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REVIEW

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Antimicrobial use and resistance in food-producing animals—How can we protect the efficacy of antibiotics for reproductive diseases?

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Abstract

The ongoing emergence of antibiotic resistance jeopardizes efficacy of antibiotics in curing animals from bacterial infections that threaten their health, welfare and productivity. This review gives an overview of antimicrobial use data in food-producing animals, a discussion on how antimicrobials are used for some infections in the reproductive system in cattle, the horse and pig in Europe where there are differences in treatment practices including options to refine the use of antibiotics, and finally, a presentation of the antibiotic resistance for some bacteria collected from the reproductive system. It is shown that there are differences in applied treatment regimens for, as well as prevention of, several reproductive diseases in Europe. Some of the treatments are not evidence-based, which should be considered by clinicians and other stakeholders. It is concluded that a more refined and restrictive use of antibiotics could be achieved by adhering to evidence-based guidelines by national and international expertise including the scientific literature when available. This may call for a re-think among the animal health stakeholders regarding the use of antibiotics and may demand new skill-sets in the animal health sphere.

KEYWORDS
antimicrobial resistance, antimicrobial use, cow, horse, pig, reproduction

1 | INTRODUCTION

Antimicrobials have contributed a lot to improved human health and animal health, productivity and welfare. However, during the last decade, antimicrobial resistance (AMR) has been identified as a major global public health issue. The fact that the use of antimicrobials drives the development of resistance, the extensive use in the livestock sector of antibiotics, the sub-set of antimicrobials effective against bacteria, has come under scrutiny (WHO, 2015). The large amounts of antibiotics use in livestock are mainly attributable to various kinds of prophylactic use and use as growth promoters, mostly administered to groups of animals. Such practices are rare in human medicine. There are reports on how resistant bacteria from animals have infected humans (reviewed by Hoelzer et al., 2017). However, how frequent this is, or how much the livestock sector contributes to the overall prevalence of resistant bacteria in humans, is largely unknown. Even so, the ongoing emergence of antibiotic resistance also jeopardizes their efficacy in curing animals from bacterial infections that threaten their health, welfare and productivity (Bengtsson and Wierup, 2006).

So, there are several good reasons to aim for a more refined and restrictive use of antibiotics within veterinary medicine. In the following, there is an overview of antimicrobial use data in food-producing animals, a discussion on how antimicrobials are used for some major infections in the reproductive system in these species in Europe. Then are differences in treatment practices highlighted including options to refine the use of antibiotics, and finally, a presentation of the antibiotic resistance for some bacteria collected from the reproductive system. The use of antibiotics associated with surgery, for example caesarean section, or for technical use, like in semen extenders, will not be covered by this review.

2 | OVERALL USE OF ANTIBIOTICS

It has been estimated that more than 70% of global antimicrobial use is in livestock and currently are the livestock riche countries China, Brazil and the USA the largest consumers, (Van Boeckel et al., 2017; Tiseo et al., 2020; Figure 1). The latter study project the amount to increase by 11.5% by 2030, primarily in Asia. The increase is primarily driven by intensification of livestock production to meet the growing demand for animal source foods in low- and middle-income countries where antimicrobial use is poorly regulated and antimicrobials are used irrationally to compensate for poor animal husbandry practices (reviewed by Magnusson et al., 2021).

In Europe, the European Medicines Agency (EMA) publish the annual report on European Surveillance of Veterinary Antimicrobial Consumption (ESVAC), where official sales and adjacent data are presented (EMA, 2021). As shown in Figure 2, there are considerable differences among countries in Europe with regard to sales per population corrected unit; most sales in some Southern and Eastern European countries and least in Northern European countries.

Also, there are monitoring systems of farm-level antibiotic use, and as of 2020, 16 countries are reported to have such systems (Sanders et al., 2020). The oldest systems are those of the Swedish Board of Agriculture, starting in 1971, and the Danish VetStat monitoring tool starting in 2000. However, the availability of the data from these monitoring programs is highly variable and it is therefore difficult to make fair comparisons.

