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Antibacterial therapy in dairy herds and the approach of veterinarians towards the issue of antimicrobial resistance in Nizhny Novgorod Oblast

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ABSTRACT

Introduction. A rational approach adopted by veterinary specialists to the selection of antibiotics is essential for successful treatment of infectious animal diseases, *inter alia* reducing the risk of developing antimicrobial resistance. Understanding the position of veterinarians regarding antimicrobial resistance and information about the extent of their knowledge on this issue are necessary for revising plans for the optimal use of antimicrobials in the field of animal husbandry.

Objective. The objective of the work was to determine the main reasons and the soundness of the use of antibacterials in dairy farming, as well as to assess the awareness of the issue of antimicrobial resistance and ways to overcome it.

Materials and methods. Rational use of antibiotics was assessed by surveying veterinarians from 44 dairy farms located in 12 raions and municipalities of Nizhny Novgorod Oblast, followed by statistical processing of the obtained data.

Results. It was found that 90.0% of the surveyed farm veterinarians kept an animal treatment log with records of antibiotic treatments, while 10.0% did not always record antibiotic prescriptions in the log. Of them, 63.0% use antibacterials to protect animals from diseases, 21.0% – to increase livestock profitability, and 16.0% – to prevent diseases. Most often, antibacterials were prescribed for treating diseases of the respiratory system (21.4%), the mammary gland (19.0%), and the reproductive organs (22.1%). More than half of the respondents stated that they do not use antibiotics for animal disease prevention, 17.3% use antimicrobials for preventing mammary gland diseases (mainly during the dry period), and 9.6% for preventing diseases of female reproductive organs after calving. Meanwhile, 50.0% of respondents do not aim to reduce their use of antibiotics. This creates high risks of the emergence of antibiotic-resistant strains of microorganisms and their spread through the food chain. The majority of veterinarians (68.0%) noted that the monitoring of residual concentrations of antibiotics in milk is a limiting factor for the widespread use of antibiotics in dairy cattle.

Conclusion. Despite the absence of a comprehensive program to reduce antibiotic use, the surveyed specialists acknowledge the existence of a mechanism that limits the spread of antimicrobial resistance. The only condition for curbing antibiotic use is the control of their content in raw milk, which dictates the need for further regulation in this area, as well as the optimization and prudent use of antibiotics.

Keywords: veterinarians, survey, use of antibiotics, antimicrobial resistance (AMR), dairy farming

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Антибактериальная терапия в молочных стадах и отношение ветеринарных врачей к проблеме антибиотикорезистентности в Нижегородской области

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РЕЗЮМЕ

Введение. Рациональный подход ветеринарных специалистов к выбору антибиотика является одним из условий успешного лечения инфекционных болезней животных, в том числе снижает риск формирования антибиотикорезистентности. Понимание позиции ветеринарных врачей относительно антимикробной резистентности и информация об объеме их знаний по данной теме необходимы для пересмотра планов по оптимальному применению противомикробных препаратов в области животноводства.

Цель исследования. Определение основных причин и степени обоснованности применения антибактериальных препаратов в молочном животноводстве, а также выяснение информированности ветеринарных врачей о проблеме антибиотикорезистентности и путях ее преодоления.

Материалы и методы. Оценку рациональности использования антибиотиков проводили методом анкетирования ветеринарных врачей 44 молочных хозяйств, расположенных в 12 районах и городских округах Нижегородской области, с последующей статистической обработкой полученных данных.
Результаты. Установлено, что 90,0% опрошенных ветеринарных врачей хозяйств вели амбулаторный журнал с записью о лечении антибиотиками, а 10,0% не всегда регистрировали назначения антибиотиков в журнале. Больше половины (63,0%) ветеринаров используют антибактериальные препараты для обеспечения благополучия животных, 21,0% – для повышения рентабельности животноводства и 16,0% – для профилактики заболеваний. Чаще всего антибактериальные препараты назначались для лечения органов дыхания (21,4%), молочной железы (19,0%) и репродуктивных органов (22,1%). Около 52,0% респондентов заявили, что не используют антибиотики для профилактики заболеваний животных, 17,3% – применяют антимикробные препараты для профилактики заболеваний молочной железы (в основном в сухостойный период) и 9,6% – для профилактики заболеваний репродуктивных органов самок после отела, при этом 50,0% опрошенных не ставят перед собой задачу сокращения применения антибактериальных средств. Это создает высокие риски появления антибиотикорезистентных штаммов микроорганизмов и распространения их по пищевой цепи. Большинство ветеринарных врачей (68,0%) отметили, что ограничивающим условием для широкого применения антибиотиков для молочного скота является контроль их остаточного содержания в молоке.
Заключение. Несмотря на отсутствие комплексной программы по сокращению использования антибиотиков, опрошенные специалисты признают существование механизма, ограничивающего распространение антибиотикорезистентности. Единственным условием сдерживания использования антибиотиков является контроль их содержания в сыром молоке, что диктует необходимость дальнейшего регулирования в данной сфере, оптимизации и рационализации антибиотикотерапии.

