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Prudent and effective antimicrobial use in a diverse livestock and consumer's world

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Introduction

The emergence of antimicrobial resistance (**AMR**) has been pointed out as a large threat to the advances that have been made in modern human medicine as well as in today's animal health, welfare, and production. It has been estimated that AMR will contribute to millions of human deaths per year in the world in the coming decades (O'Neill, 2016). Acknowledging that the threat is substantial, it has been emphasized that the current global estimates of the burden of AMR are not that informative. The estimates must be improved based on comprehensive population-based surveillance data from around the world (de Kraker et al., 2016). In the livestock sector, the production of animal source foods in low-income countries is at a particular risk with an estimated loss of 10% by 2050, if the emergence and spread of AMR are not curbed (World Bank Group, 2017). Thus, AMR is an issue for medicine as well as veterinary medicine that does not respect national borders and is, therefore, a true One Health, One World challenge (Robinson et al., 2016).

Notably, the development of AMR occurs naturally among microbes but is augmented by the use of antimicrobials (Holmes et al., 2016). In order to protect the efficiency of antimicrobials, it is thus wise to aim for reduced use and limit the use to medically rational use. In this review, four aspects of antibiotic use and resistance are discussed: firstly, the resistance related to livestock and human health; secondly, the access to antibiotics in the livestock sector; thirdly, the use of antibiotics in the sector; and finally, the reduction of use and livestock productivity.

AMR and Livestock and Human Health

Humans and livestock share several pathogenic as well as commensal bacterial species. This means that we may use the same antimicrobials, antibiotics in this case as it is about bacteria, in medicine and veterinary medicine (Cantas and Suer, 2014; WHO, 2017; OIE, 2018a). Hence, the development of resistance mechanisms that the use of these antibiotics drive is the same in bacteria isolated both from humans and from livestock. In a One health perspective, it is thus the resistances to antibiotics that are the most relevant kind of AMR. Notably, the World Health Organization has produced a list of antibiotics that is critically important for humans (WHO, 2017). Thus, several countries have established regulations or recommendations related to this list for the use of antibiotics in veterinary medicine.

Currently, the livestock sector is a significant contributor to the global pool of resistant bacteria in the biota given that the sector is the largest user of antibiotics worldwide (Van Boeckel et al., 2015). There are several reports on the association between resistant bacteria in livestock and humans (for review, see Hoelzer et al., 2017). However, except for cases where farmworkers have been infected with resistant bacteria from livestock, the importance of the sector as a contributor to resistant microbes to the human population as a whole is at large not known (Tang et al., 2017). Even so, for the risk of transmission of resistance to humans and for the sake of animal health, it is reasonable to reduce the use of antibiotics in the livestock sector, where there is an excessive use (e.g., Robinson et al., 2016). In support to this, O'Neill (2016) found in a literature in the PubMed database that 100 "academic papers" supported

Abbreviations

AMR	antimicrobial resistance
EU	European Commission
PCU	population correction unit

limiting antibiotic use in agriculture, 7 against limiting use, and 36 were neutral. Academic papers were defined as those that were exclusively written by academics.

Access to Antibiotics in the Livestock Sector

The access to antibiotics varies a lot for farmers around the world and sometimes within a country. Particularly in low-income countries it is the access to antibiotics, especially of good quality, that is the challenge as demonstrated in human medicine. (Kelesidis and Falagas, 2015; Laxminarayan et al., 2016). There are, for instance, estimates that suggest that substandard and non-registered drugs at a value of 400 Millions US dollars a year are sold in the livestock sector in Africa, which is similar to the official market (Kingsley, 2015).These antibiotics may be falsely branded or expired, thereby containing a lower, or no, active ingredient than indicated, or harmful ingredients.

