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NOAH response to final O Neill AMR review report July 2016

A. Introduction

In May 2016, "Tackling Drug Resistant Infections Globally: Final report and recommendations" was published by the O Neill Review on Antimicrobial Resistance. The report makes a number of recommendations for both human and veterinary medicine. Whilst NOAH welcomes certain recommendations, a number specific to the veterinary sector lack context and evidence, which we seek to address here.

Antimicrobials and Antibiotics

- Antibiotic resistance is only part of the wider problem of antimicrobial resistance.
- An **antimicrobial** is the general term for any compound with a direct action on microorganisms, used for treatment or prevention of infections.
- Antimicrobials include anti-bacterials, anti-virals, anti-fungals and anti-protozoals.
- Antimicrobial resistance (AMR) is resistance to any compound with a direct action on micro-organisms, used for treatment or prevention of infections.
- Antimicrobial resistance is a broader term than antibiotic resistance.
- The key focus in animal and public health is antibiotic resistance rather than antimicrobial resistance.
- Antibacterial compounds have a direct action on bacteria, reducing or inhibiting their growth or killing them completely. An antibiotic is the same as an antibacterial.
- Antibiotic resistance is the ability of bacteria to grow or survive in the presence of an antibiotic that is usually sufficient to inhibit or kill bacteria of that species.

B. Animal medicines sector position on antibiotics and antimicrobial resistance (AMR)

The animal medicines sector, represented in the UK by NOAH, remains committed to limiting the development of antibiotic resistance by promoting responsible use and stewardship of antibiotics and to preserve them for future generations.

Antibiotics are powerful tools that help fulfil our ethical and legal obligations to the animals in our care. They play a role in sustainable livestock production, preventing waste and losses caused by disease, and supporting a safe supply of food from healthy animals for everyone. Animal keepers prevent bacterial infections through their animal husbandry techniques, by maintaining high standards of bio-security and the use of vaccines, however there are occasions when animals still become sick and require treatment with an antibiotic.

Currently available veterinary medicines are an essential element of the veterinarian's armoury, especially with fewer new veterinary medicinal products being developed for animal use. By themselves, antibiotics are not a panacea for dealing with health problems in man or animal, however there will always be a

need for them. Effective disease control does not rely on one class of medicine alone. It requires a balanced approach, including attention to good hygiene, nutrition and the use of preventive measures such as vaccination, where available.

The report rightly raises concern about human deaths as a result of HIV, TB and malaria. It must be noted that animal health and the use of antibiotics in animals has no impact on treatment issues relating to HIV or malaria in humans. The use of antibiotics in agriculture does not affect the important issue of human TB treatment. TB infected animals are culled as part of disease eradication programmes and are never treated for the condition. Furthermore, the strains of mycobacteria that cause human and bovine TB infections in the UK population today are different.

The animal medicines sector advocates responsible and judicious use of antibiotics, advising on use and handling to limit the potential for selecting for resistant bacterial strains. Antibiotics must be used according to label recommendations, under veterinary prescription, and only when necessary.

Future policies and national strategies on antibiotics must promote responsible use by veterinarians and farmers, supported by antibiotic use data.

C. Use of antibiotics in agriculture

The report states that globally *'The quantity of antibiotics used in livestock is vast, and often includes those medicines that are important for humans. In the US, for example, of the antibiotics defined as medically important for humans by the FDA, over 70 percent of the total volume used (by weight) is sold for use in animals. Many other countries are also likely to use more antibiotics in agriculture than in humans but they do not even hold or publish the information.'*

NOAH believes that the development of improved global data collection systems for antibiotic use in both people and animals would be a positive step, providing an accurate picture of what is being used, where and by whom. Indeed, this is a step which our sector has consistently supported.

