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Study:

Antimicrobial Resistance (AMR) in Livestock and its Global Impact on Public Health

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Preamble

The dramatic increase of antimicrobial resistance (AMR) has become one of the most prominent global threats. In 2018, the United Nations predicted that, "…if no action is taken", human infections with multi-drug resistance will become the death reason No. 1 and climb to worldwide 10 million people per year in 2050, surpassing the death rates of cancer and car crashes. Even the three latest G-20 Summits have put the growing threat of AMR on their agendas. There is a general understanding that the use of antimicrobial agents in animal and especially in livestock production is contributing to the emergence of AMR, since, with only few exceptions, the available antimicrobial substances are equally used in human and veterinary medicine. Thus, all stakeholders of the production chain for food of animal origin, most of all farmers and veterinarians, are called upon to curb AMR. First and foremost, the need for antibiotic treatments must be minimized to the most possible prudent use of drugs. Only the close surveillance of the use of antibiotics and the resistance of isolated pathogens will halt the rise of AMR in humans, animals and the environment. It is a moral obligation to develop a sustainable livestock production with the highest possible animal health status and the lowest possible use of antibiotics to maintain the power of antimicrobial agents for generations to come.

1. The History of Antimicrobial Agents

For the longest span of mankind's history, infectious diseases were by far the main reason of lingering illness and early death of people. The discovery of small living creatures or 'animalcules' by Antonie van Leeuwenhoek (1632 – 1723) in 1676 started the study of bacteriology. The pioneers of hygiene and disinfection against infectious diseases such as Ignaz Semmelweis (1818 – 1865) and Joseph Lister (1827 – 1912) started to make use of the growing knowledge about the contagiousness of many diseases (see Fig. 1).

In the late 1800s, Robert Koch (1843 – 1910) and Louis Pasteur (1822 – 1895) were able to establish the association between individual species of bacteria and diseases through their propagation in animals and on artificial media [1].

Paul Ehrlich (1854 – 1915) started working on the antibacterial effects of dyes, which marks the beginning of the modern era of antimicrobial chemotherapy. Ehrlich's early interest was in developing stains for the histological examination of tissues, in particular the basis of the Ziehl–Neelson stain for tuberculosis and the Gram's stain. He noted that some stains were toxic for bacteria. "Salvarsan", an arsenic-based chemical discovered by Ehrlich and his team in 1909, proved an effective treatment for syphilis and was probably the first modern, truly antimicrobial agent, though it was not an antibiotic in the strict sense of the word [2].

Alexander Fleming (1881 – 1955) discovered, more or less by chance, penicillin in 1928 [3]. He realized that there was great potential in penicillin, but there were significant challenges in translating what could be demonstrated in the laboratory into a medicine that could be made widely available. Fortunately, in the same year Howard Florey (1898 – 1968), a pharmacologist and pathologist, and Ernst Chain (1906 – 1979), a biochemist working in Oxford, published a paper describing a purification technique. This breakthrough ultimately led to penicillin becoming available for limited use in 1945. Undoubtedly a lifesaver, penicillin had in the beginning some problems, due to its very short biological half-life and poor bioavailability, which step by step had been solved.

While Fleming was trying to purify penicillin, scientists at “Bayer” in Germany led by Gerhard Domagk (1895 - 1964) were following Ehrlich's lead and exploring the antibacterial effects of dyes. Combining sulfanilamide with the dye Protonsil proved effective in treating streptococcal infections in mice in 1931. In 1933, a boy dying of staphylococcal septicaemia was given the drug with miraculous success. In 1935, researchers realized that the dye component was unnecessary, as Prontosil was metabolized to sulfanilamide, and so the sulfonamide era had begun [5].

These developments of powerful antimicrobial drugs are regarded as a milestone in mankind’s history. Thus, Gerhard Domagk became a Nobel laureate in 1939, as well as Alexander Flemming together with Howard Florey and Ernst Chain in 1945, and Selman Waksman (discoverer of streptomycin) in 1952.

The growing availability of very effective antimicrobial agents caused Selman Waksman to proclaim during his Nobel laureate acceptance speech: “We soon will have overcome the threat of bacterial infections and live in a post-infection era”. However, this optimism seems premature in hindsight due to the phenomenon of antimicrobial resistance (AMR), which poses an alarmingly increasing risk to our ability to treat bacterial infections.

2. The History and Magnitude of AMR

Since the introduction of the first effective antimicrobials, namely, the sulfonamides in 1937, the emergence of resistance has hindered their therapeutic use. Sulfonamide resistance was originally reported in the late 1930s [6]. In 1940, several years before the introduction of penicillin as a therapeutic agent, a bacterial penicillinase was identified. [7]. Alexander Flemming said in his Nobel price acceptance speech in 1945 that microbes will be able to develop resistance mechanisms against penicillin, especially if it is used inappropriately.

