Critique of the 2015 O'Neill Review on Antimicrobial Resistance (AMR)

Introduction

In December 2015, the Report "Antimicrobials in agriculture and the environment: reducing unnecessary use and waste" was released. The report makes policy suggestions which are not always based on the latest available scientific evidence. These are considered below, as are omissions and inaccuracies.

Industry position on antibiotics and AMR

The Animal Health industry is committed to limiting the development of antibiotic resistance by promoting their responsible use in order to preserve them for future generations. Antibiotics are powerful tools that help fulfil our moral and legal obligation to the animals in our care. They have a role to play in sustainable livestock production by preventing waste and inefficiencies caused by disease, and help provide a safe supply of food from healthy animals. Even where great efforts are made to prevent bacterial infections through animal husbandry techniques, bio-security and use of vaccines, there are occasions when animals become sick and require treatment with an antibiotic.

These veterinary medicines are an essential element of the veterinarian's toolbox, and not many new products are being developed in this domain. By themselves, antibiotics are not a panacea for dealing with health problems in man or animal, but there will always be a need for them. Veterinarians, farmers and pet owners must appreciate that effective disease control does not rely on one class of medicines alone. It requires a balanced approach involving attention to good hygiene, nutrition and the use of other preventive measures such as vaccination.

The animal health industry advocates for responsible and judicious use of antibiotics, advising on how they should be used and handled to limit their potential for stimulating the development of resistant bacterial strains. Antibiotics should always be used according to label recommendation, under veterinary prescription, and only when necessary. Future policies and national strategies on antibiotics need to promote responsible use among veterinarians and farmers and collect antibiotic use data.

Review of the policy suggestions

The review makes three broad policy recommendations. Each is analyzed here.

Recommendation 1: "*A global target to reduce antibiotic use in food production to an agreed level per kilogram of livestock and fish, along with restrictions on the use of antibiotics important for humans.*"

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. One of the more important features of the plan is the call on countries to develop and implement their own tailored national plans, and many countries had already developed such national strategies - like the UK Five Year strategy or the US national strategy for combatting antibiotic resistant bacteria. Recommendation 1 comes on top of the agreed WHO recommendations. Given the experiences of trying to achieve consensus at the WHO, it is unrealistic, unachievable and unfair to assume any other country will accept top-down targets set by others.

The overarching target should focus on reduction of the development and dissemination of AMR, as the problem is not use *per se*. A singular focus on use does not take into account the diversity in production systems, climate conditions, regional/national need to increase food animal production, differences in potency between antibiotics and the need to react quickly to manage emerging infectious disease. A global reduction target runs the risk of being commandeered by processors, retailers or others for commercial motives, resulting in a "rat race to zero," with significant downsides for animal health and welfare, and public health.

A global reduction target for antibiotics used in food production is counter-productive for the following reasons:

- Experience has shown that reduction targets lead to improper use e.g. shortened treatment duration, or reduced dosage and illegal access (bypassing record keeping) that could increase the problem. The target should be to limit the need for antibiotic treatment courses by improving health management on the farm. Reasonable and realistic targets depend on species, age/weight of the animals. Proper treatment of diseased animals should never be punished as this would be detrimental to animal health, animal welfare and also food safety.
- The easiest way to reduce use (in Kg Active ingredient) is to shift to antibiotics with higher potency, often listed as critically important antibiotics (CIAs) by WHO. (Impact: some shifts can result in >80% quantitative reductions).
- The reduction of 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. (Impact: skipping last day in a five day treatment results in a 20% quantitative reduction).
- The reduction of dosage, e.g., a below-optimal dosage, will allow the least-sensitive bacteria to survive and is a trigger for development of resistance.
- Farmers may be reluctant to call their veterinarian to seek treatment after the first signs of disease, hoping that the symptoms will disappear without treatment, which will require heavier and longer treatment a few days later and for a longer period before animal health and welfare is restored.