Simple, crude comparisons of the tonnage of antibiotics used in the human and animal health markets are meaningless and misleading. There are many, many more individual livestock and pet animals than there are people globally, with livestock presenting a considerably larger biomass. For example, in the UK alone, a country of 65 million people, 18 million broiler chickens are slaughtered per week (circa 1 billion chickens per year). It must also be noted that a fully grown beef animal could weigh the same as up to eight average adult humans, which impacts on the amount and weight of antibiotic required to treat an infection in that animal. A recent 'One Health' report published by Public Health England and the United Kingdom's regulatory agency, the Veterinary Medicines Directorate, identified that the total human use of antibiotics in the UK was 2.4 times that of veterinary use, when measured on biomass i.e. allowing for the comparative weights of the human and animal populations (1).

Table 1: Summary of UK livestock, poultry and human population numbers in 2015

Category	Numbers (millions)
Beef & dairy cattle[2]	9.9
Sheep and Lambs[2]	33.3
Pigs[2]	4.7
Poultry	
Laying hens[2]	37
Chickens[3]	957
UK population estimate 2015[4]	65.1

Fact: Consumption of antibiotics in humans was 2.4 times the sales of antibiotics for food producing animals based on biomass (135mg/kg for people versus 55.6 mg/kg animals)[1]

The review does not present a fair scientific evaluation of the relative risk of clinically significant AMR developing in people from antibiotic use in animals compared to human use. In the United States the Food and Drug Administration (FDA) has warned against the use of volumes of antibiotics used data to measure risk. The figure of 70% of total volume used, quoted in the report is an inappropriate way to use the data and is misleading If we apply the same method, it should be noted that the Danish report, DANMAP 2014 figures would show that 68% of antibiotics sold by weight in Denmark were used in animals, however the review identifies Denmark as a model to follow (5).

In the absence of accurate information, assumptions may be made that farming contributes a similar percentage to the overall risks from resistant bacteria.

D. What is the risk? What are the benefits?

The report states the following; *'…we reviewed 280 published, peer-reviewed research articles that address the issue of antibiotic use in agriculture. We found that 139 of these were published by academics; of these, only five percent concluded that there was no evidence of a link between antibiotic use in animals and resistance in humans, while nearly three quarters concluded that there is evidence of such a link.'*

Overall, the methodology of ranking the papers simply as positive or negative lacks scientific credibility and does not take into account the quality of the papers, the objective of the papers, peer-reviewed (refereed) status, etc. This statement fails to recognise the scientific consensus that the biggest driver of AMR in humans is human use. This is confirmed time and again, and most recently by Europe's pre-eminent group of regulatory assessors at the European Medicines Agency Committee for Medicinal Products for Veterinary Use (CVMP), which says in its draft strategy on antimicrobials that:

> *"it is recognized that the biggest driver of AMR in people is the use of antimicrobials in human medicine" (6).*

Other publications, such as the UK Department of Health 5 year Strategy on Antimicrobial Resistance, published in 2013, contain similar statements. It stated that whilst antibiotic use in animals is an important factor:

> *"Increasing scientific evidence suggests that the clinical issues with antimicrobial resistance that we face in human medicine are primarily the result of antibiotic use in people, rather than the use of antibiotics in animals."(7)*

The report fails to acknowledge numerous recent scientific papers, (e.g. the Mather *et al* Salmonella paper and the Wu *et al* paper on ESBLs (8, 9)) which conclude that considerable differences exist in bacteria between pigs, poultry and humans in Europe.

The report does not consider the increased protein needs of the growing population globally – consumption of meat, milk and eggs will continue to increase and there will need to be more livestock to fulfil these nutritional demands. Even where great efforts are made to prevent bacterial infections, there will be occasions when animals become sick and require treatment with an antibiotic. Nor does the report consider the important role of livestock in developing nations' economic development – attested to by the work of international bodies and charities like the FAO, OIE and the Bill and Melinda Gates Foundation (10, 11). The report overlooks the positive impact of animal health and productivity on sustainability, as healthy animals are the most efficient producers of safe, healthy, economically- and environmentally-sustainable food products. The report neglects the public health impact of food-animal produce originating from untreated or insufficiently-treated infected animals, or by direct contact with these animals.

