ANALYSIS OF DOSAGE INSTRUCTIONS IN PACKAGE INSERTS FOR VETERINARY ANTIBACTERIAL MEDICATIONS AND IDENTIFICATION OF POTENTIAL RISKS OF BACTERIAL RESISTANCE

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ABSTRACT: Veterinarians must follow several criteria before prescribing antibacterials, and one fundamental step is selecting the correct dosage from specialized literature. Occasionally, professionals use the dosage recommended in the package insert, but several report discrepancies between the package insert and the dosage recommended in the literature. Thus, the aim of this study was to compare the dosage presented in package inserts of antibacterials from the veterinary line with the dosage recommended in the updated scientific literature. Package inserts of all antibacterials produced by laboratories associated with the National Union of Animal Health Products Industry (SINDAN) indicated for systemic use in dogs, cats, horses, and cattle were analyzed. The percentage of observations with inserts showing dosage concordant with the consulted reference literature was 50.0% for dogs, 54.2% for cats, 3.8% for horses, and 23.6% for cattle. Of the total observations of veterinary line antibacterials produced by SINDAN-affiliated laboratories, 32% present a dose and interval concordant with the consulted literature, which may favor the expected therapeutic effect; 35% combine a dose below and/or an interval above the reference, which may favor bacterial resistance, a relevant issue for public health; 5% combine a dose above and/or an interval below the reference, which may cause iatrogenic intoxication; and 28% present other combinations, with an undefined effect. These possible consequences were not evaluated directly in this study.

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Most package inserts of antibacterials from the veterinary line produced by SINDAN-affiliated laboratories in Brazil show divergences in posology compared with the consulted reference literature. The most frequent type of divergence identified was a combination of dose below and/or interval above the reference, a pattern that could favor bacterial resistance if this association is confirmed by studies directly assessing this outcome.
KEYWORDS: Animals; Antibiotics; Microbial resistance.

ANÁLISE DA POSOLOGIA DE BULAS DE MEDICAMENTOS ANTIBACTERIANOS VETERINÁRIOS E IDENTIFICAÇÃO DE POTENCIAIS RISCOS DE RESISTÊNCIA BACTERIANA

RESUMO: O médico veterinário precisa seguir diversos critérios antes de prescrever antibacterianos, e um dos fundamentos é selecionar a posologia correta com base na literatura especializada. Ocasionalmente, utiliza-se a posologia recomendada nas bulas, e diversos profissionais relatam discrepância entre a posologia das bulas e o que se recomenda na literatura. Assim, o objetivo deste estudo foi comparar a posologia apresentada nas bulas de antibacterianos da linha veterinária com a posologia recomendada na literatura científica atualizada. Foram analisadas as bulas de todos os antibacterianos produzidos pelos laboratórios associados ao Sindicato Nacional da Indústria de Produtos para a Saúde Animal (SINDAN) indicados para uso sistêmico em cães, gatos, equinos e bovinos. Observou-se que o percentual de observações com bulas que apresentavam posologia concordante com a literatura consultada foi de 50,0% para cães, 54,2% para gatos, 3,8% para equinos e 23,6% para bovinos. Do total de observações de antibacterianos da linha veterinária produzidos por laboratórios associados ao SINDAN, 32% apresentam dose e intervalo concordantes com a literatura consultada, o que pode favorecer o efeito terapêutico esperado; 35% combinam dose abaixo e/ou intervalo acima da referência, o que pode favorecer a resistência bacteriana, uma questão relevante para a saúde pública; 5% combinam dose acima e/ou intervalo abaixo da referência, o que pode causar intoxicação iatrogênica; e 28% apresentam outras combinações, com efeito indefinido. Essas possíveis consequências não foram avaliadas diretamente neste estudo. Conclui-se que a maioria das bulas dos antibacterianos da linha veterinária produzidos por laboratórios associados ao SINDAN no Brasil apresenta divergências na posologia em relação ao que recomenda a literatura consultada. O tipo de divergência mais frequente foi uma combinação de dose abaixo e/ou intervalo acima da referência, padrão que pode favorecer a resistência bacteriana caso essa associação seja confirmada por estudos que avaliem diretamente esse desfecho.
PALAVRAS-CHAVE: Animais; Antibióticos; Resistência microbiana.