The document 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 useful because it fails to recognize that the conditions outside Denmark (or those in north Western Europe), are very different. The choice of Denmark as an example should also be questioned. It should be considered that in Denmark and other comparable countries, organic compounds like ZnO are broadly used in feed for pigs to compensate. It is likely that with the extreme selective use of tetracyclines and ZnO, a selection of MRSA was achieved, which has caused Denmark challenges with pig meat export. One should wonder if this is such a good example, if it is known such problems will arise. In recent years use of antibiotics in Denmark has not been further reduced when one takes into account their decrease in livestock numbers.

Recommendation 2: ***"The rapid development of minimum standards to reduce antimicrobial manufacturing waste released into the environment."***

The recommendation does not reflect the reality that there are different situations around the world in different countries. There are already clear enforced standards regarding waste from pharmaceutical production plants in most important producing countries. These need to also be applied in other countries' manufacturing sites, especially in some Asian countries. Many companies already ask for higher environmental standards in India and China from suppliers than local rules require and are working to raise them. Instead of creating new standards, existing standards should be applied and monitored, and non-compliance should be sanctioned globally. The absence of a level playing field results in economic advantages for the undesired direction.

Recommendation 3: ***"Improved surveillance to monitor these problems, and progress against global targets."***

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 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 and other surveillance systems 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.

Omissions and inaccuracies

The report does not mention, or only summarily mentions, highly relevant issues that have a direct and important bearing on AMR. These issues are at the core of any discussion on antibiotic use.

1. Though numerous international organizations including the World Health Organization (WHO), the Food and Agriculture Organization (FAO) and the World Organisation for Animal Health (OIE) have recognized the need for a holistic approach to the use of antibiotics in animals, the O'Neill report appears to overlook this large body of work. A holistic approach focuses on reducing the need for antibiotics through prevention (vaccines), nutrition, housing and better management, as well as the use of antibiotics if needed.

2. In the Executive Summary the report states that "*…antibiotic use in animals is a factor in promoting resistance in humans and provides enough justification for policy makers to aim to reduce global use in food production to a more optimal level.*" What it fails to mention in the report is 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 preeminent 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 humans or human health."* 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 that: "*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."*

3. The report considers antibiotics and all bacteria together. This unscientific approach fails to recognize that all uses are not the same. As a result, the main policy recommendation is less use, not better use. The ineffectiveness of this approach is demonstrated by the DANMAP data that shows elimination of the use of avoparcin in animals has been followed by an increase in Vancomycin Resistant Enterococci (VRE). The report fails to acknowledge numerous recent scientific papers, (like the Mather et al salmonella paper and the Wu et al paper re ESBLs) which conclude that considerable differences exist in bacteria between pigs, poultry and humans in Europe.

4. Important assumptions are based on non-existing or unreliable data. For example, the first sentence of the report says that: "*the precise quantity of antimicrobials used in food production globally is difficult to estimate, but the evidence suggests that it is at least as great as the amount used by humans".* This is akin to saying: "We *don't know enough to estimate how much, but whatever it is, it is equal or more than human use".* The reality is that today there is no data in many countries.

The second and third sentences state that "*…in the US…more than 70 percent of medically important antibiotics are used in animals".* The FDA has warned against the use of the sales data to measure risk. The 70% figure used in the report is an inappropriate way to use the data, according to the FDA. If 70% in the U.S. is meaningful to the authors then it should be noted that DANMAP 2014 shows it is 68% in Denmark. Unless told otherwise, people will make an assumption that farming contributes a similar percentage to the overall risks from resistant bacteria. But it is important to point out that the products used in human and veterinary treatments are often not the same.

Comparisons of the tonnage of antibiotics used in the human and animal health markets are meaningless because there are many, many more livestock and pet animals than there are people globally but also the considerably larger biomass of the livestock. For example, in the UK alone, a country of 64 million people, 18 million broiler chickens are slaughtered per week (circa 1 billion chickens per year). Also consider that a fully grown beef bull could weigh the same as up to six average adult humans.

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.

Additionally many of the products used in livestock were introduced decades ago, are generally less potent than modern medicines and so may have to be used in higher doses.

