this will become mandatory for all member states of the European Union by 2030 at the latest (21)."

In some countries, like the Netherlands, "AMs for veterinary use are sold to companion animal owners (or farmers) by veterinarians exclusively" (15) and, consequently, "antimicrobial procurement data are supposed to reflect the total amount of AMs used in animals," becoming an additional data source for AMU metrics based on the amount of AMs. The number of units of AM products purchased by owners was also used in the UK (3) for quantifying the kilograms of AMs. Nevertheless, this approach is not applicable in Spain.

Another putative source of data of AMU in dogs is the full dosage in clinical records. Among the studies summarized in **Table 1**, Buckland et al. (12) used the dosage data existing in the VetCompass database for the calculation of the quantity of AMs used. Joosten et al. (16) used data provided by practitioners (the commercial antimicrobial name, the frequency of administration [per day], and the duration of treatment) and data from the Summary of Product Characteristics (SPC) as sources for AMU indicators. Nevertheless, in our experience, the complete data set of a prescription (including dosage and duration) is not always recorded in our country, precluding any approach for calculating the amounts of AMs based on these data. For instance, from the 480 AM treatments recorded in this study, only 56 (11.7%) have the full posology data (dosage and duration). Compliance with SPC data will help to solve this gap of data, but we are not confident that Spanish vets habitually use the SPC data for prescription.

However, almost all case histories of companion animals usually had some information, mostly including the active substance or the medicinal product, that allows us to identify an AM treatment, and these data can be used for AM exposure calculations based on treated animals. Although this procedure does not take into account whether the dosage is correct or not, it has the advantage that real information about the number of treated animals is used. Consequently, metrics using AM treatments or treated animals as the numerator are a good alternative for a preliminary quantification of AM exposure when more detailed information is not available.

The first option (proportion of appointments where an AM has been administered or prescribed) has been applied in some studies attaining figures of 35.5% (9) and 18.8% (13) in UK and 14.5% (17) in Australia, whereas our figure, 19.7% (423/2148), was in between.

The second one (proportion of dogs with a prescription or administration of AMs) has been also reported, but with different study periods. This indicator should be higher when using a follow-up design compared to the cross-sectional one, since the longer the follow-up period, the higher the probability that a dog was AM treated. It is also interesting to note that this indicator has the same interpretation as those based on DCDAs. Figures of 45.1% (10) (1-year period), 25% (16) (1-year period), 28.4% (13) (2-year period), and 18.2% (14) (4-year period) have been provided, whereas our figure was higher (63.3% [157/248 in a 1-year period]). Nevertheless, it is not clear that the mentioned periods can indicate a follow-up of dogs (see the paragraph below).

Study Design

A cross-sectional design was indicated in some studies (11, 16) and probably also used in others (9, 12, 13) since follow-up of dogs is not mentioned. Nevertheless, this approach requires a high sample size if the outcome of interest has low prevalence. Bearing in mind that animals treated with an AM remain at risk to be treated with other AMs if they suffer a new bacterial disease, a longitudinal design computing multiple occurrences of AM treatments is a good approach for the assessment of AM exposure. In addition, if the duration of the follow-up period by dog is recorded, a denominator based on dog-days units (as in the classical incidence rate used by epidemiology) can be computed providing an alternative indicator. Indeed, for open populations and different follow-up periods, the preferred option for the denominator is computing animal-time units. This approach calculating the incidence rate of exposure to AMs was used in Australia by Hardefeldt et al. (14), obtaining a value of 5.8 prescriptions per 10 d-y, whereas our data were also higher (18.4 treatments per 10 d-y).

Metrics Based on DDDAs

For the numerator, the calculation of metrics based on DDDAs requires information regarding amounts of AMs used (obtained from packages or from prescriptions), standard dosage from the SPC, and animal weight (from animal records or standard weight tables). This approach has been used in some studies reporting figures corresponding to the number of DDDAs per year from 2.22 to 1.88 in the Netherlands (18) and 3.3 in Belgium, Italy, and the Netherlands (16). Bearing in mind that DDDAs are the number of days per year a dog was treated with AMs (15), an alternative calculation procedure can be applied from our data. In our study, treatment duration was available for 192 (40%) treatments; nevertheless, data from the SPC could be assigned for up to 415 (86.5%) treatments; 279 of these were systemic treatments totalizing 1,834 days and 136 topical treatments (1,140 days). For long-acting products, treatment duration was established according to the SPC and considering the time for a second administration (14 days for cefovecin-containing products and 2 days for amoxicillin-containing products). Extrapolating these data to all the systemic and topical treatments, respectively, the supposed numbers of DDDAs per year in our study were 8.1 and 5.3, for systemic and topical use, respectively. It is interesting to note that the primary indicator used by Joosten et al. (16) is treatment incidence (TI), "which resembles the percentage of a full year that the animal has been treated with a standard dose of AMs," that is, a metric based on the yearly proportion of days with treatment.

Antimicrobials Used and Administration Route

Although the main objective of our study using population at risk as the denominator was not to specifically assess the most frequently used AMs, our data confirm, like others, that the above-mentioned ranking in dogs is led by amoxicillin clavulanate (14, 16, 17). Nevertheless, the use of different reporting criteria for the administration route (all AMs aggregated or segregated into systemic vs. topical) or AMs (by active substance or grouped by critical importance or choice) also makes it more difficult to compare published data.

Finally, there is no current agreement regarding an indicator for quantifying AM exposure in dogs, precluding the assessment of data from different sources. In addition to other well-established measures in other animal species, the simplest indicators based on the most frequently available information should be also reported as a compromise for permitting a preliminary comparative analysis of the different scenarios.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

AUTHOR CONTRIBUTIONS

MM performed sampling and a data analysis and revised the drafted manuscript. MAM designed the study, revised the data analysis, and drafted the manuscript. All authors contributed to the article and approved the submitted version.

ACKNOWLEDGMENTS

The authors would like to thank all the veterinary practitioners collaborating in the study. We also want to thank AMVAC for providing support for recruiting veterinary practitioners.

REFERENCES

1. Schechner V, Temkin E, Harbarth S, Carmeli Y, Schwaber MJ. Epidemiological interpretation of studies examining the effect of antibiotic usage on resistance. *Clin Microbiol Rev*. (2013) 26:289–307. doi: 10.1128/CMR.00001-13
2. The Copenhagen Recommendations. *Report from the Invitational EU Conference on The Microbial Threat Copenhagen*. Denmark. Available online at: https://www.reactgroup.org/uploads/react/resources/430/The%20Copenhagen%20Recommendations.en.504.pdf (accessed March 24, 2020).
3. Chauvin C, Madec F, Guillemot D, Sanders P. The crucial question of standardisation when measuring drug consumption. *Vet Res.* (2001) 32:533–43. doi: 10.1051/vetres:2001145
4. Jensen VF, Jacobsen E, Bager F. Veterinary antimicrobial-usage statistics based on standardized measures of dosage. *Prev Vet Med.* (2004) 64:201–15. doi: 10.1016/j.prevetmed.2004.04.001
5. Grave K, Jensen VF, McEwen S, Kruse H. Monitoring of antimicrobial drug usage in animals: methods and applications. In: Aarestrup F, editor. *Antimicrobial Resistance in Bacteria of Animal Origin.* Washington, DC: ASM Press (2006). p. 375–96. doi: 10.1128/9781555817534.ch22
6. Collineau L, Belloc C, Stark KDC, Hemonic A, Postma M, Dewulf J, Chauvin C. Guidance on the selection of appropriate indicators for quantification of antimicrobial usage in humans and animals. *Zoonoses Public Health* (2017) 64:165–84. doi: 10.1111/zph.12298
7. Moreno MA, Collineau L, Carson CA. Editorial: antimicrobial usage in companion and food animals: methods, surveys and relationships with antimicrobial resistance in animals and humans. *Front Vet Sci*. (2020) 7:63. doi: 10.3389/fvets.2020.00063
8. European Medicines Agency, European Surveillance of Veterinary Antimicrobial Consumption, 2019. *'Sales of veterinary antimicrobial agents in 31 European countries in 2017'*. (EMA/294674/2019)
9. Radford AD, Noble PJ, Coyne KP, Gaskell RM, Jones PH, Bryan JG, et al. Antibacterial prescribing patterns in small animal veterinary practice identified via SAVSNET: the small animal veterinary surveillance network. *Vet Rec.* (2011) 169:310. doi: 10.1136/vr.d5062
10. Mateus A, Brodbelt DC, Barber N, Stark KD. Antimicrobial usage in dogs and cats in first opinion veterinary practices in the UK. *J Small Anim Pract.* (2011) 52:515–21. doi: 10.1111/j.1748-5827.2011.01098.x
11. Escher M, Vanni M, Intorre L, Caprioli A, Tognetti R, Scavia G. Use of antimicrobials in companion animal practice: a retrospective study in a veterinary teaching hospital in Italy. *J Antimicrob Chemother.* (2011) 66:920–7. doi: 10.1093/jac/dkq543
12. Buckland EL, O'Neill D, Summers J, Mateus A, Church D, Redmond L, et al. Characterisation of antimicrobial usage in cats and dogs attending UK primary care companion animal veterinary practices. *Vet Rec.* (2016) 179:489. doi: 10.1136/vr.103830
13. Singleton DA, Sanchez-Vizcaino F, Dawson S, Jones PH, Noble PJM, Pinchbeck GL, et al. Patterns of antimicrobial agent prescription in a sentinel population of canine and feline veterinary practices in the United Kingdom. *Vet J.* (2017) 224:18–24. doi: 10.1016/j.tvjl.2017.03.010
14. Hardefeldt LY, Selinger J, Stevenson MA, Gilkerson JR, Crabb H, Billman-Jacobe H, et al. Population wide assessment of antimicrobial use in dogs and cats using a novel data source - A cohort study using pet insurance data. *Vet Microbiol.* (2018) 225:34–9. doi: 10.1016/j.vetmic.2018.09.010
15. Hopman NEM, van Dijk MAM, Broens EM, Wagenaar JA, Heederik DJJ, van Geijlswijk IM. Quantifying antimicrobial use in dutch companion animals. *Front Vet Sci.* (2019) 6:158. doi: 10.3389/fvets.2019.00158
16. Joosten P, Ceccarelli D, Odent E, Sarrazin S, Graveland H, Van Gompel L, et al. ntimicrobial Usage and Resistance in Companion Animals: A Cross-Sectional Study in Three European Countries. *Antibiotics.* (2020) 9:E87. doi: 10.3390/antibiotics9020087
17. Hur BA, Hardefeldt LY, Verspoor KM, Baldwin T, Gilkerson JR. Describing the antimicrobial usage patterns of companion animal veterinary practices; free text analysis of more than 4.4 million consultation records. *PLoS ONE.* (2020) 15:e0230049. doi: 10.1371/journal.pone.0230049
18. Gómez-Poveda B, Moreno MA. Antimicrobial prescriptions for dogs in the capital of Spain. *Front Vet Sci.* (2018) 5:309. doi: 10.3389/fvets.2018.00309
19. Watson AD, Maddison JE. Systemic antibacterial drug use in dogs in Australia. *Australian Vet J.* (2001) 79:740–6. doi: 10.1111/j.1751-0813.2001.tb10888.x

20. Rantala M, Holso K, Lillas A, Huovinen P, Kaartinen L. Survey of condition-based prescribing of antimicrobial drugs for dogs at a veterinary teaching hospital. *Vet Rec.* (2004) 155:259–62. doi: 10.1136/vr.155.9.259
21. European Parliament and The Council. *Regulation (EU) 2019/6 of the European Parliament and of the Council of 11 December 2018 on Veterinary Medicinal Products and Repealing Directive 2001/82/EC*. European Parliament and The Council (2019). Available online at: https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32019R0006&from=EN (accessed March 25, 2020).

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Veterinary Science

ORIGINAL RESEARCH
published: 15 December 2020
doi: 10.3389/fvets.2020.566529

Antimicrobial Usage Among Different Age Categories and Herd Sizes in Swiss Farrow-to-Finish Farms

Thomas Echtermann[1]*, *Cedric Muentener*[2], *Xaver Sidler*[1] *and Dolf Kuemmerlen*[1]

[1] *Division of Swine Medicine, Department for Farm Animals, Vetsuisse Faculty, University of Zurich, Zurich, Switzerland,*
[2] *Institute of Veterinary Pharmacology and Toxicology, Vetsuisse Faculty, University of Zurich, Zurich, Switzerland*

In the Swiss pig sector, the usage of antimicrobials has been recorded, evaluated and systematically reduced on a voluntary basis since 2015. This monitoring has been carried out using various methods thereby enabling continuous national scrutiny as well as international comparisons. To gain a better understanding of the dynamics of the antimicrobial usage on Swiss farms, consumption data of farrow-to-finish farms were analyzed for (i) the within-herd relationships among different age categories and (ii) the influence of the herd size. The data were collected on 71 farms for the year 2017, encompassing the amount of active ingredients and number of defined daily doses Switzerland (nDDDch) in total, and stratified for the different age categories of piglets, weaners, fattening pigs, and sows. The differences in nDDDch per animal among the age categories were determined by a Wilcoxon test and subsequent *post-hoc* analysis according to Bonferroni. The within-herd relationship among the individual age categories as well as the influence of the herd size on nDDDch per animal measured as kept sows were analyzed by simple linear regression. The evaluation of the treatment days showed that 50% of the nDDDch were used in piglets, 44% for weaners, and 3% each for fattening pigs and sows. Compared to the other age categories, the examination of the number of nDDDch per animal showed a significantly higher number for sows, whereas for fattening pigs the number was significantly lower ($P < 0.01$). The farm-based analysis using linear regression showed a relationship between antimicrobial usage in sows and piglets ($P < 0.001$; adj. $R^2 = 0.19$). Similarly, a significant relationship between larger herd size and increased antimicrobial usage was observed ($P = 0.02$; adj. $R^2 = 0.06$). The present study provides an insight into the antimicrobial treatment dynamics of farrow-to-finish farms. In particular, the age categories piglets and sows—with their higher number of treatment days in total or per animal—are of interest regarding the potential reduction in antimicrobial usage. Likewise, larger farms with higher management requirements were found to be of particular importance for the reduction of antimicrobial usage. Monitoring programs should therefore evaluate different age categories separately to identify problems for individual farms.

Keywords: antimicrobial drug usage, defined daily dose, age category, herd size, monitoring systems, pigs, Switzerland

OPEN ACCESS

Edited by:
Lucie Collineau, Agence Nationale de Sécurité Sanitaire de l'Alimentation, de l'Environnement et du Travail (ANSES), France

Reviewed by:
Andreia Goncalves Arruda, The Ohio State University, United States
Lis Alban, Danish Agriculture and Food Council, Denmark

***Correspondence:**
Thomas Echtermann
techtermann@vetclinics.uzh.ch

Specialty section:
This article was submitted to Veterinary Epidemiology and Economics, a section of the journal Frontiers in Veterinary Science

Received: *28 May 2020*
Accepted: *19 November 2020*
Published: *15 December 2020*

Citation:
Echtermann T, Muentener C, Sidler X and Kuemmerlen D (2020) Antimicrobial Usage Among Different Age Categories and Herd Sizes in Swiss Farrow-to-Finish Farms. Front. Vet. Sci. 7:566529. doi: 10.3389/fvets.2020.566529

INTRODUCTION

Awareness of the spread of antimicrobial-resistant genes is an important issue at the public health interface between human and veterinary medicine (1). The general transfer of these genes between both disciplines is well documented (2–4). One of the most important drivers to reduce this spread is optimized and prudent antimicrobial drug usage (AMU) (5). This approach of careful usage is consistently demanded for our farm animals and is also reflected by the report of the European Surveillance of Veterinary Antimicrobial Consumption (ESVAC), where Switzerland performs moderately within a European context (6). In addition to the guidelines of the World Health Organization (WHO) (7), countries like Switzerland have therefore published guidelines describing the evidence-based usage of antimicrobials for the important livestock species cattle and pigs (8).

In addition to treatment guidelines, the first important step is setting up a powerful AMU monitoring system, which allows for correlations with resistance data (9) and is linked to animal performance and certain aspects of biosecurity and prevention (10–13). Such monitoring systems may be based on several different measurement methodologies, which, although valid and reliable by themselves, could nevertheless complicate comparisons among different regions and species (14). Such differences in the calculation must be taken into account. An established and common monitoring strategy is based on the measurement of so-called defined daily doses, which allow for the estimation of the potential number of treatment days from the used amount of antimicrobial ingredients (15, 16). This measurement method, originally developed for human medicine (17), was adopted in veterinary medicine and examined in several studies monitoring the AMU in pigs (18, 19). Furthermore, the European Medicines Agency (EMA) developed a detailed description for the assignment of defined daily doses and treatment course doses in animals (20), supplemented by values for defined daily doses (DDDvet) and defined course doses (DCDvet) for the livestock sector (21).

According to this description, nationally defined doses (DDDch/DCDch) were developed for the pig sector in Switzerland and compared with the values of the EMA in the field (22, 23). These defined doses of Switzerland were used in a further study to determine the usage of Highest Priority Critically Important Antimicrobials according to WHO (HPCIAs) and the Swiss Federal Ordinance on veterinary medicines as well as to investigate the association between AMU and different types of farms (24, 25).

In addition to comparing different types of farms, the relationship among AMU and different age categories within farrow-to-finish farms has also been examined and described with other monitoring systems (26). This study found a positive relationship among the AMU within the studied age categories, so the AMU in one age category was positive related to the AMU in another age category on the farm. The influence of larger herd size on increasing antibiotic consumption has also been investigated by several authors using different monitoring strategies, with some studies observed (27, 28) while other studies found only weak correlations (29) or not observed (30), such a relationship.

The objectives of this study were (1) to investigate the association among AMU and animal age category on farrow-to-finish farms and (2) to investigate the association between AMU and herd size on farrow-to-finish farms. The hypotheses of this study were that (1) AMU would differ among age categories on farrow-to-finish farms, and (2) AMU would differ among herd sizes on farrow-to-finish farms. AMU was measured using DDDch, and herd size was measured in the number of sows kept.

MATERIALS AND METHODS

Data Collection

In collaboration with the Swiss Pig Health Service (SSHS), AMU data were collected from 71 Swiss farrow-to-finish pig farms in 2017. The study farms joined a nationwide voluntary program known as Suissano/Safety+, which evaluates the AMU on their farms to improve transparency along the pig production process. Overall, 598 out of 6,406 pig farms throughout Switzerland participated in the Suissano/Safety+ program in 2017, which represents a proportion of 9% (31). Out of the 598 farms, 71 farms were defined as farrow-to-finish by the SSHS as farms housing at least 10% of the piglets from birth until the time of slaughter. The farms were independent of each other and not part of a larger system. The distribution of the study farms corresponds to the distribution of Swiss pig production with its higher animal populations in the cantons of Lucerne and St. Gallen. Only farms with complete documentation for antimicrobial preparations purchased in 2017 were included in the study. According to the Swiss Federal Ordinance on veterinary medicines, purchased preparations containing antimicrobial ingredients must be used within a maximum time period of 3 months (25). The study farms were required to document all veterinary prescriptions of antimicrobial ingredients for that year, including exact information on the name and quantity of the products used. Supported by the herd veterinarian and the SSHS, farmers had to allocate the prescribed antimicrobial agents to four different categories (piglets, weaners, fatteners, and sows). The age categories were defined in such a way that a piglet was counted from birth until the end of the 4th week of life, a weaner from the 5th week of life until the end of the 12th week of life, and a fattening pig from the 13th week of life until slaughter. Gilts and boars were counted as sows from the age of 7 months. This classification was communicated by the SSHS when a farm was included in the Suissano/Safety+ program. In addition to the AMU records, the number of pigs kept (sows) or produced annually (all other age groups) were recorded.

AMU Quantification

To quantify AMU, the amount of prescribed antimicrobial ingredient from the study farms during 2017 was divided by the defined daily doses Switzerland (DDDch) of each corresponding antimicrobial classes multiplied by the standard weights of the different age categories as defined by the European Surveillance of Veterinary Antimicrobial Consumption (ESVAC) (piglets:

4 kg; weaners: 12 kg; and fatteners: 50 kg and sows: 220 kg) (32).

$$\text{Number of defined daily doses Switzerland (nDDDch)} = \frac{\sum \text{total amount ofprescribed antimicrobial ingredient (mg)}}{\text{DDDch}\left(\frac{mg}{kg}\right) * \text{standard weight of age category (kg)}}$$

The required information describing the doses in mg/kg was taken from the product leaflets which are available in the Swiss Veterinary Medicines Drug Compendium (33). The detailed procedure for defining the national doses and all values for DDDch have been published in previous work from our research group (22).

The number of DDDch (nDDDch) and the amount of prescribed antimicrobial ingredients were calculated in total, as were the different age categories and the different used antimicrobial classes.

For the evaluation of the AMU among different herd sizes and to compare the consumption by different categories, the number of kept (sows) or produced pigs (piglets, weaners, and fatteners) in the year 2017 were considered according to the following formula:

$$nDDDch/animal/year = \frac{\sum \text{total amount of prescribed antimicrobial ingredient per farm and age category (mg)}}{\text{DDDch}\left(\frac{mg}{kg}\right) * \text{standard weight of age category (kg)} * \text{number of pigs per farm and age category}}$$

This calculation was performed separately for each prescribed antimicrobial ingredient used on the farm, and the resulting numbers were added up for each age category. Finally, the results of the different age categories were summarized as the total nDDDch per pig in 2017. The herd size was defined as the number of sows kept.

Data Processing and Statistical Analysis

The preparation of all operating farm data and the calculation of the number of defined doses were carried out using Microsoft Excel 2016 (Microsoft, Redmond, WA, USA). The statistical analysis and preparation of graphs to visualize the results were performed with R (https://cran.r-project.org). Differences among the tested groups having a $P \leq 0.05$ were considered statistically significant. The data for calculated AMU on the farm level were tested for normal distribution and the differences among the individual age categories were investigated using the Kruskal-Wallis test followed by a *post-hoc* pairwise analysis (Bonferroni correction). The relationship between the herd sizes and the nDDDch/animal/year on farms was examined by a simple linear regression. Both were set as continuous variables with herd size as the predictor and nDDDch/animal/year as the response variable. Similarly, simple linear regression was used to compare the nDDDch/animal/year for the different age categories. The nDDDch/animal/year of sows or the respective younger age category was determined as the predictor variable and was examined with the nDDDch/animal/year of another age category as the response variable. The nDDDch/animal/year of the six different models of predictor-response variables (sows-piglets, sows-weaners, sows-fatteners, piglets-weaners, piglets-fatteners, and weaners-fatteners) was therefore analyzed. Homoscedasticity tests and plots were examined to check whether assumptions of normality and homoscedasticity were fulfilled and scatterplots were prepared to visualize the results.

TABLE 1 | Total and relative (%) distribution of antimicrobial consumption within the different age categories (piglets, weaners, fatteners, and sows) measured either as number of defined daily doses Switzerland (nDDDch) or as active antimicrobial ingredients.

	nDDDch	%	Active ingredient in kg	%
Piglets	314,743	50%	9.8	10%
Weaners	276,038	44%	44.0	44%
Fatteners	18,399	3%	9.2	9%
Sows	17,799	3%	36.1	36%
Overall	626,979		99.1	

RESULTS

AMU Quantification per Age Category

The total and relative distribution of the antimicrobial consumption within different age categories measured as nDDDch as well as the active antimicrobial ingredient is given in **Table 1**. In terms of AMU monitoring calculated as nDDDch, piglets (50%) and weaners (44%) were the most frequently observed age categories, while weaners (44%), and sows (36%) were the most frequently observed age categories for administered active ingredients. The antimicrobial consumption in fatteners was 18,399 nDDDch (3%) and 9.2 kg of active ingredient (9%), respectively.

The overall distribution as well as the distribution within the different age categories of the used antimicrobial classes analyzed either as nDDDch or as active ingredient are shown in **Figure 1**. Penicillins were the most frequently observed used antimicrobial classes overall with 298,311 nDDDch (48%) and 37.8 kg (38%) measured active ingredients, respectively. Apart from the measured active ingredients in weaners, penicillins were also the most frequently observed antimicrobial class in the different age categories. For the weaners, 19.6 kg (44%) sulfonamides and 12.5 kg (28%) tetracyclines were observed when measuring active ingredients. Analyzing the HPCIAs cephalosporins, fluoroquinolones, macrolides, and polypeptides, the overall proportions of these antimicrobial classes were 21% for the calculated nDDDch results and 7% for the amount of active ingredients, respectively.

Table 2 summarizes the descriptive statistics for the distribution of the number of animals per farm. These herd size numbers for the different age categories were included for each individual farm to calculate the number of DDDch per animal in the year 2017.