3 | OPTIONS FOR REFINING AND REDUCING ANTIBIOTIC USE FOR REPRODUCTIVE DISEASES

Currently, there is no harmonized collection of antibiotic use data by indication by species available from Europe or from any country. For instance, 'injectable products' reported in the ESVAC are used for various diseases, including reproductive diseases (EMA, 2021). In the reporting of the distribution of sales of antimicrobials by product form by country show that the formulas exclusive for reproductive diseases, 'Intramammary products' and 'Intrauterine products', constitute a minor share of the total use of antibiotics in most countries (Figure 3). However, there are some substantial differences among the countries in the proportions of sales of intramammary and intrauterine products. This may be attributable to composition of the animal population in the country of concern or national guidelines or tradition in veterinary practices as discussed below.

Thus, it is not possible to compare among countries the quantity of antibiotics used for reproductive diseases in different species. However, there are different kinds of sources indicating differences in using antibiotics for the same kind of reproductive disease: treatment guidelines from the livestock industry, professional associations, vet schools or actual surveys among clinicians (e.g. Drillich et al., 2007; Eppe et al., 2021; Espinosa-Gongora et al., 2021; Köhne et al., 2020; Sølverød et al., 2011; Timonen et al., 2021). In the following, with focus on the situation in Europe, such sources are the basis for elaborations on how to refine and reduce the use of antibiotics for some major reproductive diseases in cows, pigs and horses where antibiotics are a significant component of the treatment regimes.

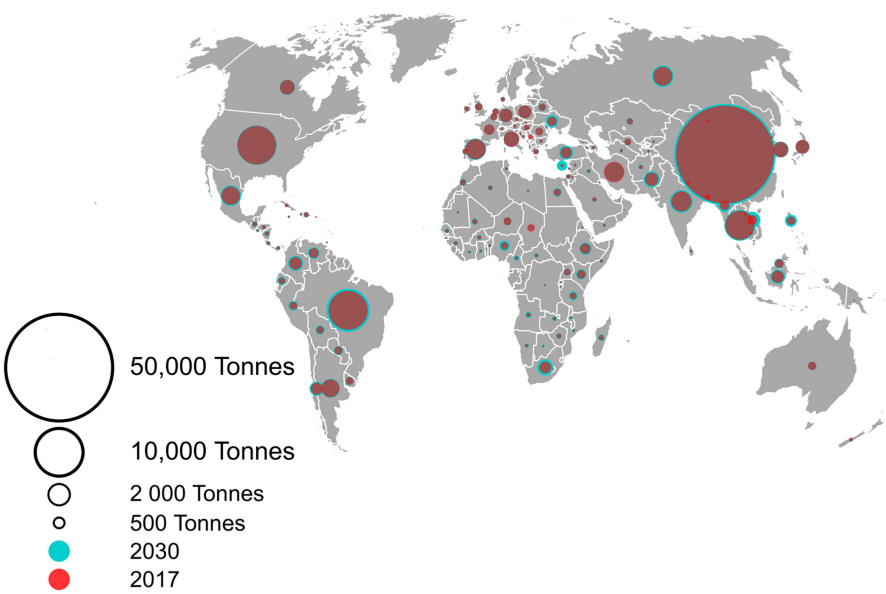


FIGURE 1 Estimated combined antimicrobial consumption in pigs, chicken and cattle per country in 2017 and 2030. The size of the circles corresponds to the amounts of antimicrobials used. Dark red circles correspond to the amounts used in 2017, and the outer blue ring corresponds to the projected increase in consumption in 2030. (Tiseo et al., 2020)