5. The report overlooks the legal responsibility to treat sick animals, a basic animal welfare issue. It should consider the basic right of animals for medicines to restore their health as quickly and completely as possible; the right of animal care providers (veterinarians and owners) to access adequate veterinary medicines; as well the ethical and often legal obligation of those responsible for animal care to use these medicines in a timely and adequate way.

6. The report overlooks the rapid (re)emergence and spread of (new) diseases, some of which are affected by climate change. This has an impact on animal health, human health and antibiotic use.

7. The report does not adequately take into account the different levels of sophistication of agriculture (developing and developed world) and as part of that, the lack of (access to) economically affordable veterinary services in many countries. There needs to be far greater emphasis on availability and training of veterinary surgeons that prescribe antimicrobials and who should act as gatekeepers for these products. There also needs to be better training for farmers on correct use of these products after they have been prescribed. Indeed availability of appropriate medical services is also an issue in human medicine in the developing world.

8. The report does not consider the increased protein needs of the growing population globally – people will continue to eat more meat, milk and eggs and there will be more livestock to fulfill 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.

9. Nor does the report consider the important role of livestock in developing nation's economic development – attested to by the work of international bodies and charities like the FAO, OIE and the Bill and Melinda Gates Foundation. 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.

10. 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.

11. It does not consider environmental production sustainability - by keeping animals healthy they perform better (less feed consumed, less grain to transport, etc. and less waste/manure produced).

12. The report creates the incorrect impression that high priority critically important antibiotics are used routinely in livestock. 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. These were one of the first antibiotics to be developed and in 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 less than 1% of all antibiotic use in US agriculture. In Europe this is around 1.9% (ESVAC 2015 report on 2013 data). 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 fluroquinolone-use in cattle giving rise to an untreatable bacterial disease in a human patient is vanishingly small – one recent study calculated that they would occur at a rate of a single case of Salmonella every 293 years in the US.

    The report fails to recognise that where classes are removed from use, it leads to greater use of the remaining classes. This 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.

    An ill-informed reader of the report could be confused by the US-based wording on "medically important". It is recommended to provide a list of all new "human" antibiotics which are not registered for veterinary uses. 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. And further restrictions may force vets to prescribe inappropriate antibiotics, which will in turn lead to severe resistance problems in animals.

13. Regarding use in the U.S. perspective, the report fails to mention a significant number of "farm to fork" risk assessments that have been published showing the very low risk to humans from antibiotic use in animal agriculture. It fails to consider the Centre for Disease control (CDC) threat report that listed 18 specific pathogens that are the greatest threat in human health and said only 2 might have a source in agriculture. This enables the focus to be put in the right place (i.e. on these two for agricultural use).

    The report's statement about growth promotion and preventive uses being more prevalent in intensive agriculture is at odds with a recent USDA report. Looking at the broiler industry, the report stated *"larger contract growers were no more likely to provide antibiotics for growth promotion or disease prevention than smaller contract operations."* The report provides no data or factual basis for the statement.

14. Literature review. Regarding the selection of research articles in the report, the statement "*We believe these papers should be representative for the wider literature,"* (page 10) is overreaching. An analysis of the literature included in the report shows the following:
    - Though nearly 200 of the 280 papers referenced in this review are more than 10 years old, they are all weighted equally, which neglects recent technological developments and corresponding insights that the contribution of transfer of resistance from the animal reservoir to human therapy is lower than previously expected. A non-exhaustive selection of more recent literature not included in the O'Neill report is provided in the annex.

- The graph on page 12 suggests that 114 out of 129 (114 supportive +/+ 15 against) papers support limiting the use of antibiotics in animals. However, a total of 280 papers were reviewed, which, using this system of classification would mean that 151 (i.e.280 - 129) papers did not reach a conclusion on this point. Therefore, a conclusion more grounded in science would be that, since more than 50% of all the papers reviewed are inconclusive, a simple solution cannot be expected for such a complex issue, nor can the issue be solved by an approach as simple as the proposed volume reduction.

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.