ANÁLISIS DE LA POSOLOGÍA EN PROSPECTOS DE MEDICAMENTOS ANTIBACTERIANOS VETERINARIOS E IDENTIFICACIÓN DE POTENCIALES RIESGOS DE RESISTENCIA BACTERIANA

RESUMEN: El médico veterinario debe seguir diversos criterios antes de prescribir antibacterianos, y uno de los fundamentos es seleccionar la posología correcta a partir de la literatura especializada. Ocasionalmente, se utiliza la posología recomendada en los prospectos (bulas), y diversos profesionales reportan discrepancias entre la posología

indicada en dichos prospectos y la recomendada en la literatura científica. Así, el objetivo de este estudio fue comparar la posología indicada en los prospectos de antibacterianos de la línea veterinaria con la posología recomendada en la literatura científica actualizada. Se analizaron los prospectos de todos los antibacterianos producidos por los laboratorios asociados al Sindicato Nacional de la Industria de Productos para la Salud Animal (SINDAN), indicados para uso sistémico en perros, gatos, equinos y bovinos. Se observó que el porcentaje de observaciones con prospectos que presentaban una posología concordante con la literatura consultada fue de 50,0% en perros, 54,2% en gatos, 3,8% en equinos y 23,6% en bovinos. Del total de observaciones de antibacterianos de la línea veterinaria producidos por laboratorios asociados al SINDAN, el 32% presentan dosis e intervalo concordantes con la literatura consultada, lo que puede favorecer el efecto terapéutico esperado; el 35% combinan dosis por debajo y/o intervalo por encima de la referencia, lo que puede favorecer la resistencia bacteriana, una cuestión relevante para la salud pública; el 5% combinan dosis por encima y/o intervalo por debajo de la referencia, lo que puede causar intoxicación iatrogénica; y el 28% presentan otras combinaciones, con efecto indefinido. Estas posibles consecuencias no fueron evaluadas directamente en este estudio. Se concluye que la mayoría de los prospectos de los antibacterianos de la línea veterinaria producidos por laboratorios asociados al SINDAN en Brasil presentan divergencias en la posología respecto de lo recomendado en la literatura consultada. El tipo de divergencia más frecuente fue la combinación de dosis por debajo y/o intervalo por encima de la referencia, patrón que podría favorecer el desarrollo de resistencia bacteriana si esta asociación se confirma en estudios que evalúen directamente este desenlace.
PALABRAS CLAVE: Animales; Antibióticos; Resistencia microbiana.

1. INTRODUCTION

Since Alexander Fleming discovered penicillin in 1928, researchers have studied and released many other antibacterials for use (Stokes *et al.*, 2020). In addition to their use in humans, antibacterials are also widely used in veterinary medicine to treat infections, reduce mortality rates, and act as growth promoters in animal production (Gonzales; Mello; Café, 2012; Landers *et al.*, 2012). More than half of the antibiotics obtained worldwide are used in animals (Regassa; Koelsch; Dean, 2015).

Several criteria guide antibacterial prescribing. The patient must have a bacterial infectious disease; the veterinarian must evaluate whether an antibacterial agent is needed and whether treatment should be systemic. The bacterial culture identifies the pathogen and the antibiogram identifies its susceptibility to different antibiotics. Among these antibacterials, the Veterinarian must select the most suitable drug based on pharmacokinetics and pharmacodynamics (Spinosa; Tárraga, 2017). In farm animals, it is still necessary to assess the drug withdrawal period and the risks of environmental contamination (Zhang *et al.*, 2021a; Zhang *et al.*, 2021b).