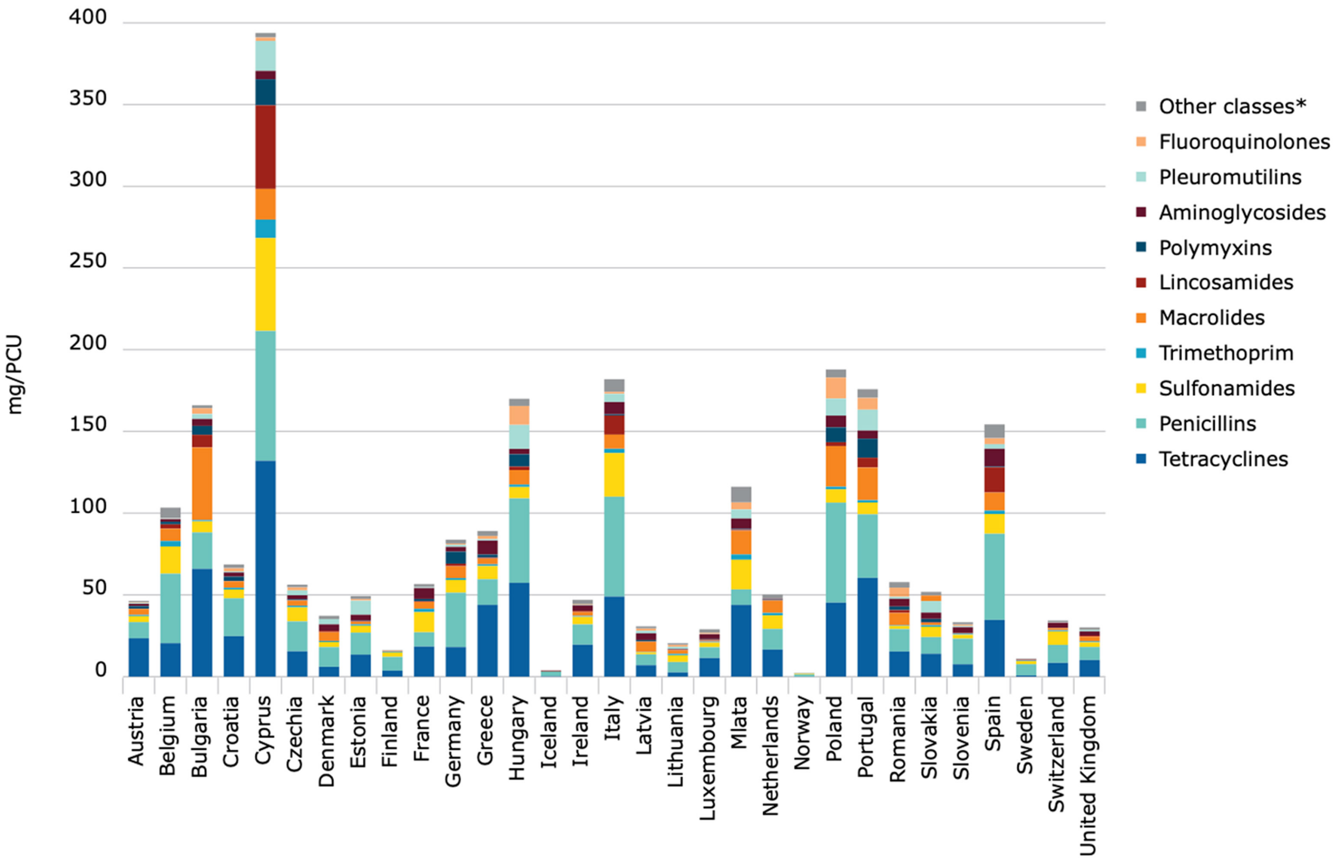
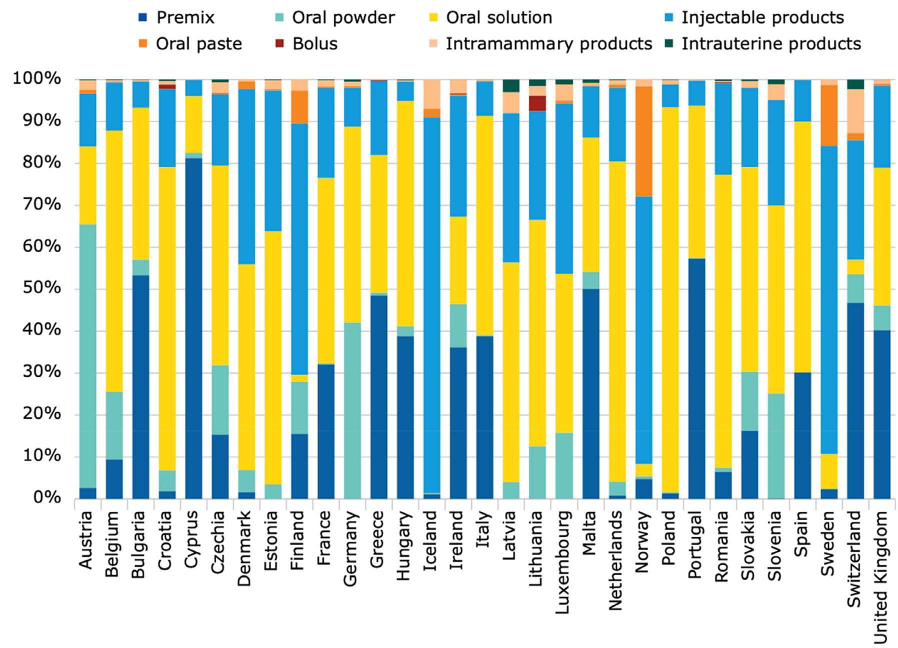