To make a real impact, it is important that policy decisions are evidence-based and proportionate to the risk involved as our common goal is to effectively tackle the human AMR crisis, while maintaining an affordable global food supply.

E. Review of recommended steps

NOAH supports many of the recommendations in the report.

1. A massive global public awareness campaign

The animal medicines sector endorses this proposal for increased public awareness of antibiotic resistance. There is a recommendation for producers, retailers and regulators to agree standards for 'responsible antibiotic use' labels to be applied to the labelling of food. This will require careful, cautious consideration as there is a risk of misuse merely as a marketing differential. It must also be acknowledged that retailers may not have the expertise to assess what constitutes 'responsible antibiotic use'. Proper oversight with technical expertise will be needed to implement this recommendation in a meaningful manner.

2. Improve hygiene and prevent spread of infection

The animal medicines sector fully endorses this proposal. Through participation in various responsible use initiatives such as the Responsible Use of Medicines in Agriculture Alliance (RUMA), the Sustainable Control of Parasites in Sheep (SCOPS) and the Control of Worms Sustainably (COWS) in the UK, our sector has been supporting disease prevention through better on-farm hygiene and bio-security, for many years. The animal medicines sector has also participated in similar initiatives at an EU level in the European Platform for the Responsible Use of Medicines in Agriculture (EPRUMA). NOAH members also produce and promote the use of products such as vaccines and teat sealants for dairy cattle, to prevent infectious disease.

3. Reduce unnecessary use of antimicrobials in agriculture and their dissemination into the environment

(i) A 10 year target to reduce unnecessary antibiotic use in agriculture

The report recommends setting targets to reduce unnecessary use and suggests that developed countries should follow the approach taken by Denmark, with usage levels of 50 mg/kg.

Member countries of the WHO have striven for over a year to achieve the WHO global AMR action plan. The WHO plan provides a holistic approach that has already been agreed by all WHO Member States. An important feature of the plan is the call on countries to develop and implement their own tailored national plans, and many countries had already developed national strategies – such as the UK Five Year Strategy or the US national strategy for combating antibiotic resistant bacteria.

It is our view that setting reduction targets for antibiotics used in food production could become counter-productive, will not address resistance concerns and can lead to compromised farm animal welfare;

• Experience has shown that reduction targets can lead to improper use e.g. shortened treatment duration, or reduced dosage and illegal access (bypassing record keeping) that can increase the problem. The target should be to limit the need for antibiotic treatment by improving preventative and active health management on the farm. Reasonable and realistic targets depend on species, age and weight of the animals. Proper treatment of sick animals should never be compromised as this is detrimental to animal health, animal welfare and food safety.

• Reduction of treatment duration, e.g., skipping the last days of treatment, will allow the least-sensitive bacteria to survive and is a trigger for development of resistance (for example: skipping last day in a five-day treatment results in a 20% quantitative reduction of total antibiotic used).

• Reduction of dosage, e.g., below-optimal dosage, will allow the least-sensitive bacteria to survive and is a trigger for development of resistance.

• If they are to be penalised, farmers may be reluctant to call their veterinary surgeon to seek treatment after the first signs of disease, hoping that the symptoms will disappear without treatment, which will lead to more intense and longer treatment a few days later and for a longer period before animal health and welfare is restored.

The report states that individual countries should be responsible for deciding how to meet any reduction in use targets. This is appropriate, as local disease, animal husbandry, economic and climate conditions will impact on countries' abilities to change existing practices.

The suggestion to reduce levels to the Danish level is not appropriate because it fails to recognise that the conditions globally, outside Denmark (or those in North-Western Europe), are very different.

