

Antimicrobial resistance – an update

Dr Gabriel J Beechinor, director of veterinary sciences, Health Products Regulatory Authority (HPRA) provides an update on European developments to control antimicrobial resistance (AMR)

The control of antimicrobial resistance (AMR)¹ remains a key priority for EU governments and regulatory authorities. This focus is well-deserved given the increasing prevalence of resistance in human and veterinary medicine over recent years, the lack of new antimicrobials being developed and the potential risks for human and animal health in the future. The use of antimicrobials in veterinary medicine has attracted significant attention from the European Commission as well as from European agencies involved in public health in recent years. Indeed, various monitoring and control measures have been put into place over the last decade. Despite recent efforts to raise awareness of the issue and to update the labelling of veterinary medicines containing antimicrobials to improve their use, the control of AMR remains elusive. This may be the reason why it is one of the key drivers in the elaboration of the draft EU legislation² on the authorisation of veterinary medicines, which is still under debate by the EU institutions in Brussels.

ONGOING SCIENTIFIC REGULATORY DEVELOPMENTS

The EU Commission revealed its new 'One Health Action Plan against AMR' in June 2017. The plan³ has three key objectives:

- To make the EU a best practice region [of the world], eg. promoting the prudent use of antimicrobials, improving infection prevention and consolidating surveillance of AMR and antimicrobial consumption.
- To boost research, development and innovation of new antimicrobials, diagnostics, vaccines and alternative treatments.
- To influence the global agenda on AMR.

The plan builds on a 2011 Commission action plan, which has been judged to have been successful in raising awareness of the topic and in spawning the elaboration of various initiatives and responsible use policies in the EU, on improved monitoring of resistance, as well as in international collaboration. However, the Commission reported that the available evidence and assessments showed that the AMR problem persists and further action is needed to tackle the issue. It noted that: "without effective action to reverse current trends, mankind could face a return to the pre-antimicrobial era, with simple wounds and infections causing significant harm and even death". It advised that there were 'considerable disparities' between member states in antimicrobial consumption in humans and animals and in the spread of AMR.

In 2016, the European Medicines Agency (EMA) and the European Food Safety Authority (EFSA) produced a joint scientific opinion on measures to reduce the need to use antimicrobial agents in animal husbandry in the EU.⁴ That report advised that reduction strategies have been

successfully implemented in some EU Member States. Such strategies include:

- national reduction targets for antimicrobial drugs;
- controls on prescribing and restrictions on use of specific critically important antimicrobials (CIAs);
- improvements to animal husbandry and disease prevention; and
- control measures.

One of the statements in the opinion is that no single option to reduce antimicrobial usage will be sufficient to make a long-lasting impact on the occurrence of AMR in livestock production and its subsequent impact on public health. A number of recommended options are proposed, including:

- development of national strategies implemented through action plans;
- development of harmonised systems for monitoring antimicrobial use and surveillance of AMR integrating data from humans, food-producing animals and food derived thereof;
- establishing targets for reduction of the use of antimicrobials in food-producing animals, especially CIAs;
- on-farm animal health management with professional input;
- increasing the responsibility taken by veterinarians for prescribing antimicrobials.
- increased oversight of preventive and metaphylactic antimicrobial use;
- training and education for veterinarians and for end users of antimicrobials, and raising public awareness;
- increasing the availability and use of rapid and reliable diagnostics and antimicrobial susceptibility tests, including at the farm level;
- improvement of husbandry and management procedures for disease prevention, control and eradication of infectious diseases in livestock production, including vaccination;
- rethinking livestock production systems – reduced reliance on antimicrobial use and exploring further the potential of alternative production systems; and
- development of treatments which are alternatives to antimicrobials.