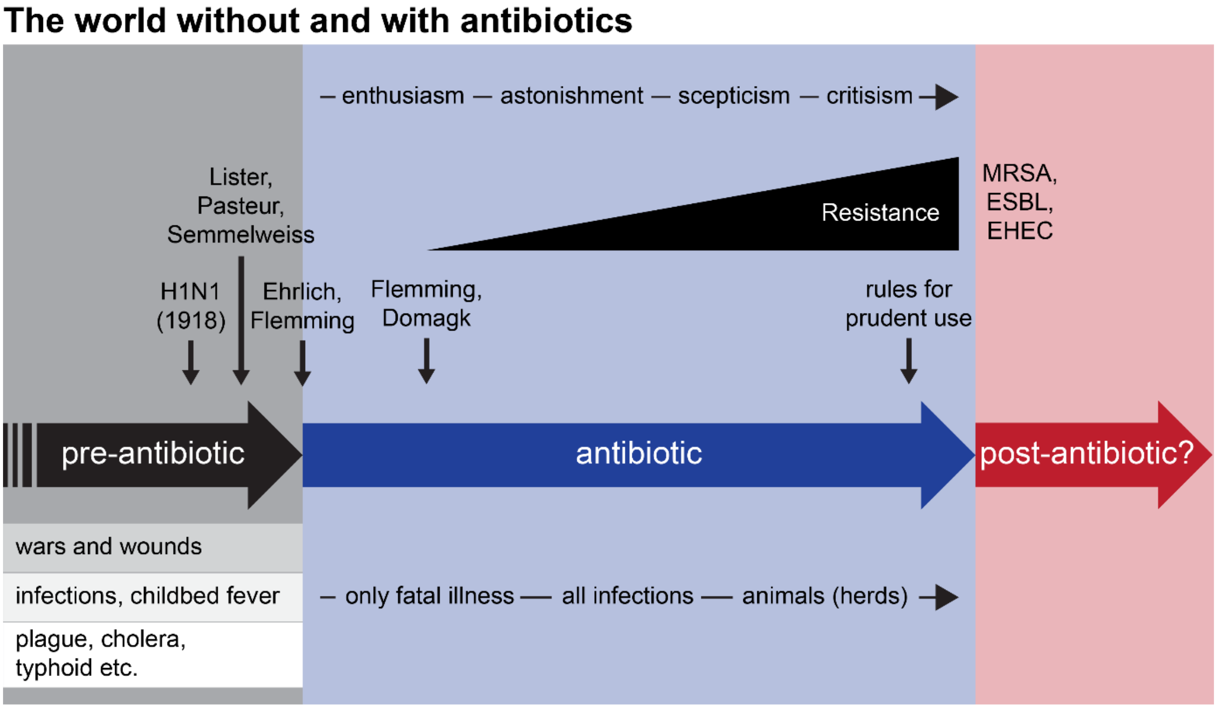


Fig. 1: The development from the enthusiasm about antimicrobials as successful weapon against bacterial infections to the criticism of their uncontrolled use (Blaha, Th., 2014 [18])

Figure 1 illustrates how the colossal need for these valuable drugs and the resulting industrial mass production of antibiotics and their ample availability have had a significant impact on its uncontrolled overuse: the emerging AMR problems increased, and the inappropriate use of antibiotics unveiled the environmental downside. In the 60 years since their introduction, millions of metric tons of antibiotics have been employed for a wide variety of purposes. Improvements in drug production have provided increasingly less expensive compounds that encourage non-prescription and off-label uses. The cost of the oldest and most frequently used antibiotics is (probably) mainly in the packaging. The planet is saturated with these toxic agents, which has of course contributed significantly to the selection of resistant strains. Their distribution in microbial populations throughout the biosphere is a result of many years of unremitting selection pressure from human applications of antibiotics via underuse, overuse, and misuse. This is not a natural process, but a man-made situation which harms nature; there is perhaps no better example of the Darwinian principles of selection and survival. And, if mankind cannot curb this development, there will be a “post-antibiotic era”.

The first report of the World Health Organization (WHO) on AMR released April 2014 stated, "this serious threat is no longer a prediction for the future, it is happening right now in every region of the world and has the potential to affect anyone, of any age, in any country. Antibiotic resistance - when bacteria change so antibiotics no longer work in people who need them to treat infections - is now a major threat to public health"[8].

Currently, the WHO estimates that more than 700,000 people die from infections with multi-drug resistant bacteria.

The European Centre for Disease Prevention and Control (ECDC) calculated that there were 671,689 infections in the EU and European Economic Area caused by antibiotic-resistant bacteria, resulting in 33,110 deaths, in 2015 alone. Most were acquired in healthcare settings [9].
The U.S. Federal Health Agency “Centers of Disease Control and Prevention” (CDC) states in its “AR Threats Report”: more than 2.8 million antibiotic-resistant infections occur in the U.S. each year, and more than 35,000 people die as a result.