The results of these calculations for nDDDch/animal/year values in the different age categories as well as the overall AMU per animal on the farms are summarized in **Table 3**

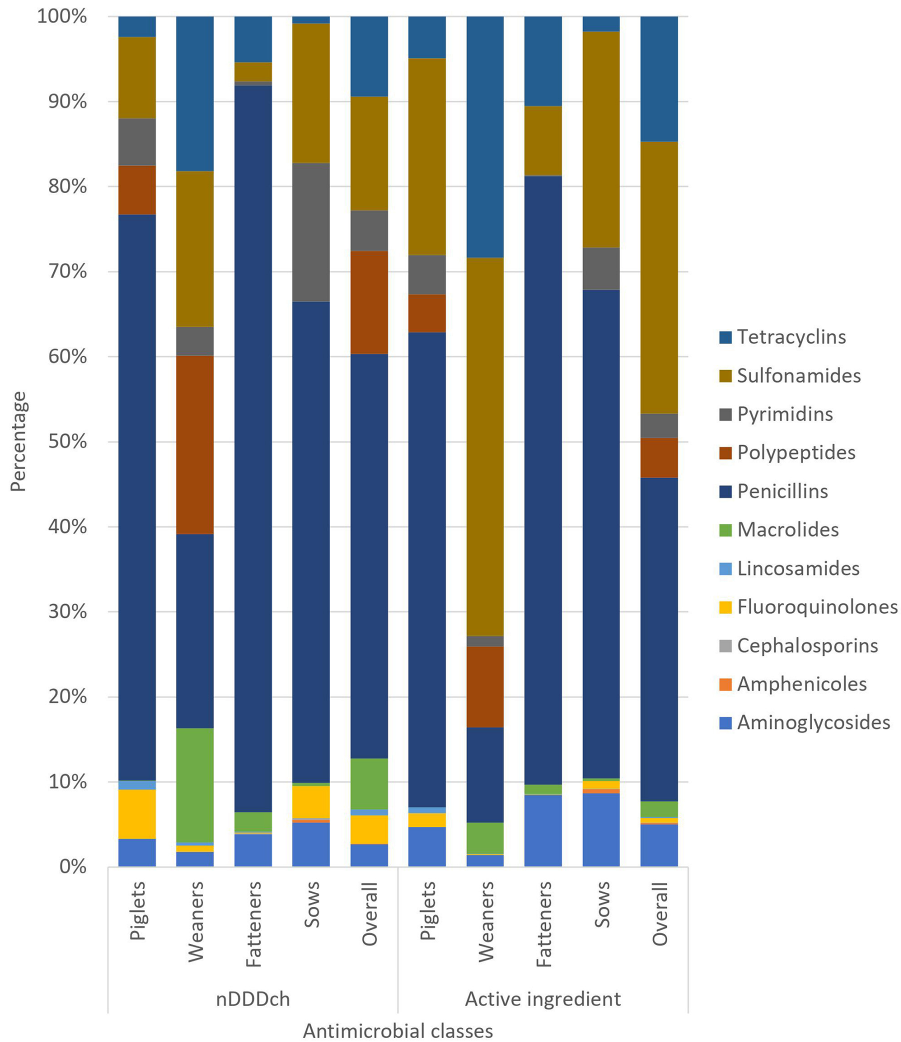


FIGURE 1 | Relative distribution of the used antimicrobial classes analyzed either as nDDDch or as active ingredient of the overall study population and separated among the different age categories (piglets, weaners, fatteners, and sows).

TABLE 2 | Descriptive statistics on the distribution of different age categories on the study farms measured as number of pigs kept (sows) and number of produced pigs per year (piglets, weaners, and fatteners) on 71 farrow-to-finish pig farms in Switzerland in 2017.

Age category	Mean	Median	CI (95%)	SD	Min	Max
Piglets	2,390	2238	2,085–2,694	1,267	359	6,040
Weaners	2,061	1,918	1,803–2,319	1,075	320	5,200
Fatteners	936	790	750–1,122	775	15	3,800
Sows	79	74	69–88	43	10	220

CI, confidence interval; SD, standard deviation; Min, minimum; Max, maximum.

TABLE 3 | Median values, minimum, and maximum and 25%/75% quartiles of the number of defined daily doses Switzerland per pig (nDDDch/animal/year) measured on 71 farrow-to-finish farms in the year 2017.

	Median	Minimum	25% Quartiles	75% Quartiles	Maximum
1. Piglets	0.5	0	0.2	1.5	11.5
2. Weaners	0.7	0	0.1	2.0	13.3
3. Fatteners	0.04*	0	0	0.3	9.9
4. Sows	2.1⁺	0	0.7	3.5	13.8
Overall	5.2	0	3.0	8.1	26.1

**$P < 0.001$ to 1, 2, and 4; $^{+}P < 0.001$ to 1, 2, and 3 by a Kruskal-Wallis test followed by a post-hoc pairwise analysis (Bonferroni correction).*

and visualized in **Figure 2**. Based on the defined daily doses, a significantly higher AMU per pig was found for sows (median of 2.1 nDDDch/animal/year) compared to the other age categories, whereas a significantly lower AMU was observed for fatteners (median of 0.04 nDDDch/animal/year) (**Figure 2**). No significant differences were observed between piglets and weaners, as indicated by their median values of 0.5 and 0.7

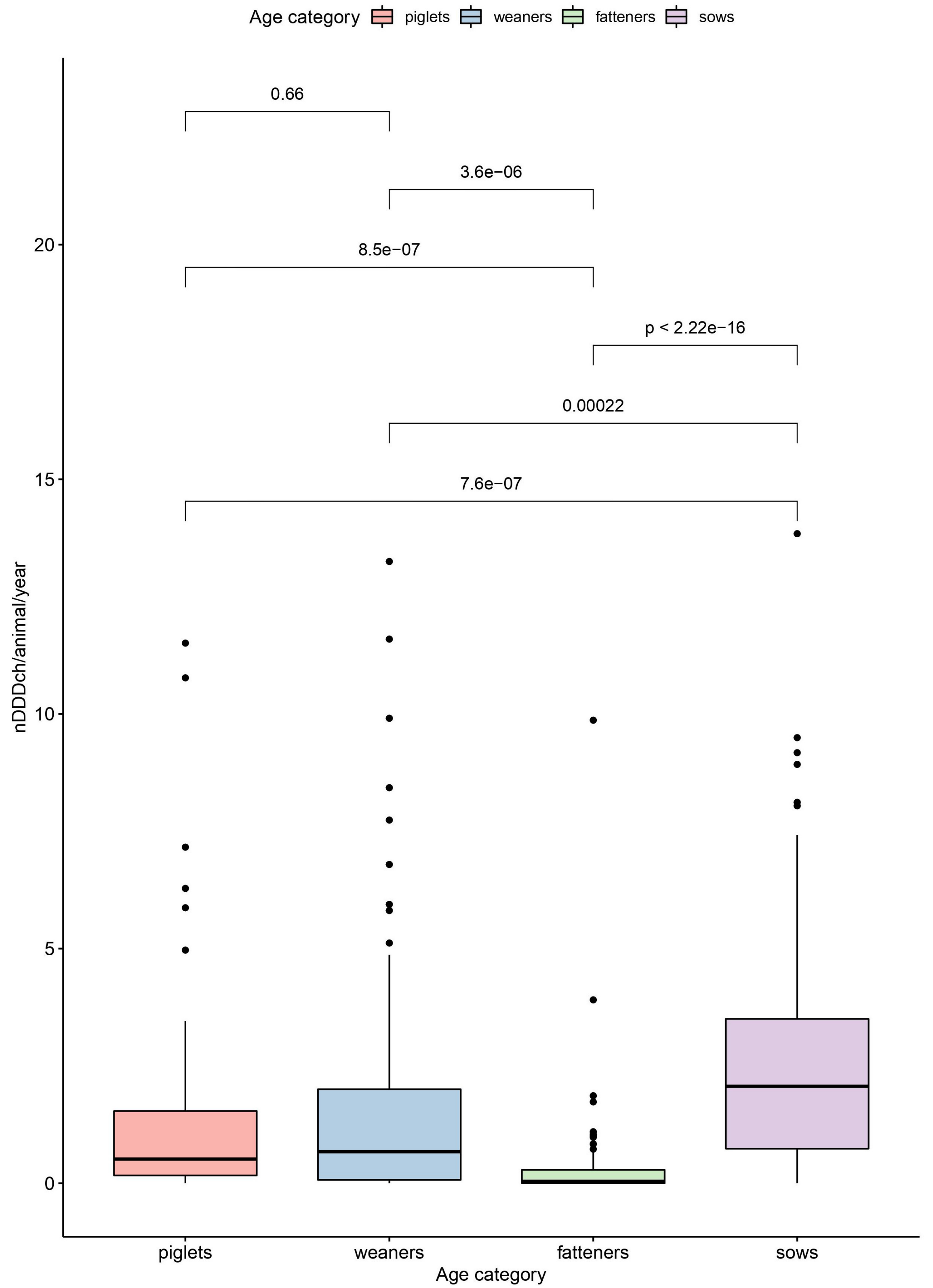


FIGURE 2 | Boxplot showing differences in the number of defined daily doses Switzerland per pig (nDDDch/animal/year) among the individual age categories (piglets, weaners, fatteners, and sows) investigated by a Kruskal-Wallis test followed by a *post hoc* pairwise analysis (Bonferroni correction).

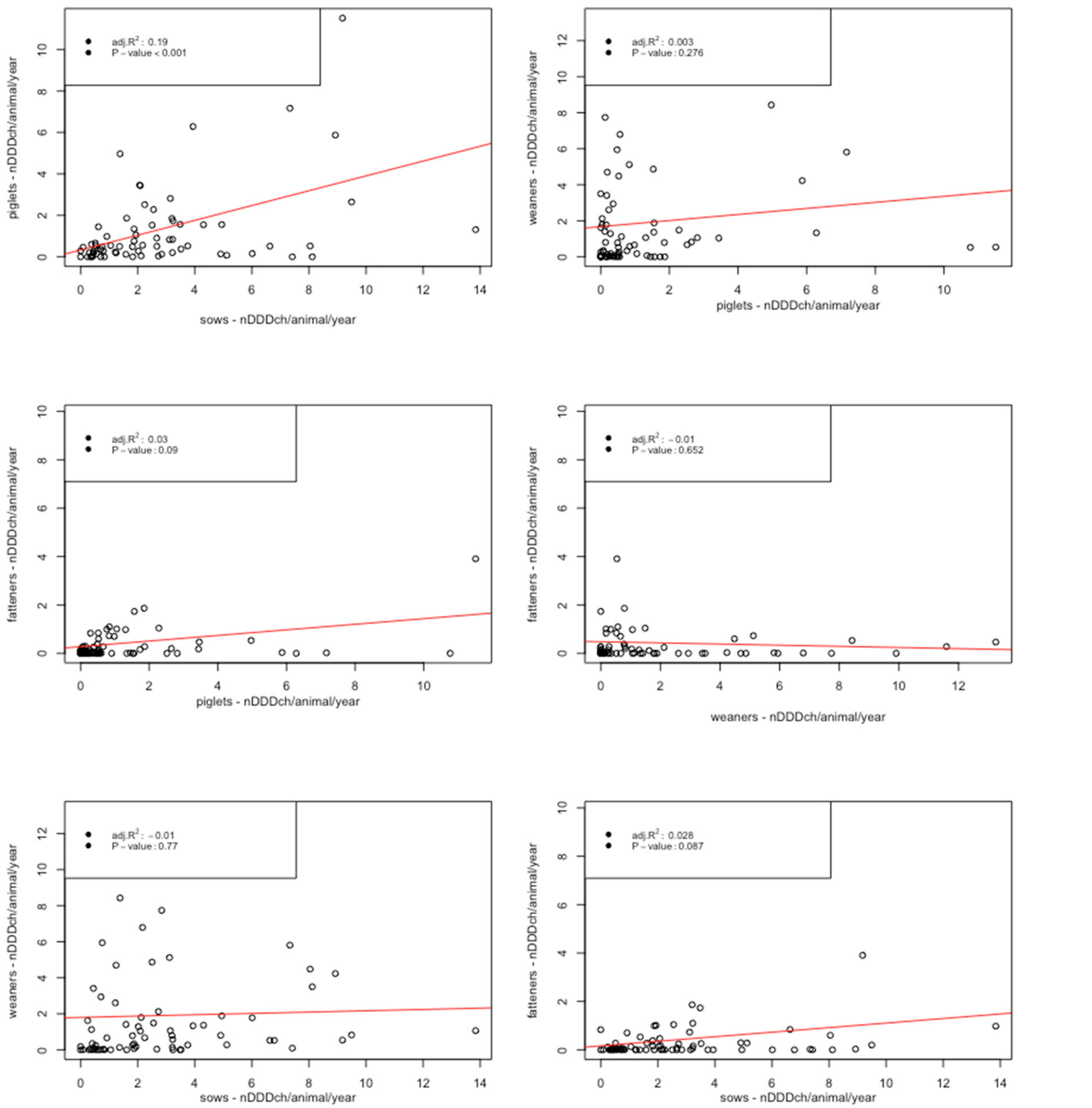


FIGURE 3 | Scatterplots and linear regressions for the within-herd relationship of the number of defined daily dose Switzerland per pig (nDDDch/animal/year) among the different age categories (piglets, weaners, fatteners, and sows) for 71 farrow-to-finish pig herds in Switzerland.

nDDDch/animal/year, respectively. The maximum values of nDDDch/animal/year on individual farms varied between 9.9 for the fatteners and 13.8 for the sows.

Relationship of AMU Among Age Categories

Considering the within-herd AMU of the different age categories measured as defined daily doses per animal and year, a significant linear relationship was found between data for sows and piglets ($P < 0.001$) (**Figure 3**). The analysis of other age category combinations showed some positive (e.g., piglets and weaners) and some negative (e.g., weaners and fatteners) relationships—none of them significant.

AMU Quantification per Herd Size

As shown in **Table 2**, the average, minimal, and maximal herd size of our study population measured as kept sows were 10, 79, and 220 animals per farm, respectively. The median value of antimicrobial drug usage was 5.2 defined daily doses per animal per year and reached a maximum of 26.1 on one farm (**Table 3**). **Figure 4** shows that both variables were connected by

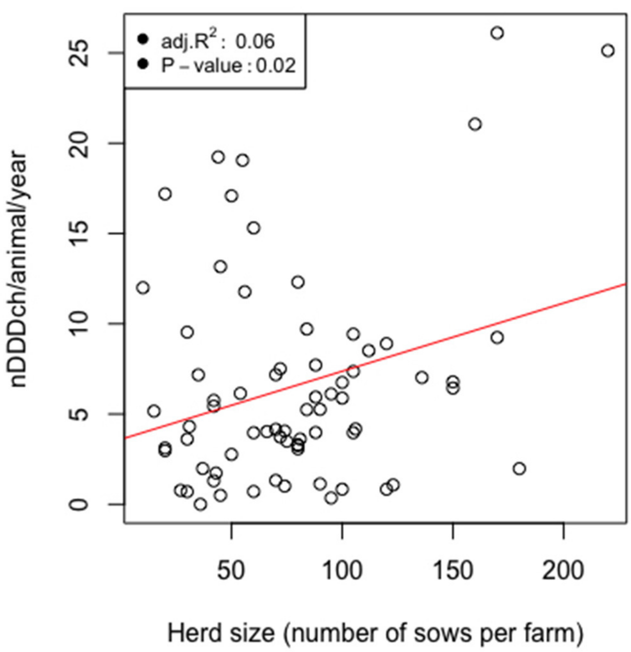


FIGURE 4 | Scatterplots and linear regressions for the relationship of the number of defined daily dose Switzerland per pig (nDDDch/animal/year) and the herd size counted as the number of kept sows for 71 farrow-to-finish pig herds in Switzerland in 2017.

a significant linear relationship between the herd size measured as kept sows and the AMU measured as defined daily doses per animal and year ($P = 0.02$).

DISCUSSION

This study found major differences in AMU among the age categories of piglets, weaners, fatteners, and sows, which varied depending on whether active ingredients or the number of defined daily doses are used as method of measurement. Due to the different weights of the age categories, 9.8 kg (10%) of all active ingredients in piglets represent 50% of the number of defined daily doses, whereas 36.1 kg (36%) in sows represents only 3% of the total number of these doses. For the weaners, the percentage for both the active ingredients and the number of defined daily doses was 44%. As previous studies have shown, the proportion of AMU measured by defined daily doses in weaners is comparatively high (18, 34). A frequent administration of antimicrobial premixes contained in the feed for a certain period in this age category has also been documented (35). In Switzerland, some of the available premixes include high concentrations of active ingredients (23), which, combined with relatively low animal weight and longer treatment duration, could explain the results obtained for weaners.

This could also partly explain that in weaners, in contrast to the other age categories, it is not penicillins, often used as an injection solutions, but sulfonamides and tetracyclines that were the most frequently observed antimicrobial classes within the amount of active ingredients. Both sulfonamides and tetracyclines are potentially part of the premixes, which are used as group treatments in weaners in Switzerland (36). This study, similarly to other Swiss (22, 37) and international studies (18, 38), observed penicillin as a frequently used antimicrobial class in the different age categories of pigs. Since penicillins are considered as the first selection for many indications in the Swiss AMU guidelines for pigs, an evidence-based usage in accordance with guidelines could be concluded from this findings (8).

This study shows that for HPCIAs, the calculated number of defined daily doses was 21% of the overall consumption. Similar results with similar measuring methods have already been shown in earlier studies, which could also demonstrate the potential for reduction over time (10, 39). Similarly to the deviations observed for the different age categories, the lower percentage of 7% HPCIAs measured as active ingredients shows the differences in output between the two measurement methods of defined daily doses and amount of active ingredients.

These differences in the output of different measurement methods were mentioned in theoretical reviews (14, 40) and observed in field trials (24, 41). They also need to be considered, for example, when evaluating comparisons of the AMU among countries or species. In principle, monitoring systems based on defined doses only allow a statistical estimation of the probable AMU since the calculation is based on prescribed amounts and the doses used on the farm could differ from the estimations. Other authors therefore prefer the so-called "used daily doses" if detailed data about the on-farm doses of individual treatments are available (42). However, the calculation behind the number of doses per animal and year as described in this study is comparable to other systems using defined doses to estimate AMU in livestock (43, 44).

The average herd size of the farms in this study was 79 kept sows, which is comparable to earlier studies describing the usage of antimicrobials on Swiss pig farms (36). Since participation in the Suissano/Safety+ program is voluntary, farmers with a higher awareness of the importance of antimicrobial treatments in their animals and the role it plays in the spread of resistance maybe more represented (45). This might result in a selection bias in the study population and could compromise the internal validity of the analyses in this study. Although participation in the program is without benchmarking or consequences, a reduction of AMU on farms could be observed as a result of the comparison to other farms (39).

This study identified significant differences in the number of defined daily doses per animal among the different age categories. Fatteners were treated less frequently, which has already been shown in a previous study (18) and could be explained by the good health status of Swiss pigs in terms of lung diseases (46) as well as a low number of oral group therapies with certain combinations of antimicrobials compared to weaners (22). As Switzerland is almost free of the lung pathogens *Mycoplasma hyopneumoniae* and *Actinobacillus pleuropneumoniae* and free of the porcine reproductive and respiratory syndrome (PRRS) virus, there are some indications missing which have been linked to increased antibiomicrobial usage in growing pigs in other countries (13, 47). The continuous development of the Suissano/Safety+ program will allow the identification of indications for treatment as well as management and biosecurity measurements on Swiss pig farms and the evaluation of these potential confounders on the AMU will be the subject of future studies. For the present study, confounders were minimized by restricted sampling that included only farms with a complete AMU data documentation of the year 2017 into the study (48).

In contrast to the lower AMU in fatteners, the AMU in sows measured as defined daily doses per animal was significantly higher compared to all other age categories. This finding was observed also by other authors (24, 38), although other studies refute it (18, 26). One of the main drivers of high AMU in sows could be the treatment of postpartum dysgalactic syndrome (PPDS) after birth. PPDS has been described as an important cause of economic losses in sows (49) and Pendl et al. (50) were able to show the potential of reducing AMU by targeted herd health management for this syndrome. Since PPDS is related to reduced colostrum production, it could also partly explain the significant relationship between the AMU of sows and suckling pigs identified in this study. The connection between reduced colostrum intake and increased mortality and susceptibility to disease such as diarrhea caused by *Escherichia coli* has been observed previously (51, 52); increased usage of antimicrobials for piglets in such cases could therefore also be assumed. In contrast to Sarrazin et al. (18) and Sjölund et al. (26), this was the only significant relationship among the different age categories in this study. Although there were some positive (e.g., piglets and weaners) and negative (e.g., weaners and fatteners) relationships between the other age categories, none of them were significant. These findings therefore indicate the importance of stratified AMU monitoring which evaluates the results of the different age categories separately and not as an overall farm assessment. The benefit of such a monitoring system is also underlined by the fact that the AMU in single farms reached high maximum values in individual age categories. This is already implemented in the Suissano/Safety+ program.

Similarly, a significant relationship between larger herd size measured as kept sows and increased AMU was observed. This underlines the findings of previous studies (27, 28) and emphasize the importance of successful herd management and appropriate external and internal biosecurity practices to avoid disease spreading and maintain standards of animal health and low antimicrobial consumption, especially on larger farms. To continue understanding the influence of various farm characteristics on AMU as well as important indications, as has been done in other studies (29), further research is needed for the Swiss pig sector.

CONCLUSION

Our study demonstrates that AMU monitoring programs should evaluate different age categories separately to identify specific points of concern and suggest possible solutions for individual farms. The categories of piglets and sows are especially important on Swiss pig farms due to their high and related AMU either in absolute terms or per animal. Likewise, a link between larger farms and increased usage was observed and should be considered through improved on-farm health management.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation, to any qualified researcher.

ETHICS STATEMENT

Ethical review and approval was not required for the animal study because since this was only data that had no influence on the actual treatment of the animals, an animal welfare permit was not required. No veterinary manipulations or similar interventions were carried out on any animals by the research team. Written informed consent was obtained from the owners for the participation of their animals in this study.

AUTHOR CONTRIBUTIONS

TE drafted the manuscript. TE, DK, and XS designed and directed the study. CM supported the pharmacological aspects of the used measurement methods. TE prepared the data processing and statistical analysis. All authors have read and approved the manuscript.

ACKNOWLEDGMENTS

We would like to thank the members of the Swiss Swine Health Service for their support with the data collection on farms and Emily Katharina Gueldner and Laura Pieper for their help in proofreading of the manuscript.

REFERENCES

1. McEwen SA, Collignon PJ. Antimicrobial resistance: a one health perspective. *Antimicrob Resist Bacteria Livestock Compan Anim.* (2018) 6:521–47. doi: 10.1128/microbiolspec.ARBA-0009-2017
2. Hoelzer K, Wong N, Thomas J, Talkington K, Jungman E, Coukell A. Antimicrobial drug use in food-producing animals and associated human health risks: what, and how strong, is the evidence? *BMC Vet Res*. (2017) 13:211. doi: 10.1186/s12917-017-1131-3
3. Scott AM, Beller E, Glasziou P, Clark J, Ranakusuma RW, Byambasuren O, et al. Is antimicrobial administration to food animals a direct threat to human health? A rapid systematic review. *Int J Antimicrob Agents*. (2018) 52:316–23. doi: 10.1016/j.ijantimicag.2018.04.005
4. Mølbak K. Spread of resistant bacteria and resistance genes from animals to humans–the public health consequences. *J Vet Med B Infect Dis Vet Public Health*. (2004) 51:364–9. doi: 10.1111/j.1439-0450.2004.00788.x
5. Filippitzi ME, Chantziaras I, Devreese M, Dewulf J. Probabilistic risk model to assess the potential for resistance selection following the use of anti-microbial medicated feed in pigs. *Food Addit Contam Part A Chem Anal Control Expo Risk Assess*. (2018) 35:1266–77. doi: 10.1080/19440049.2018.1461257
6. European Medicines Agency ESoVAC. *Sales of Veterinary Antimicrobial Agents in 31 European Countries in 2017*. (EMA/294674/2019). (2019).