There is evidence that in countries where the use of antibiotics in feed for pigs has been restricted, it has led to increasing use of alternative organic compounds such as Zinc oxide (ZnO). This has created extreme selective pressure and the occurrence of a new selection of MRSA, creating challenges with pig meat exports. It must be asked - is this such a good example, if it is known such unintended consequences can and do arise?

(ii) Restrictions and/or bans on certain types of highly critical antibiotics.

The report provides a misleading impression that high priority critically important antibiotics are used routinely in livestock which is incorrect. One major class of veterinary antibiotics is the tetracycline group which makes up 40% of the total veterinary antibiotic market in the countries where use is reported. Tetracyclines were one of the first groups of antibiotics to be developed and many countries have limited use in human patients. But despite their use in animals, veterinarians have found little evidence of resistant strains causing hard to treat infections in their animal patients. Treatment failure in animals as a result of resistance remains a rarity.

There is overlap in the use of many medically valuable antibiotic groups including, fluoroquinolones and 3rd and 4th generation cephalosporins; the latter is only used for individual animal treatment. Veterinary fluoroquinolones, for example, make up only 1.9% of all antibiotics used in Europe (ESVAC 2015 report on 2013 data (12)). These are effective treatments for cattle and pigs with respiratory diseases but are only available for use through a veterinarian's prescription. When used appropriately, the likelihood of fluoroquinolone-use in cattle giving rise to an untreatable bacterial disease in a human patient is very small – one recent study calculated that they would occur at a rate of a single case of Salmonella every 293 years in the US (13).

The report fails to recognise that where classes of antibiotics are removed from use, it can lead to greater use of the remaining classes. The increased selection pressure on the remaining few antibiotics classes can in turn lead to increasing resistance among the remaining classes. A better strategy is to retain heterogeneity of the veterinary antimicrobial classes used, with all classes being used responsibly, only where necessary and where measures to prevent infection are in place e.g. bio-security and vaccination. It is recommended to provide a list of all new "human" antibiotics which are not registered for veterinary use. It should be pointed out that an overlap for the remaining therapeutic antibiotics is close to 100% and a further reduction of this already limited arsenal in veterinary medicine could easily lead to disease situations that are very difficult or not manageable. Further restrictions may force vets to prescribe inappropriate antibiotics, which will in turn lead to severe resistance problems in animals.

We agree with the recommendations of the report on the need for a harmonised approach to identify those antibiotics of greatest importance to human health. This should be led by the European Medicines Agency, the World Health Organisation, the OIE and the FDA to avoid variations in approach by either sectors or national

states. It is essential that these products are available for the veterinary sector, used responsibly, to ensure vets can access the products they need to treat the range of conditions they encounter.

We also agree with the recommendations for the development of better systems of veterinary oversight in low and middle income countries and endorse the OIE's efforts in this regard.

4. Improve global surveillance of drug resistance and antimicrobial consumption in humans and animals

The recommendation to improve surveillance is not new, and is already being acted upon. First, the OIE is leading the Tripartite (OIE/FAO/WHO) project to develop a global database of use of veterinary products around the world. Second, countries do collect data on usage in their area. For example, in the largest markets - US, EU and others, there are sophisticated data collection and surveillance systems in place. In the EU, there are proposals to improve these systems in the draft new European Veterinary Medicines Regulation.

Enhanced surveillance of use patterns can help to identify and support best practices. However, enhanced insight into use patterns is only a secondary objective. The primary objective should be enhanced surveillance of resistance prevalence to obtain better insights into the potential relationships between use, management practices, etc., and resistance at the specific 'drug/bug' level.

The report does not address the achievements of state-of-the-art research, such as whole-genome sequencing, that points to a much lower impact from resistance in the animal reservoir on resistance in human isolates than was previously expected.

Nonetheless, as the recent reports of colistin resistance illustrate, there are important gaps in our current surveillance systems, (considering that a resistance gene had been there since 2011 without being detected) that must be addressed. The Chinese surveillance systems and those in many other countries need to be enhanced. Monitoring is needed to try to detect the extent of co-resistance and spread of the gene. More information on colistin use is needed and the OIE database is the obvious tool to address this.