All international organisations that are involved in public health (WHO, FAO, O.I.E. and the ECDC) agree on the fact that the magnitude of AMR is on the rise worldwide and that there is an urgent need for coordinated actions to curb this threatening development.

In order to be able to understand and to counteract this development, it is necessary to understand the mechanisms of how bacteria become resistant to one or more antimicrobial agents.

3. The Emergence of AMR

3.1. The Major Molecular Mechanisms that Cause Antimicrobial Resistance

1. Drug inactivation or modification: for example, enzymatic deactivation of penicillin G in some penicillin-resistant bacteria through the production of β-lactamases [10].

2. Alteration of target- or binding site: for example, alteration of the binding target site of penicillin in MRSA and other penicillin-resistant bacteria. Another protective mechanism are ribosomal protection proteins. These proteins protect the bacterial cell from antibiotics that target ribosomes to inhibit protein synthesis [11].

3. Alteration of metabolic pathway: for example, some sulfonamide-resistant bacteria turn to using preformed folic acid, like mammalian cells. Hereby, they circumvent the effects of sulfonamides, which inhibit the folic acid synthesis pathway [12].

4. Reduced drug accumulation: by decreasing drug permeability or increasing active efflux (pumping out) of the drugs across the cell surface [13,14].

Some bacteria are naturally resistant to certain antibiotics; for example, gram-negative bacteria are resistant to most β-lactam antibiotics due to the presence of β-lactamase. Antibiotic resistance can also be acquired as a result of either genetic mutation or horizontal gene transfer. The most common mechanism of horizontal gene transfer is the transfer of plasmids carrying antibiotic resistance genes between bacteria of the same or different species via conjugation allowing the fast spread of resistance within a species [15, 16].

3.2. The Epidemiological Mechanisms that Cause the Increasing Spread of Antimicrobial Resistance Worldwide

As seen above, antimicrobial resistance mechanisms belong to the “survival strategy” of microorganisms and develop in response to the use of antimicrobial agents. However, antimicrobial agents are not only causing AMR, but they are also responsible for the increasing spread of AMR. Every use of antimicrobial substances creates an evolutionary pressure (better: selection pressure). The death or weakening of susceptible bacteria will always provide a huge advantage for those then unhindered resistant bacteria. Thus, there is no way to prevent AMR. Even the most appropriate use of antibiotics will exacerbate AMR [17]. However, the use of antibiotic substances according to the general rule of “prudent use” can stave off AMR emergence. “Prudent use” requires that antibiotics are to be only prescribed when inevitably needed and only as much as needed [18].

Further reasons for the widespread use of antibiotics and the emergency of AMR in human and veterinary medicine include:

- Increasing global availability of affordable antimicrobials over time since the 1950s.
- The pressing demand for more antibiotics than necessary by patients (human medicine) and animal owners (veterinary medicine) all over the world.
- Uncontrolled sale in many low- or middle-income countries, where they can be obtained over the counter without a prescription, enabling antibiotics being used when not indicated [19].
- Antibiotic use in livestock feed at low doses for growth promotion and for so-called prophylactic purposes is an accepted practice in many industrialised countries and is known to lead to increased levels of resistance [20, 21].
- Releasing large quantities of antibiotics into the environment during pharmaceutical manufacturing through inadequate wastewater treatment [22].

Other (indirect) major causes that amplify the worldwide spread of AMR include:

- The steep increase of the global movement of people potentially carrying resistant bacteria and resistance genes around the world in short time spans.
- The enormous international trade of animals, plants as well as food and products of animal origin around the globe which are potentially contaminated with resistant bacteria and resistance genes.

3.3. Antimicrobial Drug Use and AMR in Livestock Production and its Impact on Human Medicine

As seen above, any use of antimicrobial substances causes both changes in the molecular mechanisms that result in antimicrobial resistance and in the population dynamics of bacteria due to the selective pressure that gives the resistant bacteria a huge advantage, which gives way to the excessive multiplication of the resistant strains. This general mechanism is identical in human and veterinary medicine. There are clearly certain pools of resistant bacteria and resistance genes that preferentially circulate either in the human population (hospitals, foster homes, antibiotic use in private homes etc.) or in animal populations (livestock, companion animals and wildlife). However, due to the multiple direct and indirect contacts between humans and animals (care for animals, food production with and from animals, food of animal origin) there is a substantial exchange of bacteria and resistance genes between the human medicine bacterial pool and the veterinary medicine bacterial pool.