7. World Health Organization. WHO guidelines on use of medically important antimicrobials in food-producing animals. Geneva: World Health Organization. Licence: CC BY-NC-SA 3.0 IGO. (2017). Available online at: http://apps.who.int/iris/bitstream/10665/258970/1/9789241550130-eng.pdf?ua=1 (Accessed May 5, 2020).
8. Eidgenössisches Departement des Innern EDI. Strategie-Antibiotikaresistenzen (StAR)-Umsichtiger Einsatz von Antibiotika: Therapieleitfaden für Tierärztinnen und Tierärzte. Bundesamt für Lebensmittelsicherheit und Veterinärwesen BLV. (2019). Available online at: https://www.blv.admin.ch/dam/blv/de/dokumente/tiere/tierkrankheiten-und-arzneimittel/tierarzneimittel/therapieleitfaden.pdf.download.pdf/therapieleitfaden-de.pdf (Accessed May 5, 2020)
9. Chantziaras I, Boyen F, Callens B, Dewulf J. Correlation between veterinary antimicrobial use and antimicrobial resistance in food-producing animals: a report on seven countries. *J Antimicrob Chemother*. (2014) 69:827–34. doi: 10.1093/jac/dkt443
10. Postma M, Vanderhaeghen W, Sarrazin S, Maes D, Dewulf J. Reducing Antimicrobial Usage in Pig Production without Jeopardizing Production Parameters. *Zoonoses Public Health*. (2017) 64:63–74. doi: 10.1111/zph.12283
11. Stygar AH, Chantziaras I, Toppari I, Maes D, Niemi JK. High biosecurity and welfare standards in fattening pig farms are associated with reduced antimicrobial use. *Animal*. (2020) 14:1–9. doi: 10.1017/S1751731120000828
12. Collineau L, Backhans A, Dewulf J, Emanuelson U, Grosse Beilage E, Lehebel A, et al. Profile of pig farms combining high performance and low antimicrobial usage within four European countries. *Vet Rec*. (2017) 181:657. doi: 10.1136/vr.103988
13. Lopes Antunes AC, Jensen VF, Toft N. Outcomes from using mortality, antimicrobial consumption, and vaccine use data for monitoring endemic diseases in danish swine herds. *Front Vet. Sci*. (2019) 6:41-. doi: 10.3389/fvets.2019.00041
14. Collineau L, Belloc C, Stark KD, Hemonic A, Postma M, Dewulf J, et al. Guidance on the selection of appropriate indicators for quantification of antimicrobial usage in humans and animals. *Zoonoses Public Health*. (2017) 64:165–84. doi: 10.1111/zph.12298
15. Jensen VF, Jacobsen E, Bager F. Veterinary antimicrobial-usage statistics based on standardized measures of dosage. *Prev Vet Med*. (2004) 64:201–15. doi: 10.1016/j.prevetmed.2004.04.001
16. World Health Organization WHO, Collaborating Centre for Drug Statistics Methodology. *DDD: Definition and General Considerations*. (2018). Available online at: https://www.whocc.no/ddd/definition_and_general_considera/ (Accessed May 5, 2020).
17. Merlo J, Wessling A, Melander A. Comparison of dose standard units for drug utilisation studies. *Eur J Clin Pharmacol*. (1996) 50:27–30. doi: 10.1007/s002280050064
18. Sarrazin S, Joosten P, Van Gompel L, Luiken REC, Mevius DJ, Wagenaar JA, et al. Quantitative and qualitative analysis of antimicrobial usage patterns in 180 selected farrow-to-finish pig farms from nine European countries based on single batch and purchase data. *J Antimicrob Chemother*. (2019) 74:807–16. doi: 10.1093/jac/dky503
19. Postma M, Sjolund M, Collineau L, Lösken S, Stärk KD, Dewulf J, et al. Assigning defined daily doses animal: a European multi-country experience for antimicrobial products authorized for usage in pigs. *J Antimicrob Chemother*. (2015) 70:294–302. doi: 10.1093/jac/dku347
20. European Medicines Agency Surveillance of Veterinary Antimicrobial Consumption. *Principles on Assignment of Defined Daily Dose for Animals (DDDvet) and Defined Course Dose for Animals (DCDvet)*. (EMA/710019/2014). (2015). Available online at: https://www.ema.europa.eu/en/documents/scientific-guideline/principles-assignment-defined-daily-dose-animals-dddvet-defined-course-dose-animals-dcdvet_en.pdf (Accessed May 5, 2020).
21. European Medicines Agency European Surveillance of Veterinary Antimicrobial Consumption. *(DDDvet) and Defined Course Doses for Animals (DCDvet)*. (EMA/224954/2016). (2016). Available online at: https://www.ema.europa.eu/documents/other/defined-daily-doses-animals-dddvet-defined-course-doses-animals-dcdvet-european-surveillance_en.pdf (Accessed May 5, 2020).
22. Echtermann T, Muentener C, Sidler X, Kümmerlen D. Antimicrobial drug consumption on Swiss pig farms: a comparison of swiss and european defined daily and course doses in the field. *Front Vet Sci*. (2019) 6:240. doi: 10.3389/fvets.2019.00240
23. Echtermann T, Müntener CR, Torgerson PR, Sidler X, Kümmerlen D. Defining daily doses and total doses for the measurement of antibiotic usage in Swiss pig production. *Schweiz Arch Tierheilkd*. (2018) 160:597–605. doi: 10.17236/sat00179
24. Kümmerlen D, Echtermann T, von Gerlach F, Müntener CR, Sidler X. Analyses of antimicrobial usage in 598 pig farms in Switzerland in 2017. *Schweiz Arch Tierheilkd*. (2019) 161:809–20. doi: 10.17236/sat00237
25. Swiss Federal Council. *Federal Ordinance on Veterinary Medicines*. (2004). Available online at: https://www.admin.ch/opc/de/classified-compilation/20030705/index.html (Accessed August 31, 2020).
26. Sjölund M, Postma M, Collineau L, Lösken S, Backhans A, Belloc C, et al. Quantitative and qualitative antimicrobial usage patterns in farrow-to-finish pig herds in Belgium, France, Germany and Sweden. *Prev Vet Med*. (2016) 130:41–50. doi: 10.1016/j.prevetmed.2016.06.003
27. Raasch S, Postma M, Dewulf J, Stark KDC, Grosse Beilage E. Association between antimicrobial usage, biosecurity measures as well as farm performance in German farrow-to-finish farms. *Porcine Health Manag*. (2018) 4:30. doi: 10.1186/s40813-018-0106-5
28. Hemme M, Ruddat I, Hartmann M, Werner N, van Rennings L, Kasbohrer A, et al. Antibiotic use on German pig farms - A longitudinal analysis for 2011, 2013 and 2014. *PLoS ONE*. (2018) 13:e0199592. doi: 10.1371/journal.pone.0199592
29. Kruse AB, Nielsen LR, Alban L. Herd typologies based on multivariate analysis of biosecurity, productivity, antimicrobial and vaccine use data from Danish sow herds. *Prev Vet Med*. 181:104487. (2018). doi: 10.1016/j.prevetmed.2018.06.008
30. Hybschmann GK, Ersboll AK, Vigre H, Baadsgaard NP, Houe H. Herd-level risk factors for antimicrobial demanding gastrointestinal diseases in Danish herds with finisher pigs: a register-based study. *Prevent Vet Medi*. (2011) 98:190–7. doi: 10.1016/j.prevetmed.2010.10.005
31. Eidgenössisches Departement des Innern EDI. *Landwirtschaftliche Strukturerhebung* 2019. (2020). Bundesamt für Statistik. Available online at: https://www.bfs.admin.ch/bfs/de/home/statistiken/land-forstwirtschaft/landwirtschaft.assetdetail.12687406.html (Accessed June 13, 2020).
32. European Surveillance of Veterinary Antimicrobial Consumption ESVAC. *Revised ESVAC Reflection Paper on Collecting Data on Consumption of Antimicrobial Agents Per Animal Species, on Technical Units of Measurement and Indicators for Reporting Consumption of Antimicrobial Agents in Animals*. (2013). (EMA/286416/2012-Rev.1). Available online at: https://www.ema.europa.eu/documents/scientific-guideline/revised-european-surveillance-veterinary-antimicrobial-consumption-esvac-reflection-paper-collecting_en.pdf (Accessed May 5, 2020).
33. Institute of Pharmacology and Toxicology Vetsuisse Faculty. *Tierarzneimittelkompendium der Schweiz*. Available online at: www.tierarzneimittel.ch (Acessed May 5, 2020).
34. Hirsiger P, Malik J, Kummerlen D, Vidondo B, Arnold C, Harisberger M, et al. Risk factors for the oral use of antibiotics and treatment incidence of weaners in Switzerland. *Schweiz Arch Tierheilkd*. (2015) 157:682–8. doi: 10.17236/sat00046
35. Sjolund M, Backhans A, Greko C, Emanuelson U, Lindberg A. Antimicrobial usage in 60 Swedish farrow-to-finish pig herds. *Prev Vet Med*. (2015) 121:257–64. doi: 10.1016/j.prevetmed.2015.07.005
36. Hartmann S, Riklin A, Müntener C, Schüpbach-Regula G, Nathues C, Sidler X. Use of antibiotics in Swiss piglet production and fattening farms. *Schweiz Arch Tierheilkd*. (2019) 161:797–808. doi: 10.17236/sat00236
37. Carmo LP, Nielsen LR, Alban L, Muntener CR, Schupbach-Regula G, Magouras I. Comparison of antimicrobial consumption patterns in the Swiss and Danish cattle and swine production. (2007-2013). *Front Vet Sci*. (2017) 4:26. doi: 10.3389/fvets.2017.00026
38. Jensen VF, Emborg HD, Aarestrup FM. Indications and patterns of therapeutic use of antimicrobial agents in the Danish pig production from 2002 to 2008. *J Vet Pharmacol Ther*. (2012) 35:33–46. doi: 10.1111/j.1365-2885.2011.01291.x
39. Echtermann T, Müntener C, Sidler X, Kümmerlen D. Impact of the Suissano Health Programme on antimicrobial usage on 291 pig farms in Switzerland. *Vet Rec Open*. (2020) 7:e000389. doi: 10.1136/vetreco-2019-000389

40. Lekagul A, Tangcharoensathien V, Yeung S, Angkana L, Viroj T, Yeung SM. The use of antimicrobials in global pig production: a systematic review of methods for quantification. *Prevent Vet Med*. (2018) 160:85–98. doi: 10.1016/j.prevetmed.2018.09.016
41. Arnold S, Gassner B, Giger T, Zwahlen R. Banning antimicrobial growth promoters in feedstuffs does not result in increased therapeutic use of antibiotics in medicated feed in pig farming. *Pharmacoepidemiol Drug Safety*. (2004) 13:323–31. doi: 10.1002/pds.874
42. Kasabova S, Hartmann M, Werner N, Kasbohrer A, Kreienbrock L. Used Daily Dose vs. Defined daily dose-contrasting two different methods to measure antibiotic consumption at the farm level. *Front Vet Sci*. (2019) 6:116. doi: 10.3389/fvets.2019.00116
43. Veldman KT, Mevius DJ, Wit B, Pelt Wv, Heederik D. MARAN 2018 Monitoring of Antimicrobial Resistance and Antibiotic Usage in Animals in the Netherlands in 2017. *MARAN 2018 Monitoring of Antimicrobial Resistance and Antibiotic Usage in Animals in the Netherlands in 2017*. (2018):78.
44. Hog BB, Bager F, Korsgaard H, Ellis-Iversen J, Pedersen K, Jensen LB, et al. DANMAP 2017 - use of antimicrobial agents and occurrence of antimicrobial resistance in bacteria from food animals, food and humans in Denmark. *DANMAP 2017 - use of antimicrobial agents and occurrence of antimicrobial resistance in bacteria from food animals, food and humans in Denmark*. (2018):150.
45. Visschers VH, Backhans A, Collineau L, Iten D, Loesken S, Postma M, et al. Perceptions of antimicrobial usage, antimicrobial resistance and policy measures to reduce antimicrobial usage in convenient samples of Belgian, French, German, Swedish and Swiss pig farmers. *Prev Vet Med*. (2015) 119:10–20. doi: 10.1016/j.prevetmed.2015.01.018
46. Sidler X, Eichhorn J, Geiser V, Bürgi E, Schüpbach G, Overesch G, et al. Lung and pleural lesions before and after implementation of a national eradication program against enzootic pneumonia and actinobacillosis as well as changes of slaughter carcass organs in slaughter pigs in Switzerland. *Schweiz Arch Tierheilkd*. (2015) 157:665–73. doi: 10.17236/sat00044
47. Kruse AB, de Knegt LV, Nielsen LR, Alban L. No clear effect of initiating vaccination against common endemic infections on the amounts of prescribed antimicrobials for Danish weaner and finishing pigs during 2007–2013. *Front Vet Sci*. (2017) 3:120. doi: 10.3389/fvets.2016.00120
48. Dohoo IR, Martin W, Stryhn HE. *Veterinary Epidemiologic Research.* Charlottetown, PE: University of Prince Edward Island (2003).
49. Niemi JK, Bergman P, Ovaska S, Sevon-Aimonen ML, Heinonen M. Modeling the costs of postpartum dysgalactia syndrome and locomotory disorders on sow productivity and replacement. *Front Vet Sci*. (2017) 4:181. doi: 10.3389/fvets.2017.00181
50. Pendl W, Jenny B, Torgerson PR, Spring P, Kummerlen D, Sidler X. Effect of herd health management on the prevalence of Postpartum Dysgalaktie Syndrome (PPDS) and the treatment incidence. *Schweiz Arch Tierheilkd*. (2017) 159:109–16. doi: 10.17236/sat00105
51. Alexopoulos JG, Lines DS, Hallett S, Plush KJ. A review of success factors for piglet fostering in lactation. *Animals (Basel)*. (2018) 8:38. doi: 10.3390/ani8030038
52. Unterweger C, Kahler A, Gerlach GF, Viehmann M, von Altrock A, Hennig-Pauka I. Administration of non-pathogenic isolates of Escherichia coli and Clostridium perfringens type A to piglets in a herd affected with a high incidence of neonatal diarrhoea. *Animal*. (2017) 11:670–6. doi: 10.1017/s1751731116001804

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Veterinary Science

ORIGINAL RESEARCH
published: 16 December 2020
doi: 10.3389/fvets.2020.576113

A Cross-Sectional Study of Antimicrobial Usage on Commercial Broiler and Layer Chicken Farms in Bangladesh

Tasneem Imam[1]*, Justine S. Gibson[1], Mohammad Foysal[2], Shetu Bhusan Das[2], Suman Das Gupta[1], Guillaume Fournié[3], Md. Ahasanul Hoque[2] and Joerg Henning[1]

[1] School of Veterinary Science, The University of Queensland, Gatton, QLD, Australia, [2] Chattogram Veterinary and Animal Sciences University, Chattogram, Bangladesh, [3] Department of Pathobiology and Population Sciences, Royal Veterinary College, University of London, London, United Kingdom

OPEN ACCESS

Edited by:
Lucie Collineau,
de l'Environnement et du Travail (ANSES), France

Reviewed by:
Omid Nekouei,
City University of Hong Kong, Hong Kong
Muhammad Hammad Hussain,
Ministry of Agriculture and Fisheries, Oman
Agnes Agunos,
Public Health Agency of Canada, Canada

***Correspondence:**
Tasneem Imam
t.imam@uqconnect.edu.au

Specialty section:
This article was submitted to Veterinary Epidemiology and Economics,
a section of the journal Frontiers in Veterinary Science

Received: 25 June 2020
Accepted: 13 November 2020
Published: 16 December 2020

Citation:
Imam T, Gibson JS, Foysal M, Das SB, Gupta SD, Fournié G, Hoque MA and Henning J (2020) A Cross-Sectional Study of Antimicrobial Usage on Commercial Broiler and Layer Chicken Farms in Bangladesh. Front. Vet. Sci. 7:576113. doi: 10.3389/fvets.2020.576113

Commercial poultry production is growing rapidly in Bangladesh to address the increasing demand for poultry meat and eggs. Challenges faced by producers include the occurrence of poultry diseases, which are usually treated or controlled by antimicrobials. A cross-sectional study was conducted on 57 commercial layer and 83 broiler farms in eight subdistricts of the Chattogram district, Bangladesh, to assess antimicrobial usage in relation to clinical signs observed in chicken flocks on these farms. Of the 140 commercial chicken farms, 137 (97.9%) used antimicrobials and 24 different antimicrobial agents were administered. On layer farms, the most commonly used antimicrobials were ciprofloxacin (37.0% of farms, 20/54), amoxicillin (33.3%, 18/54), and tiamulin (31.5%, 17/54), while on broiler farms, colistin (56.6%, 47/83), doxycycline (50.6%, 42/83), and neomycin (38.6%, 32/83) were most commonly administered. Only 15.3% (21/137) of farmers used antimicrobials exclusively for therapeutic purposes, while 84.7% (116/137) of farmers used them prophylactically, administering them either for prophylactic purposes only (22.6% of farmers, 31/137) or in combination with therapeutic purposes (62.1% of farmers, 85/137). About 83.3% (45/54) of layer farmers were selling eggs while antimicrobials were being administered compared to 36.1% (30/83) of the broiler farmers selling broiler chickens while administering antimicrobials. Overall, 75.2% (103/137) of farmers reported clinical signs for which they administered antimicrobials, while 24.8% (34/137) of farmers reported no clinical signs but still administered antimicrobials. Respiratory signs (71.8% of farms with clinical signs, 74/103) were most commonly reported, followed by enteric signs (32.0%, 33/103) and increased mortality (16.5%, 17/103). About 37.2% (51/137) of farmers bought antimicrobials exclusively from feed and chick traders, followed by veterinary medical stores (35.0%, 48/137). Purchasing antimicrobials from feed and chick traders was more common among broiler than layer farmers. It is recommended that commercial poultry farmers should keep records of antimicrobials used with dosage and duration of administration along with indication of use. This would allow farmers and veterinarians to review if antimicrobial usage had the desired effects and to evaluate the appropriate use of antimicrobial agents under an antimicrobial stewardship approach.

Keywords: antimicrobial usage, commercial chicken farms, broiler, layer, Chattogram, Bangladesh

INTRODUCTION

Poultry meat production has increased substantially over the past decades in South and South East Asia (1). In Bangladesh, where 20% of all protein consumed is derived from poultry products, most poultry species raised in Bangladesh are chickens (90%), followed by ducks (8%) and other species such as quail, pigeons, and geese (2%) (2).

Two poultry production systems are found in Bangladesh, commercial and backyard production. About 89% of households rear poultry with an average flock size of seven birds (2–4). Commercial chicken production can be classified into broiler and layer farming. In broiler farming, chickens are reared for meat while on layer farms, and chickens are reared for egg production although unproductive layer birds are also sold for meat (5).

The biggest challenge for commercial chicken producers is the occurrence of diseases (6). In Bangladesh, salmonellosis, colibacillosis, mycoplasmosis, and necrotic enteritis were the most frequent bacterial diseases reported from commercial chicken farms between 2002 and 2018, while infectious bursal disease, Newcastle disease, avian influenza, infectious bronchitis, avian leucosis, and fowl pox were the most common viral diseases reported during that period (7–11). Avian influenza in particular had a devastating effect on commercial chicken production in Bangladesh, resulting in a decrease of commercial chicken farms from 115,000 in 2007 to 55,000 in 2013 (12). Coccidiosis and ascaridiosis were the most common parasitic diseases reported in commercial poultry (7–11).

Thus, commercial poultry production requires comprehensive animal husbandry practises, which include antimicrobial therapy and vaccinations (13). Therapeutic application focuses on the treatment of birds with clinical signs of an infectious disease while prophylactic or preventive application refers to reduction of the risk of disease occurrence (14). In Bangladesh, antimicrobials are generally used for the treatment and prevention of poultry diseases, but some farmers use them also for growth promotion in order to increase feed conversion (15).

While the application of antimicrobials has contributed to the decline of mortality and morbidity rates in animals, misuse of antimicrobials is considered to be one of the biggest threats to human health (16). Antimicrobial resistance associated with inappropriate application of antimicrobials (17–20) can result in treatment failures for animal (21) and human diseases (22). This has significant economic and public health consequences, such as prolonged treatment duration of patients and longer hospital stays, which may further promote transmission of resistant pathogens in hospital (23), and represents an economic burden to the families of patients (24). The consumption of contaminated animal-source food (25, 26), direct contact with animals (27), or environmental exposure (28, 29) may promote the transmission of antimicrobial resistant bacteria to humans. In addition, animal-source food might contain antimicrobial residues if farmers do not adhere to recommended withholding periods for antimicrobial usage (30). Inappropriate use of antimicrobials in commercial chicken production is, therefore, a primary concern (17–20).

In Bangladesh, the extent of antimicrobial usage in livestock production is unknown (31) and data on national sales of antimicrobials are unreliable (32). In addition, frequent sales of antimicrobials through feed and chick traders and pharmaceutical company representatives (33) highlight the lack of governance on antimicrobial use in Bangladesh.

In the National Drug Policy 2016, the Bangladesh government published a list of priority drugs for the treatment of humans, which should not be sold "over the counter" (34). Unfortunately, a similar list of veterinary drugs not to be sold "over the counter" has not yet been published (34). Furthermore, there are neither regulations on veterinary drug registration and labelling (34) nor specific guidelines for the usage of antimicrobials in food animals available in Bangladesh (32). In addition, it has been shown that farmers in Bangladesh often do not follow the manufacturers' recommended dose and duration when administering antimicrobials to livestock (31).

Thus, this study aimed to assess (1) the frequency, purpose of usage, and sources of antimicrobials on commercial broiler and layer chicken farms in Chattogram, Bangladesh; (2) whether antimicrobial usage was associated with farmers' and farms' characteristics; (3) and the clinical signs for which antimicrobials were administered. In addition, compliance with the antimicrobials' withholding periods was evaluated.

MATERIALS AND METHODS

Study Location

A cross-sectional study was conducted to collect data on antimicrobial usage on commercial broiler and layer farms in Chattogram district of Bangladesh.

The Chattogram district in the southeastern part of Bangladesh was selected as the study location because it is one of the main districts in the country in terms of chicken production. It is also the main region supplying chickens to Chattogram city, the second urban centre of the country (35). In 2014, 1,796 farmers in Chattogram reared commercial chickens on 289 layer and 1,507 broiler farms (36).

Sampling Approach

In the absence of a registry of commercial farms in the district, the farms included in this study were selected from a sampling frame of 1,748 commercial chicken farms that was created in 2017 (37). The sampling frame was developed by Gupta et al. (37) through consultation with the Bangladesh District Livestock Services, feed and chick traders, pharmaceutical representatives, and government and private practitioners. Gupta et al. (37) then selected farms using simple random sampling. The same farms were recruited in the current study, but some farms were excluded ($N = 25$) as they were no longer operating or had no chickens at the time of the field visits. Thus, 140 commercial chicken farms (83 broiler and 57 layer farms) in eight subdistricts (*upazilas*) of the Chattogram district were visited between February and May 2019 (**Figure 1**).

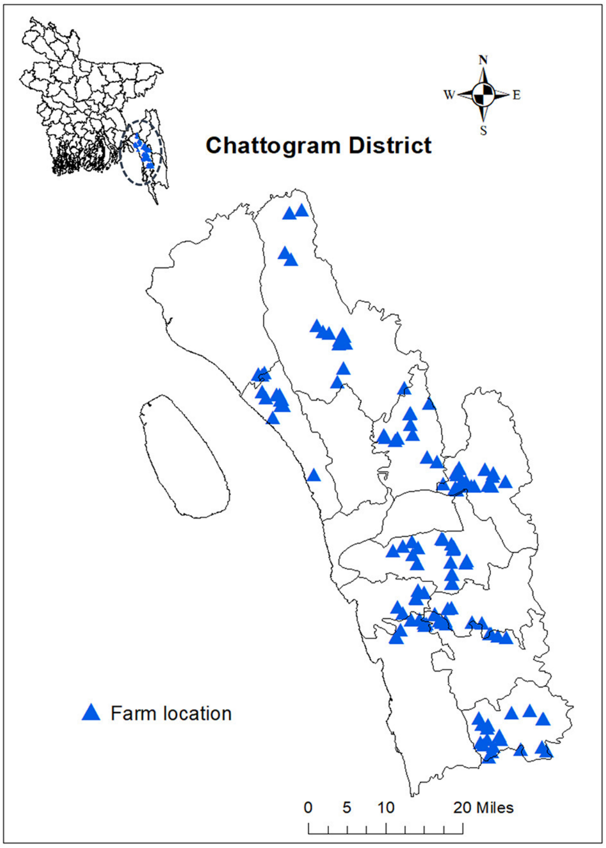


FIGURE 1 | Location of studied commercial chicken farms in Chattogram, Bangladesh.

Questionnaire and Interviews

A structured questionnaire was developed. It included sections on demographic/socioeconomic characteristics of the commercial chicken farmers and chicken management characteristics (flock size, chicken strains, number of sheds, age of chickens, type of the production system). It was piloted on five layer and five broiler farms.

Antimicrobial usage data was collected using a count-based approach, representing the use (yes/no) of an antimicrobial during the current production cycle (38). In addition, data on trade names of antimicrobials with active ingredients derived from trade name labels, purpose of antimicrobial application, frequency, dosage, duration, and route of administration of antimicrobials, adherence to withholding periods, sources from where antimicrobials were obtained, and sources of advice on antimicrobial administration and on sales of antimicrobials by chicken farmers were collected.

We also collected data on clinical signs and diseases observed by farmers in the current production cycle and information on biosecurity practises on farms and on attitudes and behaviours of farmers towards the usage of antimicrobials (**Supplementary Material**).

All collected data related to the current production period for one flock (poultry shed) at the time of the field visit.

When there were several chicken flocks or sheds, the following criteria were used to select the flock or the shed from which the data were collected:

- If the same number of antimicrobials was used in all sheds, the shed with the oldest chickens was selected.
- If the number of antimicrobials used across sheds differed, then the shed with the highest number of antimicrobials used was selected.

People most actively involved in chicken management on the visited farm were interviewed. Consent was obtained from the interviewees before the start of the interview. The interviews were conducted by a team of trained and experienced researchers from Chattogram Veterinary and Animal Sciences University (CVASU). All interviewers were fluent in English and Bangla. The interview was conducted in Bangla and responses were entered by the interviewers in the questionnaire in English. An interview lasted for about 1 h.

Although data on antimicrobial products used was obtained from the interviewees, photographs of antimicrobial packages were also taken to cross-check the information. Photographs of the drug registration book kept on the farms, if available, were also taken.

Data Analysis

Frequencies were computed for farmer demographics (education, experience in poultry production) and antimicrobial usage (percentage of farms using antimicrobials, route of administration, source of antimicrobials, purpose of usage, adherence to withholding periods, sale of antimicrobials, and the occurrence of clinical signs on farms).

An association between any two categorical variables was investigated using a Fisher's exact test (39).