FIGURE 2 Sales for food-producing animals (incl. Horses), in milligram per population corrected unit*, of the various antimicrobial classes, for 31 European countries in 2020. (EMA, 2021). * PCU = the animal population and the estimated weight of each particular animal at the time of treatment with antibiotics (EMA, 2021)

FIGURE 3 Distribution of sales antimicrobial veterinary products for food-producing animals, in milligram active substance per population correction unit, by product form, in 31 European countries, in 2020 (EMA, 2021)



The use of antibiotics for bovine mastitis of different microbiological origin has been reviewed thoroughly previously and points out some different treatment approaches (Pyörälä et al., 2014), which also may be the case within the same country (Timonen et al., 2021). One such treatment is the use of blanket dry cow therapy that is still in practice in some countries, but has never been used in the Nordic countries. There instead, the dry cow therapy has been individually tailored for each udder quarter based on its infectious status and thereby reducing the use of antibiotics substantially. (Rajala-Schultz et al., 2021). Also, even now is the use of microbiological diagnosis as basis for choice of antibiotics in treating mastitis not applied in all settings. With regard to mastitis caused by *E. coli*, it should be noted that evidence for the efficacy of antibiotic treatment is very limited. In mild-to-severe cases, a non-antimicrobial approach (anti-inflammatory treatment, frequent milking and fluid therapy) should instead be the first-hand option (Suojala et al., 2013). Also, the first-hand choice for treating mastitis in general should be an antibiotic with a narrow spectrum, that are less prone to select for resistance, for example benzyl penicillium for gram positive bacteria that is not producing beta-lactamase (Sølverød et al., 2011). By applying the best practices described above over time, together combined with sound preventive measures, it is possible to reduce the incidence of clinical mastitis and thereby the need for antibiotics (Figure 4; Landin, 2020; FAO, 2020).

There is no consensus in the scientific literature about the definition and about the most efficient treatment of subclinical endometritis in the cow (reviewed by Haimerl et al., 2017; Wagener et al., 2017). Is injection with prostaglandins in cows with intact corpus luteum enough, or should it be combined with antibiotic treatment or should the cow be treated with antibiotics only? However, one may conclude that the use of ceftiofur is outdated as it is a third-generation cephalosporin now on the WHO list on critically important antimicrobials for humans (CIA) (WHO, 2019).

There are good evidence that cows with retained fatal membranes and systemic affection like fever, is best treated with antibiotics parenterally (preferentially penicillin, ampicillin or oxytetracycline), without intrauterine treatment or manual placenta removal (Drillich et al., 2006; Pyörälä et al., 2014). It is global wisdom since long that manual removal has limited or no benefit for the health of the cow, instead reports indicate that the prevalence and severity of uterine infection are often become worse (Bolinder et al., 1988; Roberts, 1986; Sheldon, 2019). However, in a recent study on treatment regimens of retained foetal membranes among practitioners in Belgium, it was reported that 94% of them attempted manual removal and that majority also treated cows without fever with antibiotics, mostly with intrauterine formula solely (Eppe et al., 2021).