The distribution channels of antibiotics do also vary around the world; in many low- and middle-income countries, one may buy antibiotics over the counter without a prescription. In a survey conducted by the European Commission (EC) in 70 non-EU countries (Table 1; EC, 2017), it was found that the prescription requirement is highest in high-income countries and lowest in low-income countries. Anecdotal, it is said that in several countries a large, sometimes the major, proportion of the income for physicians and veterinarians comes from the sales of antibiotics and other pharmaceuticals. In a survey conducted by the Federation of Veterinarians in Europe based on self-reporting, it was found that in some large European countries, between 24% and 20% of the revenues come from sales of medicines, whereas in other countries, it is about 1% to 3 % (FVE, 2015). These differences may attributable to the difference in legalization, general health status, disease spectrum, or different medical approaches to animal health issues or other factors. Remarkably, within the relatively economically and legislative homogenous Europe, there are immense differences between countries in the use of antibiotics in the livestock sector, with the lowest use in the Nordic countries and highest in the Southern countries (see Figure 1; ESVAC, 2019). Possibly, the reasons for these differences are similar to those for the differences in revenues from the sales of antibiotics as described above.

The trade over the internet is a new, challenging, and unregulated source of antibiotics. However, solid reports on the volumes, or importance, of this trade is currently not at hand.

Table 1. Antimicrobial prescriptions required in animals, percentages by income group. Data from 70 non-EU countries (EC, 2017)

World Bank income group	Yes, in all cases, %	Yes, some cases, %	No, %	No. of countries
High income	42	42	16	12
Upper middle income	48	26	26	11
Lower middle income	20	45	35	20
Low income	10	45	45	27

Use of Antibiotics in the Livestock Sector

It is widely acknowledged that there is a positive relationship between the amount of used antibiotics in the livestock sector and the development of antibiotic resistance (Bengtsson and Wierup, 2006; Chantziaras et al., 2014; Tang et al., 2019). Thus, to protect the efficiency of antibiotics in livestock farming for curing diseases and maintain productivity and animal welfare, it is crucial to apply a restrictive approach and only use antibiotics when exclusively needed.

One of the large differences between the use of antibiotics in the livestock sector and human health sector is that in the former there is a large prophylactic use and a use of antibiotics as "growth promoters." There have been estimates of the global use of antimicrobials in the livestock sector (Van Boeckel et al., 2015, 2017), but proper data are in general weak when looking for data in low- and middle-income countries (Cuong et al., 2018). Also, comparisons between OECD countries are challenging as different measures are used. Within the European Union, there is a harmonized system in which the use is equalized by using a population correction unit (ESVAC, 2019). The World Animal Health Organisation, OIE, has in their annual reports on the use of antimicrobials in animals, progressed their data collection methodology (Góchez et al., 2019). However, the data in these reports are aggregated on regional levels in the world.

When it comes to the total use in the livestock sector, China is by far the largest user, followed by the United States and Brazil according to the recent estimates (Van Boeckel et al., 2017). Notably, these countries are all very large livestock producers. Also, they do have substantial populations of intensive farmed pig and poultry, which are the livestock systems where most of the antibiotics are used.

The use of antibiotics for prevention and as growth promotors are most prevalent in pig and poultry rearing but may be avoided by instead applying adequate preventive measures (Magnusson et al., 2019). On the regulatory side, Sweden was the first country in the world to ban the use of antibiotics as growth promotors in 1986, the entire EU followed in 2006, and the United States in 2017. Still, OIE reports that 45 countries, out of the 155 providing data to their annual reports on antimicrobials, allow the use of antibiotics for growth promotion (OIE, 2018b). A global ban on the use of antibiotics for growth promotion seems, therefore, justified.

The wide-spread regular, preventive use of antibiotics in some livestock systems may be phased out by applying other disease preventive measures as discussed in the following section. Another challenge is the medically irrational and arbitrary use, often seen in the settings with weak animal health service (Ström et al., 2018). In these cases, there is a call for a more medically rational use of antibiotics as outlined in Magnusson et al., 2019: 1) just use quality-assured medicines; 2) do not use antimicrobials as growth promotors and avoid regular preventive use of antibiotics; 3) avoid using Highest Priority Critically Important Antibiotics for human medicine in livestock; 4) only use antibiotics based on a diagnosis of the disease by an animal health professional and only for authorized indications; and 5) strive for individual treatment of animals with the correct dose and duration, and avoid using antimicrobials for group treatments, especially via feed. Also when possible, the selection of antibiotics for therapeutic use may be based on sensitivity testing. Such a medically rational use will in several settings improve animal health and reduce the use of antibiotics.