Univariable logistic regression models (40) were developed to assess whether using a given antimicrobial was associated with farm (farm type, flock size) and farmer characteristics (education, experience in poultry farming) the observation of a set of clinical signs during the current production cycle, the source of antimicrobials (veterinary medical stores, feed and chick traders), the purpose of usage, and the sale of antimicrobials by the farmer. Variables associated with a p-value < 0.2 were then considered for the multivariable analysis. A backward stepwise elimination procedure at a 5% level of significance was used to produce the final multivariable logistic regression model. The distributions of the outcome variables and predictors are shown in **Supplementary Tables 5–12**. Once a model with significant predictors was found, the confounding effect was examined by adding omitted predictors again and evaluating a change of the odds ratios by more than 20% (41). Biological plausible interactions were also evaluated in the final models. The overall model fit was examined by the Hosmer–Lemeshow test. The predictive ability of the models was evaluated by computing the area under the curve (AUC) of receiver operating characteristic (ROC) curves.

TABLE 1 | Socioeconomic and demographic characteristics of commercial layer and broiler chicken farmers and a description of the chicken farms in Chattogram, Bangladesh.

Characteristics of the study population			Layer farmers (*N* = 54) % (*N*)	Broiler farmers (*N* = 83) % (*N*)	Fisher's exact *p*-value
Characteristics of chicken farmers	Education level	No education/primary	7.4 (4)	21.7 (18)	0.032
		Secondary/graduate/post graduate	92.6 (50)	78.3 (65)	
	Experience in poultry raising	≤1 year	3.7 (2)	8.4 (7)	0.074
		1–5 years	11.1 (6)	26.5 (22)	
		6-10 years	24.1 (13)	15.7 (13)	
		>10 year	61.1 (33)	49.4 (41)	
	Poultry farming as the only source of income	No	31.5 (17)	41.0 (34)	0.283
		Yes	68.5 (37)	59.0 (49)	
	Sex	Male	100.0 (54)	98.8 (82)	1.000
		Female	0.0 (0)	1.2 (1)	
	Religion	Muslim	92.8 (77)	79.6 (43)	0.038
		Hindu	7.2 (6)	18.5 (10)	
		Buddhist	0.0 (0)	1.9 (1)	
Characteristics of chicken flocks	No. of sheds	1	81.5 (44)	96.4 (80)	0.006
		>1	18.5 (10)	3 (3.6)	
	Flock size	≤500	3.7 (2)	3.6 (3)	<0.001
		501–2500	55.6 (30)	86.6 (72)	
		>2500	40.7 (22)	9.6 (8)	
		Median flock size	2150 birds (Range: 120 to 7880)	1300 birds (Range: 120 to 4880)	
	Age	Mean age	334 days	19 days	
		Median age	357 days (Range: 26 to 720)	18 days (Range: 5 to 45)	

STATA 16 was used for the analysis (1985–2019, StataCorp). Farm locations were plotted across Chattogram district using ArcMAp 10.8 (ArcGIS, 1995–2019 Esri Inc.).

RESULTS

From 140 farms surveyed, 137 (97.9%) used antimicrobials. Data from these 137 farms, which comprised of 60.6% (83/137) broiler and 39.4% (54/137) layer farms, were analysed.

Overview of the Study Population

Flock Characteristics

A total of 81.5% (44/54) of layer and 96.4% (80/83) of broiler farms had one shed only.

Layer flocks, with a median size of 2,150 chickens, were larger than broiler flock, with a median of 1,300 chickens ($p < 0.001$) (**Table 1**). The median age was 357 days for layer and 18 days for broiler flocks (**Table 1**).

The most common layer breed was White Hyline Brown (61.1%, 33/54), followed by Novogen Brown (16.7%, 9/54), Bovans Brown (7.4%, 4/54), White Shaver 579 (5.6%, 3/54), and Hisex Brown (3.7%, 2/54). On broiler farms, Indian River (39.8%, 33/83) and Cobb 500 (38.6%, 32/83) were the most common breeds, followed by 12.0% of Hubbard Classic (10/83) and 8.4% of Ross 308 (7/83). However, for 5.6% (3/54) of the layer and 1.2% (1/83) of the broiler farms the breed was not specified.

Farmer Characteristics

People most actively involved in chicken management on the visited farm were interviewed. In most cases, they were either the farm owner (77.4%, 106/137), or the main farm worker (22.6%, 31/137).

More layer farmers (92.6%, 50/54) had a higher educational qualification (secondary, higher secondary, graduate, or postgraduate level) than broiler farmers (78.3%, 65/83) ($p = 0.032$) (**Table 1**).

Layer farmers were marginally more experienced in poultry farming compared to broiler farmers ($p = 0.074$) (**Table 1**).

Antimicrobial Usage

Antimicrobial Agents, Their Purpose, and Route of Administration

A total of 24 different antimicrobial agents were administered in the current production cycle at the time of the study in 449 different ways (either alone or in combination with other antimicrobials) (**Supplementary Table 1**). Eight of these 24 antimicrobials were most commonly applied (either alone or in combination with other antimicrobials), representing 71.5% (321/449) of the overall usage of antimicrobials on the farms. These eight antimicrobials (colistin, ciprofloxacin, tylosin, neomycin, amoxicillin, trimethoprim sulfonamides, doxycycline, and tiamulin) represent the most frequently used antimicrobials in each of the eight antimicrobial classes (polymyxins, quinolones, macrolides, aminoglycosides, beta lactams, tetracyclines, sulfonamides, and pleuromutilins). Further data analysis focused on these eight antimicrobials.

On layer farms, the most commonly administered antimicrobial was ciprofloxacin 37.0% (20/54), followed by amoxicillin 33.3% (18/54) and tiamulin 31.5% (17/54). On broiler farms, the most commonly administered antimicrobial was colistin 56.6% (47/83), followed by doxycycline 50.6% (42/83) and neomycin 38.6% (32/83). Doxycycline, neomycin and colistin were more frequently applied on broiler farms compared to layer farms ($p < 0.05$), while tiamulin was not used on broiler farms (**Table 2**).

The number of antimicrobials used on farms was categorised in the following groups: 1, 2–3, 4–5, 6, or more. Overall, these (categorised) number of antimicrobials used did not differ between layer and boiler farms ($p = 0.120$). However, most farmers used 2–3 antimicrobials (59.3% of layer and 38.6% of broiler farmers), while usage of 4–5 antimicrobials was more common on broiler than on layer farms (37.3% vs. 22.2%) (**Figure 2**).

Antimicrobials were administered in water by 97.1% (133/137) of farmers (with 91.3% (125/137) of farmers providing them in water only and 5.8% (8/137) in both water and feed) and in feed by 8.7% (12/137) of farmers (with 2.9% (4/137) of farmers providing it in feed only).

Only 15.3% (21/137) of farmers used antimicrobials exclusively for therapeutic purposes, while 84.7% (116/137) of farmers used them prophylactically, administering them either for prophylactic purposes only (22.6% (31/137) of farmers) or in combination with therapeutic purposes (62.1% (85/137) of farmers). The purpose of using antimicrobials did not differ between layer and broiler farms ($p = 0.328$, **Supplementary Table 2**). None of the farmers indicted they used antimicrobials as growth promoters.

Eggs and birds were sold while antimicrobials were still administered in flocks, with 83.3% (45/54) of layer farmers selling eggs, and 36.1% (30/83) of broiler farmers selling birds while administering antimicrobials ($p < 0.001$). The most common antimicrobials used on layer farms while selling eggs were ciprofloxacin (40.0%, 18/45), trimethoprim sulfonamides (35.6%, 16/45), and amoxicillin (33.3%, 15/45). On broiler farms, colistin (66.7%, 20/30), doxycycline (53.3%, 16/30), and ciprofloxacin (46.7%, 14/30) were the most common antimicrobials administered, while broilers were sold. Except for trimethoprim sulfonamide usage on layer farms, there was no difference at $p < 0.05$ between farms selling eggs or broilers and not selling eggs or broilers while administering antimicrobials for the type of antimicrobials used (**Supplementary Table 3**). Broiler farmers (63.9%, 53/83) who stopped using antimicrobials before selling their birds stopped on average 4.2 (95% CI: 3.6, 4.8) days (Median: 3) before the sale of birds.

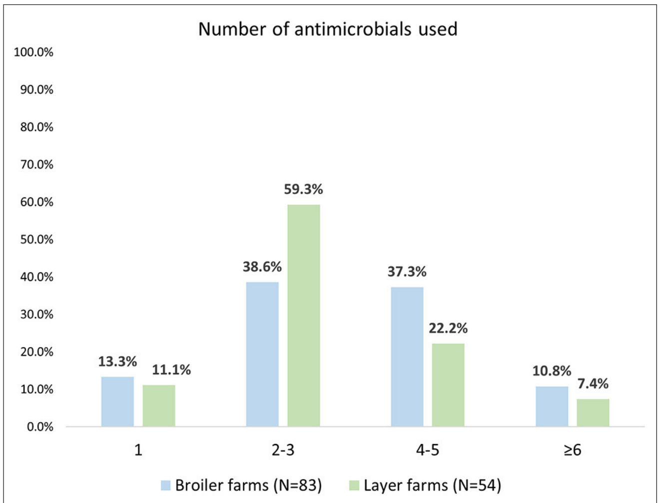


FIGURE 2 | Number of antimicrobials used on layer and broiler farms in Chattogram, Bangladesh.

Clinical Signs for Which Antimicrobials Were Used

Overall, 75.2% (103/137) of farmers reported clinical signs (alone or in combination) during the production period, while 24.8% (34/137) of farmers did not observe any clinical signs of disease.

Antimicrobials were most frequently used for respiratory signs (alone or in combination with other signs) (71.8%, 74/103), followed by enteric signs (32.0%, 33/103). Antimicrobials were used to address increased mortality (alone or in combination with other signs) on 16.5% (17/103) of farms, while 16.5% (17/103) of farmers administered antimicrobials to prevent and/or treat swollen head, ascites, in-appetence, and eye problems. Decreased egg production or poor-quality eggs were specified by 20.4% (11/54) of layer farmers as a reason for using antimicrobials (**Supplementary Table 4**).

Colistin and ciprofloxacin were the most frequently used antimicrobials on farms reporting respiratory signs (41.9%, 31/74; 41.9%, 31/74), enteric signs (48.5%, 16/33; 45.5%, 15/33), and increased mortality (29.4%, 5/17; 35.3%, 6/17), as well as single miscellaneous signs, such as swollen head, ascites, in-appetence, and/or eye problem. However, doxycycline (45.5%, 5/11) and tiamulin (45.5%, 5/11) were preferred to address a reduction in egg production. In the absence of clinical signs, colistin (47.1%, 16/34), doxycycline (32.4%, 11/34), and amoxicillin (29.4%, 10/34) were the most frequent antimicrobials administered (**Figure 3**).

TABLE 2 | Antimicrobials used (according to medical importance) on commercial layer and broiler farms in Chattogram, Bangladesh.

Importance of antimicrobials[a]	Usage of antimicrobials on commercial chicken farms[b]		Layer farmers (*N* = 54)	Broiler farmers (*N* = 83)	Fisher's exact test *p*-value
			% (*N*)	% (*N*)	
Highest Priority Critically Important	Colistin	Yes	27.8 (15)	56.6 (47)	0.001
		No	72.2 (39)	43.4 (36)	
	Ciprofloxacin	Yes	37.0 (20)	33.7 (28)	0.717
		No	63.0 (34)	66.3 (55)	
	Tylosin	Yes	16.7 (9)	20.5 (17)	0.659
		No	83.3 (45)	79.5 (66)	
High-Priority Critically Important	Neomycin	Yes	7.4 (4)	38.6 (32)	<0.001
		No	92.6 (50)	61.4 (51)	
	Amoxicillin	Yes	33.3 (18)	32.5 (27)	1.000
		No	66.7 (36)	67.5 (56)	
Highly Important	Trimethoprim sulfonamides (SXT)	Yes	29.6 (16)	18.1 (15)	0.144
		No	70.4(38)	81.9 (68)	
	Doxycycline	Yes	25.9 (14)	50.6 (42)	0.005
		No	74.1 (40)	49.4 (41)	
Important	Tiamulin[c]	Yes	31.5 (17)	0.0 (0)	<0.001
		No	68.5 (37)	100.0 (83)	

Usage relates to the application of antimicrobials in the current production cycle at the time of the survey in 2019 (mean age of layers: 334 days, mean age of broilers: 19 days).
[a]Classified as per WHO Critically Important Antimicrobials for Human Medicine 6th revision.
[b]Most frequently used antimicrobials, representing 71.5% of overall usage.
[c]Tiamulin was not used on commercial broiler farms during the time of the survey.

Source of Antimicrobials

Farmers bought antimicrobials most frequently (sole source or in combination with other sources) from feed and chick traders (43.8%, 60/137), veterinary medical stores (44.5%, 61/137), and pharmaceutical representatives (5.1%, 7/137). More specifically, farmers bought antimicrobials only from feed and chick traders in 37.2% (51/137) of cases and from veterinary medical stores only in 35.0% of cases (48/137). Broiler farmers were more likely to purchase antimicrobials only from feed and chick traders (45.8%, 38/83) compared to layer farmers (24.1%, 13/54) ($p = 0.012$).

The usage of individual antimicrobials on farms was not associated with the supply of antimicrobials through feed and chick traders ($p > 0.05$) **Supplementary Tables 5-12**. Doxycycline and colistin were the antimicrobials used by farmers that were less likely purchased from veterinary medical stores ($p = 0.017$ and $p = 0.041$, respectively) **Supplementary Tables 6**, **11**.

About 16.1% (22/137) of farmers sold antimicrobials to other farmers.

Factors Associated With Antimicrobial Usage

Univariable logistic regression models for each of the most commonly used antimicrobials, namely, colistin, ciprofloxacin, tylosin, neomycin, amoxicillin, trimethoprim sulfonamides, doxycycline, and tiamulin, are shown in **Supplementary Tables 5-12**.

Factors with p-values < 0.05 in the multivariable models were identified for trimethoprim sulfonamides and neomycin.

Farmers were 3.1 times (95% CI: 1.3–7.8) more likely to administer trimethoprim sulfonamides for respiratory signs (**Table 3**). Farmers were also 3.1 (95% CI: 1.3–7.7) more likely to use trimethoprim sulfonamides for enteric signs (**Table 3**). The model for trimethoprim sulfonamides usage showed a good fit (Hosmer–Lemeshow p-value = 0.681, AUC = 0.68).

The odds of using neomycin was higher in broiler than layer farms (OR = 8.3, 95% CI = 2.7–25.6) and among farmers selling antimicrobials (OR = 3.2, 95% CI = 1.1–9.1) (**Table 4**). The model for neomycin usage showed a good fit (Hosmer–Lemeshow p-value = 0.201, AUC = 0.74).

DISCUSSION

Our study highlighted that usage of antimicrobials is very common in the commercial poultry industry of Bangladesh, with almost all broiler and layer farmers administrating antimicrobials to their flocks. Use of medically important antimicrobials, non-adherence to withholding periods, usage of antimicrobials despite the non-occurrence of any clinical signs, and sales of antimicrobials without veterinary advice were frequently reported.

There is little reliable data on the extent of antimicrobials usage in the livestock production system across South East Asia (42–44) and in particular, from commercial poultry farms in Bangladesh (15, 32). We were able to provide detailed data of antimicrobial usage in the commercial layer and broiler industry of Bangladesh. In addition, while previous studies used convenience sampling to describe antimicrobial usage on

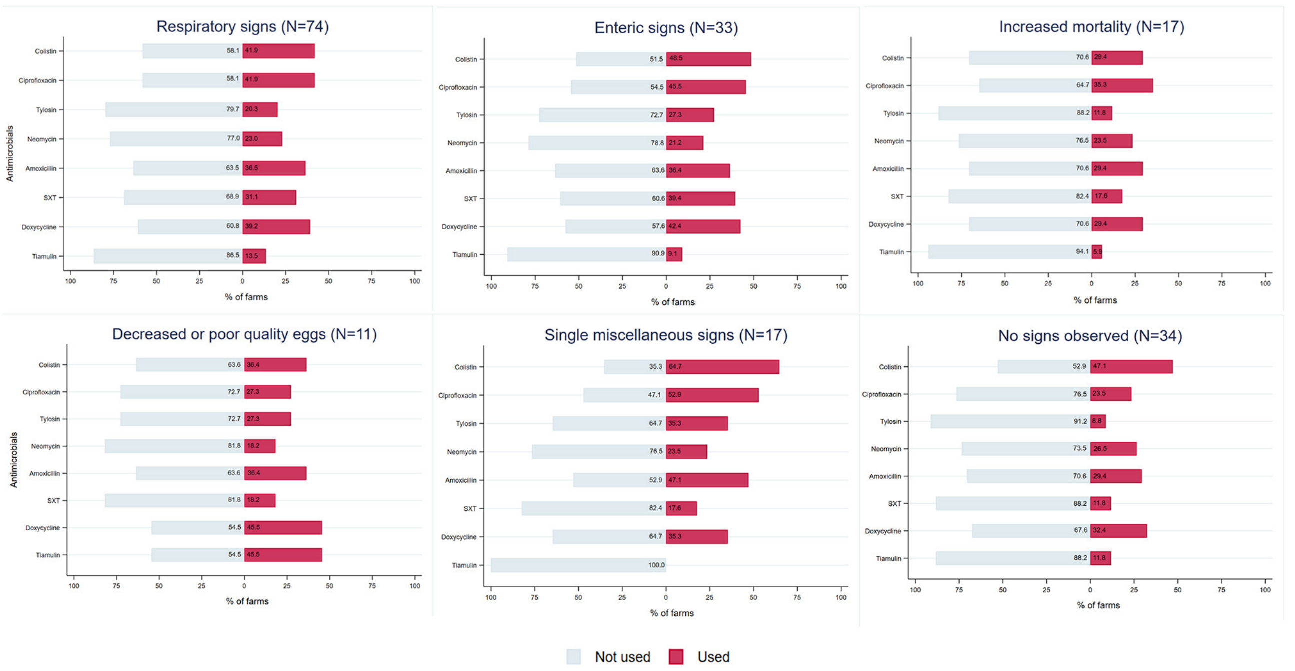


FIGURE 3 | Types of antimicrobial used (percent usage) by commercial layer and broiler farmers in Chattogram, Bangladesh, for clinical signs reported on these farms. Usage relates to the application of antimicrobials in the current production cycle at the time of the survey in 2019 (mean age of layers: 334 days, mean age of broilers: 19 days). Most frequently used antimicrobials are presented here, representing 71.5% of overall usage.

TABLE 3 | Results of the multivariable analysis for risk factors associated with the use of trimethoprim sulfonamides on commercial chicken farms in Bangladesh in 2019.

Risk factors	Category	OR[a] (95% CI[b])	Logistic regression *p*-value
Occurrence of respiratory signs	No	Ref	0.014
	Yes	3.1 (1.3–7.8)	
Occurrence of enteric signs	No	Ref	0.012
	Yes	3.1 (1.3–7.7)	

[a]*Odds ratio.*
[b]*Confidence interval.*

commercial poultry farms (45, 46), we used a random sampling approach, increasing the external validity of our study findings.

The majority of farmers used antimicrobials for prophylactic purposes. Prophylactic administration of antimicrobials may be conducted to compensate for substandard farm management conditions, to prevent frequently occurring poultry diseases (13) or because vaccinations against poultry diseases were not conducted. Furthermore, cost associated with veterinary treatments (47) might result in farmers administering drugs prophylactically in order to prevent severe clinical events that require substantial, and expensive, veterinary interventions. Farmers may also have difficulties in accessing veterinary services to diagnose diseases. Laboratory confirmation of livestock, including poultry, diseases in Bangladesh is only conducted in District Veterinary Hospitals, Regional Field Diseases Investigation Laboratories, and the Central Disease Investigation Laboratory of Department of Livestock Services (48), which represents only a small number of laboratories compared to the number of poultry farms in Bangladesh. Thus, farmers might be unable to use these laboratories to diagnose diseases from samples collected, which could result in a widespread prophylactic administration of antimicrobials based on farmers' perceptions of disease risk or their own experience.

It has been shown that antimicrobial usage on commercial poultry farms is strongly driven by advice provided from antimicrobial suppliers; in particular, feed and chick traders who closely work with representatives of drug companies to achieve target sales, may have influenced farmers' behaviours in using antimicrobials (33). A large proportion of commercial chicken farmers were supplied with antimicrobials from feed and chick traders. The use of antimicrobials may be influenced by contractual agreements with the feed and chick traders who supply all production inputs (e.g., day-old chicks and feed) in credit to farmers and then purchase the poultry products from farmers at pre-arranged prices (33). This practise is more common among broiler than layer farmers; thus,

TABLE 4 | Results of the multivariable analysis for risk factors associated with the use of neomycin on commercial chicken farms in Bangladesh in 2019.

Risk factors	Category	OR[a] (95% CI[b])	Logistic regression *p*-value
Farm type	Layer	Ref	<0.001
	Broiler	8.3 (2.7–25.6)	
Sale of antimicrobials to other commercial chicken farmers	No	Ref	0.030
	Yes	3.2 (1.1–9.1)	

[a]*Odds ratio.*
[b]*Confidence interval.*

these transactional arrangements likely explain the differences observed between the two production types in this study.

Farmers did not report the use of antimicrobials as growth promoters. It has been suggested that the use of antimicrobials for growth promotion might represent a considerable cost for farmers, and therefore, they might refrain from using antimicrobials for this purpose (15).

Eight antimicrobials were most frequently administered in our study area (either alone or in combination with other antimicrobials). These antimicrobials are commonly used in the poultry industry and included colistin, ciprofloxacin, and tylosin, which are considered as "Highest Priority Critically Important Antimicrobials" for public health (49). Indeed, Colistin is used as last resort for the treatment of infections with *Enterobacteriaceae* and *Pseudomonas aeruginosa*, while tylosin is used for *Legionella*, *Campylobacter* spp., MDR *Salmonella* spp., and *Shigella* infections, and ciprofloxacin for the treatment of *Campylobacter* spp. and *Salmonella* spp. infections (50). It is recommended that ciprofloxacin and colistin should not to be administered in animals as first-line therapy and should only be used after obtaining culture and susceptibility test results. In fact, ciprofloxacin and colistin should not be administered at all to any food-producing animals including chickens in the absence of any clinical signs (51). Surprisingly, many farmers used antimicrobials (including ciprofloxacin, tylosin, and colistin) without observing any clinical signs, and even when they did observe some, the decision to use those antimicrobials was rarely informed by veterinarians.

The use of colistin, doxycycline, and neomycin was higher on broiler farms compared to layer farms. Doxycycline was also more commonly administered by less experienced broiler farmers and was often administered in combination with other antimicrobials, including colistin. The frequent use of colistin may reflect the fact that they are considered as an "essential" antimicrobial in the poultry industry and have been used there for a long time (52).

Neomycin was more frequently used on broiler farms and by farmers who sell antimicrobials. The relatively low cost of neomycin may be the reason for its frequent usage (53) but also its re-sale by commercial farmers.

Similar to previous research, farmers in our study mostly mixed antimicrobials into water (33). This is in accordance with the Bangladesh Fish Feed and Animal Feed Act 2010, which highlights that antimicrobials are not permitted to be added into feed (54). However, some farmers in our study were breaching the Act by administering antimicrobials in feed.

Layer farmers reported selling eggs and broiler farmers selling chickens while administering antimicrobials. Antimicrobial residues was previously found in poultry in Bangladesh (55–57). For instance, trimethoprim sulfonamides, which were frequently used by layer farmers while selling eggs, are not approved to be used in laying chickens as the trimethoprim residues can be detected in egg yolk as well as albumen for more than 7 days after its administration (58). Farmers in Bangladesh may not be aware of withholding periods and the residual effects of antimicrobials (32). There may also be a lack of information from veterinarians on withdrawal periods of antimicrobials (32). Furthermore, continuous occurrence of clinical signs might result in farmers deciding to constantly use antimicrobials on their chickens until the time of sale of their poultry products (59).

A lack of monitoring from governmental agencies had been previously identified as a reason why withholding periods were not adhered to by farmers (32). This includes monitoring of farm management practises but also monitoring antimicrobial residues according to Codex standards (60). Unfortunately, there are limited facilities in Bangladesh to conduct residue analysis in tissues of animal origin (61). Establishing government or private laboratories with infrastructure and expertise in identifying residues will assist in residue detection and in monitoring appropriate antimicrobial use. However, it is uncertain if farmers would actually submit samples for residue testing—such residue monitoring is usually conducted by regulatory bodies.

In Bangladesh, only registered veterinarians are authorised to prescribe antimicrobials as per the Bangladesh Veterinary Practitioners Ordinance, 1982 (62) and only registered pharmacists are permitted to sell antimicrobials with a prescription as per Drug Act 1940 (63). Thus, veterinarians only prescribe, but do not sell, antimicrobials in Bangladesh. However, in practise, antimicrobials are available in Bangladesh "over the counter" from veterinary medical stores without prescriptions.

Sixteen percent of farmers sold antimicrobials to other farmers. These arrangements make antimicrobials very accessible in Bangladesh and increase the risk of their improper use on poultry farms. Easy access to antimicrobials is not unique to Bangladesh and has also been described for other Southeast Asian countries such as India, Indonesia, Nepal, Bhutan, Thailand, Sri Lanka, and Maldives (44).