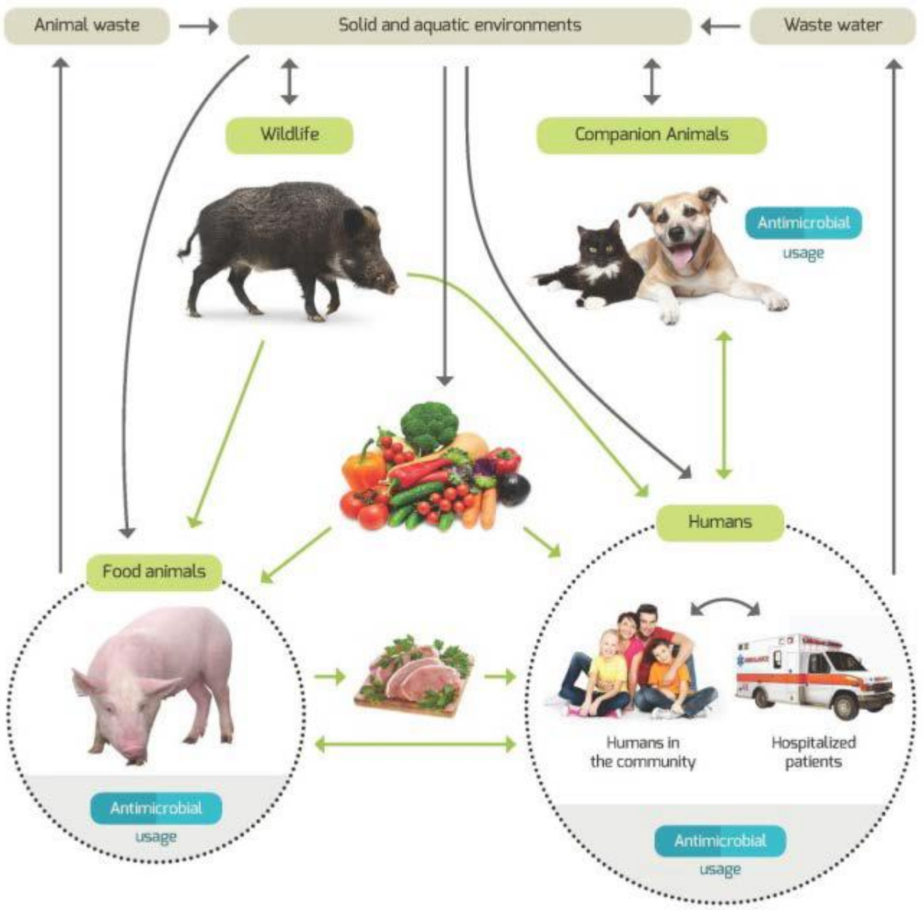


Fig. 2: The multidimensional exchange of the human and animal pools of AMR (EFFORT, 2018)

Figure 2 illustrates that additionally to the direct exchanges between these pools, the environmental compartments that are contaminated likewise by human and animal AMR sources contribute considerably to this exchange.

One of the best understood contributions to AMR in human medicine is the example of Methicillin-resistant Staphylococcus aureus (MRSA). For decades, the circulation of MRSA in human populations has been identified: those that have a connection to hospitals (= hospital-acquired MRSA, haMRSA) and those that occur sporadically in the general society (= community-acquired MRSA, caMRSA) was known. In the early 2000s however, the occurrence of a clonal line of MRSA (CC 398) that is mainly circulating in pig and cattle herds as well as in poultry flocks, i.e. a livestock-associated (laMRSA), was identified [23].

In the years afterwards, the ecology of laMRSA and its impact on human health was estimated as follows: persons that have direct contact to livestock animals (farmers and veterinarians) have a high risk of a nasal contamination with laMRSA [24]. These persons have a certain risk of developing a problematic infection with MRSA, after receiving an operation such as a hip replacement. Furthermore, they are potential carriers of MRSA into hospitals and foster homes, both as patients and visitors, thus, contributing to the increase of AMR in human medicine [25].

Another case of multi-resistant bacteria is the extended-spectrum ß-lactamase producing (EBSL) Enterobacteriaceae that disseminate their resistance genes into the environment. The risks to public health of livestock treatments targeting ESBL are less clear. However, the use of antimicrobial substances in livestock is undoubtedly contributing to the increased spread of resistant bacteria, and especially of resistance genes, into the environment and, by extent, the general population, e.g. by contaminated food. The resulting increased likelihood of introducing ESBL-producing bacteria in hospitals and foster homes poses a risk to human medicine [26], as it is demonstrated in Figure 2.

The fact that the use of antimicrobial substances in livestock has been internationally more and more scrutinised led to the ban of antimicrobial growth promotors in some parts of the world, e.g. in the European Union, in the early 2000s [27]. This adoption has resulted in legal efforts and programmes in many countries to monitor and reduce the amount of antimicrobial agents in livestock production.