Reduction of Antibiotic Use and Productivity

Northern European countries have a very low use of antibiotics per livestock biomass compared with other OECD-countries (e.g., ESVAC, 2019). Reducing the use of antibiotics to those levels in other parts of the world without implementing disease-preventing measures would, of course, be detrimental for animal health and productivity. The change in antibiotic use must be tightly matched with improved animal health management in a stepwise manner over time. If properly implemented, this transition will maintain the animal health status and productivity, with a limited and transient reduction in profit for the producers (Wierup, 2001). Actually, in Sweden that banned antibiotics as feed additives in 1986 with limited new preventive measures in place, the use of antibiotics initially increased (Figure 2; Swedres-Svarm, 2018). This was attributable to an increased need of antibiotics for curing an increased disease incidence before appropriate preventive measures were in place. However, nowadays, the productivity per dairy cow and sow in Sweden are in pair with the highest in the world; 26.7 weaned piglets per year per sow (weaning age 32 d) and 10,493 kg Energy Corrected Milk per year per Swedish Holstein Cow (Swedish WinPig, 2019; Växa, 2019).

The following basic principles would reduce the need of antibiotics and often increase animal health and productivity (Magnusson et al., 2019): 1) the basis is the rearing of robust animals by providing sufficient and good quality feed and water in adequate facilities, 2) second to apply good external and internal biosecurity measures to prevent infections from entering the farm and spread within the farm (Davies and Wales, 2019),

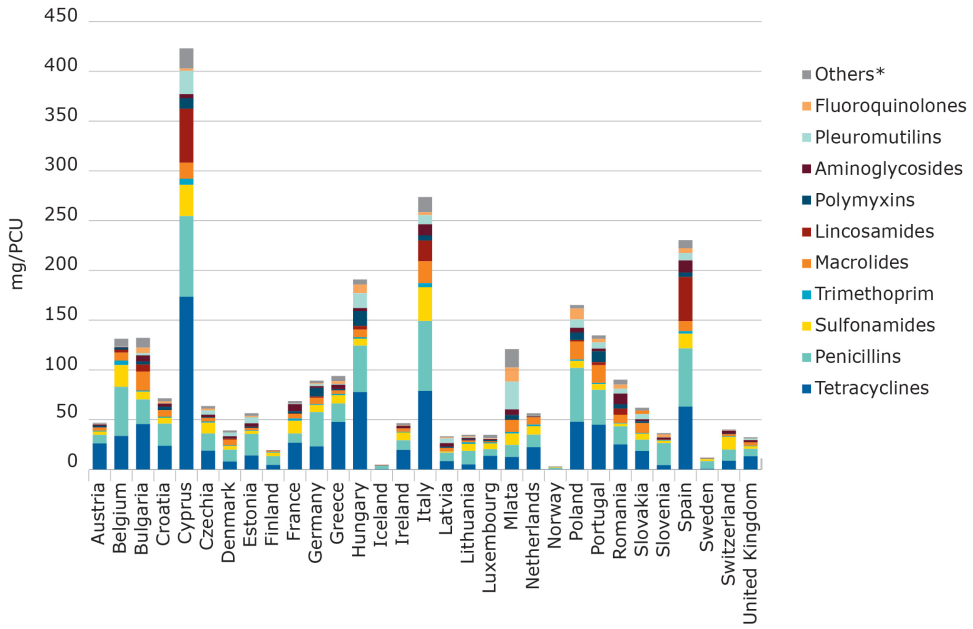

Figure 1. Sales for food-producing species, in mg per population correction unit (mg/PCU), of the various veterinary antimicrobial classes, for 31 European countries, in 2017 (ESVAC, 2019).