Ключевые слова: ветеринары, опрос, использование антибиотиков, устойчивость к противомикробным препаратам, молочное животноводство

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INTRODUCTION

Since its discovery, antibacterial substances have been widely used in medicine and agriculture. Antibiotics are used in livestock farming for the treatment and prevention of diseases and like growth promoters. For therapeutic purposes, antibacterials are typically administered in doses and courses prescribed by their manufacturers. To stimulate growth, they are introduced into the animal's body over a long period, and for prevention, they are used in small doses [1, 2, 3, 4]. More frequent use of antibiotics and their improper prescription exert selective pressure on clinically significant bacteria, which causes the development of antimicrobial resistance (AMR). This complicates the treatment of diseases they cause and makes first-line antimicrobial agents ineffective, leading to the overuse of second- and third-line antibacterials [4, 5]. Furthermore, the use of antibiotics leads to their accumulation in animal products, through which they can enter the human body [6, 7]. Also, the presence of antibiotics in milk reduces its technological properties, hindering fermentation by bacterial cultures when producing fermented dairy products and cheese [8]. Antibiotics can enter aquatic and terrestrial ecosystems through farm wastewater [9]. The close attention of scientists and practitioners to the problem of AMR has contributed to the adoption of documents at the global and national levels aimed at prudent use of antibiotics. For example, in 2017, the World Health Organization (WHO) developed a classification of antibiotics designed to systematize their use for treatment purposes. All antibiotics were divided into three groups: Access, Watch, and Reserve [10].

In our country, in 2017, the Strategy to Prevent the Spread of Antimicrobal Resistance in the Russian Federation to 2030 was approved. It is aimed at preventing and limiting the spread of microorganism resistance to antimicrobials, as well as informing and increasing the knowledge level of physicians and veterinary specialists on these issues [11]. In addition, Russian national standards do not permit the presence of antibiotics in milk and cattle meat [12]. Despite various existing regulatory documents, residual amounts of antibacterials are sometimes detected in milk and beef, indicating their uncontrolled use on livestock farms.

To understand risks to human and animal health associated with the use of antibiotics for therapeutic and preventive purposes in dairy farming, it is important to determine conditions and motivations for the use of antimicrobials on farms. Consequently, global efforts are currently underway to assess the awareness of the general public, physicians, and veterinary specialists about antibiotic use and AMR. In 2015, the WHO developed a questionnaire to evaluate public awareness and behavior related to antibiotic use [13]. Studies using surveys and interviews among the public, physicians, and veterinarians have been conducted in several European and Asian countries [14]. Such research is part of the system aimed at monitoring and evaluating knowledge about AMR.

In Russia, no similar investigations involving surveys of veterinarians working with food producing animals have been conducted. It is necessary to understand the perspective of veterinarians on AMR and the level of their awareness about the issue in order to revise plans for the prudent

use of antimicrobials in livestock farming. Therefore, this study was conducted among veterinarians on livestock farms to assess their practical and theoretical knowledge of antibiotic use and the emergence of resistance resulting from their use.

MATERIALS AND METHODS

Study area. The study was conducted in Nizhny Novgorod Oblast, an area with developed dairy and beef cattle, poultry, and pig farming. In total, there are 383 industrial livestock farms in the region, including 345 dairy farms with a total population of 243,400 cattle, of which 104,300 are cows (including heifers and beef cows). The average milk yield per dairy cow is 7,306.0 kg per year, with a total yield of 536.9 million kg per year. The consumption of milk and dairy products per person is 289.2 kg per year, and for the entire population of the region, it is 890.7 million kg per year, which is 65.9% more than what is produced [15].