It can be summarised: The multitude of factors that trigger and amplify AMR in the area of antibiotic use, especially in the livestock industry, ask for a very complex approach to a solution, which need to involve various stakeholders and coordination efforts on a local, regional and global level according to the paradigm: “One World – One Health”.

4. The One Health-Concept and AMR

The One Health concept recognises that the health of people is connected to the health of animals and the environment. The One Health approach is characterised by coordinating the activities of physicians, veterinarians, ecologists, and many others to monitor and control public health threats and to learn how diseases spread among people, animals, and the environment [28].

There are many examples that show how the health of people is related to the health of animals and the environment. For instance, some diseases can be transmitted between animals and humans. These diseases are known as zoonotic diseases. Examples include: Rabies, Salmonella infection, West Nile virus fever and Q-Fever (Coxiella burnetii). ***However, not only diseases are transmitted between animals and humans, but also bacteria that are resistant***

to antimicrobial agents such as Methicillin-resistant Staphylococcus aureus (MRSA), extended-spectrum ß-lactamase producing (ESBL) Enterobacteriaceae, Vancomycin-resistant Enterococci (VRE) and many other pathogens with a multi-drug-resistance (MDR). Antibiotics can trigger biochemical mechanisms of cross-resistance, and bacteria can share their "infectious" resistance genes with other bacteria of the same species, but also with bacteria of other bacteria species.

One Health is not a new concept, but it has become more important in recent years, mainly due to the worldwide emergence and steady increase of AMR [29]. It is the basis for all international, national, regional, and local action programmes and policies to reduce AMR.

5. Reducing Antimicrobial Use in Livestock Production

Already in 1969, the UK government's "Swann Report," formally the Joint Committee on the Use of Antibiotics in Animal Husbandry and Veterinary Medicine (headed by Dr M. M. Swann), proposed that rising rates of multi-drug resistant bacteria are caused by veterinary use [30]. Thus, the growing magnitude of antimicrobial resistance was slowly, but increasingly recognised by more and more physicians and public health as well as animal health professionals. However, it took about 30 years before in the mid-1990s, the World Health Organisation (WHO) hosted two international workshops in Geneva on the "Impact of the Veterinary Use of Antibiotics on Human Medicine". The result of these publications and scientific congresses was the development of the **concept of prudent use of antibiotics** both in human and veterinary medicine, which focuses on using antibiotics in humans and animals in a way that provides a ***maximum of efficacy against the target pathogen with minimally provoking the development and spread of resistant bacteria. The most important means to choose the "right" antimicrobial substance to meet the prudent use criteria is carrying out a laboratory "resistance test" to determine the susceptibility of the bacterium that causes the infection prior to the treatment***.

For several years, it was thought that the prudent use principles were able to curb the problem of antimicrobial resistance. However, despite the concept of prudent use the AMR problems grew and grew. With the emergence of MRSA and ESBL-producing Enterobacteriaceae as well as other multi-drug resistant opportunistic pathogens, the world recognised that the focus on only the target pathogens was missing the fact that not only the targeted disease-causing bacteria, but all bacteria in and on humans and animals treated with antibiotics are exposed to the selective pressure as described in Chapter 3.2. This triggered the worldwide understanding that apart from the prudent use of antibiotics, a substantial reduction of the use of antibiotics in humans and animals is required to lower the selective pressure that promotes the multiplication of resistant bacteria and the spread of resistance genes.

The first **Global Action Plan on Antimicrobial Resistance** was endorsed at the 68th World Health Assembly in May 2015 to tackle antimicrobial resistance. It was followed by the first OIE Annual report on the use of antimicrobial agents in animals at the end of 2016: "Better understanding of the global situation". In the framework of the Global Action Plan, a tripartite collaboration of OIE, FAO, and WHO has taken the lead to build a global database on the use of antimicrobial agents in animals. The OIE's partners acknowledge this accomplishment as a major milestone in the global effort to contain antimicrobial resistance.

The **European Union (EU)** issued the EU strategy to fight antimicrobial resistance at the OECD workshop on the Economics of Antimicrobial Use in the Livestock Sector and Development of Antimicrobial Resistance in October 2015. One part of this strategy is that the European Medicines Agencies (EMA) monitors the estimated use of antimicrobial drugs per animal unit in the EU-Member States. The total sale of veterinary antimicrobial drugs adjusted for the food animal base per country in 30 European countries measured in mg/PCU (population correction unit) varies hugely from < 10 mg/PCU in Norway and Sweden to > 350 mg/PCU in Cyprus and Spain (see Fig. 3). This type of information is essential to identify possible risk factors that could lead to the development and spread of antimicrobial resistance in animals. In part, this led to several nations introducing reduction programmes, e.g. Denmark, The Netherlands, Belgium, UK, Austria, and Germany.