Persistent breeding-induced endometritis (PBIE), that is when a mare does not manage to clear the normal 'physiological' inflammatory response after breeding within 48 h, do predispose for bacterial endometritis and is a very common cause for veterinary interventions. Common treatment practices are uterine lavage, and the use of ecbolic agents like oxytocin and prostaglandin as recently reviewed by Morris and colleagues (Morris et al., 2020). Also, antibiotics are used, but there is currently no scientific consensus if systemic or intrauterine antibiotic treatment is the best. On the other hand, there is an agreement that microbiological diagnosis should be conducted before antibiotic treatment (Canisso et al., 2020; Morris et al., 2020). With these recommendations about antibiotic management in mind, the outcome of a recent online survey among 680 equine practitioners in Germany is interesting (Köhne et al., 2020). Among the 117 vets that responded about their management of PBIE and chronic endometritis, it was found that none of the vets that managed a large number of mares used antibiotics for treating PBIE, whereas 38% of the vets managing a small number of mares did. For treatment of chronic endometritis, 78% applied systemic

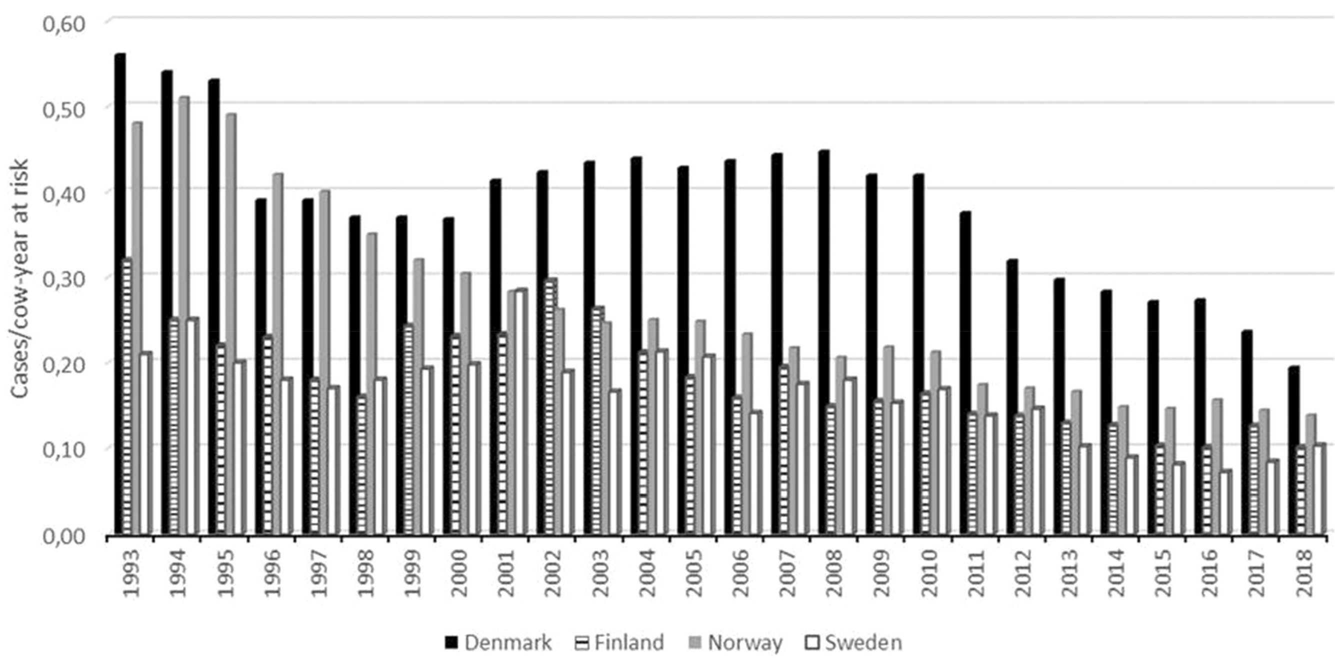


FIGURE 4 Incidence rate of clinical mastitis (treatments administered or initiated by a veterinarian) from 1993 to 2018 in four Nordic countries (Rajala-Schultz et al., 2021)

treatment with antibiotics, whereas intrauterine antibiotics were just used for this diagnosis by <20% of the responding vets. For both conditions, it was common to collect microbiological samples, either for diagnosis or as follow-up after treatment, respectively. It should be noted though that the reported practices varied by geographic region and size of the stud practice and that the response frequency was quite low (17.2%).