Our study had a number of limitations. Firstly, due to the retrospective nature of the data collection, we could not observe the clinical signs and relied on farmers' reports. Recall bias might have also impacted the reporting by farmers. Furthermore, this study only collected data on clinical signs reported during the production period and antimicrobials used in that production period. However, farmers did not keep records of the antimicrobials they used in response to which clinical signs and for what duration. We collected data on the dosage of antimicrobials administered to chickens, but the data quality was poor and did not permit a reliable analysis. A prospective study with detailed (daily) observations on clinical signs, diseases antimicrobial usage (including dosage and duration), and treatment outcomes would be able to better explore the association between antimicrobial usage and the motivations for its application.

Based on the results of this study, it is recommended that farmers should keep records of antimicrobials used with dosage and duration of administration along with the use of specific antimicrobials against which diseases or clinical signs. This would certainly allow farmers and veterinarians to evaluate if antimicrobial usage had the desired outcome and allow adherence to withholding periods.

Education or extension programs for poultry farmers on the use of antimicrobials are highly warranted. Such training should encompass information on withholding periods for antimicrobial usage and should highlight the importance of vaccinations to control viral and bacterial infections in poultry. The association between good biosecurity and infection control practises and diseases needs to be highlighted in order to reduce the further use of antimicrobials. Extension programs are implemented in Bangladesh by government and nongovernmental agencies. The Department of Livestock and Services in Bangladesh drafted a "National Livestock Extension Policy 2013" and highlighted the importance of establishing collaborative livestock extension services that include all stakeholders (64). In case of antimicrobial applications in the poultry industry, this would include, in addition to the poultry farmers, also suppliers of antimicrobials (e.g., feed and chick traders and veterinary medical representatives).

Changing regulatory frameworks is most challenging. Currently, no enforced national strategy for the control of antimicrobials in food animals exists for Bangladesh. The Ministry of Health and Family Welfare has developed a national action plan (2017–2022) for antimicrobial resistance containment in Bangladesh (65), but unfortunately relevant policies have not been implemented yet (66).

Also, prohibiting over-the-counter sales of antimicrobials without the prescription from a registered veterinarian is not enforced in Bangladesh. Recently, a ruling of the High Court Division of the Supreme Court of Bangladesh highlighted that sales of antimicrobials should only be conducted with prescription (67). It is recommended to closely work with farmers' to evaluate societal factors influencing poultry management practises in order to develop evidence-based and practical policies for farmers to reduce and modify antimicrobial usage.

In conclusion, our research highlights the challenges faced by commercial poultry producers in Bangladesh and outlined opportunities to improve the appropriate use of antimicrobial agents under an antimicrobial stewardship approach.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Human Ethics. Approval for the interviews was obtained from the University of Queensland Institutional Human Ethics Committee on the 7 December 2018 (Approval number: 2018002266). Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements. Ethical review and approval was not required for the animal study because the respondents were farmers of commercial chicken farms.

AUTHOR CONTRIBUTIONS

JH, GF, and MH designed the research study and obtained the funding for the field research. The questionnaire was developed by TI with inputs from JH, JG, and SG. The data collection strategy was developed by JH, GF, MH, TI, and SG. Data collection was conducted by MF and SD. TI conducted data analysis under the guidance of JH, GF, and JG. TI prepared the initial draft, figures, tables, and supplementary materials, with edits provided by JH and JG. All authors have read, contributed to, and approved the final version of the manuscript.

FUNDING

This field data collection was supported by the BALZAC research program Behavioural adaptations in live poultry trading and farming systems and zoonoses control in Bangladesh (BB/L018993/1), a joint research initiative between the Biotechnology and Biological Sciences Research Council, the Defence Science and Technology Laboratory, the Department for International Development, the Economic and Social Sciences Research Council, the Medical Research Council, and the Natural Environment Research Council. TI was supported by Australia Awards Scholarship.

ACKNOWLEDGMENTS

We are grateful to the farmers for participating in the survey. Also, we thank the CVASU research team for helping with the data collection. We also acknowledged the support provided to GF, MH, and JH by the UKRI GCRF One Health Poultry Hub (Grant no. BB/S011269/1), 1 of 12 interdisciplinary research hubs funded under the UK government's Grand Challenge Research Fund Interdisciplinary Research Hub initiative.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fvets.2020.576113/full#supplementary-material

REFERENCES

1. Thornton PK. Livestock production: recent trends, future prospects. *Phil Trans R Soc.* (2010) 365:2853–67. doi: 10.1098/rstb.2010.013
2. Das SC, Chowdhury SD, Khatun MA, Nishibori M, Isobe N, Yoshimura Y. Poultry production profile and expected future projection in Bangladesh. *World Poult Sci J.* (2008) 64:99–117. doi: 10.1017/S0043933907001754
3. Chowdhury S. Family poultry production in Bangladesh: is it meaningful or an aimless journey? *World Poult Sci J.* (2013) 69:649–65. doi: 10.1017/S0043933913000652
4. Hamid M, Rahman M, Ahmed S, Hossain K. Status of poultry industry in Bangladesh and the role of private sector for its development. *Asian J Poult Sci.* (2017) 11:1–13. doi: 10.3923/ajpsaj.2017.1.13
5. Dolberg F. *Poultry Sector Country Review, Bangladesh*. Rome: FAO. (2008).p. 17-28.
6. Food and Agriculture Organisation. *Change in the Livestock Sector*. (2009). Available online at: http://www.fao.org/3/i0680e/i0680e02.pdf [Accessed February 11, 2020].
7. Badruzzaman A, Noor M, Mamun M, Husna A, Islam K, Alam K, et al. Prevalence of diseases in commercial chickens at Sylhet Division of Bangladesh. *Int Clin Pathol J.* (2015) 1:104–8. doi: 10.15406/icpjl.2015.01.00023
8. Bari MS, Rana EA, Abid MH, Akter N, Sayeed MA. Prevalence of poultry diseases in winter season in Chittagong and efficacy of challenge vaccine against Newcastle disease. *Res Agric Livest Fish.* (2018) 5:201–8.
9. Hassan MK, Kabir MH, Hasan MAA, Sultana S, Khokon MSI, Kabir SL. Prevalence of poultry diseases in Gazipur district of Bangladesh. *Asian J Med Biol Res.* (2016) 2:107–12. doi: 10.3329/ajmbr.v2i1.27575
10. Rahman M, Adhikary G. Poultry diseases in some selected areas in Sylhet district of Bangladesh. *J Sylhet Agril Univ.* (2016) 3:1.
11. Uddin M, Ahmed S, Hassan M, Khan S, Mamun M. Prevalence of poultry diseases at Narsingdi, Bangladesh. *Int J Biol Res.* (2010) 1:6.
12. Raha S. *Poultry Industry in Bangladesh: Present Status and Future Potential.* Mymensingh: Agricultural University of Mymensingh. (2000).
13. Roess AA, Winch PJ, Ali NA, Akhter A, Afroz D, El Arifeen S, et al. Animal husbandry practices in rural Bangladesh: potential risk factors for antimicrobial drug resistance and emerging diseases. *Am J Trop Med Hyg.* (2013) 89:965–70. doi: 10.4269/ajtmh.12-0713
14. World Organisation for Animal Health. *OIE Annual Report on Antimicrobial Agents Intended for Use in Animals: Better Understanding of the Global Situation.* (2020). Available online at: https://www.oie.int/fileadmin/Home/eng/Our_scientific_expertise/docs/pdf/AMR/A_Fourth_Annual_Report_AMR.pdf [Accessed September 22, 2020].
15. Islam KBMS, Shiraj-Um-Mahmuda S, Hazzaz-Bin-Kabir M. Antibiotic usage patterns in selected broiler farms of Bangladesh and their public health implications. *J Public Health Dev Ctries.* (2016) 2:276–84.
16. Franco DA, Webb J, Taylor CE. Antibiotic and sulfonamide residues in meat: Implications for human health. *J Food Prot.* (1990) 53:178–85.
17. Agunos A, Gow SP, Léger DF, Carson CA, Deckert AE, Bosman AL, et al. Antimicrobial use and antimicrobial resistance indicators integration of farm-level surveillance data from broiler chickens and turkeys in British Columbia, Canada. *Front Vet Sci.* (2019) 6:131. doi: 10.3389/fvets.2019.00131
18. Luiken REC, Van Gompel L, Munk P, Sarrazin S, Joosten P, Dorado-García A, et al. Associations between antimicrobial use and the faecal resistome on broiler farms from nine European countries. *J Antimicrob Chemother.* (2019) 74:2596–604. doi: 10.1093/jac/dkz235
19. Nhung N, Cuong N, Thwaites G, Carrique-Mas J. Antimicrobial usage and antimicrobial resistance in animal production in Southeast Asia: a review. *Antibiotics.* (2016) 5:37. doi: 10.3390/antibiotics5040037
20. Persoons D, Haesebrouck F, Smet A, Herman L, Heyndrickx M, Martel A, et al. Risk factors for ceftiofur resistance in Escherichia coli from Belgian broilers. *Epidemiol Infect.* (2011) 139:765–71. doi: 10.1017/S0950268810001524
21. Weese J, Giguère S, Guardabassi L, Morley P, Papich M, Ricciuto D, et al. ACVIM consensus statement on therapeutic antimicrobial use in animals and antimicrobial resistance. *J Vet Intern Med.* (2015) 29:487–98. doi: 10.1111/jvim.12562
22. Ferri M, Ranucci E, Romagnoli P, Giaccone V. Antimicrobial resistance: A global emerging threat to public health systems. *Crit Rev Food Sci Nutr.* (2017) 57:2857–76. doi: 10.1080/10408398.2015.1077192
23. Gandra S, Barter DM, Laxminarayan R. Economic burden of antibiotic resistance: how much do we really know? *Clin Microbiol Infect.* (2014) 20:973–9. doi: 10.1111/1469-0691.12798
24. Cosgrove SE, Carmeli Y. The impact of antimicrobial resistance on health and economic outcomes. *Clin Infect Dis.* (2003) 36:1433–7. doi: 10.1086/375081
25. Ho P-L, Wong RC, Lo SW, Chow K-H, Wong SS, Que T-L. Genetic identity of aminoglycoside-resistance genes in *Escherichia coli* isolates from human and animal sources. *J Med Microbiol.* (2010) 59:702–7. doi: 10.1099/jmm.0.015032-0
26. Hoelzer K, Wong N, Thomas J, Talkington K, Jungman E, Coukell A. Antimicrobial drug use in food-producing animals and associated human health risks: what, and how strong, is the evidence? *BMC Vet Res.* (2017) 13:211. doi: 10.1186/s12917-017-1131-3
27. Johnson JR, Sannes MR, Croy C, Johnston B, Clabots C, Kuskowski MA, et al. Antimicrobial drug–resistant *Escherichia coli* from humans and poultry products, Minnesota and Wisconsin, 2002–2004. *Emerging Infect Dis.* (2007) 13:838–46. doi: 10.3201/eid1306.061576
28. Gerd H, Heike Theresia P, Silke S, Heinz N, Jörg H. Antibiotics in dust originating from a pig-fattening farm: a new source of health hazard for farmers? *Environ Health Perspect.* (2003) 111:1590–4. doi: 10.1289/ehp.6288
29. Shawn GG, Christopher FG, Patrick MT, Linda CM, Kristina DM, Pasquale VS. Isolation of antibiotic-resistant bacteria from the air plume downwind of a swine confined or concentrated animal feeding operation. *Environ Health Perspect.* (2006) 114:1032–7. doi: 10.1289/ehp.8910
30. Nisha A. Antibiotic residues - a global health hazard. *Vet World.* (2008) 2:375–7. doi: 10.5455/vetworld.2008.375-377
31. Khatun R, Howlader MAJ, Ahmed S, Islam MN, Hasan MA, Haider MS, et al. Impact of training and monitoring of drug used by small scale poultry farmers at different location of Bangladesh. *AJFSH.* (2016) 2:134–40.
32. Ferdous J, Sachi S, Zakaria Al Noman S, Hussani YAS, Sikder MH. Assessing farmers' perspective on antibiotic usage and management practices in small-scale layer farms of Mymensingh district, Bangladesh. *Vet World.* (2019) 12:1441–7. doi: 10.14202/vetworld.2019.1441-1447
33. Masud AA, Rousham EK, Islam MA, Alam M-U, Rahman M, Mamun AA, et al. Drivers of antibiotic use in poultry production in Bangladesh: dependencies and dynamics of a patron-client relationship. *Front Vet Sci.* (2020) 7:78. doi: 10.3389/fvets.2020.00078
34. Directorate General of Drug Administration. National Drug Policy 2016. *Ministry of Health & Family Welfare, Government of the People's Republic of Bangladesh*. (2016). Available online at: https://www.dgda.gov.bd/index.php/laws-and-policies/261-national-drug-policy-2016-english-version/file [Accessed September 29, 2020].
35. Moyen N, Ahmed G, Gupta S, Tenzin T, Khan R, Khan T, et al. A large-scale study of a poultry trading network in Bangladesh: implications for control and surveillance of avian influenza viruses. *BMC Vet Res.* (2018) 14:12. doi: 10.1186/s12917-018-1331-5
36. DLS. *Annual Report on Livestock 2014.* The Department of Livestock Services (DLS), Ministry of Fisheries and Livestock, Government of the People's Republic of Bangladesh (2014). Available online at: http://blri.portal.gov.bd/sites/default/files/files/blri.portal.gov.bd/page/035f0e9b_397c_4e24_83ec_b42dff87e9c8/ANNUAL%20REPORT%202014.pdf [Accessed September 16, 2020].
37. Gupta SD, Hoque MA, Fournié G, Henning J. Patterns of Avian Influenza A (H5) and A (H9) virus infection in backyard, commercial broiler and layer chicken farms in Bangladesh. *Transbound Emerg Dis.* (2020) 00:1–15. doi: 10.1111/tbed.13657
38. Pim S, Wannes V, Mette F, Klemens F, Walter O, Agnes A, et al. Monitoring of farm-level antimicrobial use to guide stewardship: overview of existing systems and analysis of key components and processes. *Front Vet Sci.* (2020) 7:540. doi: 10.3389/fvets.2020.00540
39. Fisher RA. On the interpretation of χ 2 from contingency tables, and the calculation of P. *J R Stat Soc.* (1922) 85:87–94. doi: 10.2307%2F2340521
40. Hosmer DW, Lemeshow S, Sturdivant RX. *Applied Logistic Regression*. Hoboken, NJ: John Wiley & Sons, Inc. (2013).p. 7.

41. Bursac Z, Gauss CH, Williams DK, Hosmer DW. Purposeful selection of variables in logistic regression. *Source Code Biol Med.* (2008) 3:17. doi: 10.1186/1751-0473-3-17
42. Coyne L, Arief R, Benigno C, Giang VN, Huong LQ, Jeamsripong S, et al. Characterizing antimicrobial use in the livestock sector in three south east asian countries (Indonesia, Thailand, and Vietnam). *Antibiotics.* (2019) 8:33. doi: 10.3390/antibiotics8010033
43. Kakkar M, Chatterjee P, Chauhan AS, Grace D, Lindahl J, Beeche A, et al. Antimicrobial resistance in South East Asia: time to ask the right questions. *Glob Health Action.* (2018) 11:1483637. doi: 10.1080/16549716.2018.1483637
44. Goutard FL, Bordier M, Calba C, Erlacher-Vindel E, Góchez D, de Balogh K, et al. Antimicrobial policy interventions in food animal production in South East Asia. *BMJ.* (2017) 358:36–41.
45. Klare I, Badstübner D, Konstabel C, Böhme G, Claus H, Witte W. Decreased incidence of VanA-type vancomycin-resistant enterococci isolated from poultry meat and from fecal samples of humans in the community after discontinuation of avoparcin usage in animal husbandry. *Microb Drug Resist.* (1999) 5:45–52.
46. Endtz HP, Ruijs GJ, van Klingeren B, Jansen WH, van Der Reyden T, Mouton RP. Quinolone resistance in campylobacter isolated from man and poultry following the introduction of fluoroquinolones in veterinary medicine. *J Antimicrob Chemother.* (1991) 27:199–208. doi: 10.1093/jac/27.2.199
47. Okeke IN, Laxminarayan R, Bhutta ZA, Duse AG, Jenkins P, O'Brien TF, et al. Antimicrobial resistance in developing countries. Part I: recent trends and current status. *Lancet Infect Dis.* (2005) 5:481–93. doi: 10.1016/S1473-3099(05)70189-4
48. Department of Livestock Services. *National Livestock Development Policy 2007.* Ministry of Fisheries and Livestock, Government of the People's Republic of Bangladesh (2007). Available online at: http://nda.erd.gov.bd/en/c/publication/national-livestock-development-policy-2007#:\sim:text=The%20National%20Livestock%20Development%20Policy,economic%20growth%20for%20reduction%20of [Accessed September 30, 2020].
49. World Health Organization. *Critically Important Antimicrobials for Human Medicine*. (2019). Available online at: https://apps.who.int/iris/bitstream/handle/10665/312266/9789241515528-eng.pdf [Accessed February 14, 2020].
50. World Health Organization. Critically Important Antimicrobials for Human Medicine: Ranking of Antimicrobial Agents for Risk Management of Antimicrobial Resistance Due to Non-Human Use (2017). Available online at: https://apps.who.int/iris/bitstream/handle/10665/255027/9789241512220-eng.pdf [Accessed February 14, 2020].
51. World Organisation for Animal Health. *OIE List of Antimicrobial Agents of Veterinary Importance.* (2019). Available online at: https://www.oie.int/fileadmin/Home/eng/Specific_Issues/docs/pdf/OIE_list_antimicrobials.pdf [Accessed February 14, 2020].
52. Lees P, Pelligand L, Giraud E, Toutain PL. A history of antimicrobial drugs in animals: evolution and revolution. *J Vet Pharmacol Ther.* (2020) 00:1–35. doi: 10.1111/jvp.12895
53. Szaniszlo B, Iuga C, Bojita M. Indirect determination of neomycin by derivative spectrophotometry. *Clujul Med.* (2011) 84:398–401.
54. Bangladesh Gazette. *Fish Feed and Animal Feed Act 2010.* (2010). Available online at: http://extwprlegs1.fao.org/docs/pdf/bgd165024.pdf [Accessed September 10, 2020].
55. Chowdhury S, Hassan MM, Alam M, Sattar S, Bari MS, Saifuddin AK, et al. Antibiotic residues in milk and eggs of commercial and local farms at Chittagong, Bangladesh. *Vet World.* (2015) 8:467–71. doi: 10.14202/vetworld.2015.467-471
56. Ferdous J, Bradshaw A, Islam SKMA, Zamil S, Islam A, Ahad A, et al. Antimicrobial residues in chicken and fish, Chittagong, Bangladesh. *EcoHealth.* (2019) 16:429–40.
57. Sattar S, Hassan MM, Islam SKMA, Alam M, Faruk SA, Chowdhury S, et al. Antibiotic residues in broiler and layer meat in Chittagong district of Bangladesh. *Vet World.* (2014) 7:738. doi: 10.14202/vetworld.2014.738-743
58. Goetting V, Lee KA, Tell LA. Pharmacokinetics of veterinary drugs in laying hens and residues in eggs: a review of the literature. *J Vet Pharmacol Ther.* (2011) 34:521–56. doi: 10.1111/j.1365-2885.2011.01287.x
59. Kigozi MM, Higenyi J. Evaluation of farmer's knowledge and application of guidelines on use of veterinary antibiotics in layer poultry production in Mukono district, central Uganda. *Livest Res Rural.* (2017) 29:176.
60. FAO. *Codex Alimentarius*. (1963). Available online at: http://www.fao.org/fao-who-codexalimentarius/en/ [Accessed September 13, 2020].
61. Haque, M. Antimicrobial use, prescribing, and resistance in selected ten developing countries: a brief overview. *Asian J Pharm Clin Res.* (2017) 10:37–45.
62. Bangladesh Gazette. *Bangladesh Veterinary Practitioners Ordinance 1982.* (1982). Available online at: https://www.dpp.gov.bd/upload_file/gazettes/384-Law-1985.pdf [Accessed January 24, 2020].
63. Bangladesh Gazette. *Drugs Act 1940.* (1940). Available online at: https://dgda.portal.gov.bd/sites/default/files/files/dgda.portal.gov.bd/law/e4b84e61_6b76_43d6_b235_3e489f68220a/drugs-act-1940.pdf [Accessed January 25, 2020].
64. Department of Livestock Services. *National Livestock Extension Policy 2013.* Ministry of Fisheries and Livestock, Government of the People's Republic of Bangladesh (2013). Available online at: http://old.dls.gov.bd/Final%20Draft%20%20of%20National%20Extension%20Policy.pdf [Accessed October 10, 2020].
65. Directorate General of Health Services. *National Action Plan. Antimicrobial Resistance Containment in Bangladesh 2017–2022*. Disease Control Division, Communicable Disease Control Program, Ministry of Health & Family Welfare, Government of the People's Republic of Bangladesh (2017). Available online at: https://www.flemingfund.org/wp-content/uploads/d3379eafad36f597500cb07c21771ae3.pdf [Accessed October 24, 2020].
66. Orubu ESF, Zaman MH, Rahman MT, Wirtz VJ. Veterinary antimicrobial resistance containment in Bangladesh: evaluating the national action plan and scoping the evidence on implementation. *J Glob Antimicrob Resis.* (2020) 21:105–15. doi: 10.1016/j.jgar.2019.09.020
67. Local Correspondent. *Prescription Now Must for Antibiotics*. The Daily Star (2019). Available online at: https://www.thedailystar.net/frontpage/news/prescription-now-must-antibiotics-1734958#: ∼ :text=The%20High%20Court%20yesterday%20directed,days%20after%20receiving%20the%20order [Accessed September 14, 2020].

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Veterinary Science

REVIEW
published: 11 March 2021
doi: 10.3389/fvets.2021.595152

Antimicrobial Use Surveillance Indicators for Finfish Aquaculture Production: A Review

Jacob A. Narbonne[1,2], *Brian R. Radke*[3], *Derek Price*[4], *Patrick C. Hanington*[5], *Amreen Babujee*[1,6] and *Simon J. G. Otto*[1,6,7]*

[1] Human-Environment-Animal Transdisciplinary Antimicrobial Resistance Research Group, School of Public Health, University of Alberta, Edmonton, AB, Canada, [2] Faculty of Veterinary Medicine, University of Calgary, Calgary, AB, Canada, [3] British Columbia Ministry of Agriculture, Abbotsford, BC, Canada, [4] Department of Fisheries and Oceans, Government of Canada, Vancouver, BC, Canada, [5] School of Public Health, University of Alberta, Edmonton, AB, Canada, [6] Antimicrobial Resistance (AMR) One Health Consortium, Edmonton, AB, Canada, [7] Thematic Area Lead, Healthy Environments, Centre for Health Communities, School of Public Health, University of Alberta, Edmonton, AB, Canada

OPEN ACCESS

Edited by:
Lucie Collineau,
Agence Nationale de Sécurité Sanitaire de l'Alimentation, de l'Environnement et du Travail (ANSES), France

Reviewed by:
Madelaine Norström,
Norwegian Veterinary Institute (NVI), Norway
Alejandro H. Buschmann,
University of Los Lagos, Chile
Brett MacKinnon,
City University of Hong Kong, Hong Kong

***Correspondence:**
Simon J. G. Otto
simon.otto@ualberta.ca

Specialty section:
This article was submitted to Veterinary Epidemiology and Economics, a section of the journal Frontiers in Veterinary Science

Received: 15 August 2020
Accepted: 08 February 2021
Published: 11 March 2021

Citation:
Narbonne JA, Radke BR, Price D, Hanington PC, Babujee A and Otto SJG (2021) Antimicrobial Use Surveillance Indicators for Finfish Aquaculture Production: A Review. Front. Vet. Sci. 8:595152. doi: 10.3389/fvets.2021.595152

Quantification and tracking of antimicrobial use (AMU) are key factors for the development of responsible antimicrobial stewardship programs and comparison between countries. Global finfish aquaculture growth and increased AMU creates the potential for exchange of antimicrobial resistance between aquatic and terrestrial environments, making AMU surveillance imperative for this industry. The objective of this review is to collate current literature on AMU surveillance indicators and their application to commercial finfish aquaculture production. A systematic search strategy was applied to five databases: Medline, Embase, Agricola, CAB abstracts, and Biosis. To be included, studies must report on at least one AMU surveillance indicator for use in animals. There is no single, standardized indicator suitable to report finfish aquaculture AMU. The type and availability of finfish aquaculture data presents unique considerations for AMU reporting. Ultimately, the indicator used should be fit-for-purpose to satisfy the objective of the surveillance program, motivation for comparison and provide useful information to the industry stakeholders. Finfish aquaculture total annual slaughter weight allows estimation of biomass for the population correction unit (PCU) to report annual total mg of active antimicrobial ingredient per PCU. These data are commonly reported by finfish aquaculture-producing countries, allowing for international comparisons. However, this precludes the ability to compare to terrestrial livestock where the PCU is based on animal numbers and an average treatment weight, which are not available for finfish aquaculture. The mg per adjusted PCU indicator provides an interesting alternative that incorporates the length of the marine grow-out phase for finfish, but is subject to the same limitations. The number of defined daily doses animal per animal-days-at-risk is useful but also limited by a lack of a defined average treatment weight. The concept of average treatment weight remains challenging for the industry as it does not accurately reflect the timing of actual AMU to fish in the system. The term "average biomass" is more reflective of the intent of AMU surveillance indicators. Defining an average treatment weight, or average biomass, will require industry engagement, which is crucial if AMU reporting is to be deemed credible and provide value back to the finfish aquaculture industry.