5. Promote new, rapid diagnostics to cut unnecessary use of antibiotics

We are fully supportive of proposals for better, rapid diagnostics to reduce unnecessary use of antimicrobials. We believe that this recommendation appears to focus primarily on the human medical sector and fails to recognise that improved diagnostics are also needed in the veterinary sector. We would call for any initiatives for improved diagnostics research such as the incentives to facilitate greater uptake and use of diagnostics, to also be applied to the veterinary sector. However, we must also recognise the unique challenges in developing practical effective veterinary diagnostics including sampling difficulties, economics/costs and the frequent occurrence of complex, mixed- aetiology disease profiles. The call for higher income countries to ensure that by 2020 all antibiotic prescribing is to be informed by data and testing technology, whilst a worthy goal, seems unrealistic in terms of the timescale envisaged.

6. Promote development and use of vaccines and alternatives

The animal medicines sector has developed many vaccines for use in the prevention and treatment of many of the important bacterial and viral diseases of animals. Again, funding models such as market entry rewards and advanced market commitments, to encourage the development of new vaccines and other alternatives to antibiotics, must also be applied to the veterinary sector in order to ensure disease solutions for animals.

7. Improve the numbers, pay and recognition of people working in infectious disease research and control

The animal medicines sector fully endorses this proposal. In particular we welcome the call for better training of veterinarians to help improve prescribing practices and animal husbandry and believe the OIE is well placed to continue its work in this area. Indeed this is an area where funding should be made available to facilitate best-practice knowledge transfer to improve the use of responsible use principles.

8. Establish a Global Innovation Fund for early-stage and non-commercial research

The animal medicines sector supports this recommendation and proposes that measures to establish a Global Innovation Fund should be applied to the veterinary sector as well as the human medicines sector. This is not clearly stated in the report but it is essential that veterinary medicine research is included to support 'One Health' aims.

9. Better incentives to promote investment for new drugs and improving existing ones

The recommendation on how to provide better incentives to promote investment for new drugs and improvements to existing ones makes numerous positive suggestions on encouragement of new product development via a global system of market entry awards. It also gives an accurate description of the practical barriers to the development of new antibiotic drugs. These barriers are equally, if not more applicable to the veterinary sector as to the human sector, given the food safety considerations that licensing processes for veterinary medicines must take account of. As a result, we believe that the proposals for market entry rewards that are not based on sales volumes should also apply to the development of new veterinary medicines and steps to improve existing products. NOAH calls for any such incentivisation to include the veterinary medicines sector.

10. Build a global coalition for real action – via G20 and the UN

NOAH supports the calls for a global approach to be taken to this matter. We also believe that antibiotic resistance is a true 'One Health' issue affecting both people and animals and as a result, both sectors must be considered. In building a global coalition for action, we believe that the extensive work already undertaken by the World Health Organisation and the World Organisation for Animal Health (OIE) provide strong pillars on which to develop a true global coalition.

F. Conclusions

The animal medicines sector welcomes many of the proposals in the O' Neill review report and applauds the efforts of the team in producing a comprehensive global report on a complex subject.

We ask that UK and international organisations do not ignore the needs of the animal medicines sector when implementing the recommendations for innovation for new antibiotics, alternatives to antibiotics and better diagnostics.

Finally, the important role that antibiotics and other veterinary medicines play in the production of an affordable, sustainable food supply must be recognised. Inappropriate targets for reduction in use, or the removal of antibiotics needed by vets and farmers to treat diseases, could lead to unintended consequences and impact on the availability of food from animals. Whilst steps can be taken to reduce unnecessary use in livestock, antibiotics will remain an important tool in maintaining animal health and welfare.

For as long as we keep and farm animals, we have an obligation to care for their health and well-being and this must include providing proper treatment and care when they are ill.

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