Questionnaire survey. Researchers from the Nizhny Novgorod Research Veterinary Institute – Branch of Federal Research Center for Virology and Microbiology developed a research tool (questionnaire) using the "Yandex Forms" service (https://forms.yandex.ru/u/6800be6084227c3e18e6892c) to conduct an online survey and collect information on antibiotic use on livestock farms. The authors of this article surveyed 44 veterinarians serving dairy farms in 12 raions and municipalities of Nizhny Novgorod Oblast. Additionally, staff from the Veterinary Committee of Nizhny Novgorod Oblast orally informed veterinarians about the online survey and the study's objectives, providing guarantees of complete anonymity for the responses. No exclusion criteria were applied to the survey participants.

Questionnaire content. The questionnaire items provided information on the livestock industry and the number of animals serviced by a specific veterinarian; the objectives and motivations for using antibacterials in practice; their types and pharmacological groups; and the age and sex structure of the animals for which they are prescribed, as well as the symptoms and diseases involved. The questions also covered methods of medicinal product administration, record-keeping of their use, and assessment of microbial sensitivity to antibiotics. The final questions aimed to ascertain the veterinarians' opinions on the problem of bacterial resistance to antibacterials and the possibility of reducing or discontinuing antibiotic use.

Data analysis. Only questionnaires containing answers to questions with single or multiple response options were used for subsequent analysis. The analysis of the collected survey data was performed using free R software (version 4.3.1, available at https://www.r-project.org). Data processing involved methods for analyzing categorical data, as well as calculating percentage distributions using the "table" function in combination with the prop.table function. Statistical significance was estimated based on the *p*-value: if it was less than 0.05, this indicated statistical significance.

RESULTS AND DISCUSSION

The survey found that 90.0% of veterinary specialists maintain a clinic log, where they record antibiotic treatments, providing verifiable documentation.

Further analysis of the reasons for using antibacterials (Fig. 1) showed that 63.0% of respondents use antibiotics

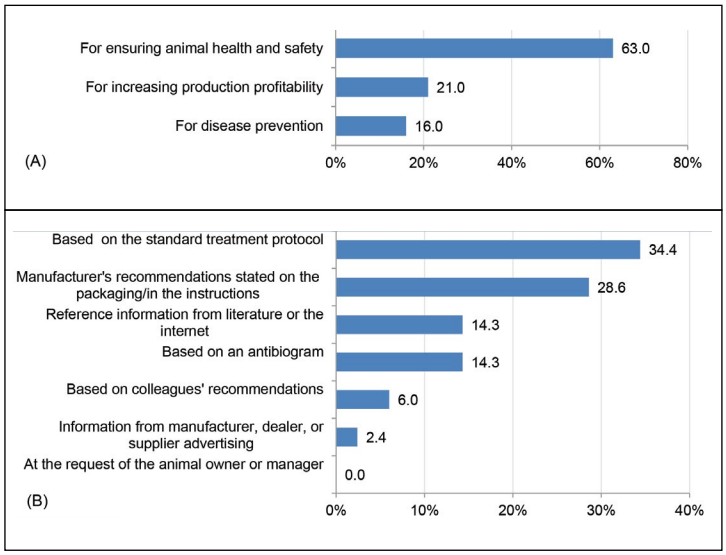

Fig. 1. Factors contributing to use of antibiotics: (A) purpose of use; (B) grounds for prescription