Correct dosing helps achieve the expected therapeutic success: fighting infection while minimizing side effects (Stokes *et al.*, 2020). However, when the systemic antibiotic is employed with incorrect posology, therapeutic failure can occur and there is a potential risk of favoring bacterial resistance when low-dose and/or medication intervals longer than the ideal are combined (Spinosa; Tárraga, 2017), or iatrogenic intoxication, when an overdose and/or medication intervals shorter than the ideal are combined (Sala *et al.*, 2019). These complications compromise treatment, can put the patient's life at risk, and can strain the relationship between the Veterinarian and the person responsible for the animal.

Unfortunately, the development of antibacterials was accompanied by the emergence of resistant microorganisms (Spinosa; Tárraga, 2017; Ritter *et al.*, 2020). Although bacterial resistance occurs naturally (Martínez, 2012; Ritter *et al.*, 2020), it is intensified by the incorrect and indiscriminate use of antibacterials (Ayukekbong; Ntemgwa; Atabe, 2017), especially their excessive use (Rambliére *et al.*, 2021); self-medication; and changes in the protocol involving low-doses, increasing the interval between administrations and early discontinuation of treatment (Holloway; Van Dijk, 2011; Spinosa; Tárraga, 2017). Bacterial resistance makes antibacterials ineffective and, consequently, leads to therapeutic failure, increasing morbidity and mortality rates (Holloway; Van Dijk, 2011; Rambliére *et al.*, 2021).

Iatrogenic intoxication occurs when the human or animal patient has drug intoxication (Reis *et al.*, 2012; Benedicto, 2019; Sala *et al.*, 2019). The National System of Toxic-Pharmacological Information, which belongs to the Oswaldo Cruz Foundation (Fiocruz), shows that in Brazil, in 2017, of the 76,961 poisonings registered, 21,591 (28.1%) resulted from the use of medicines or veterinary products by humans or animals (SINITOX, 2017). Iatrogenic intoxication in animals can occur through accidental ingestion, administration by the responsible person without a previous prescription, or through the treatment recommended by the veterinarian. To prevent iatrogenic intoxication from a veterinary prescription, the professional must evaluate the patient's general condition, the animal's history, and whether the patient is receiving other concomitant treatments, and then the Veterinarian can prepare the prescription with an adequate therapeutic protocol for the patient (Reis *et al.*, 2012; Sala *et al.*, 2019).

To avoid bacterial resistance or iatrogenic intoxication, the veterinarian should consult the literature to establish the best protocol. Although not ideal, some professionals occasionally rely on the package inserts that accompany the medications before prescribing, as the material is expected to provide the correct and necessary technical information. Although it should never happen, the same occurs when the clerk or person responsible for the animal chooses to use the drug without prior consultation with the Veterinarian; they also rely on the package insert, as they do not have access to specialized literature. However, many Veterinarians report that they have already found differences between the posology presented in package inserts and the recommendations in the literature. For antibacterials, this divergence can favor bacterial resistance or iatrogenic intoxication.

Thus, the aim of this study was to compare the posology presented in the package inserts of veterinary-line antibacterials indicated for dogs, cats, horses, or bovines with the posology recommended in the updated scientific literature and, where they diverge, identify the possible risks.

2. MATERIAL AND METHODS

We accessed veterinary antibacterials' package inserts and recorded their posology between August/2019 and November/2020. For the selection of antibacterials from the veterinary line, the following criteria were established: I - be produced by one of the laboratories linked to the National Union of Animal Health Products Industry (SINDAN); II - be indicated for systemic use (injectable and/or oral) in dogs, cats, horses or cattle. Eye drops, ear drops, topical medications, and other forms of antibacterials were excluded.