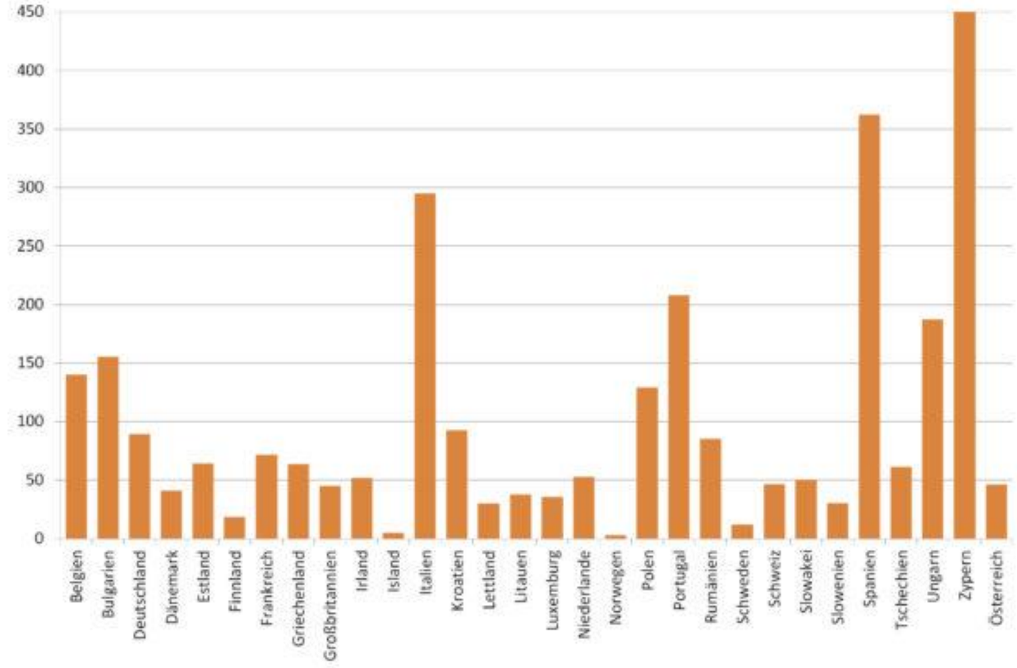


Fig. 3: The comparison of 30 European countries by their use of antimicrobial drugs in livestock production per animal unit (measured as production correction units) in 2016

In **Germany,** the approach to reducing the use of antibiotics in livestock production was to issue the 16th Amendment of the German Drug Legislation in 2014, which made the monitoring of the national use of antimicrobial drugs per animal in livestock herds and flocks mandatory. The principle of the monitoring is that each farmer must enter the antibiotic use in their herd or flock on a regular basis into a database. Thus, Germany has an ongoing record of the use of antimicrobial drugs per animal in all pig herds and poultry flocks. The employed measure is the Animal Treatment Frequency (ATF), which is calculated by the following formula:

$$\text{ATF} = \frac{\text{No. of treated animals} \quad \text{X} \quad \text{No. of treatment days}}{\text{No. of animals in the herd or flock}}$$

Thus, the ATF is a measure for: On how many days were statistically all animals in the herd or flock in question treated with an antimicrobial drug in the last six months. This results in ATF values between 0 to more than 60. The continuous recording of the ATFs of all pig herds and poultry flocks leads to a database that each six months reports the distribution of pig herds and poultry flocks according to their current six-month-ATFs. Figure 4 demonstrates exemplarily the typical distribution of the pig herds of Germany according to their ATF at a certain point in time. Each column contains the farms with the same ATF. In the data base, the farms are anonymised using a farm code, but each farmer knows his or her ATF.