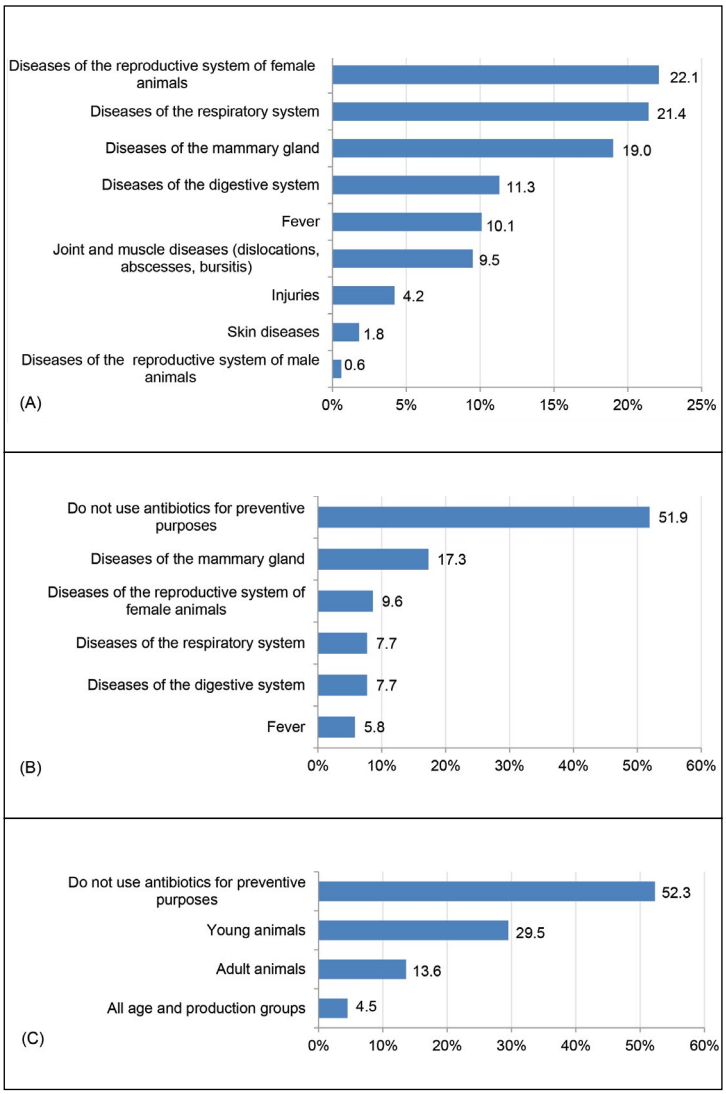

Fig. 2. Use of antibiotics: (A) for treating diseases in organs and systems; (B) for disease prevention in organs and systems; (C) for prevention purposes in animal groups. (Multiple responses allowed.)

to treat sick animals, 21.0% to ensure farm profitability, and 16.0% to prevent diseases. The majority of veterinary specialists (34.4%) used antibacterials according to a standard treatment protocol, while 28.6% followed the manufacturer's recommendations specified in the instructions for use. Additionally, 14.3% of respondents prescribed medicinal products after consulting reference literature or the internet and based on an antibiogram. Only 6.0% acted on the recommendations of colleagues, and a mere 2.4% relied on information from manufacturer (supplier) advertising.

The survey results established (Fig. 2A) that antibacterials were most frequently used to treat the reproductive system of female animals (22.1%), the respiratory system (21.4%), and the mammary gland (19.0%). Additionally, 11.3% of respondents used these medicinal products for digestive tract diseases, 10.1% for fever, 9.5% for joint and muscle conditions (dislocations, abscesses, bursitis), and 4.2% for injuries. A small number of respondents used antibacterials for treating skin diseases (1.8%) and diseases of the reproductive system of male animals (0.6%).

A little more than half of the surveyed veterinary specialists (51.9%) did not use antibiotics for preventive purposes (Fig. 2B). When used, they were primarily administered to prevent diseases of the mammary gland (17.3%) and the reproductive system of female animals (9.6%), respiratory and digestive organs (7.7% each), and fever (5.8%).

More than half of the veterinarians in Nizhny Novgorod Oblast (52.3%) did not prescribe antibacterials to any specific group of animals for prevention. However, 29.5% of respondents prescribed them to young stock, 13.6% to adult animals, and only 4.5% used these medicinal products for preventive purposes across all age and production groups (Fig. 2C).

Antibiotics (according to the AWaRe classification) from the Access group were used by 59.5% of veterinarians (Fig. 3). Specifically, they used penicillins, penicillins with *β*-lactamase inhibitors, ampicillins and amoxicillins, tetracyclines (oxytetracycline, Nitox®, etc.), 1st generation cephalosporins (cephaloridine, cephalothin, cephapirin, cephradine, cefazolin, cefalexin, cefadroxil), aminoglycosides (streptomycin, gentamicin, kanamycin, neomycin/gentamicin, tobramycin, netilmicin, sisomicin/amikacin/isepamicin), metronidazole, chloramphenicol (Levomekol®), lincomycin, sulfonamides (streptocide, Ditrim®, Norsulfazole, Ethazole, Sulfadimezin, sulfadimethoxine, trimethoprim, etc.), nitrofuran medicinal products (furacilin, furazolidone, etc.), and feed antibiotics.