In the first semester of 2019, we consulted the SINDAN website to identify its member laboratories. The website of each laboratory was then accessed individually to verify whether it produced antibacterial medicines meeting the eligibility criteria; when it did, the medicine was included in the list, and its package insert was accessed directly on the laboratory’s website. The authors acknowledge that this strategy may not have captured every veterinary antibacterial laboratory in the country; however, restricting the survey to companies already known to the researchers posed a greater risk of regional and marketing bias. Therefore, we linked the selection to SINDAN, an industry union that groups relevant and consolidated veterinary pharmaceutical companies, to obtain a broad and diversified sample. Accordingly, the results presented here should be interpreted as representative of an expressive share of the veterinary antibacterials produced by

SINDAN-affiliated laboratories in Brazil, rather than the totality of antibacterials marketed in the country.

We consulted the package inserts of these selected antibacterials and analyzed their posology. In the case of antibacterials indicated for two or more species, each product was evaluated once per indicated species, generating one product-species observation for each combination; each observation therefore corresponds to a product-species combination and not necessarily to an independent commercial product. Overall, 208 distinct commercial products were identified, of which 123 were indicated for a single species and 85 for two or more species, resulting in 303 product-species observations; this last unit was used to calculate the percentages presented in the Results. Whenever the package insert expressed the posology directly in mg/kg, the dose was compared on that basis. When the package insert instead indicated a fixed quantity (e.g., a number of tablets or a volume) for an adult animal, without specifying a dose per kilogram, a standard body weight was adopted to allow the mg/kg calculation: 10 kg for dogs, 5 kg for cats, and 500 kg for horses and cattle.

Next, we verified the posology recommended in the literature for each active ingredient of the selected antibacterials. When the package inserts were collected (2019–2020), this comparison was first carried out using the 4th edition of Guia Terapêutico Veterinário, by Fernando A. Bretas Viana, published in 2019 (Viana, 2019). In 2025, the collected data were reanalyzed and compared with the updated recommendations in the 5th edition of the same reference, published in 2024 (Viana, 2024), whose results are reported in the present study. The authors recognize that therapeutic recommendations, and possibly the package inserts themselves, may have changed between 2019–2020 and 2024; this time interval is considered a limitation of the study and is further addressed in the Discussion.

For the comparison between the posology stated in the package insert and the value recommended in the reference literature, we considered a divergence whenever the insert’s dose differed by more than 10% from the reference value. When the reference recommended a fixed dose, this dose was used directly as the comparison value; when the reference recommended a dose range, the arithmetic mean of the range was used, and the same 10% threshold was applied. The same criterion was used to classify the dosing interval as below, in accordance with, or above the reference. Doses and intervals within this 10% margin were considered in accordance with the consulted literature and are referred to hereafter as concordant; those below the threshold were classified as below the reference, and those above as above the reference. Following this rationale, the descriptors "correct", "low-dose", "overdose" and "correct interval" used in an earlier version of this manuscript were replaced throughout by concordant, below the reference, and above the reference, since determining whether a given dose is clinically adequate, subtherapeutic, or excessive also depends on other factors — such as the clinical indication, the species, the pharmacokinetic and pharmacodynamic properties of the antibacterial, the susceptibility of the causative agent, and the safety margin — which were not evaluated in this study.

For antibacterial medicines containing two or more active ingredients, each active ingredient was compared individually with the corresponding recommendation in the reference literature. When at least one of the active ingredients presented a divergent posology, the entire product-species observation was classified in the category "combination with divergent posology in at least one active ingredient"; this classification groups together combinations in which only one, several, or all of the active ingredients diverged from the reference, and was adopted to keep the presentation of results manageable.

Finally, the posology comparison was made between the package inserts and the scientific literature to verify whether differences existed and, when present, what their nature was — that is, whether the divergence involved the dose, the interval, or both, and in which direction. The results were presented descriptively according to this classification. The possible clinical implications of each type of divergence for bacterial resistance, iatrogenic intoxication, or therapeutic failure were not evaluated directly in this study and are discussed, with due caution, as potential — not demonstrated — consequences.