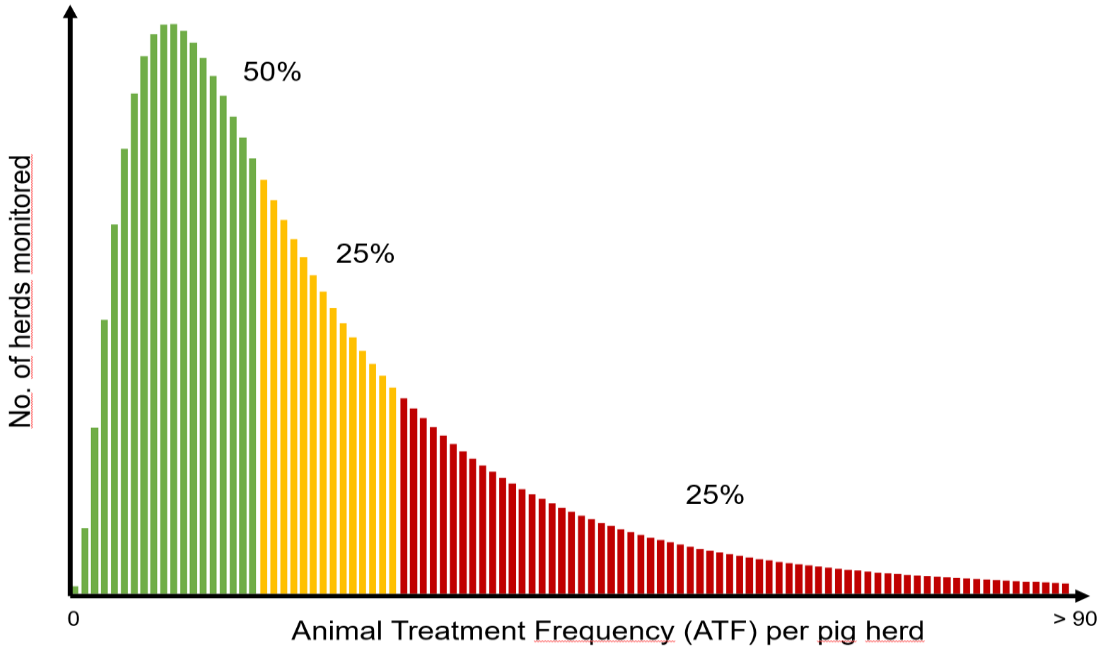


Fig. 4: The distribution of the German pig herds on a scale of their ATF from 0 to >90

Those farmers with an ATF in the 4th quartile of the curve (= the red part of the curve) have to start implementing measures for reducing their antibiotic use, and have to write a report for the veterinary authority in charge explaining how they plan to reduce the amount of applied antimicrobials per animal in the weeks and months to come. In case of no reduction over time, the veterinary authority will visit the farmer and impose provisions aiming for a reduction of the antibiotic use by ordering (non-antibiotic) measures that will improve the health of the animals.

The effect of this German national programme, that started only in 2014, is that the amount of antimicrobial substances applied to the German national livestock population has been reduced by remarkable 57% (see Fig 5).

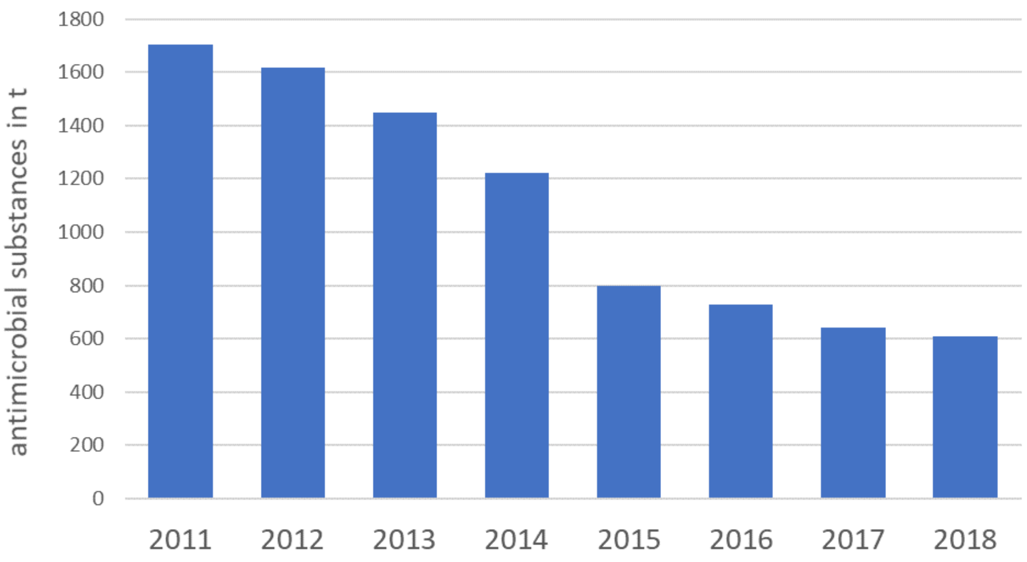


Fig. 5: The yearly amount in tons of antimicrobial substances used in Germany's livestock population

Of course, this reduction will level out, since it is a moral obligation of any animal caretaker to treat their animals in case of serious bacterial infections, which means: the reduction will slow down when only those animals are treated that really need treatment. Any further reduction of using antimicrobial substances in livestock populations is only possible by measurable improvements of the animal health status, especially the frequency of bacterial infections, by increasing the biosecurity and the hygiene status to minimise the risk of infectious diseases.

The fact that the Scandinavian countries (Norway, Sweden and Finland) have a considerably lower level of antibiotic use in livestock animals than all other countries proves that there is a great potential worldwide for reducing the enormous amounts of antimicrobial drugs used in the global livestock production, as demonstrated by several European countries (Denmark, The Netherlands, Belgium, the UK and Austria) that have successfully lowered their use of antimicrobial substances in farm animals up to >60%.