Antibacterials from the Watch group were used by veterinarians in 36.7% of cases. This group was represented by medicinal products such as 2nd generation cephalosporins (cefuroxime, cefaclor, cefamandole, cefotiam, cefsulodin, cefoxitin), 3rd generation cephalosporins (cefotaxime, cefoperazone, ceftriaxone, ceftibuten, ceftazidime, cefixime, cefpodoxime, cefodizime, cefetamet), fluoroquinolones (ciprofloxacin, norfloxacin, ofloxacin, pefloxacin, lomefloxacin, sparfloxacin, levofloxacin, moxifloxacin, gemifloxacin, gatifloxacin, sitafloxacin, trovafloxacin, delafloxacin, enrofloxacin: Enroflon®, Enroflox, Enroxil®, Renrovet, Iroflox, Baytril, Enrofarm, Enrosept, etc.), macrolides (tylosin, Pharmazin®, Tylan, Tylanic, Disparcol, Draxxin, Floritil, Endometramag-T®, Spirovim, Pulmotil®, Aquatyl, Aivlosin®, etc.), and rifamycins (rifampicin, Rifacyclin, Rifapol, etc.).

The use of Reserve group antibiotics was minimal – 3.8%, including 4th generation cephalosporins (cefpirome,

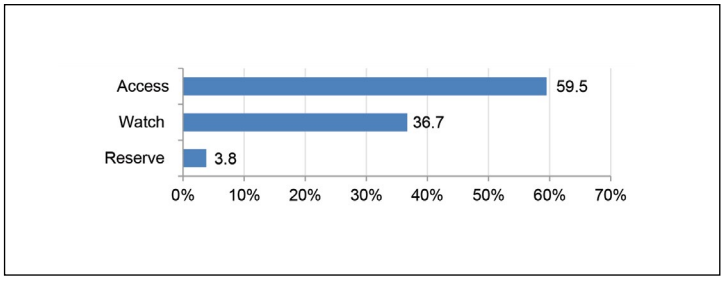

Fig. 3. Antibacterials of the Access, Watch, and Reserve groups used for livestock treatment on farms in Nizhny Novgorod Oblast

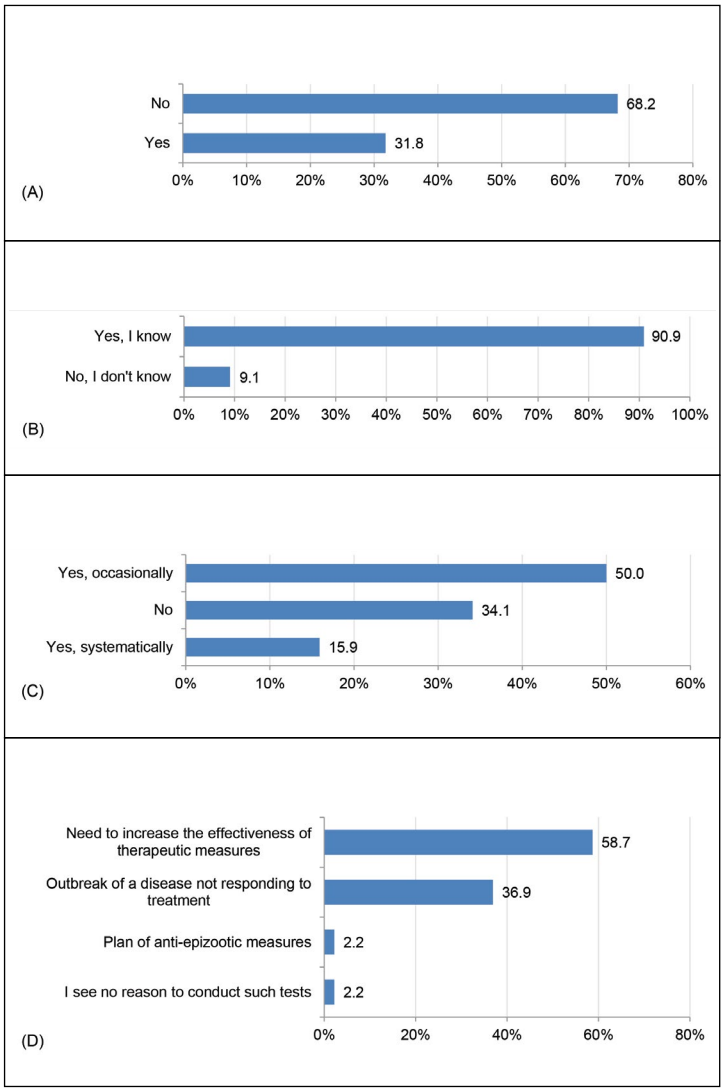

Fig. 4. Antibiotic resistance awareness analysis: (A) Have you ever participated in a survey regarding the prevention of antimicrobial resistance? (B) Are you aware of the issue of bacterial resistance to antibiotics? (C) Do you perform laboratory tests to determine the sensitivity of microorganisms to antibiotics? (D) In which cases do you conduct antibiotic sensitivity testing (multiple responses allowed)?

cefepime), 5th generation cephalosporins (ceftobiprole, ceftaroline, ceftolozane), and polymyxins (polymyxin M, polymyxin B).