15. The article draws inappropriate comparisons to smoking bans and waste control when considering how to reduce antibiotic use in agriculture. Such comparisons are wholly out of context. Smoking is something with no public good and, in fact, is directly responsible for many human health problems. The products produced by the veterinary medicines industry, including antibiotics, help maintain animal health and welfare and ensure a sustainable, affordable food supply. While industry recognises the importance to society of acting against antibiotic resistance and wishes to see antibiotics used responsibly to preserve their long term efficacy, they should never be compared to products such as cigarettes that do not serve any public good. Antimicrobials, including veterinary antimicrobials, are a global public good.

16. The section on 'Public awareness' should also acknowledge the importance of correct and hygienic slaughtering, processing, handling, storage and cooking in reducing the risk of transmission of bacteria (including resistant) from animals to people via the food chain. Any efforts to move towards 'antibiotic free' production and labelling are likely to lead to adverse effects on animal health and welfare such as the withholding of necessary treatment. The report does reference papers from the 1st world that state that many consumers wish for 'antibiotic-free' meat and that they would be willing to pay more for such meat, though experiences with organic sales show that during periods of economic downturn sales of organic plummet. In the context of a global report, it is unlikely that much of the developing world would share such a sentiment, where access to affordable food from animals is unfortunately still a significant issue.

17. Vaccines: The cost of vaccines in animal health is typically a tenth or less than similar products in human health. Cost is not the direct issue. In fact antimicrobials often cost more than vaccines. To put the low use of vaccines down to a perception of high prices is a gross simplification and ignores many sociological and psychological factors behind the health belief ratio (the benefits against the drawbacks of using a vaccine).

The drivers behind the use of vaccines are complex and multifactorial but an important component is the assessment of risk. The use of vaccines requires a recognition and acceptance of the risk from disease and that risk needs to be deemed medium to high in order to stimulate action. The use of antimicrobials is a reaction to a situation and therefore much easier for human nature than a proactive response. Effectively vaccines are an attempt at "insurance" against a possible risk. If that risk is not considered significant or if there are other priorities at the time then the investment in insurance will not be made.

Prophylactic antimicrobial usage is often towards diseases for which there are no vaccines. Even for respiratory disease, where there are effective vaccines against certain pathogens, vaccination cannot protect against all pathogens and so a farmer may vaccinate and still see disease – a definite disincentive to vaccination.

As stated in the report, many vaccines are available. This leads to difficulties for a farmer to successfully integrate all the vaccines into a herd or flock programme. It is not feasible to vaccinate animals every other week and therefore farmers have to select for what is most likely. While vaccines are available for a large number, or even majority, of viral diseases, there are fewer vaccines to prevent the bacterial diseases, treated by antimicrobials.

While development of animal vaccines does involve a lower investment than human vaccines, it still represents significant investment. Vaccine development is driven by market demand which means that the targeted diseases need to be common.

Adding taxes to antimicrobials may reduce their use but it will not necessarily drive an increased use of appropriate vaccines as it does not address the sociological or market factors. Instead it runs a risk of leading to more disease going untreated, increasing suffering, harming animal welfare, and putting sustainable food at risk.

18. The report bases many of its core arguments on data from a highly speculative study entitled: "*Global trends in antimicrobial use in food animals*" which estimates global consumption of antibiotics in agriculture will increase by 67% from 2010 to 2030. This study has major flaws. It is based on a number of inappropriate, lopsided and inaccurate assumptions. The papers' conclusions are deemed statistically questionable, speculative and scientifically of little value.

- For example, the article makes conclusions on global consumption based on data from a limited number of countries. It states "*data are scarce…estimates could be obtained for only 32 countries, all of which were high income".* Despite this, the article draws widespread conclusions for 228 countries about low/middle income countries. Such extrapolation is misleading.
- The article does not pay sufficient attention to the fact that volume of use does not fully correlate to resistance levels. Judicious or responsible use can be achieved while preserving effectiveness, by paying attention to the type of antibiotic used, the purpose of the treatment, the disease threat, etc.
- The article assumes continuous use of antimicrobial growth promoters, which are already banned in Europe in 2006 and are in the process of being phased out in the US, well ahead of the reports 2030 trajectory. The report also assumes no further decrease of antibiotic use in Europe. The article assumes that the current levels of antibiotic use to produce a kg of meat will be replicated in a linear fashion as meat production increases. It does not take into account the global efforts towards disease prevention where possible, development of new vaccines, and responsible use and stewardship campaigns. These measures are likely to lead to global reductions in the quantity used per kg of meat.
- The article contains out of context statements, or statements that lack substantive data. Example: *'… extensive farming systems will be replaced by large-scale intensive farming operations that routinely use antimicrobials in sub-therapeutic doses'.* There is no data to support this comment.