Keywords: antimicrobial use, antimicrobial resistance, integrated surveillance, antimicrobial stewardship, finfish aquaculture

INTRODUCTION

Quantification and tracking of antimicrobial use (AMU) are key factors in the development of responsible antimicrobial stewardship policy and programs (1). Antimicrobial use in livestock production has been linked to increased selective pressures for resistance to various antimicrobial drugs (AMDs) in bacteria in both agricultural and human settings (2). This spread of antimicrobial resistance (AMR) between human and animal settings can be due to environmental contamination (3, 4) or direct transmission of resistant bacteria or the genes that encode for AMR (5, 6). With the growing threat of AMR, stakeholders require robust, standardized methods to monitor and report AMU in food animal agriculture (7). The threat of trade restrictions from AMR (8) and the need to assess and promote antimicrobial stewardship means that countries and agricultural industries must be able to compare their AMU in a standardized and robust manner (9).

The worldwide growth of finfish aquaculture production has resulted in marked increases in therapeutic and prophylactic use of antimicrobial drugs in marine and freshwater settings (10–12). This presents the opportunity for exchange of resistance determinants between water and terrestrial environments (13). The potential for environmental exposure to AMR organisms and genes from finfish aquaculture operations poses a unique One Health threat (13). These resistance determinants can spread from farmed to wild fish populations and antimicrobial residues from fish feeds can settle in the benthic zone of the ocean (13, 14). As a result, surveillance of AMR that can integrate AMU data from the finfish aquaculture industry is of paramount importance to guide future stewardship efforts. Application of AMU surveillance indicators to finfish aquaculture AMU data will be pivotal to inform future stewardship programs and allow for international comparisons.

As AMR continues to be a preeminent One Health threat, indicators for analyzing and reporting AMU are increasingly important tools. The design and improvement of AMU surveillance programs must consider these indicators to best promote antimicrobial stewardship (15–17). Some European Union (EU) countries (Denmark and the Netherlands) set and enforce AMU benchmarks for livestock production that rely on AMU data and indicators (18, 19). However, most indicators have been developed for terrestrial food animals. There is no international consensus on the preferred, standardized AMU indicators for terrestrial animals, let alone finfish aquaculture species. It is widely recognized that the purpose of surveillance directly affects the choice of surveillance indicator and subsequent data collection (16). Regardless of the policy intent of collecting AMU data, which can range from informing industry-driven stewardship programs to benchmarking and between-country comparisons, robust indicators are required.

Government organizations create and define AMU indicators because they typically bear the responsibility of monitoring AMU over time (17), but the outputs of surveillance must be fit for the purposes of both government and agriculture industries. The lack of standardized indicators makes it difficult to compare AMU between different countries and species. This is further compounded by differences in items important for their derivation, such as animal average treatment weights (ATWs), defined dosing standards, and variable production practices and animal cycle lengths between countries (20, 21). In addition to this lack of standardization and comparability, all AMU indicators suffer from their own respective limitations based on poor data availability, or uncertain assumptions such as animal weights and drug label and used doses (22). Regulators must be transparent in how indicators are derived and used to clearly reflect the burden of AMU in a population and allow for comparison. A recent publication, based on a 2016 literature search, reviewed and categorized commonly used AMU indicators for food animal production (9). The objective of this review is to collate current literature on AMU surveillance indicators and to consider how these can be applied to AMU surveillance in commercial finfish aquaculture production, with specific focus on the Canadian finfish aquaculture context.

REVIEW METHODOLOGY AND RESULTS

A systematic search string was developed with the assistance of a librarian. The complete search strategy and results can be found in **Supplementary Material**. Published articles were obtained by executing the search on January 20, 2020 in five scientific databases: Medline via Ovid®, Agricola® *via* ProQuest®, CAB Abstracts *via* Web of Science™, Biosis® via Web of Science™, and Embase via Ovid®. Key search words were broken into five categories in order to capture articles of interest: surveillance/monitoring, antimicrobials, use, metrics/indicators of interest, and animal species of interest. Searches were limited to January 1st, 2016 onwards in order to capture literature not covered by the recent review (9). Articles were then sorted and screened based on defined inclusion and exclusion criteria. To be included, studies must report on at least one AMU surveillance metric or indicator for use in animals. Studies were excluded if they did not include discussion of an AMU surveillance metric or indicator, if they did not discuss AMU surveillance in animals, if they were not written in English, or if they were theses or dissertations. All articles were screened at two levels by one reviewer (JN). All articles were managed, deduplicated and screened using Mendeley® (Elsevier, 2020). First level screening included titles and abstracts. Second level screening included full article text. Government and intergovernmental/international reports on AMU metrics and indicators in livestock and finfish aquaculture settings were identified based on investigator knowledge. Supplementary articles and reports were identified by hand-searching the reference lists of included articles and knowledge of the investigators. See **Supplementary Material** for the complete results of database searches and article screening. **Supplementary Figure 1** includes the detailed results of the search and screening. There were 1,660 articles after deduplication, of which 38 progressed to second-level screening. A total of 27 articles (20 peer-reviewed and seven governmental reports) were included in the final review. A complete list of articles with extracted data are included in **Supplementary Table 2**.

AN OVERVIEW OF ANTIMICROBIAL USE METRICS AND INDICATORS

The use of the term metric vs. indicator varies in the AMU surveillance literature. Some use the terms interchangeably, while others differentiate between them and define an AMU metric to be a technical unit of measurement (e.g., frequency of use) and an indicator to be an AMU measurement in relation to a denominator such as animal biomass, population size or time unit (17). This becomes confusing when considering, for example, the Population Correction Unit (PCU) and Defined Daily Dose Animal (DDDvet) for a given antimicrobial (17, 20, 23, 24). The PCU and DDDvet, by definition, are not AMU metrics because they do not quantify AMU. They are, however, useful population or drug-specific metrics that are used to derive AMU indicators. For the purpose of this review, we focus on indicators as the estimate of AMU that standardizes a measure of the frequency of use by a denominator with consideration of their application to finfish aquaculture production. All AMU indicators are reported over a period of time (typically 1 year, unless otherwise specified) and another unit or combination of units to standardize use by the population being considered. Sometimes these denominators include technical units of measurement specific to the population and/or drug in question.

Werner et al. (9) considered two overarching categories of commonly used AMU indicators based on quantity of AMD used and the course of AMD application. Quantity-based indicators characterize the amount of AMU in terms of the weight of AMD distributed, sold or administered/used per kg of body weight, standardized weight, or number of doses used. Course-based indicators specify if and how often AMU occurred by estimating the number of drug treatments or courses an animal or group of animals receives over time (9, 25). For this review, we consider the terms AMD, "drug" and "active ingredient" to mean a single active antimicrobial ingredient, to be distinguished from antimicrobial products that contain more than one active ingredient. A dose of active ingredient is the amount of AMD administered in a single application whereas dosage is the amount of AMD administered per kilogram of bodyweight (9).

TABLE 1 | Examples of antimicrobial use (AMU) surveillance indicators linked to underlying AMU and population metrics.

	AMU or population metrics	AMU indicators
Quantity-based indicators	Weight of active ingredient	
	Biomass—Population Correction Unit (PCU)	Total weight/PCU
	Biomass—Adjusted PCU (APCU)	Total weight/APCU
	Number of animals	Total weight/number of animals
	Defined daily dose animal (DDDvet)	Number of DDDA (nDDDvet)
	Used daily dose animal (UDDA)	Number of UDDA (nUDDA)
	UDDA	Treatment frequency (TF)
	DDDvet and PCU or APCU	Treatment incidence (TI)*
Course-based indicators	Defined course dose animal (DCDvet)	Number of DCDA (nDCDvet)
	DCDvet and PCU or APCU	Treatment incidence (TI)*

**Quantity or course-based definition of Treatment Incidence depends on the metric used to derive the indicator.*

However, the terminology in the literature is not consistent in the use of the dose vs. dosage. A treatment is all administrations of an AMD given to one animal in 1 day (9). A course is a full regimen (the number of days) of treatment with an AMD as outlined by the instructions on the drug label (1). **Table 1** includes examples of AMU and population metrics used to derive the resulting AMU indicators.

Total Weight of Active Antimicrobial Ingredient

The total weight of active ingredient for AMDs used for a population over a given period of time (usually 1 year) is a rudimentary measure of AMU (25). It simply relies on collecting and collating the total amount of active ingredient distributed, sold or administered/used over a period of time. The Canadian Integrated Program for AMR Surveillance (CIPARS) reported total annual weight of AMDs distributed for animal use for over a decade (26). Future reporting will be broken down by province and animal species (e.g., finfish aquaculture) (27). The 2017 DANMAP (Danish Integrated AMR Monitoring and Research Program) report included the total annual amount of AMDs sold in kilograms to the Danish finfish aquaculture industry (28). In 2016, Norway reported total kilograms of AMDs in finfish aquaculture prescribed by finfish species, production stage, and total biomass (29).

Unfortunately, total weight of active ingredient is insufficient for AMU surveillance when used alone due to several problems inherent with the lack of standardization by drug dosage or population size and animal weight at risk. This measure can only be used to meaningfully compare the AMU of two essentially identical farms, regions or countries using the same AMDs (with identical doses) for identical livestock populations due to its tendency to inflate the AMU of a farm/country with a larger population of animals (30, 31). It can also result in erroneous comparisons of AMU between species of different sizes (e.g., chicken, fish, cattle, or humans) or with drugs with higher (e.g., tetracyclines) or lower (e.g., macrolides) mg/kg dosages (21). This measure is, however, commonly used as a numerator in other AMU indicators that standardize the total annual amount of active ingredient by the different denominators in other quantity and course-based indicators.

Population Correction Unit and mg/PCU Indicator

The PCU is the theoretical estimate of the biomass or weight (kg) of animals that could be exposed to a given total weight of active AMD ingredient used in a country to standardize national AMD sales by a population at risk of AMU (32). It is a useful tool to pool all animal biomass to assess collective animal AMU, but can also be broken down to use and biomass per animal species. Biomass and weight are often used synonymously and by definition are the same thing, but this can be confusing when considering the PCU. Biomass in the PCU context is a population weight over a period of time (a year) (33) whereas weight implies a specific weight of an animal(s) at a specific point in time. We propose that biomass is a better representation of a population at risk of AMU over time for PCU estimation. The PCU for each species and sub-category of animal is calculated by multiplying the total number of living and slaughtered animals by a standardized theoretical weight, referred to as the average treatment weight (ATW). The European Surveillance of Veterinary Antimicrobial Consumption (ESVAC) program of the European Medicines Agency (EMA) derived the formula for the PCU shown in Equation 1 (32). The number of animals incorporates the different components of a typical production chain (Equation 1.1).

$$PCU_{species}(kg\ biomass) = number\ of\ animals\ x\ ATW\ (kg) \quad (1)$$

$$Number\ of\ animals = animals\ present + slaughtered + imported - exported \quad (1.1)$$

The mg/PCU indicator (Equation 2) simply divides the total mg of AMD by the PCU estimate for the given population. This allows for the comparison of AMU between farms/countries with differing amounts of exposed animal biomass while controlling for animal demographics (34). The mg/PCU indicator standardizes the total weight of AMD distributed/sold/administered by the biomass of the animal population. When the demographics of the animal populations differ between countries, it is possible that this will influence the resulting estimates of national AMU, but the mg/PCU indicator at least accounts for variations in animal numbers and weights across populations (25). For example, it has a marked effect on the comparison of total AMU between animals and humans when one considers total weight of active ingredient comparisons vs. those using mg/PCU. Canadian AMU reporting is included in reports from both CIPARS and the Canadian AMR Surveillance System (CARSS) (35, 36). Total active ingredient reporting shows that ∼80% of antimicrobials sold/distributed are for use in animals and crops, compared to 20% in humans (35–37). However, when you piece together the mg/PCU analyses for 2018, animal AMU is 1.4 times that of human use when standardizing by the respective population PCUs. These results are not explicitly included in any of the reports but were presented in CIPARS stakeholder meetings (results taken from presentations). This highlights the importance of context when considering the underlying population at risk of exposure. First, the population of animals in Canada greatly exceeds that of humans (35). This, combined with the relative sizes of, for example, cattle, chickens and humans, will impact the population PCU and the subsequent mg/PCU results when comparing humans and animals using this indicator. It is a stark contrast to the annual total active weight of active ingredient results.

$$mg/PCU_{species}(mg/kg\ biomass) = \frac{total\ AMD\ used\ (mg)}{PCU_{species}} \quad (2)$$

The ATW in Equation 1 has variably been termed average treatment weight, average or estimated weight at treatment, and theoretical weight at the time most likely for treatment (32, 38). The ESVAC reports the weights they use and typically reference the original publications for these values (32, 39–42). These include body weights for categories of livestock, some of which are analogous to the animal categories used in the PCU calculations. Montforts (39) defined the term "average body weight" for animals that are reared from a starting weight onwards, compared to animals kept at their mature body weight, for which maximum body weight is used (39). Montforts and Tarazona Lafarga further proposed that body weights at treatment should be based on adult weights for mature animals and the mean of starting and slaughter weights for production animals (41). Other definitions for ATW state that these weights represent the most likely size of an animal treated with an AMD (26, 32, 34).

The interpretation of the ATW in the PCU is a common point of confusion when working with specific industry stakeholders because it does not necessarily indicate the actual treatment practice for a given food animal species or category. Different diseases and drugs are used at different points in the production cycles for different species, meaning that it truly is a theoretical "average" weight of the overall animals at risk of AMU in that population for a given period of time rather than the typical weight at treatment. For example, most farmed Atlantic salmon in western Canada with yellow mouth, caused by *Tenacibaculum maritimum*, are treated with antimicrobials early in the marine grow-out phase when they are well below their mean marine production weight (43). Use of the constant body weight of mature livestock as the ATW is eminently reasonable. However, for animals reared for slaughter there is a lack of evidence or rationale to support that antimicrobials are typically administered at their ATW (i.e., their average weight in the population). For animals at slaughter, the term ATW can be confusing in the interpretation of the PCU calculation. Average biomass is more synonymous with the average weight of an animal in the population that is at risk of AMU. It is a more accurate label in the PCU calculations, rather than the term ATW. The ATW is also used to derive other indicators with the same concerns (see nDDDvet and nDCDvet below).

It is still debatable if the ATW for a given animal species (e.g., beef cattle or farmed salmon) should be constant between the populations being compared in different countries. The specified ATW can vary by country, animal species or breed (34, 44). As a hypothetical example, consider one country that produces predominantly Atlantic salmon with an average slaughter weight of 5 kg (45, 46) and an estimated ATW of 2.5 kg (41). The comparator country produces mostly Pacific Coho salmon, with an average slaughter weight of 2.5–3.5 kg and ATW of 1.25–1.75 kg (47). Using a constant ATW of 2.5 kg allows for an apparent "apples-to-apples" comparison of AMU between these countries. However, the numbers may not accurately reflect the population demographics of the second country. This is evident in the CIPARS reporting of AMU that compares mg/PCU estimates for terrestrial livestock using either ESVAC or Canadian-derived ATWs (26). **Supplementary Table 1** shows a comparison of ATWs used by ESVAC and those averaged over 28 European countries (34). If animal reporting is available by weight group or production type within a given species, then a more accurate estimate of ATW and PCU is possible. CIPARS reports two mg/PCU indicators derived using the ESVAC defined ATWs and the Canadian ATWs agreed upon by animal commodity groups (35). This allows for comparison between the EU and Canada using a common ATW and a more Canadian representation of AMU based on Canadian ATWs.

For terrestrial species, ESVAC uses the reported numbers of existing and slaughtered livestock from European countries for Equation 1.1, and CIPARS uses Canadian numbers (26, 32). However, finfish production is typically reported by total annual slaughter weight and does not include reporting of animal numbers by any country or producing entity in the world (32). Some regions, such as Chile and the Canadian province of British Columbia, report total annual slaughter weights by Atlantic and Pacific salmon species (48, 49), while others (Canada overall, Norway, and the UK) report total finfish aquaculture slaughter weight without species breakdown (50–52). International reports of finfish aquaculture are also available from the Food and Agricultural Organization (FAO) Fisheries and Aquaculture Department (53) and its subsequent FishStatJ app (54), both of which rely in part on industry reporting from producing nations/regions. As ESVAC does not specify an ATW for farmed finfish or the number of fish slaughtered, they report the farmed finfish PCU as the total annual slaughter weights (55). This is consistent with 2018 OIE determination of PCUs for finfish aquaculture (56). The rationale for finfish PCU departing from the terrestrial animal PCU approach of using animal numbers and ATW is unclear, other than data availability, as is the effect of this departure on the resulting national PCUs and mg/PCU indicators for AMU. A recent study by Schar et al. (57) reported current and projected trends in global aquaculture AMU using the mg/PCU metric where the PCU was also based on total annual production weights by species class (57) from the FAO FishStat data (54).

As an example, Atlantic salmon make up about 96% of recent finfish aquaculture production in British Columbia, with an average slaughter weight of 5 kg (58). A reasonable estimate of ATW is approximately half of this (2.5 kg), based on the method Montforts and Tarazona Lafarga (41) using the mean of initial (0 kg) and final weight (5 kg). The number of fish can be estimated by dividing the total annual slaughter weight by the 5 kg average slaughter weight. The number of fish and the average animal weight of 2.5 kg can then be used to derive the PCU. The net effect of these calculations is that the finfish PCU biomass (which is analogous to the PCU biomass of terrestrial species) is half the total annual finfish slaughter weight. Either method assumes that only slaughtered fish are eligible for AMD treatment and ignores the live fish (brood-stock and early growing fish) and fish mortality, which can range from 5 to 15% (59). This is similar to poultry where the PCU includes only slaughtered broilers and turkeys, but does not include breeder flocks (26). In British Columbia, the average grow-out length of Atlantic salmon can range from 18 to 24 months (45, 46, 60), meaning that the annual slaughter weight also does not account for the animals in early growing phase of production. It also relies on the standard slaughter weight for the fish in question, which could vary by fish species and production region or country. Grow-out cycle length, and sometimes slaughter weight, is highly dependent on degree days from water temperature and varies by oceanic region (61). The marine grow-out cycle occurs in saltwater and ignores the freshwater phase of production for salmon and finfish where this applies, a feature unique to the finfish aquaculture industry. However, if applied in the same manner to different populations for comparison, the $PCU_{finfish}$ metric is useful for relative comparison of AMU between countries. Like CIPARS, one can consider using region and/or species-specific slaughter weights and ATWs to show the relative comparisons of using the same values vs. regional specific values (26).

The mg/PCU indicator is adept at identifying low and high users of AMDs due to its straightforward interpretation when the comparison groups have similar animal species demographics (30). However, the comparison of AMU between farms/countries can be problematic due to either under or over-representing AMU across operations with differing ATW (e.g., cattle in North America vs. Europe) (21, 25). These can vary between countries, regions and farms as the result of different breeds and variable production practices such as feeding protocols (1). For example, while ESVAC estimates the mean slaughter cattle ATW to be 425 kg (32), the standard slaughter weight for beef cattle in Canada ranges between 500 and 640 kg (21) and averages 627 kg in 28 EU countries (34). Countries where production practices result in markedly different treated and mature animal weights should consider developing their own animal weight standards in order to make more accurate estimates of representative AMU (25), but there remains debate about how to compare these estimates between countries using different weights. This also creates the ability for a reporting country to manipulate their PCU and subsequent mg/PCU results based on the used ATWs. The indicator incorporates country-specific ATW, reducing bias from variable production practices, but must be accompanied with transparency in their specification of weights and units for weight-based metrics like mg/PCU (21, 34).

There is some concern about comparing mg/PCU estimates between countries that include all antimicrobials and all animals when there is variation between food animal production (e.g., relative levels of chicken, cattle, pigs and finfish) (34). Use of the mg/PCU indicator to compare AMU of countries using total PCU values including different livestock demographics should be interpreted with these differences in mind, as AMU intensity and duration can differ between species for reasons such as variations in production practices of the nation, or the varying length of life of different livestock species. The mg/PCU indicator treats AMU in different species or risk categories equally when this may not be the case. For example, AMU in broiler chicken production may pose a different risk of selection for and transmission of AMR through the food chain than beef cattle due to differing lifespans and timing of AMU in the production cycle (34). Another example is beef vs. dairy cattle that use different types and overall weights of AMDs in feed or by parenteral or intramammary administration at different points in the production cycle, with markedly different mg/kg drug dosages. However, the standardization using PCU biomass is more appropriate for comparison than simple total weight of active ingredient in this regard. If one desires more specific species comparisons, then mg/PCU broken down by animal species can provide this relative comparison at a specific industry level (if data are available). National surveillance from CIPARS and ESVAC reports total mg/PCU for all livestock species, but species-specific mg/PCU is possible (32, 51).

The mg/PCU indicator cannot account for AMDs with different dosages (e.g., the total mg of active ingredient will be less for a drug with a lower mg/kg dose) (21), but drug-specific mg/PCU estimates are also possible (51). Given that drug doses can vary between categories of importance to human medicine (62), use of drugs with higher doses (e.g., tetracyclines) may inflate mg/PCU estimates compared to those with lower doses (e.g., macrolides) (21). This creates difficulty in assessing the relative prudence of AMU between countries using mg/PCU that includes all AMDs and all livestock (25, 63).

The mg/PCU indicator can also be calculated using more specific animal weights, such as the actual weight of animals at the time of drug administration or actual slaughter weights of animals linked to their individual AMU, if data are available, but these are extremely difficult to procure for large populations. The census of AMU data in 2.6 million feedlot cattle in Western Canada were accompanied by actual market weight data (31), but the availability of such granular data are not commonplace for livestock surveillance systems. This method offers the advantage of accuracy for a specific population, but unless comparators are also using real data, it offers no advantage over using ATW other than an assumed increase in the real-world accuracy of the PCU denominator. A potential alternative to mg/PCU uses actual production data as a denominator instead of standard or true animal weights, such as mg AMD/100,000 head of feedlot cattle (21), mg AMD/1,000 L of milk produced in dairy operations (25), or mg AMD/10,000 broiler chickens or eggs produced in poultry operations. This removes the need for estimating ATWs of different populations of animals. However, it only allows for within-species comparisons and has also created consumer confusion that AMDs are actually present in animal products (25). The use of production data as a denominator is highly limited to the type of operation for its application as many livestock systems do not produce an easily measured quantity such as number of head, kg of milk or number of eggs.

For finfish aquaculture, producing countries (Norway, Chile, the United Kingdom, and the European Union) and the OIE report AMU in mg/PCU using total annual slaughter weight for their PCU estimate (49–51, 55, 56). Total annual slaughter weight represents the most accurate data available. It can be used to estimate the ATW as described by Montforts and Tarazona Lafarga (41) and approximate the mg/PCU method that relies on real production data that is arguably more representative of the true population of slaughtered fish (31). The total annual slaughter weight of fish is a corollary to the example of using actual production data for a denominator that is applicable for finfish aquaculture production. Using a total annual slaughter weight PCU to compare finfish AMU between countries is advantageous because there is no need to define an ATW, especially if the ATW is variable between nations. The limitations of using slaughter weight are real, but it provides the benefits of transparency and consistency. Accounting for missing fish in the population and/or estimating an ATW would simply apply a scale factor to the mg/PCU result. Consistency for the PCU estimation is key to allow for international comparison.

Adjusted Population Correction Unit and mg/APCU Indicator

Radke proposed the adjusted PCU (APCU) as an alternative interpretation to the PCU (34). The PCU does not consider the lifespan of animals in its estimate of the biomass at risk of treatment (21, 34). Risk of animal exposure to AMU is related to their weight and length of life (34). The APCU accounts for the total weight of animals in a population and their length of life to calculate the total animal biomass for possible AMD exposure, resulting in life-adjusted weights for animal categories (Equations 3 and 3.1) (34). The consideration of an animal's average lifespan improves comparability between different species where length-of-life differs greatly, such as in the case of cattle, swine, poultry and finfish. It also accounts for the increased possibility of exposure to AMD for animals as they live longer (64).

$$APCU_{species}(kg\ biomass) = number\ of\ animals\ x\ life\text{-}adjusted\ treatment\ weight\ (kg) \tag{3}$$

$$Life\text{-}adjusted\ treatment\ weight\ (kg) = ATW\ x\ length\ of\ life\ (years) \tag{3.1}$$

$$mg/APCU_{species}(mg/kg\ adjusted\ biomass) = \frac{total\ AMD\ used\ (mg)}{APCU_{species}} \tag{4}$$

Radke (34) found differences between PCU and APCU estimates of Canada and eight European countries when using the same number of animals for both. The APCUs for longer-lived animals (cattle) increased compared to shorter-lived animals (pigs, poultry, sheep, and goats). This has the effect of reducing the relative AMU in a long-lived species by increasing the size of the denominator in the mg/APCU indicator (Equation 4), with the opposite effect in shorter-lived species. The data required to determine length of life used by Radke (34) was obtained from the literature.