Most of the surveyed veterinary specialists used antibacterials most frequently during transitional seasons: 46.1% in the spring and 35.2% in the autumn. This is explained by the fact that this period is one of the most challenging stages in the production cycle of dairy cattle and their offspring, as the main problem for cows after calving is the imbalance between the body's reserves and the nutrient requirements for milk production. The sharp increase in metabolic rate associated with calving and the onset of lactation leads to greater susceptibility to stress, which contributes to the occurrence of various disorders in cows and even calves.

The problem of AMR is highly relevant; therefore, several questionnaire items addressed this topic. 90.9% of the surveyed veterinary specialists are aware of the issue of AMR, while 9.1% reported being unaware. Regarding the prevention of AMR, 68.2% of respondents had been previously surveyed on the matter, while 31.8% had not. Only 15.9% of veterinary specialists consistently determine microbial sensitivity to antibiotics, 50.0% perform resistance testing occasionally, and 34.1% of specialists do not conduct such tests at all.

For specialists who perform antibiotic sensitivity testing, the primary reason in most cases (58.7%) is the need to increase the efficacy of therapeutic measures. In 36.9% of cases, the reason is an outbreak of a disease unresponsive to treatment, in 2.2% of cases – it is the fulfillment of an anti-epizootic measures plan, and in 2.2% of cases – respondents see no grounds for conducting the aforementioned testing (Fig. 4).

When studying the conditions for the possible reduction of antibiotic use in the future, it was found that the majority of respondents (47.1%) believe that the use of vaccines and sera would contribute to this, 41.1% – the implementation of veterinary and sanitary measures (disinfection, disinsection, and deratization), 4.0% – suggested other options (adherence to animal feeding and animal keeping rules), and 7.8% of specialists stated that there are no grounds for reducing the volume or changing the strategy of antibiotic use (Fig. 5A).

The majority of veterinary specialists (40.9%) believe that the antibiotics used for animals are becoming ineffective, meaning microorganisms develop resistance to them (based on laboratory sensitivity testing), 36.4% of respondents doubt this (judging by the reduced effectiveness of therapeutic measures), and 22.7% of respondents believe that resistance to antimicrobials does not develop (Fig. 5B).

None of the respondents would be able to completely stop using antibacterials; 47.7% of respondents definitely would not stop using them, and 52.3% believe they could reduce the use of antibiotics (Fig. 5C).

An analysis of awareness regarding antibiotic use recommendations revealed that in the majority of cases (50.0%), respondents had not been tasked with reducing antibiotic use in animals; 31.8% of veterinarians were instructed by farm management, and 18.2% by the raion/municipality veterinary administration.

An analysis of the reasons for refusing or reducing antibiotic use in dairy farming showed that most surveyed veterinarians (68.0%) limit their use due to the monitoring of residual amounts in milk and meat. 26.0% of specialists