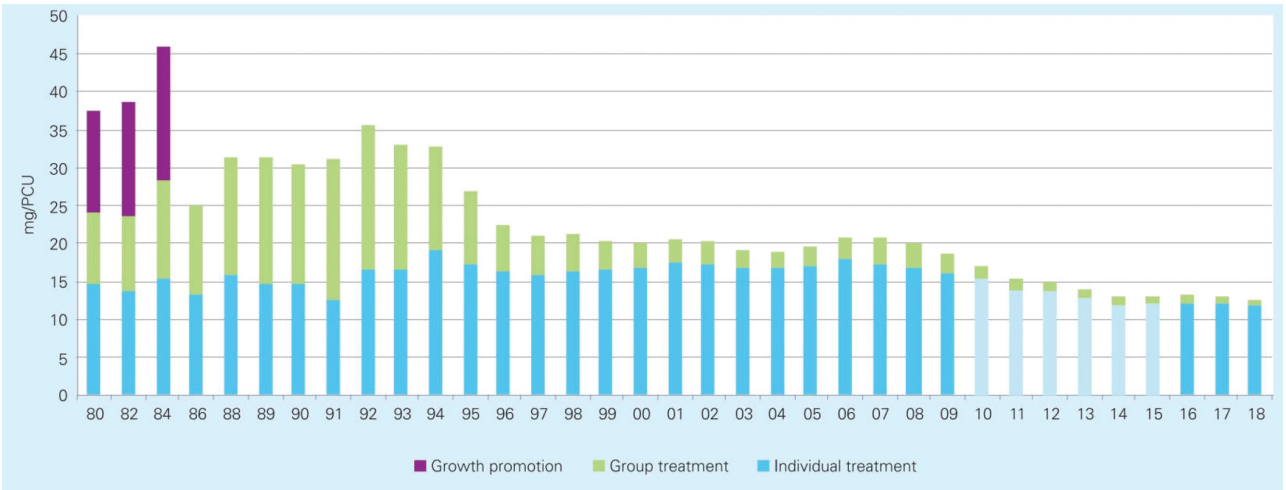

Figure 2. Sales of antibiotics for animals in Sweden expressed as mg per population correction unit (PCU) (Swedres-Svarm, 2018).

and 3) finally applying relevant vaccination schemes for specific diseases (Hoelzer et al., 2018). In many settings, this requires a new skill set for veterinarians: to move from only diagnosing and curing, toward more infection epidemiology thinking, knowledge about vaccine schemes, and a general herd management.

Besides acquiring these animal health management skills and applying a medically rational use of antibiotics, a supportive policy environment will enhance the transition toward prudent and effective use of antibiotics. For instance, the access of antibiotics over-the-counter for layman should be banned; antibiotics should only be sold on prescription. Another issue is the lack of proper quality control of animal medicines in general and antibiotics in particular; regulations or such control must be enforced. Also, another regulatory mean that may contribute to the restrictive use of antibiotics is to state the withdrawal periods after antibiotic treatment where meat, milk, or egg is not allowed for human consumption. Notably, to enforce such a regulation, efficient monitoring programs must be in place along the food chain to check the compliance and there must be corrective measures.

Conclusions

The importance of the resistance in bacteria in the livestock sector for the overall resistance emergence in the human population is not fully elucidated. Still, it is wise to try to mitigate the resistance in the livestock sector. This is best done by combining sound policies and regulations with appliance of a prudent and medically rational use of antibiotics in the sector. However, this approach requires a matching by good disease preventive measures, based on good animal management that generates robust and disease-resistant animals, high biosecurity, and effective vaccination programs. Experience from Sweden and other Nordic countries show that good health and high productivity may be maintained. However, the approach does require, in several settings, new skills and mindsets among producers, animal health professionals, and other extension personnel.

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Conflict of interest statement

The author declares no conflict of interest.

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