3. RESULTS AND DISCUSSION

Using the SINDAN website, 77 members companies were found. Altogether, 208 distinct commercial antibacterial products met the eligibility criteria, of which 123 were indicated for a single species and 85 for two or more species, resulting in 303 product-species observations (see Material and Methods). Analysis by species (Table 1) showed that, for dogs, 28 pharmaceutical laboratories produced 64 antibacterial observations for systemic use, involving 29 different active ingredients. Of these 64 observations, 49 are antibacterials with only one active ingredient, and 15 are antibiotic combinations. Regarding cats, 27 pharmaceutical laboratories account for 59 observations from 23 different pharmacological bases. Of these 59 observations, 45 contain only one active antibacterial ingredient, and 14 are combinations. For horses, 23 laboratories account for 53 observations involving 23 active ingredients. Of the 53 observations, 20 have only one active ingredient, and the other 33 are combinations of antimicrobials. In cattle, 27 pharmaceutical laboratories account for 127 antibacterial observations across 42 different active ingredients. Of the 127 observations, 84 are antibacterial only and 43 are antimicrobial combinations.

Table 1. Profile of antibacterials of veterinary line available for domestic animals in Brazil.

	Dogs	Cats	Equine	Cattle	Total
Antibacterial medicines	64	59	53	127	303
Medicine with one active ingredient	49 (76.6%)	45 (76.3%)	20 (37.7%)	84 (66.1%)	198 (65.3%)
Medicine with two or more active ingredients	15 (23.4%)	14 (23.7%)	33 (62.3%)	43 (33.9%)	105 (34.7%)

By analyzing the package insert of each of the antibacterial drugs and comparing them to the reference literature, it was observed that the proportion of drug observations with posology in accordance with the reference (concordant posology) was 50.0% for dogs, 54.2% for cats, 3.8% for horses, and 23.6% for cattle (Table 2).

Table 2. Comparison of the posology presented in veterinary antibacterial package inserts with the dosage recommended in the reference literature consulted.

	Dogs	Cats	Equine	Cattle
Concordant dose and interval	32 (50.0%)	32 (54.2%)	2 (3.8%)	30 (23.6%)
Concordant dose and interval above the reference	4 (6.3%)	5 (8.4%)	8 (15.1%)	33 (26.0%)
Dose below the reference and concordant interval	14 (21.8%)	6 (10.2%)	7 (13.2%)	8 (6.3%)
Dose below the reference and interval above the reference	2 (3.1%)	3 (5.1%)	5 (9.3%)	12 (9.5%)
Concordant dose and interval below the reference	-	1 (1.7%)	1 (1.9%)	1 (0.8%)
Dose above the reference and concordant interval	7 (10.9%)	4 (6.8%)	-	-
Dose above the reference and interval above the reference	1 (1.6%)	3 (5.1%)	3 (5.7%)	5 (3.9%)

Dose below the reference and interval below the reference	-	1 (1.7%)	2 (3.8%)	-
Undefined dose and concordant interval	-	1 (1.7%)	-	-
Concordant dose and undefined interval	-	-	1 (1.9%)	1 (0.8%)
Combination with divergent posology in at least one active ingredient	4 (6.3%)	3 (5.1%)	22 (41.5%)	30 (23.6%)
Not mentioned in the consulted literature	-	-	2 (3.8%)	7 (5.5%)
Total	64 (100%)	59 (100%)	53 (100%)	127 (100%)

Concordant dose/interval: dose or interval in accordance with the consulted literature. Dose/interval below the reference: dose or interval lower than that stated in the consulted literature. Dose/interval above the reference: dose or interval higher than that stated in the consulted literature. Categories are based exclusively on the numerical comparison between the package insert and the reference literature (Material and Methods); clinical implications were not evaluated directly and are discussed in the text.