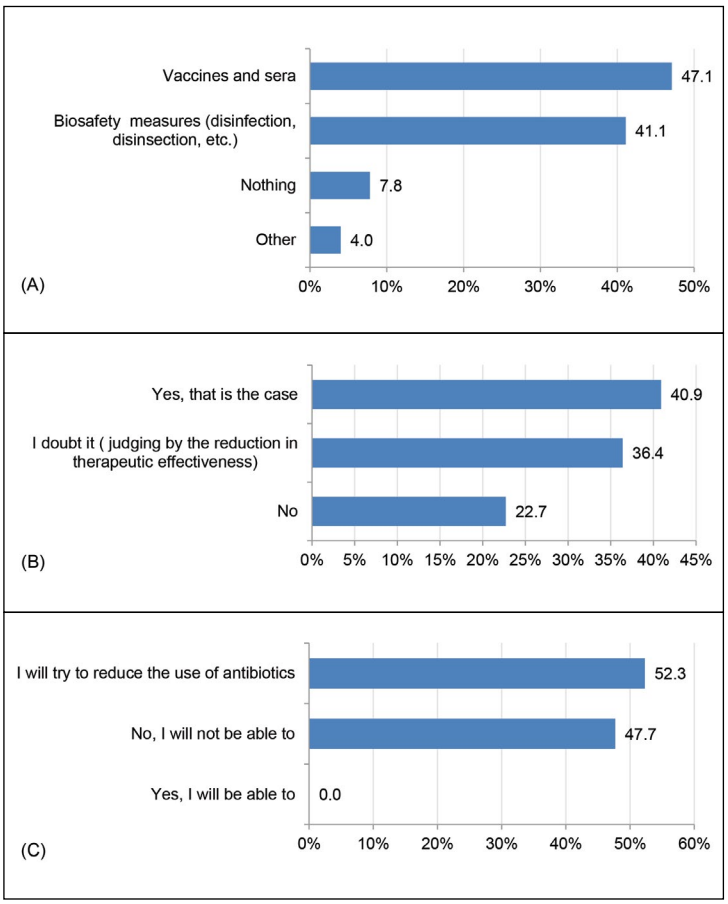

Fig. 5. Analysis of factors reducing future use of antibiotics: (A) In your opinion, what factors would lead to a reduction in antibiotic use (multiple responses allowed)? (B) Do you believe that some antibiotics you use for livestock treatment have become ineffective (due to the development of resistance)? (C) Will you be able to completely stop using antibiotics in your practice in the foreseeable future?

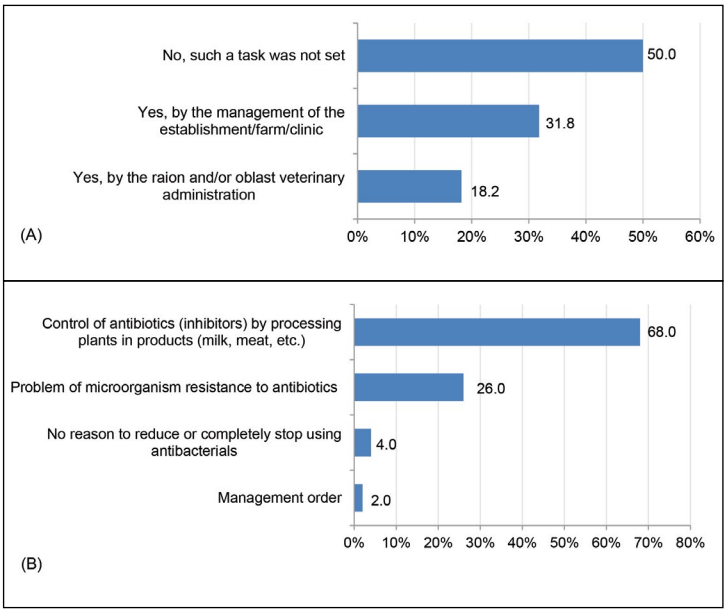

Fig. 6. Analysis of information on the use of antibacterials by veterinary specialists in Nizhny Novgorod Oblast: (A) Has management set a goal for you to reduce the use of antibiotics in animals? (B) What is the reason for the reduction or complete cessation of antibiotic use (multiple responses allowed)?

attribute their refusal of widespread antibiotic use to the development of microbial resistance, 2.0% – to instructions from farm management, and 4.0% believe there are no grounds for reducing or completely abandoning the use of antibiotics in dairy farming (Fig. 6).

This is the first documented study in Russia involving only veterinary practitioners working on dairy farms. The survey showed that 100.0% of specialists in Nizhny Novgorod Oblast use antibiotics in their practice. At the same time, 59.5% of veterinarians prescribed antibiotics from the Access group, 36.7% – from the Watch group, and the use of Reserve antibiotics was minimal (3.8%). Veterinarians in Nizhny Novgorod Oblast did not use medicinal products from the 'not recommended' group. The most frequently prescribed antibiotics were tetracyclines (12.4%), macrolides (12.4%), and 3rd generation cephalosporins (10.0%). These findings are similar to data on antibiotic use in European countries. For instance, in Sweden, Access group antibiotics, particularly penicillins, were used significantly more often than others (84.0%). The use of Watch group antibiotics was more frequently reported in Germany (42.0%), while in Sweden, medicinal products from this group were not used [16].