19. The following are some detailed comments related to inaccuracies on a page by page basis:

- Page 4 text box, "The Work of the Review" 2nd paragraph: The references to tuberculosis, malaria, HIV do not relate to the topic of use of antibiotics in livestock at all. TB is mainly non-animal source, malaria is a parasitic disease (cannot be treated by antibiotics) and HIV is caused by a virus, therefore the economic cost mentioned is of no relevance for this topic.
- Page 5, 3rd paragraph: A comparison between human and animal use on absolute quantities (KG AI) cannot be considered proper science. Comparing animal use to human use needs to be done on a parameter that addresses differences in active ingredients, potencies, etc. In The Netherlands this comparison has been made, based in Defined Daily Dosages – DDDs for 2013 Dutch animal use[1] and human use 2012[2] in Europeans, resulting in the following ranking:

[1] Usage of Antibiotics in Agricultural Livestock in the Netherlands in 2013, http://www.autoriteitdiergeneesmiddelen.nl/Userfiles/pdf/SDa-rapporten/sda-report-usage-of-antibiotics-in-agricultureal-livestock-in-the-netherlands-in-2013--september-2014.pdf

[2] Surveillance of antimicrobial consumption in Europe 2012, http://www.ecdc.europa.eu/en/publications/_layouts/forms/Publication_DispForm.aspx?List=4f55ad51-4aed-4d32-b960-af70113dbb90&ID=1174

Average DDD (animal/human daily dosage of antibiotics):

- Suckler cow (Netherlands): 0,7
- Dairy (Netherlands): 2,8
- Dogs and cats (Netherlands): 3,4
- Humans (Netherlands): 4,1
- Fattening pigs (Netherlands): 5,7
- Humans (Denmark): 6,0
- Humans (UK): 7,3
- Humans (Europe average): 7,8
- Humans (France): 10,8
- Humans (Belgium): 10,9
- Piglets (and sows) (Netherlands): 10,9
- Broilers (Netherlands): 11,5
- Humans (Greece): 11,6

* It should be noted that the Dutch have the lowest antibiotic consumption in humans, whereas the consumption in animals is moderate compared to the European average DDD.
* Page 6: This comparison of mere quantities is of very limited value, as this gives the impression that the antibiotics used, e.g. their quality, their identity, overlap as well. The reality is that penicillins, the most commonly used antibiotic for humans, only makes up 6% of the quantity used in animals, whereas tetracyclines, the commonly used antibiotic for animals only make up for 4% of the human use and ionophores, the second-most used group in animals, are not used for humans at all (US data)
* Page 8: fungicide use: Neglects major use in wood conservation.
* Page 10: Overlooks the CDC report, “Antibiotic resistance Threats in the US, 2013” mentioning 18 drug/bug combinations whereof only two are (partially) related to use in animals.
* Page 14: 17 out of the 31 mentioned do not appear on WHO list of CIA, HIA or IA for human medicine (3rd edition), whereas the graph on this page suggests so.
* Page 16: more recent data are available for Europe from ESVAC reports.
* Page 20-21: see above, 1st bullet of the three interventions proposed.
* Page 24, 3rd paragraph: This needs to be a major objective. Reduction of use levels should not be the primary target, but the “future efficacy of the antibiotic arsenal,” e.g. reduction of AMR.
* Page 25: The economic and public health impact of diseased animals and their produce is not included.
* Page 25-26, re vaccines: Using vaccines properly, routinely, timely, etc. is a bigger issue than availability. Correct and adequate use should be stimulated to make progress. It should also be recognized that vaccine development can only start after the causative pathogen is known, which results in a time gap between need and access. Antibiotics are often the sole option to treat sick animals during this period before vaccines become available. The average time needed for vaccine development is 6 – 8 years.
* Page 26, public awareness: The outcome of studies regarding consumer willingness to pay extra and the actual behavior when shopping shows a serious gap.