The remaining drug observations presented some type of divergence in the posology compared to the reference literature; based on the type of divergence identified, about 35% of them combined a dose below the reference and/or an interval above the reference, and about 5% combined a dose above the reference and/or an interval below the reference (Figure 1). As discussed below, these two patterns could potentially favor bacterial resistance and iatrogenic intoxication, respectively, although this study did not evaluate these outcomes directly.

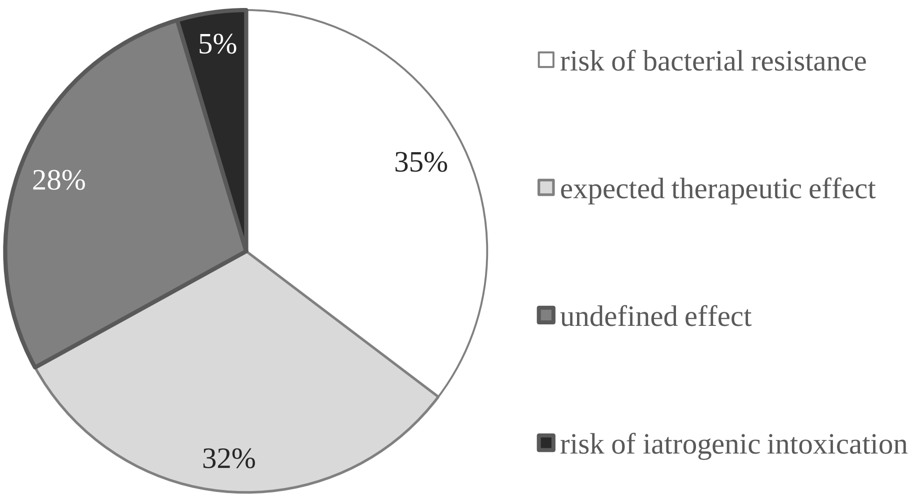

Figure 1. Possible consequences of medicating domestic animals with antibacterial medicines from the veterinary line available in Brazil, following the posology suggested in the package insert.
Source: Inserir fonte da imagem.

At first glance, what stands out most in this survey is the high rate of package inserts that differ in posology from what is recommended in the scientific literature. Next, when analyzing the type of divergence, it is surprising to find that more than a third of inserts for antibacterials in the veterinary line can favor bacterial resistance.

Among the four species evaluated, horses presented the lowest proportion of package inserts with posology concordant with the reference (3.8%) and, together with cattle, the highest proportion of combination products with divergent posology in at least one active ingredient (22/53, 41.5%, versus 30/127, 23.6%, in cattle; Table 2). Horses were also the species with the highest proportion of antibacterial combinations among the medicines analyzed (33/53, 62.3%; Table 1), which may partly explain the high frequency of this category in the species, since a combination product is classified as divergent whenever at least one of its active ingredients diverges from the reference, increasing its chance of falling into this category relative to single-ingredient products. Even so, the data in this survey do not allow a definitive explanation for why horses showed comparatively higher divergence than the other species, and future studies should investigate this finding further.

Bacterial resistance is inevitable because when using an antibacterial, bacteria will emerge that are or will become resistant, and resistance will be genetically transferred to daughter cells (Martínez, 2012; Spinosa; Tárraga, 2017; Ritter *et al.*, 2020). However, it is the responsibility of those who produce, prescribe, and use antimicrobials to avoid favoring this process by: (i) do not make indiscriminate and exaggerated use of antibacterials (Ayukekbong; Ntemgwa; Atabe, 2017; Rambliére *et al.*, 2021); (ii) do not practice self-medication from the misuse of leftover antibacterials stored; (iii) do not change the protocol proposed by health professionals, especially no reduce doses, prolong intervals between medications, or carry out early suspension of treatment (Holloway; Van Dijk, 2011), as this way the antibacterial acts selectively against the most sensitive bacteria, allowing the most resistant microorganisms to survive and proliferate, giving rise to resistant strains (Spinosa; Tárraga, 2017); (iv) to support the changes in favor to prohibit the free sale of veterinary antibiotics; and (v) to reduce maximally the antibiotics in animal feed (Regassa; Koelsch; Dean, 2015). Rational antibiotic use is essential to minimize the onset of bacterial resistance (Ayukekbong; Ntemgwa; Atabe, 2017; Rambliére *et al.*, 2021).