DEVELOPMENTS IN RESPECT TO ANTIMICROBIAL DRUGS

The vision of the EMA in respect of antimicrobials⁵ is to ensure the availability of effective antimicrobial medicines for the treatment of important infectious diseases of animals with, at the same time, minimum risks to animals or humans arising from their use. The efforts are focused on a number of areas as follows:

- clarifying and bolstering the data requirements for new antimicrobials that are intended for use in food-producing animal species;
- supporting the categorisation of the World Health Organization (WHO) and OIE of antimicrobials, to ensure that CIAs are used thoughtfully and selectively and that antimicrobials which are used as a last resort for the treatment of life-threatening disease in humans are excluded from veterinary use where this measure is supported by the findings of a suitable risk assessment;



- improving the labelling of currently used antimicrobials, to ensure that the warnings for the various antimicrobial classes are clear and appropriate, and are commensurate with the WHO and OIE categorisation (this exercise has been ongoing for several years already);
- reviewing and harmonising the dosage and indications for older antimicrobials, to reflect the current state of scientific knowledge;
- improving knowledge of antimicrobial consumption and risk management measures under the European Surveillance of Veterinary Antimicrobial Consumption (ESVAC) programme.⁶

In relation to human CIAs (as classified by the WHO), the work of the EMA includes a categorisation of these substances according to their importance in human medicine as well as the risk of spread of resistance from animals to humans:

- **CATEGORY 1:** Antimicrobials used in veterinary medicine where the risk for public health is estimated as low or limited. This group includes penicillins, macrolides, tetracyclines and polymyxins. These antimicrobials are not considered to be devoid of negative impact on resistance development and spread. To keep the risk from use of these classes within Category 1 as low as possible, the principles of responsible use in everyday practice should be followed. Non-responsible use, including unnecessary use and unnecessarily long treatment periods, should be avoided and group treatment restricted to situations where individual treatment is not feasible.
- **CATEGORY 2:** Antimicrobials used in veterinary medicine, where the risk for public health from veterinary use is only considered acceptable, provided that specific restrictions are placed on their use (ie. fluoroquinolones and systemically administered [parenteral and oral] third and fourth-generation cephalosporins). These reserved antimicrobials should be used only when there are no alternative antimicrobials authorised for the respective target species. Two other classes of antimicrobials are also included currently in this category, pending a risk assessment. These are aminoglycosides and extended-spectrum penicillins that are active against enterobacteriaceae and which have a high risk for transfer of resistance (eg. amoxicillin and clavulanic acid).
- **CATEGORY 3:** Antimicrobials that are not approved for use in veterinary medicine.

In respect of aminoglycosides, the EMA has recently produced a draft reflection paper⁷ that searchingly reviews the current knowledge on their use, their potential to induce resistance development and the potential impact of this resistance on animal and human health. That paper advises of the need to review any indications for use beyond seven days treatment duration, and also calls into question the rationale for combinations of aminoglycosides

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¹Kynetec VetTrak Sales Data, MAT values (July 2017)

²Study conducted by the Royal Veterinary College,
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with other aminoglycosides, as well as with other classes of antimicrobials. This draft reflection paper was recently published for a three month period of public consultation (end of consultation, October 31, 2017). It is expected that, once finalised, this reflection paper will lead to the development of further risk management measures which may impact on the use of the products concerned. In respect of many older antimicrobials, the EMA periodically receives applications to harmonise the conditions under which they are used in member states, in particular where they have different dosages, indications or withdrawal periods. One of the challenges for regulators in this evaluation exercise is the paucity of up-to-date, good quality, evidence-based clinical studies; the medicines themselves no longer have data protection and few companies are willing to invest in generating new studies that might raise doubts on the soundness of an existing dosage or indication. Moreover, the older products often had quite broad, general indications for use compared to the precise conditions that are specified for newer products. However, at the same time, learned clinical societies in member states and in regional areas are expected to develop 'treatment protocols' for treating diseases, which might not be in agreement with the authorised conditions of use (eg. use of a drug for an indication not on the labelling or at a different dosage). This development is expected to

pose a challenge to all concerned, lest it leads to a further round of harmonisation referrals.