E. coli—mastitis in the sow at parturition is by several studies indicated to be a key component in the agalactia or dysgalactia postpartum, sometimes including metritis, syndrome (Kemper, 2020; Kemper et al., 2013; Magnusson et al., 2001; Persson et al., 1996), even if other factors likely contribute to this syndrome. Similar to *E. coli* mastitis in the cow, non-antibiotic treatments including oxytocin, which also may help curing metritis (Björkman et al., 2018), and NSAIDs are often recommended except for severe cases with high fever when antibiotics against gram-negative bacteria is justified (Farmer et al., 2019). However, as the clinical signs, as well as possible aetiologies, of this syndrome is variable there is a challenge in pinpointing the most precise therapy, especially since the diagnostic criteria differ between studies (Kemper, 2020).

In summary, there is a wide range of practices about how to use antibiotics within large animal reproduction. There are some general paths towards a refined use of antibiotics that may help curbing the emergence of antibiotics: (i) improve diagnostics and treatment precision by bacteriological sampling (ii) use narrow-spectrum antibiotics as the first-hand choice and never CIAs and (iii) consider non-antibiotic therapy whenever possible. Especially for cattle and pigs, it is also critical to apply appropriate disease preventive measures on herd level (FAO, 2020; Magnusson et al., 2019).

4 | ANTIBIOTIC RESISTANCE IN BACTERIA CAUSING REPRODUCTIVE DISEASES

Comparisons of resistance prevalence in bacteria among countries or regions do have inherent challenges: differences in sampling frames, sample collection procedures or analytic methods for determine resistance. The best available system for comparing the situation among countries is the EU-run one. In this system, the same sampling frame for collection of samples is applied and harmonized methods are used for analysis of on resistance in some zoonotic bacteria and indicator commensal *E. coli* from humans, animals and food by species by country by antibiotics (European Food Safety Authority, & European Centre for Disease Prevention and Control, 2021). In short, there are substantial differences between countries included in the analysis for the various antibiotics tested for. However, these data do not specifically target reproductive diseases or the samples are not collected from the reproductive organs. So, data on the resistance to antibiotics in bacteria associated with reproductive diseases are often scarce and mostly limited to one country and sampled in a way that is not allowing an assessment of prevalence. Still, such data are of interest for the clinician, that does not have the time or logistic resources to conduct a microbiological analysis including resistance testing, for guiding her to the best-bet of antibiotics.

There is a need for local or domestic and continuous updates on the antibiotics resistance situation as the resistance may vary between locations and over time. For instance, in studies of penicillin resistance in the bovine mammary pathogen *Staphylococcus aureus* sampled in Switzerland and Sweden, there were considerable differences between the two countries: 14% and 3% of the isolates, respectively, were resistant (Duse et al., 2021; Käppeli et al., 2019). The Swedish study also stress that in order to maintain optimal treatment, it is important to have current knowledge about the causative agents.

Variable results from studies on the microbiology and antibiotic resistance in equine endometritis from different parts of Europe and at different time points calls for microbiological diagnosis before antibiotic treatment in order to refine the treatment (Albihn et al., 2003; Pisello et al., 2019; Díaz-Bertrana et al., 2021; Table 1). The gram-negative *E. coli* is the most common isolated bacteria, though with a large range of occurrence (17%–68%), whereas the occurrence of Streptococci species was more similar in three countries. These differences may actually reflect true difference among geographically different horse populations, but may also reflect differences in inclusion criteria, transportation of samples to laboratories or analytic procedures.