It is important to note that the microorganism acquires resistance, not the host (Martínez, 2012; Spinosa; Tárraga, 2017), and the microorganism does not differentiate whether the antibacterial will be used in human or animal treatment. Thus, errors in veterinary medicine have consequences for human medicine, and vice versa (Zhang *et al.*, 2021b; Regassa; Koelsch; Dean, 2015; Booton *et al.*, 2021). Therefore, the correct prescription of antibacterials and their control of sale is an important public health problem (Yadav; Kapley, 2021), as microbial resistance must be avoided regardless of whether the drug is registered with the Ministry of Health and is sold in a drugstore or is registered with the Ministry of Agriculture, Livestock and Supply and be sold in pet shops or farm animals shops.

The World Health Organization (WHO) classifies antimicrobial resistance as a serious threat to global public health (Ritter et al., 2020; Yadav; Kapley, 2021) and maintains a specific, updated online page on the subject (WHO, 2021). Microbial resistance compromises public health by making several antimicrobials ineffective, hindering and even preventing treatment of widespread and emerging diseases (Holloway; Van Dijk, 2011; Rambliére *et al.*, 2021). A reduced pharmacological arsenal increases the number of patients with serious diseases in Intensive Care Units, with high treatment costs and high mortality rates (Loureiro *et al.*, 2016; Prusakov *et al.*, 2021). In Veterinary Medicine, negative effects related to bacterial resistance in pets (Umber; Bender, 2009) and production animals (Zhang *et al.*, 2021a; Zhang *et al.*, 2021b) are also observed. In 1998, the World Health Assembly passed a resolution calling on its Member States to take action against antimicrobial resistance, and since then WHO has proposed several global strategies (WHO, 2001). In 2015, the 68th World Health Assembly approved the Global Plan of Action to Combat Antimicrobial Resistance (ECDC, 2008).

In Brazil, in 2011, the National Health Surveillance Agency (ANVISA), linked to the Ministry of Health, published RDC n. 20/2011, which sets criteria for prescribing, dispensing, controlling, packaging, and labeling antimicrobial drugs for prescription use, characterized or associated (ANVISA, 2011). Since then, pharmacies have sold antibacterials only with a duplicate copy of the prescription. In 2017, ANVISA published the National Plan for the Prevention and Control of Microbial Resistance in Health Services, with the general objective of establishing actions to prevent, detect, control, and reduce microbial resistance in national health services. One of the plan's axes aims to promote the rational use of antimicrobials in human and animal health (ANVISA, 2017).

However, this resolution was not extended to medicines registered at the Ministry of Agriculture, Livestock and Supply (MAPA), and currently, it is still possible to purchase veterinary antibacterials nationwide without prescription.

Veterinary medicine was recognized as a profession in the health area by the Ministry of Health through Resolution n. 287/1998 of the National Health Council (CNS, 1998). Subsequently, Ordinance n. 2488/2011 approved the National Primary Care Policy for the Unified Health System and included Veterinary Medicine in the Family Health Support Centers (MS, 2011). As health professionals, Veterinarians must help reduce the risk of bacterial resistance through actions such as (i) the establishment of animal health programs based on vaccination and good management practices in order to avoid infectious diseases; (ii) reduction in the use of antimicrobials as additives in animal feed; and (iii) the implementation of measures that prevent the free sale of antibacterials, making it mandatory to retain a prescription signed by a Veterinarian at the time of purchase of medicines (Spinosa; Tárraga, 2017).

