
Background

The emergence of antimicrobial resistance (AMR) is seen worldwide as one of the most important health problems in human and veterinary medicine. This was reinforced by international organizations such as the World Health Organization (WHO), the World Organisation for Animal Health (OIE), or the Food and Agriculture Organization (FAO) as well as on national level in many countries (e.g. Germany with DART). Therefore, the fight against AMR is a global task for the society as a whole in order to preserve the (veterinary) medical therapy of bacterial infectious diseases and must be tackled in a One Health approach according to the unanimous opinion of the organisations mentioned. The WHO advocates to use their list of the Critically Important Antibiotics (CIA) for use in humans in conjunction with the OIE’s list of antimicrobials of veterinary importance in order to fulfil the demands of the One Health approach.

Regulation (EU) 2019/6 of the European Parliament and of the Council of December 11, 2018 came into force on January 27, 2019 and will apply as from January 28, 2022. One of the goals of the regulation is to strengthen the European Union (EU) in the fight against AMR. On the basis of Regulation 2019/6, the European Medicine Agency (EMA) was requested by the European Commission (EC) to issue recommendations on the criteria which antibiotics should be reserved for human medical use only. The recommendations were sent by the EMA to the EC on October 31, 2019 and were implemented in a Delegated Act (DEA 2021/2718) on “Criteria for the designation of antimicrobials to be reserved for the treatment of certain infections in humans”.

This proposal was objected on the grounds that the Commission delegated regulation sets the bar for the designation of HRAM unduly high and gives undue consideration to animal health concerns in its criteria. Part of the objection was also the demand to ban the use of so-called "reserve antibiotics" in animal husbandry. The treatment of individual animals with a clinically diagnosed severe, life-threatening disease which, if improperly treated, would lead to significant morbidity or mortality, should be excluded from this ban.

Regarding the last point, the scientific evidence available is summarized here below on the exchange of AMR bacteria between animals and humans in Germany and on the use of HP CIA in animals:

Epidemiological Evidence

From a One Health perspective, the following scientific facts (from monitoring programs and special studies) on the AMR problem can currently be summarised, which show that there is a large number of overlaps of antimicrobial resistance in human and veterinary medicine:

(1) According to the WHO, the number of approved antibiotic substances is at least 296 in human medicine (WHO 2018) and according to OIE, 124 in veterinary medicine (OIE 2019). Of these active ingredients, a total of 22 active ingredients are used in veterinary medicine in Germany, which can be assigned to the classes of fluoroquinolones, 3rd and 4th generation cephalosporins, polypeptides and macrolides on the WHO HP CIA list. Of these 22 active ingredients, five active ingredients (erythromycin, spiramycin, bacitracin, polymyxin B and colistin) are used jointly by human and veterinary medicine in Germany.
The evaluations of an AMR working group funded by the European Centre for Disease Prevention and Control (ECDC) (Cassini et al., 2019) showed that 63.5% of all deaths caused by AMR and 75% of the life lost as a result in humans are caused by behaviour characteristics in humane health care systems.

A model from the Netherlands estimated that around 60% of the asymptomatic colonization of humans with specifically frequently occurring multi-resistant pathogens (ESBL and AmpC-producing E. coli) is due to transmission from person to person, whereas transmission from products of animal origin accounts for 17.8% and from domestic animals for 7.9% (Mughini-Gras et al., 2019).

A final assessment of the relative amount of transferred AMR from animals to humans, including from humans to animals and the interactive significance of the environment, is currently not available, as an additional distinction must be made between specific pathogens or active substances (JIACRA-III).

The entry of antimicrobial substances into the environment through wastewater from private households, medical facilities, nursing and retirement homes as well as animal husbandry has been observed, but its impact on AMR in humans has not yet been sufficiently quantified (Umweltbundesamt, 2018).

For Germany, the studies on the 16th amendment to the Medicines Act (central documentation requirements for farmers, BMEL, 2019), the DIMDI pharmaceutical regulation (central documentation requirement for pharmaceutical companies, Wallmann et al., 2020) as well as scientific studies among farmers and veterinarians (Kasabova et al., 2021) show that

(a) between 2011 and 2019, the amount of antibiotics sold to German veterinarians declined by a total of around 61% (thereof minus 63% for 3rd and 4th generation cephalosporins, minus 27% for fluoroquinolones, minus 68% for macrolides and minus 48% for polypeptides)

(b) a change in veterinary therapy behaviour between 2013 and 2020, which can be very different depending on the active ingredient class and animal species, e.g. in

(i) 3rd and 4th generation cephalosporins: +5.9% in beef cattle, -21.7% in dairy cows
(ii) Fluoroquinolones: -11.4% in broilers, + 0.4% in shoat pigs
(iii) Macrolides: -7.2% in broilers, + 27.3% in piglets
(iv) Polypeptides: -13% in broilers, -8.6% in piglets.

In Germany, the regulation on veterinary domestic pharmacies (TäHAV) was changed in order to restrict structurally the use of 3rd and 4th generation cephalosporins and fluoroquinolones for explicitly justified cases only. In addition, mandatory antimicrobial susceptibility testing has been included.

Conclusions

In our opinion, the tabled objection on the Delegated Act does not sufficient consider that there is so far little reliable evidence of restrictive measures (prohibition of “reserve antibiotics” in animal husbandry) on the population-related impact on AMR in humans regarding the extent and active ingredients. The authors, who are organized in the Research Network “Zoonotic Infectious Diseases” and in the German National Research Platform for Zoonoses, therefore point out that available scientific
evidence shows that the AMR problem can only be solved in a One Health approach, as there are many interactions exist between the microbial colonization of animals, humans and their environment.

For this reason, we advocate largely to avoid the use of antimicrobial substances that are particularly important for human medicine in animals and for measures that are suitable for limiting this use.

However, there is currently no evidence as to whether a blanket ban on the use of drugs containing the active ingredient groups fluoroquinolones, 3rd and 4th generation cephalosporins, polypeptides and macrolides in animals would have a substantial and lasting effect on the occurrence of resistance in human medicine.

Authors of the opinion
The working groups and research associations on the subject of AMR in the research network Zoonotic Infectious Diseases (https://www.zoonosen.net/forschungsnetz).

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Abbreviations
AMR Antimicrobial Resistance
AVI Antimicrobials of Veterinary Importance
CIA Critically Important Antimicrobials
DART Deutsche Antibiotikaresistenz Strategie (German antibiotic resistance strategy)
ECDC European Center for Disease Prevention and Control
EMA European Medicines Agency
FAO Food and Agriculture Organization
OIE World Organization for Animal Health
TäHAV Tierärztliche Hausapothekeverordnung (Regulation on Veterinary Domestic Pharmacies)
WHO World Health Organization

References


Umweltbundesamt (2018): Antibiotics and Antibiotic Resistances in the Environment Background, Challenges and Options for Action. ISSN 2363-829X