It is challenging to compare the resistance situation in the three horse populations as not the same panel of antibiotics were used in the sensitivity testing (Table 1). Even so, the sensitivity of isolated *E. coli* to ampicillin and gentamycin was tested in all three studies, showing a sensitivity of 87%, 10% and 17% for ampicillin and 96%, 87% and 53% for gentamycin, in Sweden, Italy and Spain, respectively. This not only displays substantial geographic differences in resistance but may also reflect a temporal difference as the Swedish study were conducted some 15 years before the other ones. Interestingly, the extensive study from Italy includes samples over a 8-year period and the antibiotic resistance increases over this time period (Pisello et al., 2019). The authors stress that the high frequency of resistance proceeds in same way as the huge antibiotic use in Italy.

5 | TOWARDS A MORE REFINED AND REDUCED USE OF ANTIBIOTICS TO PROTECT THEIR EFFICIENCY

The regulations about the use of antibiotics in livestock have not been discussed here as it to a very large extent is the same among the majority of European countries, especially since the 28th of January 2022 when the new Veterinary Medicinal Products Regulation became applicable and updated the rules on the authorization and use of veterinary medicines in the European Union (EMA, 2022). Even so, one aspect that is not covered in this regulation is the right for veterinarians to dispense antibiotics to animal

TABLE 1 Most common bacteria isolated from the uterus in mares with fertility problems collected in three European countries and the antibiotics to which *E. coli* and common gram-positive bacteria were least sensitive to

	Albihn et al. (2003) Sweden	Pisello et al. (2019) Italy	Díaz-Bertrana et al. (2021) Spain
Definition of disorder	Fertility problems	Sub fertile	Repetitive infertility
Kind of study and sampling technique	Prospective—double guarded swab (dgs)	Retrospective of laboratory records-dgs	Retrospective—dgs
Number of mares sampled and number of samples with microbiological growth	239/152	4,122/3,171	363/323
Most common bacteria isolated	*E. coli* 64% *Strept beta haemolytic* 20% *Strept zooepidemicus* 14%	*E. coli* 28% *Strept zooepidemicus* 25% *Pseudomonas spp* 11%	*E. coli* 17% *Staphylococcus spp* 16% *Streptococcus spp* 14%
The three antibiotics to which *E. coli* was least sensitive to[a,b], percentage of sensitive isolates	Cephalothin 18% Streptomycin 51% Oxytetracyline 81%	Ampicillin 10% Rifampin 11% Ceftiofur 18%	Doxycyline 5% Cephalosporidine 15% Ampicillin 17%
The three antibiotics to which the most common gram-positive bacteria were least sensitive to[a], percentage of sensitive isolates	*Strept beta haemolytic* Neomycin 13% Gentamycin 19% Oxytracyline 29%	*Strept zooepidemicus* Gentamycin 2% Amikacin 2% Enrofloxacin 6%	*Strept ssp* Cephalosporidine 15% Apramycine 17% Doxycyline 17%

[a]Note that the same panel of antibiotics for sensitivity testing were not used in the three studies.
[b]Penicillin excluded.

owners. In several countries in Europe, this is allowed and may contribute to a significant share of the veterinarians income as it does in many low- and middle-income countries, thereby potentially counteract a reduced use of antibiotics (Magnusson, 2020; Magnusson et al., 2021).

An important aspect of reducing the need, and thereby use, of antibiotics, that is just briefly mentioned in this review is disease prevention. This applies of course for reproductive diseases and for all species, but has likely its best leverage for pigs and cattle, and do include all dimensions of good animal husbandry, biosecurity and vaccination schemes (e.g. Magnusson et al., 2021). To be efficient, such an approach needs a good cooperation between animal keepers, veterinarians and other stakeholders and an appropriate skillset by the veterinarian in preventive medicine including sound antibiotic stewardship (Espinosa-Gongora et al., 2021; Vidović et al., 2022).

The key message in this review is that more refined and restrictive use of antibiotics could be achieved by adhering to evidence-based guidelines by national and international stakeholders including the scientific literature when available. Thus, actions to be implemented are in particularly in the areas of improved precision in diagnosis and treatment. As shown above, there are differences in applied treatment regimens for, as well as prevention of, several reproductive diseases. Some of the treatments are not evidence-based, which should be considered by clinicians and other stakeholders, to protect the antibiotics' efficacy for the sake of animal health, productivity and welfare.

DATA AVAILABILITY

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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