OTHER SCIENTIFIC STUDIES AFFECTING ANTIMICROBIALS

The environmental impact of antimicrobials is another area that is receiving attention. In both humans and animals as much as 30-90% of antimicrobials consumed are released into the manure and urine. Indeed, it has been reported⁸ that animal excreta can contaminate the environment with antimicrobial resistant bacteria and antimicrobials. It seems likely that human waste is similarly problematic. In a report by the European Food Safety Authority⁹ in 2016, it was concluded that milk from cows receiving antimicrobial treatment during lactation contains substantial residues during the treatment and withdrawal period and that consumption of such milk will lead to increased faecal shedding of antimicrobial-resistant bacteria by calves. The report recommended that the feeding to calves of colostrum and milk containing residues of antimicrobials that could select for antimicrobial-resistant bacteria should be avoided, particularly those selecting for resistance to highest priority CIAs. The report also recommended that further studies be performed to consider the significance of antimicrobials in faeces of treated animals and the development of AMR in the farm environment.

THE FUTURE OF OFF-LABEL USE OF ANTIMICROBIAL DRUGS

As the conditions of use of veterinary antimicrobials have been subject to increasing scrutiny, so too has attention been focused on their off-label use.¹⁰ While such use has been seen as necessary and pragmatic in the past, it is recognised that unless carefully and expertly applied it can pose unnecessary risks.¹¹ Particular areas of concern are the use of antimicrobials when they involve group treatments and/or the use of CIAs. The blanket use of antimicrobials as a 'welcome shot' to prevent infection in groups of newly-gathered animals, for practical or economic reasons, is of high concern. It is recommended that prescribing under the cascade should be supported by a full diagnostic investigation, where possible, and restricted to treatment of individual animals, where feasible. It is also recommended that in order to safeguard human-only authorised antimicrobials, any veterinary use should be kept to an absolute minimum and veterinarians should be particularly careful and carry out a benefit-risk assessment before prescribing them in individual companion animals. Furthermore, when prescribing any antimicrobial drug under the cascade, veterinarians should take into account the importance of the antimicrobial to human medicine and the risk for transmission of AMR from treated animals to humans. The development of evidence-based treatment guidelines to support off-label use to address local or regional AMR situations is encouraged.

OTHER DRIVERS OF AMR

It is reported that¹² the genes coding for AMR can

potentially confer resistance to many more chemicals, including both naturally derived and xenobiotics. Biocides and metals have been used for centuries for their antimicrobial properties. However, bacterial resistance against different types of biocides also has been reported,¹³ with some resistance mechanisms being common to both biocides and antimicrobials. Noting that more research was needed to characterise the resistance in the environment, the Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR) advised that it was paramount to prevent the emergence of bacterial resistance and cross-resistance that biocides be used appropriately and prudently. The Norwegian Scientific Committee for Food Safety (VKM)¹⁴ reported that the most commonly used chemical substances with the potential to induce AMR and cross- or co-resistance in bacteria are the heavy metals, copper, zinc and cadmium. Copper and zinc have been used in animal feeds for several years and, more recently, zinc has been authorised for use in certain veterinary medicines for the control of post-weaning diarrhoea in piglets. The use of copper and zinc increases the supply to the agricultural environments, and to both land and water by runoff, thereby constituting a selection pressure on local microbiota. Indeed, in June 2017 the EU decided to phase out the use of zinc oxide in piglets before June 2022, in response to a decision of the EMA that the benefit/risk balance was negative (although the issue of primary concern related to the toxicity of zinc for the environment).

CONCLUSIONS

AMR remains a significant threat to human and animal health. Current efforts to address the veterinary use of antimicrobials have had limited effects on reducing resistance, although they serve to heighten awareness of the issues. There is a growing appreciation of the complexity of the problem, including the drivers of resistance, the effects of non-antibacterial chemicals and the nature and interlinkages between reservoirs of resistance in the wider environment. Despite the existence of many knowledge gaps, the EU seems set to continue to target veterinary antimicrobials for new risk management measures. For the veterinary practitioner, the need for exemplary behaviour in using and prescribing antimicrobials has never been more important. New antimicrobials, if developed, are expected to be reserved exclusively for human use. Excellent stewardship of our existing repertoire of antimicrobials is therefore required to preserve their effectiveness into the future.

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