Annex 1: UK, European and global initiatives and information sources

Video dispelling commonly held myths: https://www.youtube.com/watch?v=1qIuroDR8Ak

EPRUMA is a multi-stakeholder platform of which IFAH-Europe is an active member, which links best practice with animal and public health http://www.epruma.eu/

Global Principles and Perspectives on the Responsible Use of Medicines in Animals: GPPRUMA http://healthforanimals.org/global-principles-and-perspectives-on-the-responsible-use-of-medicines-in-animals-gppruma/

"Antibiotics and antibiotic resistance in veterinary science" http://healthforanimals.org/antibiotics-and-antibiotic-resistance-in-veterinary-science/

The challenges of developing new antibiotics are considered in this 2015 article "*New Veterinary Antibiotics: Barriers, Consequences and Solutions" found here:* http://animalhealthmedia.com/investment-in-new-veterinary-antibiotics-barriers-consequences-and-solutions/

Annex 2: Literature references not included in O'Neill's list of publications, relevant to the quantification of the contribution of the animal reservoir to efficacy in human antimicrobial therapy, are listed below.

Quantification of the contribution and relevance of the animal reservoir to compromised efficacy in human antimicrobial therapy has been scientifically debated for several decades. Recent publications provide some clarity and indicate that the impact and relevance needs to be reconsidered. Their conclusions are cited here:

- In the report, "Antibiotics in food animal production and resistant bacteria in humans," the Dutch Health Council concluded in 2011 that, "*The relationship between the use of antibiotics in food animal production and the occurrence of VRE (Vancomycin Resistant Enterocci) in hospitals is not as clear as once thought years ago.*"[1]
- A research team using more sophisticated methods (whole-genome sequencing) than previously available[2] has concluded that, "*The relatively large genomic differences observed between chicken, chicken meat and human E. coli strains suggests that clonal transmission of ESBL-producing E. coli from chickens to humans is a rare event.*" [3,4] A review by B.Lazarus et al. published in 2015 in *Clinical Infectious Diseases*;60(3):439–52, in which a previous study by this research group prior to the use of whole-genome sequencing period was referenced, motivated the authors to send a letter to the editor[5] pointing out that the state-of-the-art in science moved forward and that their conclusion differs significantly from Lazarus et al.
- Uhlemann et al[6] concluded that carriage of LA-MRSA ST398 by farmers is transient, and human-to-human transmission of LA-MRSA ST398 does not appear readily, probably due to the loss of expression of proteins required for human host colonization and transmission.
- Mather et al[7]., in *Science* (Sept 27, 2013), performed a study using whole-genome sequencing of 142 human and 120 animal S.Typhimurium DT104 isolates and concluded: *"We demonstrate that the bacterium and its resistance genes were largely maintained within animal and human populations separately and that there was limited transmission, in either direction."* And, *"This study challenges current views on the contribution of the animal reservoir as source for Salmonella and AMR in humans"* and points out the relevance of *'acquiring targeted genotypic data set.,"*
- UK Dept of Health and Dept DEFRA published (Sept, 2013) the UK Five Year Antimicrobial Resistance Strategy 2013-2018[8]. On page 8, the contribution of the animal reservoir is addressed as follows: "*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. Nevertheless, use of antibiotics in animals (which includes fish, birds, bees and reptiles) is an important factor contributing to the wider pool of resistance which may have long term consequences."*
- The MARAN report, "Monitoring of Antimicrobial Resistance and Antibiotic Usage in Animals in the Netherlands in 2012"[9] (published June 2013) provides in Appendix 1 the results of a study on ESBL-producing Enterobacteriaceae in the Netherlands and concludes: *"This demonstrates that the perceived attribution of ESBL/AmpCs to humans from meat sources needs to be carefully evaluated and reported. It can only be based on detailed genetic analysis of genes, strains and mobile genetic elements and thorough epidemiological analysis." (page 42-43)*
- The 2012 SVARM report, "Swedish Veterinary Antimicrobial Resistance Monitoring,"[10] (published in 2013) summarized a study on indications of spread of Escherichia coli carrying blaCMY-2 from broilers to human clinical settings as follows: "*Ín conclusion, it was shown that the overlap between isolates of E.coli producing ESBL and AmpC in Sweden from humans and broilers appears to be limited."* The corresponding article is published by Börjesson S, et al. (2013, Clin Microbiol Infect)[11]
- G.Wu et al.[12] (Sept 26, 2013) used virulence and resistance gene microarrays to investigate isolates from Germany, The Netherlands and the UK obtained from humans, food producing animals and animal food products. A subset of these isolates was also characterized by multi-locus sequence typing (MLST) to assist in elucidating the clonal relationship of isolates. They concluded: "*Among animal isolates subjected to MLST (n=258), only 1.2% (n=3) were more than 70% similar to human isolates in gene profiles and shared the same MLST clonal complex with the corresponding human isolates. The results suggest that minimising human-to-human transmission is essential to control the spread of ESBL-positive E. coli in humans."*