Application of the APCU to finfish is an interesting premise as the animals are small relative to cattle, but have a relatively long lifespan. However, its derivation is more difficult due to the lack of reporting of animal numbers or a defined ATW and the length of life for different finfish species. It is also still limited in that it does not account for the variable relative mg/kg doses of different AMDs. An interesting consideration is the application of the length of grow-out cycle to a total slaughter weight for finfish and derived fish numbers and biomass. Using the concept of life-adjusted weights (34), one could estimate the APCU for fish to align with the approach used for terrestrial animals. At this time, we are not aware of any governments that are using mg/APCU to report finfish AMU data. Its utility for application to finfish aquaculture requires further research.

Defined Daily Dose Animal and Number of DDDvet Indicator

The DDDvet (also known as the DDDA), an adaptation of the human DDD, is the "assumed average dose (of antimicrobial) per kg of animal per day" of treatment (Equation 5), expressed in mg/kg/day (23, 26, 65, 66). The DDDvet was described by ESVAC and the EMA as part of an effort to develop a system for the collection of harmonized data on AMU in the European Union (23, 65, 66). By definition, the DDDvet for each active drug ingredient is specific to the EU as it represents the average dosage (the arithmetic mean) of the daily dosages of that ingredient based on the dosage labels from European countries (23, 65). The DDDvet for specific AMD active ingredients are only assigned by ESVAC if they possess an Anatomical Therapeutic Chemical classification code (67).

$$DDDvet_{drug}\left(mg/kg/day\right) = \frac{mg/kg\ drug\ dose}{day\,(s)\ \ duration\ of\ effect} \quad (5)$$

$$nDDDvet_{drug} = \frac{total\ AMD\ used\left(mg\right)}{DDDvet_{drug}\left(mg/kg/day\right)\ x\ ATW\left(kg\right)} \quad (6)$$

The nDDDvet indicator adjusts the weight of active ingredient distributed/sold/administered by the DDDvet of the AMD and the ATW of the animal in question (Equation 6) (20). This calculation is AMD and animal specific, making its derivation comparable between populations using similar AMDs with similar livestock demographics (44). The DDDvet for combination products including more than one active antimicrobial ingredient measure use by counting the DDDvet of each single ingredient product separately, with specific methods for synergistic combinations (9, 23, 65). The nDDDvet also accounts for long-acting parenteral formulations by dividing the single administered dose by the number of days of the duration of therapeutic effect (65). The duration of effect is an important consideration for quantifying AMU in terms of evaluating selective pressure and the development of AMR (21). To compare AMU for a population with a mixed animal demographic, species-specific nDDDvets can be calculated and summed to consider total AMU. However, comparison of total nDDDvets for all animals between countries with dissimilar populations without accounting for numbers, types and ATWs of animals is questionable for similar reasons as outlined for the mg/PCU.

The use of European standard doses is advantageous to compare AMU in European countries that operate under the customs and production practices where ESVAC standard doses apply. Current, defined DDDvets from ESVAC for AMDs exist for swine, cattle, and broiler chickens (66). While the nDDDvet offers a standardized dose-based indicator compared to the mg/PCU biomass-based indicator, it is still difficult to interpret and compare between countries with different doses, production practices, animal populations and ATWs (1). Countries outside the EU may have different approved drug label dosages that lead to country-specific DDDvet definitions. Canada has defined Canadian industry-specific DDDvetCAs for swine, chickens, turkeys and cattle (20, 24, 30). Typical drug labels for in-feed or water administration for these species use inclusion rates of mg AMD per 1,000 kg of feed or 1,000 L of water. ESVAC and CIPARS use a conversion factor to estimate the daily dose per kg animal for AMDs administered in feed or water by estimating feed or water intake (26, 65). Conversely, finfish aquaculture drug dosage labels provide a mg/kg/day values, negating the need to apply this conversion factor for standard feed intake of fish (68).

The DDDvet is a technical unit of measure that represents a compromise between all European label dosages for an AMD (23, 25, 26, 65). As a result, it is a compromise of existing dosages and is intended for reporting AMU data, but it does not necessarily reflect the daily dosages recommended or prescribed for use in animals. The nDDDvet by itself does not provide any information as to the number of animals treated or the population at risk of treatment that is provided by mg/PCU (9). It also does not provide the length of treatment (the number of days of consecutive or total therapy), the actual daily dose applied, or the total amount of AMD used. The nDDDvet also relies on defining the ATW and is subject to the same concerns that this poses for PCU estimates. Inconsistent ATWs between countries create concerns for international comparisons. This is compounded by inconsistent DDDvets between countries.

The nDDDvet can be considered for finfish aquaculture AMU, but there are important limitations. Approved label dosages exist within countries for commonly used AMDs, such as oxytetracycline and florfenicol, but neither ESVAC nor Canada have defined DDDvets for these drugs in finfish aquaculture species at this time (23, 26, 65, 66). The lack of an ESVAC or Canadian ATW for finfish also raises uncertainty for the application of nDDDvet. There are methods to estimate the ATW using the total annual slaughter weight, as described for the mg/PCU. However, there is no simple way to do this knowing that average slaughter weights and industry salmon species demographics vary between countries and regions. There is no way to incorporate total annual slaughter weight directly into the nDDDvet calculation like there is for mg/PCU. This makes the nDDDvet less transparent and subject to variation depending on the assumptions for the ATW as well as non-standard DDDvets.

Used Daily Dose Animal and Number of UDDA Indicator

The UDDA is the daily dose of an active ingredient per animal that is typically administered to an animal (mg drug/animal/day—Equation 7) (9, 69–71). Alternatively, the $UDDA_{kg}$ (UDDA per kg—Equation 8) is the actual administered dosage of an active ingredient per day per kg of body weight of a treated animal (9). These require the actual number of treated animals, their weights and the number of days of treatment to be known. As a result, they are based on real data rather than the theoretical value presented by the consensus of several doses that make up the DDDvet. The UDDA allows for comparisons of AMU between populations using the same active ingredient.

$$UDDA_{drug}(mg/animal/day) = \frac{total\ AMD\ used\ (mg)}{\#\ treated\ animals\ x\ \#\ treatment\ days} \quad (7)$$

$$UDDA_{kg\ drug}(mg/kg/day) = \frac{total\ AMD\ used\ (mg)}{\#\ treated\ animals\ x\ treatment\ weight\ (kg)\ x\ \#\ treatment\ days} \quad (8)$$

The number of UDDA (nUDDA) indicator is the sum of daily applications in a population (Equation 9) (9). It represents the amount of actual administered AMD doses for a given animal population (9, 44). It does not indicate how much active ingredient is being used, it simply reflects the frequency of treatments with AMD (72). It requires granular data such as the number of animals treated, the number of days treatment occurred, and the number of active ingredients administered (72, 73). It is also only specific for similar populations being analyzed at a point in time using the same active ingredients for treatment (9, 20).

$$nUDDA = \#\ treated\ animals\ x\ \#\ active\ ingredients\ x\ \#\ treatment\ days \quad (9)$$

With the increased level of specificity at the farm level, indicators like nUDDA can be used as tools to show actual AMU for benchmarking between similar farms. One study compared the nDDDvet and nUDDA to quantify AMU at the farm level using similar data sets (71). There were differences in observed AMU due to the use of actual vs. standard animal weights. Comparisons between populations are further limited by a lack of standardization of the UDDA between farms, specific treated animals within populations, veterinarians, and producers (71, 73). Due to the presumed real-world accuracy of the UDDA for comparing AMU between similar populations with similar dosing practices, the ratio between the UDDA and DDDvet of AMU in a population can reflect the suitability of dosing (44). The higher the ratio between these two metrics, the more excessive the AMU is when compared to baseline expectations of AMU built into the DDDvet metric (in the form of expected average dosages). In reality, the nUDDA relies heavily on granular data for each food animal industry, making its use for comparison limited unless these data are collected at the national level. The lack of these specific data for number of treated fish and actual treatment weights in finfish aquaculture make the nUDDA a poor candidate for estimating AMU in this industry.

Defined Course Dose Animal and Number of DCDvet Indicator

The Defined Course Dose Animal (DCDvet) does not have a human counterpart and is defined as the "average dose per kilogram of animal per species per treatment course," or the product of the treatment length and the DDDvet for that drug (Equation 10) (1, 23, 25, 65, 66). The number of DCDvet (nDCDvet) adjusts the total weight of active ingredient by the DCDvet and ATW (Equation 11).

$$DCDvet_{drug}(mg/kg_{course}) = DDDvet_{drug}\ (mg/kg/day)\ x\ treatment\ length\ (days) \quad (10)$$

$$nDCDvet_{drug} = \frac{total\ AMD\ used\ (mg)}{DCDvet_{drug}\ (mg/kg_{course})\ x\ ATW\ (kg)} \quad (11)$$

Course-based indicators can give estimates on the likelihood and propensity an animal will be treated with AMDs in a specified period of time (74). They require increasingly granular data ranging from simply applying an animal-time-at-risk denominator of an overall population to finding the exact dose and number of days that animals are exposed to that dose for benchmarking a population (74, 75). These can be powerful tools in developing a broader view of AMU when used in conjunction with quantity-based indicators (30). Similar to the DDDvet, the recommended treatment/course length for the DCDvet can vary substantially between countries and on a case by case basis, depending on the animal species, diagnosis, prescriber and end-user. This influences the comparability of AMU based on nDCDvet between different populations using different treatment courses (1). Countries with proprietary and/or drug label treatment practices that differ substantially from those outlined by the ESVAC DCDvet are difficult to quantify without defined treatment courses. Antimicrobial use would be underestimated if a recommended course is shorter than its comparator group (1).

Unfortunately, unlike mg/PCU calculations, the DCDvet does not account for topical AMU applications like foot bathing and intramammary infusions (65). To this end, one UK study defined intramammary therapy as four tubes per cow to be a single course of AMD administration, but foot bathing antimicrobials were not included in nDDDvet or nDCDvet analyses (63). In another UK study, the nDCDvet was used in conjunction with nDDDvet and mg/PCU estimates of AMU on British dairy farms to incorporate intramammary dry cow therapy by assignment of four applications per DCDvet (25). They demonstrated how the nDCDvet was increased by intramammary administration with relatively little change on mg/PCU due to the low mg/kg dosage of these products.

A study on Norwegian finfish aquaculture sought to evaluate AMU by considering the total weight of AMDs prescribed divided by a DCDvet for fish ($DCDvet_{fish}$) metric similar to the DCDvet (76). They defined the $DCDvet_{fish}$ due to special properties related to how fish, as poikilothermic animals, consume feed at variable rates based on water temperature. As a result, the total course dose per biomass of fish was the prescribed treatment regimen rather the daily dose and number of treatment days. One $DCDvet_{fish}$ represented the amount of a specific AMD prescribed for the treatment of 1 kg of fish under standard conditions. The $nDCDVet_{fish}$ of an AMD was the biomass of farmed fish that could be treated with a certain amount of AMD. The annual $nDCDVet_{fish}$ divided the total active ingredient for an AMD by the $nDCDVet_{fish}$ for that drug. The examples of $DCDvet_{fish}$ were 100 mg for florfenicol, 150 mg for flumequine, 800 mg for oxytetracycline, and 320 mg for trimethoprim/sulfadiazine (1:5). They used this metric to report on temporal trends for AMU of these various AMDs in the Norwegian finfish aquaculture industry, but they did not comment specifically on the use of $nDCDvet_{fish}$ as an indicator.

The nDCDvet for finfish aquaculture is subject to the same limitations as the nUDDA and terrestrial species regarding the need for granular data and a defined ATW. Typical finfish aquaculture operations do not report the numbers of animals treated or the course length for that treatment within AMU reporting programs. The Norwegian $DCDvet_{fish}$ presents an interesting concept, but is highly data dependent and may not be generally applicable to current AMU surveillance reporting for finfish aquaculture as these data are not available. Interestingly, the Norwegian study also stated the limitation of brood stock being excluded from their biomass estimations, similar to the issue of using total slaughter weight for the mg/PCU indicator.

Treatment Frequency and Treatment Incidence Indicators

Treatment frequency (TF) and treatment incidence (TI) can be equated to two epidemiological measures, cumulative incidence (risk of treatment) and incidence density/intensity (rate of treatment), respectively (9). On its own, TF is the average number of treatments per animal and is simply calculated by dividing the nUDDA by the number of animals (Equation 12) (9, 44, 71, 72). The TF indicator does not give an indication of the rate of treatment, but rather how many days on average an animal in a population is treated with an active ingredient, from which the risk of treatment for an average animal can be extrapolated (9).

$$Treatment\ Frequency\ (doses/animal) = \frac{nUDDA}{number\ of\ animals\ in\ the\ population} \quad (12)$$

The TF can be used as a farm-level benchmarking indicator as it uses data from the real farm situation for actual applied dosages and true animal weights and numbers (71). Differing TFs between populations could be explained by varying disease pressures or AMU protocols if the populations are much different, making relative comparisons challenging. Germany uses TF as a benchmarking metric for AMU, calculated twice a year for all species and age groups in the country (71). One study used this approach without knowing the total quantity of active ingredients or animal weights because the nUDDA and animal numbers were available due to German law (72). The number of single applications can be extrapolated from the nUDDA indicator if the total quantity of AMDs used is known (9). The nDDDvet could also be used to calculate TF, but does not reflect the actual application of AMDs. Using the nUDDA to calculate sum of single applications would provide information on the actual number of animals treated, as well as the ability to assess each individual dose of AMD if the total amount of AMU is also recorded (72). Using nDDDvet could bias TF depending on the DDDvet and ATWs.

Treatment incidence (TI) has been defined in different ways for different purposes. Generally, it standardizes an indicator by a population time-at-risk. For example, CIPARS standardizes the nDDDvetCA by animal time-at-risk (Equation 13) (17, 26). The nDDDvetCA/1,000 animal-days-at-risk (ADR) is interesting to compare to the PCU and APCU. It presents an indicator that standardizes by both a drug dose and an actual number of animal days at risk. The denominator for Equation 13 is equivalent to the animal PCU (Equation 1) multiplied by the animal lifespan, which is the equivalent of the APCU (Equations 3 and 3.1). This presents an interesting option, but again requires that the numbers of animals, average treatment weights and lifespans are defined as accepted standards or are known from real data. The Canadian estimates from CIPARS use industry-reported ADRs (i.e., animal grow cycle lengths, or lifespans) that change annually based on data (26).

$$nDDDvetCA\ per\ 1,000\ ADR = \frac{nDDDvetCA}{total\ animals\ x\ ATW\ x\ days\ at\ risk} x\ 1,000 \quad (13)$$

Werner et al. (9) defined TI as the overall total amount of applied active ingredient divided by the same denominator from Equation 13, which is also equivalent to the nUDDA divided by the product of animal days at risk and the number of animals. The only difference is that the estimates from CIPARS represent the theoretical DDDvet compared to the actual AMU from the UDDA for the latter. A European study on broiler chickens calculated TI using three different methods that incorporated DDDvet, UDDAs, and the DCDvet into Equation 13 (73). The correlation between the different methods varied depending on within-flock, between-flock and between-farm comparisons, but this was not the main objective of the study. Another study on poultry farms in Vietnam found poor correlation between TI and mg AMD per reported kg biomass using mg AMD at sale or treatment (64). These results suggest that TI may reveal trends in AMU not apparent using quantity-based indicators. The discrepancies may be explained by differences in the strengths of AMD, timing of use, and variable mortality in flocks. Treatment indicence may be more balanced because it incorporates dosing and animal time-at-risk variability into its derivation, but it suffers from the same challenges inherent to the DDDvet, DCDvet and UDDA metrics.

The nDDDvetCA per 1,000 ADR is a fascinating consideration for finfish aquaculture AMU. Label dosages exist within countries for commonly used products, such as oxytetracycline and florfenicol, but neither ESVAC nor Canada have defined DDDvets for these drugs in finfish aquaculture species. The lack of defined ATWs for finfish and reported number of fish also create uncertainty for its application. Alternatively, given the link to the PCU and APCU derivations, the nDDDvetCA for finfish could use the APCU denominator to derive this estimate of TI for finfish if the total slaughter weight and lifespan are used to estimate the APCU. Given that farm-level data are typically not available, the alternative TI estimates based on UDDA or DCDA are not available for finfish aquaculture.

DISCUSSION—AN EXAMPLE APPLICATION OF AMU INDICATORS TO FINFISH AQUACULTURE DATA

Tables 2, **3** demonstrate the application of the different AMU indicators to a hypothetical finfish population and florfenicol AMU data. In Canada, the label dose for florfenicol in fish is 10 mg/kg/day with a treatment course of 10 days (77). This example illustrates how the calculations are performed and highlights the data limitations for their application when considering the availability of international, and particularly Canadian, finfish data. It is common practice for countries to report annual slaughter weights and total kg of AMD used in their finfish industries. Conversely, they do not collect data on or report the numbers of fish or drug dosages by individual fish. These are not easy pieces of information to glean from typical production records as fish are grown and managed in pens. The concept of ATW is also confusing as its hypothetical meaning is often at odds with typical industry practice for reasons already discussed (43). As a result, national finfish AMU estimates are often standardized by a PCU for biomass that is based on the total annual slaughter weight of fish (49–51, 55).

These hypothetical data illustrate the differences when using total slaughter weight compared to an ATW and number of fish for the mg/PCU and mg/APCU indicators. Based on this example, the use of total slaughter weight reduces the resulting indicator for both by approximately half. The length of the grow-out cycle also decreases the mg/APCU indicator compared to the mg/PCU. If the objective for estimating AMU is to compare between countries, it is best to use common and consistent PCU for biomass. The availability of total slaughter weight is a transparent and consistent approach for finfish AMU comparison using the mg/PCU indicator. However, it precludes direct comparison of mg/PCU or mg/APCU to terrestrial animals within a country such as Canada where the latter is based on animal numbers and average treatment weights (26). The lack of a defined ATW for finfish creates problems for the derivation of the nDDDvet, nDCDvet and nDDDvetCA per 1,000 ADR indicators. The lack of ESVAC or internationally recognized DDDvet values

TABLE 2 | Hypothetical data for derivation of antimicrobial use indicators for finfish aquaculture.

Variable	Value	Considerations
Number of fish	100,000	Unknown—countries typically do not report
Average treatment weight (kg)*	2.5	Value not described for Canadian or global industry
Total fish slaughter weight (kg)	500,000	Countries commonly report
Marine grow-out cycle length (years)	1.5	Estimate for Canadian west coast Atlantic salmon
Antimicrobial active ingredient	Florfenicol	Labeled for use in Canadian finfish
$DDDvetCA_{florfenicol}$ (mg/kg/day)	10	Canadian label dose for florfenicol
Dose course for florfenicol (days)	10	Canadian label dose for florfenicol
Number of fish treated	50,000	Unknown—countries do not report
Average actual weight at treatment (kg)	1.0	Unknown and variable with region, disease
Total florfenicol used (kg)	5,000	10 d * 10 mg/kg * 50,000 fish * 1 kg

**Average treatment weight (kg) = hypothetical average of the slaughter (5 kg) and starting weights (0 kg) per Montforts and Tarazona Lafarga (41).*
DDDvetCA, Defined Daily Dose Animal for Canadian animals.

for common finfish aquaculture antimicrobials also presents challenges for standardized nDDDvet estimates (65, 66). As is the case in Canada, it is common for countries to define their own values, such as the nDDDvetCA that reflect their region-specific drug labels (26). The lack of granular, farm-level data precludes the ability to estimate the nDCDvet. The link between the formula for nDDDvetCA per 1,000 ADR and the APCU does allow for the alternative calculation of this estimate of TI for finfish, whereby the APCU based on either total slaughter weight or ATW, and marine grow-out lifespan is used for calculation. This does allow for an estimate of TI for finfish, but again suffers from the lack of an international DDDvet for florfenicol and the need to estimate an ATW.

Another important consideration is that a PCU based on the total annual slaughter weight for finfish does not account for existing, live fish in the population at a given time or the fish that die. It excludes brood stock and any freshwater grow-out phase for a given fish species. This is similar to the PCU approach to poultry whereby breeder stock are not included in the calculations as is time spent in the hatchery. Generally, the mg/PCU indicator does not account for drug potency, but species-level comparisons are possible if the data are available (21, 25, 63). The DDDvet accounts for varying drug doses/indications and AMU at more granular levels such as animal species and breed (34), but is limited in application for finfish without DDDvet and ATWs. Unfortunately, the DCDvet metric is highly data dependent with high resource demands such as dose and indication information for AMU and species or animal standard weights (34, 44). These are not available in finfish aquaculture at this time. While the DDDvet has become a

TABLE 3 | Application of antimicrobial use indicators to finfish aquaculture data.

Metric/Indicator	Value	Considerations
$mg/PCU_{average\ treatment\ weight}$ (mg drug/kg biomass)	20	=5,000 kg/(100,000 fish * 2.5 kg)
$mg/PCU_{total\ slaughter\ weight}$ (mg drug/kg biomass)	10	=5,000 kg/500,000 kg
$mg/APCU_{average\ treatment\ weight}$ (mg drug/kg biomass)	13.33	=5,000 kg/(100,000 fish * 2.5 kg * 1.5 years)
$mg/APCU_{total\ slaughter\ weight}$ (mg drug/kg biomass)	6.67	=5,000 kg/(500,000 kg * 1.5 years to market kg)*
$nDDDvetCA_{florfenicol}$	200,000	= 5,000 kg/(10 mg/kg/day * 2.5 kg)
$DCDvet_{florfenicol}$ (mg/kg)	100	= $DDDvet_{florfenicol}$ 10 mg/kg * course 10 d
$nDCDvet_{florfenicol}$ (# of treatment courses)	20,000	= 5,000 kg/($DCDvet_{florfenicol}$ 100 mg/kg * 2.5 kg)
$UDDA_{florfenicol}$ (mg/fish/day)	10	=5,000 kg/(50,000 fish * 10 days)
$UDDA_{kg\ florfenicol}$ (mg/kg of fish/day)	10	=5,000 kg/(50,000 fish * 1.0 kg * 10 days)
$nUDDA_{florfenicol}$ (# used daily doses)	500,000	=50,000 fish * 1 drug * 10 days
Treatment $frequency_{total\ population}$ (doses/fish)	5	=nUDDA/100,000 fish
Treatment $frequency_{treated\ population}$ (doses/fish)	10	=nUDDA/50,000 fish
Treatment incidence (nDDDvetCA per 1,000 ADR)	0.73	=$nDDDvetCA_{florfenicol}$/(500,000 kg * 1.5 years * 365/1,000 days)**

*Total grow-out length $mg/APCU_{total\ slaughter\ weight}$–the slaughter weight was multiplied by the average grow-out cycle length to give the life-adjusted slaughter weight.
**The nDDDvetCA per 1,000 animal days at risk used the APCU for total slaughter weight as the denominator and scaled per 1,000 fish days at risk.
PCU, population correction unit; APCU, adjusted PCU; nDDDvetCA, number of Defined Daily Doses animal for Canadian data; UDDA, Used Daily Doses Animal; $UDDA_{kg}$, UDDA/kg of animal; ADR, animal days at risk.

popular standard metric in the EU, the PCU is still used by over 25 countries as a means of AMU standardization (34). With this in mind, the PCU is likely to hold high importance for finfish aquaculture at this time. The APCU shows some utility, but requires further investigation and consideration of its derivation from reports of total annual slaughter mass for finfish and weight of antimicrobials used.

This review adds important information about the application of AMU metrics and indicators to finfish aquaculture AMU and production. Werner et al. (9) reviewed AMU metrics and indicators broadly for all animals, with a focus on terrestrial animals. There was no discussion about specific application to and data sources for global finfish aquaculture AMU and production data. This review provides this specific finfish aquaculture lens as this industry continues to grow in importance as a global protein source. In particular, the papers included in the review discuss the PCU metric and mg/PCU indicator, which are increasingly used as reporting tools for national surveillance programs such as CIPARS and ESVAC (26, 55) and recent global aquaculture AMU projections (57) based on FAO production statistics (54). Radke (34) proposed the APCU metric as a means to consider the variable lengths of life of different food animal species. New data from a census of AMU for 2.6 million feedlot cattle in western Canada also explored the nDDDvet, mg/100 cattle-at-risk, and mg/PCU indicators, with resulting differences in results between them (21, 31). This review also explores the potential difficulties and confusions when defining and applying ATW values for food animal species. This review will support future work to consider the application of these indicators and metrics to finfish aquaculture AMU data as the pressure increases on this industry to demonstrate antimicrobial stewardship.

CONCLUSIONS

There is no single AMU indicator that is suitable for all intended purposes for surveillance and reporting of finfish aquaculture AMU data. This review highlights the common AMU indicators and inherent AMU and population metrics developed for different purposes in terrestrial animal livestock production and surveillance. Specific consideration for the finfish aquaculture industry illustrates that the mg/PCU based on total annual slaughter weight is common, consistent and transparent for international comparisons for trade or stewardship assessment purposes. Further work on ATWs and DDDvets is required to be able to apply other indicators to the industry with confidence. This work is required for further assessment of antimicrobial stewardship, farm-to-farm comparison, or should it become required, benchmarking. Ultimately, the indicator used should be fit-for-purpose in that it must satisfy the objective of the surveillance program and motivation for comparison. It must also provide meaningful and useful data back to the industry and other stakeholders. Commonly available data for finfish aquaculture, such as total slaughter weight, present an alternative biomass estimate for the industry to calculate mg/PCU for AMU. This strategy may miss some fish biomass in the system, but provides for a common denominator that can be applied across the major finfish producing countries that report these and AMU data. This allows for international comparisons of mg/PCU indicators of AMU, whether it be to inform antimicrobial stewardship policy or trade decisions. The PCU concept of ATW continues to present challenges for industry interpretation as it often does not reflect actual industry AMU practice. We argue that the term "average biomass" is a better reflection of what the value actually represents. Ultimately, the mg/PCU and mg/APCU indicators provide the means for international comparison of finfish aquaculture AMU. The ability to use nDDDvet or nDDDvet per animal-days-at-risk will be limited until progress is made to define an ATW. This will require industry engagement and buy in, which is crucial if AMU reporting and estimation is to be deemed credible and provide value back to the finfish aquaculture industry.