More than a third of the surveyed veterinarians (34.4%) prescribe antibiotics based on a standard treatment protocol, and 28.6% based on manufacturer recommendations. Only 14.3% base their choice of medicinal products on the results of laboratory sensitivity testing of the herd microflora. We assume that an important factor in choosing an antibacterial could be its cost.

Data from other researchers indicate that antibiotics are most commonly used to treat infectious diseases in cows (mastitis, endometritis) and young stock (respiratory and digestive diseases) [17]. Our results show that veterinary specialists most frequently use antimicrobials to treat diseases of the reproductive organs of female animals (22.1%), respiratory system (21.4%), and mammary glands (19.0%).

The preventive use of antibiotics is also very widespread all over the world [18]. Researchers believe that using antibiotics for prevention has both advantages and disadvantages. The main advantage is maintaining the maximum number of healthy animals, while the risk lies in the fact that antimicrobial use leads to the emergence of resistant bacterial strains and serotypes, which can ultimately enter the human body [18, 19]. The most favorable time for antibiotic therapy of bovine mastitis is the dry period [17]; therefore, 17.3% of the surveyed veterinarians prescribe antibiotics for mastitis prevention specifically during this timeframe. After calving, the period of milking and calf feeding begins. During the time when milk is not sent to processing plants and there is no risk of a milk batch being returned, treatment and prevention of uterine and birth canal diseases are performed. Our results show that antimicrobials are used for the treatment and prevention of reproductive organ infections in cows (22.1 and 9.6% of cases, respectively). However, this leads to the excretion of residual amounts of the medicinal product in milk, which is then fed to calves.

Calves are the group of animals most susceptible to diseases on dairy farms. In the first weeks of life, there is a high risk of digestive system diseases, and in the first 2–3 months, respiratory diseases [20]. Therefore, various therapeutic and preventive measures are performed for this animal group, which may include the use of antibiotics. We have previously demonstrated [21] that 21.4 and 11.3% of veterinarians use antibacterials to treat respiratory and digestive diseases, while antibiotics are most frequently used for preventive purposes in young stock (29.5% of cases). In particular, 7.7% of respondents consciously use them for the prevention of digestive and respiratory diseases.

As can be seen, antibacterials are deliberately and widely used in dairy farming to increase the effectiveness of therapeutic measures or disease prevention. Almost half (50.0%) of the surveyed veterinarians did not set a goal to reduce antibiotic use. At the same time, monitoring the development of AMR in the herd microflora is weak: only 15.9% of veterinarians regularly determine the sensitivity of isolated microorganisms to antibacterials, while a third never do so; 47.7% of veterinarians affirmatively state that they will never stop using antibiotics, even though they are aware of the AMR problem. Thus, despite awareness of the problem, there are no restrictions on the use of antibacterials at the farm and establishment level.

There are several factors limiting the use of antibiotics, such as administrative or industry-specific restrictions. For instance, the Strategy to Prevent the Spread of Antimicrobal Resistance in the Russian Federation to 2030 outlines several key areas, such as informing the public about the use of antimicrobials and resistance issues, and improving the training and awareness of physicians and veterinarians on these issues [11]. The survey revealed that 68.0% of veterinary specialists limit antibiotic use only because of the monitoring of their presence in raw milk by dairies. Thus, an important production factor restraining the use of antibacterials is GOST 31449-2013 Raw cow's milk. Specifications'[1], which do not allow residual amounts of antibiotics in milk; if they are detected, farms suffer losses. Despite this, only 26.0% of surveyed veterinarians, recognizing the significance of AMR, are reducing antibiotic use in cows and calves. Such an attitude among veterinarians contributes to the development of AMR and the spread of resistant microorganisms through the food chain, creating a risk of untreatable bacterial infections in both animals and humans.

CONCLUSION

Thus, the use of antibiotics in dairy farming in Nizhny Novgorod Oblast is widespread. Antibacterials are integrated into treatment protocols for most common diseases in dairy cows and calves and are also used for preventive purposes. This contributes to the development of AMR in on-farm bacteria and the dissemination of resistant strains beyond the farm environment via raw milk. The only functional tool for restraining antibiotic use is the monitoring of residual levels in raw milk by dairies. However, the concept of a conscious refusal to use antibiotics is not widely supported by veterinarians, highlighting the urgent need for further regulatory measures in this sector, as well as enhanced training and outreach for both veterinary specialists and farm management.

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