- D. Hetem et al[13] performed a 6-month (June 1–November 30, 2011) nationwide study to quantify the single-admission reproduction number, R_A, for LA-MRSA in 62 hospitals in the Netherlands and compared this transmission capacity to previous estimates. They used spa typing for genotyping and concluded: *"R_A values indicated that transmissibility of LA-MRSA is 4.4 times lower than that of other MRSA (not associated with livestock)."*
- C. Belmar Campos et al[14] performed a study on the prevalence of ESBL-producing Enterobacteriaceae in stool samples from ambulatory patients (University Medical Centre Hamburg-Eppendorf) with gastrointestinal complains and in chicken meat samples from the Hamburg region. All samples were analysed and compared with respect to ESBL-genotypes, sequence types and antibiotic resistance profiles. They concluded: "*Chicken meat is not a major contributor to human colonization with ESBL-carrying Enterobacteriaceae*."
- H. Sharp et al[15], performed a Risk Assessment of the transfer of ESBL-producing Escherichia coli to humans in Germany, concluding that the majority of cases of colonizations with ESBL-producing E. coli among humans cannot be directly linked to livestock and food-producing animals as reservoirs. (article in German with English summary)
- In January 2015, the European Centre for Disease Prevention and Control (ECDC), the European Food Safety Authority (EFSA) and the European Medicines Agency (EMA) published their first integrated report[16] analyzing the possible relationships between the consumption of antimicrobial agents and the occurrence of antimicrobial resistance in humans and food-producing animals. The main findings of this report are:
  - Marked variations between countries both in the overall consumption figures, and between antibiotic classes in both human and veterinary medicine
  - Positive associations between consumption of selected antimicrobials in food-producing animals and occurrence of resistance in human bacterial isolates were only observed for fluoroquinolone-resistance in E.coli, macrolide-resistance in Campylobacter and tetracycline resistance in Salmonella and Campylobacter
  - Epidemiology of resistance is complex, and several other factors aside antimicrobial consumption influence occurrence of resistance
- SVARM 2014[17] reports on a study to investigate food as a potential source and dissemination route for ESBL-producing E. coli to humans: *"In conclusion the study indicated that food on the Swedish market is a limited contributor to the occurence of ESBL-producing E. coli within the healthcare sector."*
- DANMAP 2014[18] reports on the investigation of bloodstream isolates from human cases of septicaemia which allows, for the first time, to assess the impact of zoonotic transmission of ESBL resistance genes. They conclude: *"The results show that humans and animals do share resistance genes and strain types. However, based on this relatively small sample from meat it is only a minority of ESBL E. coli bacteremias in humans that are caused by strains of possible animal origin."*

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