AUTHOR CONTRIBUTIONS

JN development and execution of the search strategy (90%), article screening (100%), data extraction (50%), writing a detailed, draft report on AMU surveillance metrics and indicators submitted to the British Columbia Ministry of Agriculture in March 2020 (75%), and review and writing of the manuscript (15%). SO conception of the work (50%), guided development of the review search strategy (10%), writing of the report to British Columbia (15%), and primary lead for writing and revising the manuscript (60%). BR conception of the work (50%), review and writing of the report (10%), and review and writing of the manuscript (10%). DP and PH review and writing of the manuscript (5%). AB data extraction (50%), reference management, review, and writing of the manuscript (5%). All authors contributed to the article and approved the submitted version.

FUNDING

Funding for this project was provided by the British Columbia Ministry of Agriculture through a contract to SO under the Canadian Agricultural Partnerships program (GSACP19-305). Funding for JN stipend was provided in part by an NSERC Discovery Grant (NSERC RGPIN-2020-04447) held by SO. AB was supported by funding from the AMR One Health Consortium (Major Innovation Fund, Alberta Ministry of Jobs, Economy, and Innovation) and Genome Canada.

ACKNOWLEDGMENTS

We thank David Leger from CIPARS for his guidance in understanding the AMU indicators and metrics used by CIPARS. We also thank Sandra Cameron for her library assistance to develop the search string for the review.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fvets.2021.595152/full#supplementary-material

REFERENCES

1. Collineau L, Belloc C, Stark KD, Hemonic A, Postma M, et al. Guidance on the selection of appropriate indicators for quantification of antimicrobial usage in humans and animals. *Zoonoses Public Health.* (2017) 64:165–84. doi: 10.1111/zph.12298
2. Mcewen SA, Fedorka-Cray PJ. Antimicrobial use and resistance in animals. *Clin Infect Dis.* (2002) 34(Suppl. 3):S93–106. doi: 10.1086/340246
3. Aarestrup FM. The livestock reservoir for antimicrobial resistance: a personal view on changing patterns of risks, effects of interventions and the way forward. *Philos Trans R Soc Lond B Biol Sci.* (2015) 370:20140085. doi: 10.1098/rstb.2014.0085
4. Scott AM, Beller E, Glasziou P, Clark J, Ranakusuma RW, et al. Is antimicrobial administration to food animals a direct threat to human health? A rapid systematic review. *Int J Antimicrob Agents.* (2018) 52:316–23. doi: 10.1016/j.ijantimicag.2018.04.005
5. Marshall BM, Levy SB. Food animals and antimicrobials: impacts on human health. *Clin Microbiol Revi.* (2011) 24:718–33. doi: 10.1128/CMR.00002-11
6. Aires-De-Sousa M. Methicillin-resistant *Staphylococcus aureus* among animals: current overview. *Clin Microbiol Infect.* (2017) 23:373–80. doi: 10.1016/j.cmi.2016.11.002
7. Dupont N, Fertner M, Kristensen CS, Toft N, Stege H. Reporting the national antimicrobial consumption in Danish pigs: influence of assigned daily dosage values and population measurement. *Acta Vet Scand.* (2016) 58:27. doi: 10.1186/s13028-016-0208-5
8. George A. Antimicrobial resistance, trade, food safety and security. *One Health.* (2017) 5:6–8. doi: 10.1016/j.onehlt.2017.11.004
9. Werner N, Mcewen S, Kreienbrock L. Monitoring antimicrobial drug usage in animals: methods and applications. *Microbiol Spectr.* (2018) 6:1–25. doi: 10.1128/microbiolspec.ARBA-0015-2017
10. Cabello FC. Heavy use of prophylactic antibiotics in aquaculture: a growing problem for human and animal health and for the environment. *Environ Microbiol.* (2006) 8:1137–44. doi: 10.1111/j.1462-2920.2006.01054.x
11. World Health Organization Food Agriculture Organization, World Organisation for Animal Health. *Antimicrobial Use in Aquaculture and Antimicrobial Resistance: Report of a joint FAO/OIE/WHO Expert Consultation on Antimicrobial Use in aquaculture and antimicrobial resistance*. Seoul (2006). Available online at: https://www.who.int/foodsafety/publications/amr-aquaculture/en/ (accesssed February 18, 2021).
12. Cabello FC, Godfrey HP, Tomova A, Ivanova L, Dolz H, Millanao A, et al. Antimicrobial use in aquaculture re-examined: its relevance to antimicrobial resistance and to animal and human health. *Environ Microbiol.* (2013) 15:1917–42. doi: 10.1111/1462-2920.12134
13. Watts JE, Schreier HJ, Lanska L, Hale MS. The rising tide of antimicrobial resistance in aquaculture: sources, sinks and solutions. *Marine Drugs.* (2017) 15:158. doi: 10.3390%2Fmd15060158
14. Office of the Auditor General of Canada. *2018 Spring Reports of the Commissioner of the Environment and Sustainable Development to the Parliament of Canada: Report 1 - Salmon Farming*. Office of the Auditor General of Canada (2018). Available online at: https://www.oag-bvg.gc.ca/internet/English/parl_cesd_201804_01_e_42992.html# (accesssed February 18, 2021).
15. Grant J, Saxinger L, Patrick D, Keen P. *Surveillance of Antimicrobial Resistance and Antimicrobial Utilization in Canada.* National Collaborating Centre for Infectious Diseases (2014). Available online at: https://nccid.ca/publications/surveillance-of-antimicrobial-resistance-and-antimicrobial-utilization-in-canada/ (accesssed February 18, 2021).
16. Otto SJG, Leger D, Radke B, Anderson M, Pasma T, Nguon S, et al. (2016). *Non-human Antimicrobial Use Surveillance in Canada: Surveillance Objectives and Options.* Otto SJG, Leger D, Radke B, Anderson M, Pasma T, Nguon S, et al. Edmonton, AB: Canadian Council of Chief Veterinary Officers - Antimicrobial Use in Animal Agriculture Committee. Available online at: https://cahss.ca/cahss-tools/document-library/Non-human-antimicrobial-use-surveillance-in-Canada-Surveillance-Objectives-and-Options (accesssed February 18, 2021).
17. Agunos A, Gow SP, Leger DF, Carson CA, Deckert AE, Bosman AL, et al. Antimicrobial use and antimicrobial resistance indicators-integration of farm-level surveillance data from broiler chickens and turkeys in British Columbia, Canada. *Front Vet Sci.* (2019) 6:131. doi: 10.3389/fvets.2019.00131
18. Aarestrup F. Sustainable farming: get pigs off antibiotics. *Nature.* (2012) 486:465–6. doi: 10.1038/486465a
19. Speksnijder DC, Mevius DJ, Bruschke CJ, Wagenaar JA. Reduction of veterinary antimicrobial use in the Netherlands. *Dutch Success Model Zoonoses Public Health.* (2015) 62(Suppl. 1):79–87. doi: 10.1111/zph.12167
20. Bosman AL, Loest D, Carson CA, Agunos A, Collineau L, et al. Developing Canadian defined daily doses for animals: a metric to quantify antimicrobial use. *Front Vet Sci.* (2019) 6:220. doi: 10.3389/fvets.2019.00220
21. Brault SA, Hannon SJ, Gow SP, Otto SJG, Booker CW, Morley PS. Calculation of antimicrobial use indicators in beef feedlots-effects of choice of metric and standardized values. *Front Vet Sci.* (2019) 6:330. doi: 10.3389/fvets.2019.00330
22. Waret-Szkuta A, Coelho V, Collineau L, Hemonic A, Buy C, Treff M, et al. How input parameters and calculation rules influence on-farm

antimicrobial use indicators in animals. *Front Vet Sci.* (2019) 6:438. doi: 10.3389/fvets.2019.00438

23. European Medicines Agency. *Principles on Assignment of Defined Daily Dose for Animals (DDDvet) and Defined Course Dose for Animals (DCDvet).* Veterinary Medicines Division, EMA/710019/2014 (2015). Available online at: https://www.ema.europa.eu/en/documents/scientific-guideline/principles-assignment-defined-daily-dose-animals-dddvet-defined-course-dose-animals-dcdvet_en.pdf (accesssed February 18, 2021).
24. Lardé H, Dufour S, Archambault M, Léger D, Loest D, Roy J-P, et al. Assignment of Canadian defined daily doses and Canadian defined course doses for quantification of antimicrobial usage in cattle. *Front Vet Sci.* (2020) 7:10. doi: 10.3389/fvets.2020.00010
25. Mills HL, Turner A, Morgans L, Massey J, Schubert H, Rees G, et al. Evaluation of metrics for benchmarking antimicrobial use in the UK dairy industry. *Vet Rec.* (2018) 182:379. doi: 10.1136/vr.104701
26. Government of Canada. *Canadian Integrated Program for Antimicrobial Resistance Surveillance (CIPARS) 2017: Design and Methods.* Guelph, ON: Public Health Agency Canada (2020). Available online at: https://www.canada.ca/content/dam/phac-aspc/documents/services/surveillance/canadian-integrated-program-antimicrobial-resistance-surveillance-cipars/cipars-reports/2017-annual-report-design-methods/2017-annual-report-design-methods.pdf (accesssed February 18, 2021).
27. Government of Canada. *Veterinary Antimicrobial Sales Reporting (VASR).* Health Canada (2019). Available online at: https://www.canada.ca/en/public-health/services/antibiotic-antimicrobial-resistance/animals/veterinary-antimicrobial-sales-reporting.html (accesssed February 18, 2021).
28. Danmap. *DANMAP 2017—Use of Antimicrobial Agents and Occurrence of Antimicrobial Resistance in Bacteria from Food Animals, Food and Humans in Denmark.* DenmarkISSN 1600-2032 (2017). Available online at: https://orbit.dtu.dk/ws/files/161713656/Rapport_DANMAP_2017.pdf (accesssed February 18, 2021).
29. Norwegian Veterinary Institute Grave K, Brun E. *Report 22—Use of Antibiotics in Norwegian Aquaculture.* Oslo, Norway: Norwegian Veterinary Institute (2016). Available online at: https://www.vetinst.no/rapporter-og-publikasjoner/rapporter/2016/use-of-antibiotics-in-norwegian-aquaculture (accesssed February 18, 2021).
30. Agunos A, Leger DF, Carson CA, Gow SP, Bosman A, Irwin RJ, et al. Antimicrobial use surveillance in broiler chicken flocks in Canada, 2013–2015. *PLoS ONE.* (2017) 12:e0179384. doi: 10.1371/journal.pone.0179384
31. Brault SA, Hannon SJ, Gow SP, Warr BN, Withell J, Song J, et al. Antimicrobial use on 36 beef feedlots in Western Canada: 2008–2012. *Front Vet Sci.* (2019) 6:329. doi: 10.3389/fvets.2019.00329
32. European Medicines Agency. *European Surveillance of Veterinary Antimicrobial Consumption (ESVAC) Sales Data and Animal Population Data Collection Protocol (version 3).* Veterinary Medicines Division, EMA/210691/2015-Rev.2 (2019). Available online at: https://www.ema.europa.eu/en/documents/other/european-surveillance-veterinary-antimicrobial-consumption-esvac-web-based-sales-animal-population_en.pdf (accesssed February 18, 2021).
33. Veterinary Medicines Directorate. *Understanding the Population Correction Unit Used to Calculate Antibiotic Use in Food- Producing Animals.* (2016). Available online at: https://www.gov.uk/government/publications/understanding-the-mgpcu-calculation-used-for-antibiotic-monitoring-in-food-producing-animals (accesssed February 18, 2021).
34. 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.
35. Government of Canada. *Canadian Integrated Program for Antimicrobial Resistance Surveillance (CIPARS): 2017 Integrated Findings.* Guelph, ON: Public Health Agency Canada (2019). Available online at: https://www.canada.ca/content/dam/phac-aspc/documents/services/surveillance/canadian-integrated-program-antimicrobial-resistance-surveillance-cipars/cipars-reports/2017-annual-report-integrated-findings/2017-annual-report-integrated-findings.pdf (accesssed February 18, 2021).
36. Government of Canada. *Canadian Antimicrobial Resistance Surveillance System Report 2018.* Public Health Agency of Canada (2020). Available online at: https://www.canada.ca/content/dam/hc-sc/documents/services/drugs-health-products/canadian-antimicrobial-resistance-surveillance-system-2020-report/CARSS-2020-report-2020-eng.pdf (accesssed February 18, 2021).
37. Government of Canada. *Canadian Antimicrobial Resistance Surveillance System (CARSS) Infographic: Antimicrobial Resistance and Antimicrobial Use in Canada in 2018.* Public Health Agency Canada (2020). Available online at: https://ipac-canada.org/photos/custom/Members/CNISPpublications/CARSS_Infographic_ENG%20(1).PDF (accesssed February 18, 2021).
38. European Medicines Agency. *Trends in the Sales of Veterinary Antimicrobial Agents in Nine European Countries (2005-2009).* (2011). Available online at: https://www.ema.europa.eu/en/documents/report/trends-sales-veterinary-antimicrobial-agents-nine-european-countries_en.pdf (accesssed February 18, 2021).
39. Montforts M. *Environmental Risk Assessment for Veterinary Medicinal Products. Part 1. Other than GMO-Containing and Immunological Products. First Update.* (1999). Netherlands: National Institute of Public Health and the Environment. Available online at: https://rivm.openrepository.com/bitstream/handle/10029/10110/601300001.pdf (accesssed February 18, 2021).
40. Montforts MH, Kalf DF, Van Vlaardingen PL, Linders JB. The exposure assessment for veterinary medicinal products. *Sci Total Environ.* (1999) 225:119–33. doi: 10.1016/s0048-9697(98)00338-6
41. Montforts MHMM, Tarazona Lafarga JV. *Environmental Risk Assessment for Veterinary Medicinal Products Part 4. Exposure Assessment Scenarios.* The Netherlands: National Institute for Public Health and the Environment (RIVM) (2003). Available online at: http://hdl.handle.net/10029/260761 (accesssed February 18, 2021).
42. European Medicines Agency. *Guideline on Environmental Impact Assessment for VMPs in Support of the VICH GL6 and GL38.* Committee for Medicinal Products for Veterinary Use (CVMP) (2016). Available online at: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-environmental-impact-assessment-veterinary-medicinal-products-support-vich-guidelines-gl6_en.pdf (accesssed February 18, 2021).
43. Morrison DB, Saksida S. Trends in antimicrobial use in Marine Harvest Canada farmed salmon production in British Columbia (2003-2011). *Can Vet J.* (2013) 54:1160–3.
44. Lekagul A, Tangcharoensathien V, Yeung S. The use of antimicrobials in global pig production: a systematic review of methods for quantification. *Prev Vet Med.* (2018) 160:85–98. doi: 10.1016/j.prevetmed.2018.09.016
45. Cermaq Global. *Value Chain.* (2020). Available online at: https://www.cermaq.com/wps/wcm/connect/cermaq/cermaq/our-salmon/value-chain/ (accessed August 14, 2020).
46. Grieg Seafood. *Life Cycle.* (2020). Available online at: https://www.griegseafoodcanada.com/our-fish/life-cycle/ (accessed August 14, 2020).
47. Food and Agriculture Organization. *Cultured Aquatic Species Information Programme—Oncorhynchus kisutch.* (2020). Available online at: http://www.fao.org/fishery/culturedspecies/Oncorhynchus_kisutch/en (accesssed February 18, 2021).
48. Government of British Columbia. *British Columbia Seafood Industry Year in Review 2018.* (2018). Available online at: https://www2.gov.bc.ca/assets/gov/farming-natural-resources-and-industry/agriculture-and-seafood/statistics/industry-and-sector-profiles/year-in-review/bcseafood_yearinreview_2018.pdf (accesssed February 18, 2021).
49. Government of Chile. *Report on the Use of Antimicrobials in the National Salmoniculture 2015.* (2018). Available online at: http://www.sernapesca.cl/busqueda?search=Antimicrobianos (accesssed February 18, 2021).
50. Norwegian Veterinary Institute. *Usage of Antimicrobial Agents and Occurrence of Antimicrobial Resistance in Norway.* (2018). Available online at: https://www.vetinst.no/en/surveillance-programmes/norm-norm-vet-report (accesssed February 18, 2021).
51. Veterinary Medicines Directorate. *Veterinary Antibiotics Resistance and Sales Surveillance Report 2018.* (2018). Available online at: https://www.gov.uk/government/publications/veterinary-antimicrobial-resistance-and-sales-surveillance-2018 (accesssed February 18, 2021).
52. Government of Canada. *Aquaculture, Production and Value, Table: 32-10-0107-01 (formerly CANSIM 003-0001).* Statistics Canada (2020). Available online at: https://www150.statcan.gc.ca/t1/tbl1/en/tv.action?pid=3210010701 (accesssed February 18, 2021).
53. FAO. *The State of World Fisheries and Aquaculture.* 2020. Sustainability in action. Rome: FAO (2020).

54. FAO. *FishStatJ—Software for Fishery and Aquaculture Statistical Time Series.* Rome: FAO (2020). Available online at: http://www.fao.org/fishery/statistics/software/fishstatj/en (accesssed February 18, 2021).
55. European Medicines Agency. *Sales of Veterinary Antimicrobial Agents in 31 European Countries in 2017*. (2017). Available online at: https://www.ema.europa.eu/en/documents/report/sales-veterinary-antimicrobial-agents-31-european-countries-2017_en.pdf (accesssed February 18, 2021).
56. World Organisation for Animal Health (OIE). *OIE Annual Report on Antimicrobial Agents Intended for Use in Animals. Better Understanding of the Global Situation, Third Report*. Paris (2018). Available online at: https://www.oie.int/fileadmin/Home/eng/Our_scientific_expertise/docs/pdf/AMR/Annual_Report_AMR_3.pdf (accesssed February 18, 2021).
57. Schar D, Klein EY, Laxminarayan R, Gilbert M, Van Boeckel TP. Global trends in antimicrobial use in aquaculture. *Sci Rep*. (2020) 10:9. doi: 10.1038/s41598-020-78849-3
58. Government of Canada. *Regulating and Monitoring British Columbia's Marine Finfish Aquaculture Facilities 2018.* Fisheries and Oceans Canada (2019). Available online at: https://www.dfo-mpo.gc.ca/aquaculture/management-gestion/mar-rep-rap-2018/index-eng.html (accesssed February 18, 2021).
59. Wade J. *Canadian Science Advisory Secretariat (CSAS): British Columbia farmed Atlantic Salmon Health Management Practices (Research Document 2017/072)*. Ottawa, ON: Deparment of Fisheries and Oceans (2017). Available online at: https://waves-vagues.dfo-mpo.gc.ca/Library/40653109.pdf (accesssed February 18, 2021).
60. Fisheries and Oceans Canada. *Pacific Region Marine Finfish Integrated Management of Aquaculture Plan*. (2016). Available online at: https://waves-vagues.dfo-mpo.gc.ca/Library/40628486.pdf (accesssed February 18, 2021).
61. Thyholdt SB. The importance of temperature in farmed salmon growth: regional growth functions for Norwegian farmed salmon. *Aquaculture Econ Manag.* (2014) 18:189–204. doi: 10.1080/13657305.2014.903310
62. Government of Canada. *Categorization of Antimicrobial Drugs Based on Importance in Human Medicine*. (2009). Available online at: https://www.canada.ca/en/health-canada/services/drugs-health-products/veterinary-drugs/antimicrobial-resistance/categorization-antimicrobial-drugs-based-importance-human-medicine.html (accessed August 14, 2020).
63. Hyde RM, Remnant JG, Bradley AJ, Breen JE, Hudson CD, Davies PL, et al. Quantitative analysis of antimicrobial use on British dairy farms. *Vet Rec.* (2017) 181:683. doi: 10.1136/vr.104614
64. Cuong NV, Phu DH, Van NTB, Dinh Truong B, Kiet BT, Hien BV, et al. High-resolution monitoring of antimicrobial consumption in vietnamese small-scale chicken farms highlights discrepancies between study metrics. *Front Vet Sci.* (2019) 6:174. doi: 10.3389/fvets.2019.00174
65. European Medicines Agency. *Principles on Assignment of Defined Daily Dose for Animals (DDDA) and Defined Course Dose for Animals (DCDA).* EMA/710019/2014 (2015). Available online at: https://www.ema.europa.eu/en/documents/scientific-guideline/principles-assignment-defined-daily-dose-animals-defined-course-dose-animals-draft_en.pdf (accesssed February 18, 2021).
66. European Medicines Agency. *Defined Daily Doses for Animals (DDDvet) and Defined Course Doses for Animals (DCDvet), European Surveillance of Veterinary Antimicrobial Consumption (ESVAC)*. Veterinary Medicines Division, EMA/224954/2016 (2016). Available online at: https://www.ema.europa.eu/en/documents/other/defined-daily-doses-animals-dddvet-defined-course-doses-animals-dcdvet-european-surveillance_en.pdf (accesssed February 18, 2021).
67. World Health Organization Collaborating Centre. *Guidelines for ATCvet Classification 2020*. (2020). Available online at: https://www.whocc.no/atcvet/atcvet_index_and_guidelines/guidelines_for_atcvet_classifica/ (accesssed February 18, 2021).
68. Kelly AM. *Medicated Feed for Food Fish*. (2013). Available online at: https://appliedecology.cals.ncsu.edu/wp-content/uploads/473.pdf (accesssed February 18, 2021).
69. Timmerman T, Dewulf J, Catry B, Feyen B, Opsomer G, Kruif A, et al. Quantification and evaluation of antimicrobial drug use in group treatments for fattening pigs in Belgium. *Prevent Vet Med.* (2006) 74:251–63. doi: 10.1016/j.prevetmed.2005.10.003
70. Persoons D, Dewulf J, Smet A, Herman L, Heyndrickx M, Martel A, et al. Antimicrobial use in Belgian broiler production. *Prev Vet Med.* (2012) 105:320–5. doi: 10.1016/j.prevetmed.2012.02.020
71. Kasabova S, Hartmann M, Werner N, Kasbohrer A, Kreienbrock L. Used Daily Dose vs. defined daily dose-contrasting two different methods to measure antibiotic consumption at the farm level. *Front Vet Sci.* (2019) 6:116. doi: 10.3389/fvets.2019.00116
72. Hemme M, Ruddat I, Hartmann M, Werner N, Van Rennings L, Käsbohrer A, et al. Antibiotic use on German pig farms—A longitudinal analysis for 2011, 2013 and 2014. *PLoS ONE.* (2018) 13:e0199592. doi: 10.1371/journal.pone.0199592
73. Joosten P, Sarrazin S, Van Gompel L, Luiken REC, Mevius DJ, Wagenaar JA, et al. Quantitative and qualitative analysis of antimicrobial usage at farm and flock level on 181 broiler farms in nine European countries. *J Antimicrob Chemother.* (2019) 74:798–806. doi: 10.1093/jac/dky498
74. Sjölund M, Postma M, Collineau L, Losken S, Backhans A, Belloc C, et al. Quantitative and qualitative antimicrobial usage patterns in farrow-to-finish pig herds in Belgium, France, Germany and Sweden. *Prev Vet Med.* (2016) 130:41–50. doi: 10.1016/j.prevetmed.2016.06.003
75. Redding LE, Bender J, Baker L. Quantification of antibiotic use on dairy farms in Pennsylvania. *J Dairy Sci.* (2019) 102:1494–507. doi: 10.3168/jds.2018-15224
76. Grave K, Hansen MK, Kruse H, Bangen M, Kristoffersen AB. Prescription of antimicrobial drugs in Norwegian aquaculture with an emphasis on "new" fish species. *Prev Vet Med.* (2008) 83:156–69. doi: 10.1016/j.prevetmed.2007.07.002
77. Compendium of Veterinary Products—Canada Edition. *Compendium of Veterinary Products—Aquaflor® (MERCK ANIMAL HEALTH).* (2020).

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Advantages of publishing in Frontiers

OPEN ACCESS
Articles are free to read for greatest visibility and readership

FAST PUBLICATION
Around 90 days from submission to decision

HIGH QUALITY PEER-REVIEW
Rigorous, collaborative, and constructive peer-review

TRANSPARENT PEER-REVIEW
Editors and reviewers acknowledged by name on published articles

Frontiers
Avenue du Tribunal-Fédéral 34
1005 Lausanne | Switzerland

Visit us: www.frontiersin.org
Contact us: frontiersin.org/about/contact

REPRODUCIBILITY OF RESEARCH
Support open data and methods to enhance research reproducibility

DIGITAL PUBLISHING
Articles designed for optimal readership across devices

FOLLOW US
@frontiersin

IMPACT METRICS
Advanced article metrics track visibility across digital media

EXTENSIVE PROMOTION
Marketing and promotion of impactful research

LOOP RESEARCH NETWORK
Our network increases your article's readership