In addition to reducing the risks of bacterial resistance, correcting the posology presented in the package inserts would also help to minimize the risks of iatrogenic intoxication, avoiding overdose and/or a shorter interval than recommended in the literature (Reis *et al.*, 2012; Benedicto, 2019; Sala *et al.*, 2019). This problem is particularly important in cats, as this species has difficulty metabolizing several drugs, including antibacterials (Gallacci; Cavalcante, 2012; Viana, 2019).

The findings of this survey are alarming and allow us to present some suggestions:

I. Only veterinarians are trained to prescribe antibacterials for animal use, and it is essential that the professional consult the literature when establishing the best therapeutic protocol because, in the Veterinary Doctor's Code of Ethics (CFMV, 2016) it is clear that it is a duty of this professional to continuously use their knowledge and use the best of scientific progress for the benefit of animals, man, and the environment;

II. The rational prescription of antibiotics is the responsibility of the Veterinarian, and it is also the duty of this professional to inform those responsible for the animals about the risks associated with the misuse of this class of drugs (Decree n. 20931 of 1932);

III. The uncontrolled sale of antibacterials from the veterinary line needs to be prohibited as a matter of extreme urgency, as it is currently still possible for those responsible for animals to acquire such drugs and they follow the posology presented in the package insert with the intention of doing the best for their animals, without knowing that they may be employing protocols that pose a risk to public health, can cause iatrogenic intoxication or have therapeutic ineffectiveness;

IV. Package inserts must provide accurate, reliable, and regularly updated information. Therefore, pharmaceutical companies producing antibacterials should use independent scientific research to verify the effectiveness of each active ingredient when preparing their inserts;

V. Competent government supervisory bodies need to ensure pharmacovigilance, evaluate the package inserts of veterinary medicines, and recommend periodic adjustments when necessary to establish a more comprehensive control system against bacterial resistance caused by the misuse of antibiotics; otherwise, efforts to prevent bacterial resistance will be insufficient.

This study presents some limitations that should be considered when interpreting its findings. First, the sample was limited to antibacterial medicines produced by SINDAN-affiliated laboratories and may not represent the full range of veterinary antibacterials commercialized in Brazil. Second, the package inserts were collected between 2019 and 2020, while the comparison reported here was based on the 5th edition (2024) of the reference guide; therapeutic recommendations, and possibly the package inserts themselves, may have changed during this interval, and this should be taken into account in future updates of this survey. Finally, this study evaluated only the divergence between the posology presented in the package insert and that recommended in the reference literature; it did not directly assess bacterial resistance, therapeutic failure, or iatrogenic intoxication, and the possible implications discussed here should be interpreted as hypotheses to be tested rather than as demonstrated outcomes.

It is clear that there must be a convergence of the posology of the package inserts of antibacterials from the veterinary line with the scientific literature to avoid microbial resistance and any other disorders related to medications, as errors in the protocols negatively compromise the health of the animal, the man, and the environment, prejudicing One Health (Booton *et al.*, 2021; Wang *et al.*, 2021). Therefore, those responsible for animals, Veterinarians, and pharmaceutical laboratories must be aware of the problem and aware of their role in this process. Those responsible for the animals will benefit, as their pet or production animal can recover more quickly and with minimal side effects. Veterinarians will have greater therapeutic success in recovering their patients and will avoid trouble with clients. The pharmaceutical industry benefits by continuing to market its antibacterial drugs without investing so many resources in researching new antibacterial molecules. Furthermore, a constant exchange of information among researchers, the pharmaceutical industry, and pharmacovigilance authorities is essential to identify discrepancies in antibiotic dosages early and ensure timely corrections to package inserts and treatments.

4. CONCLUSION

Most package inserts of antibacterials from the veterinary line produced by SINDAN-affiliated laboratories in Brazil show divergences in posology compared with the reference literature consulted. The most frequent type of divergence identified was a combination of dose below the reference and/or interval above the reference, a pattern that could potentially favor bacterial resistance if this association is confirmed by further studies directly assessing this outcome.

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