However, reducing the use of antimicrobial substances in livestock production will never lead to non-use, since most bacterial diseases, especially those caused by opportunistic pathogens, cannot be eradicated, and infected animals deserve antibiotic treatment. Thus, additional stewardship measures are required that make the necessary use of antimicrobials as prudent (cf. chapters 3.2., 5 and 6.) as possible.

6. Applying the Principles of Antimicrobial Atewardship

As a reminder: Any use of antimicrobials for treating infected humans and animals as well as for other purposes triggers antimicrobial molecular resistance mechanisms and epidemiological selective pressure. However, the decision on the choice of the type of antimicrobial substance and the dose and duration of application can considerably determine, whether the resistance mechanisms and selective pressure are promoted or depressed. The measures that minimise AMR when antibiotics are needed are called “antimicrobial stewardship”.

6.1. WHO Classes of Critically Important Antimicrobial Agents (CIA)

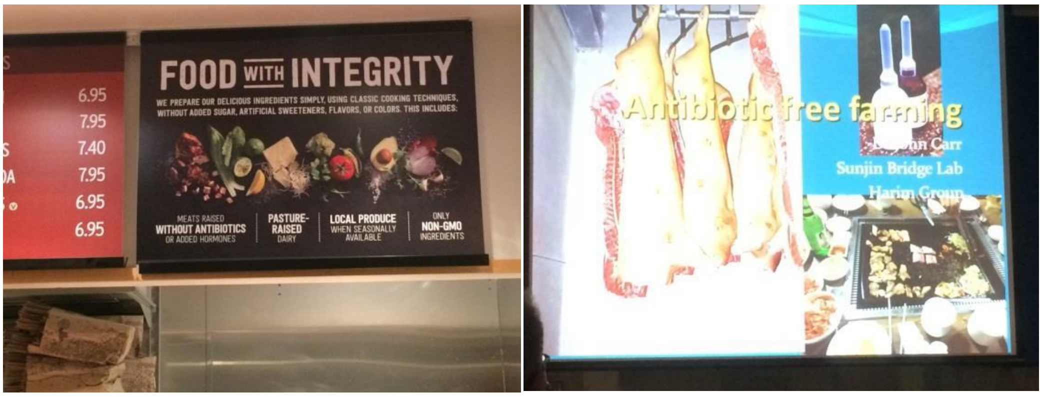
Use of antimicrobials in food animals can create an important source of antimicrobial resistant bacteria that can spread to humans through the food chain. Improved management of the use of antimicrobials in food animals, particularly reducing those critically important for human medicine, is an important step towards preserving the benefits of antimicrobials for people. The WHO has developed and applied criteria to rank antimicrobials according to their relative importance in human medicine. Clinicians, regulatory agencies, policy makers and other stakeholders can use this ranking when developing risk management strategies for the use of antimicrobials in food production animals. The use of the list will help preserve the effectiveness of currently available antimicrobials.

The first WHO list of CIA was developed in the 1st WHO Expert Meeting on Critically Important Antimicrobials for Human Health held in Canberra, Australia, in 2005. During the meeting, participants considered the list of all antimicrobial classes used in human medicine and categorized antimicrobials into three groups of critically important, highly important, and important based on the two criteria developed during the meeting:
Criterion 1 (C1): The antimicrobial class is the sole, or one of limited available therapies, to treat serious bacterial infections in people, and
Criterion 2 (C2): The antimicrobial class is used to treat infections in people caused by either: (1) bacteria that may be transmitted to humans from non-human sources, or (2) bacteria that may acquire resistance genes from non-human sources. Using these two criteria, the three WHO-groups of antimicrobial substances are:
Critically important for human medicine = antimicrobial classes which meet both C1 and C2;
Highly important for human medicine = antimicrobial classes, which meet either C1 or C2;
Important for human medicine = antimicrobial classes used in humans which meet neither C1 nor C2.
Although the intentions of the three WHO-groups with additional prioritisations are somewhat more complex the general meaning of the three CIA groups for the use in livestock is:
a) use important antimicrobials in farm animals whenever it is possible,
b) use highly important antimicrobials only in justifiable cases, and
c) refrain completely from using critically important antimicrobials.

The compliance with the rules of prudent use of antimicrobials and with the intentions of the CIA-classification are the most important aspects of the antimicrobial stewardship. However, there are additional attempts to reduce the risk of AMR such as the development of closed so-called “drug-free” production chains for producing food labelled as “produced without using antibiotics”.

6.2. Establishing “Drug-Free” Livestock Production Chains

In several industrialised countries, individual food industry companies have discovered the chance to attract consumers by offering “drug-free” food. Especially in the USA (e.g. the food chain “Chipotle” and the fast-food chain “Subway”), but also in some other countries such as South Korea (e.g. Sunjin Bridge Lab, Harim), a growing number of food enterprises are offering “food with integrity”, which attracts consumers that look for more sustainability, animal welfare and no antibiotics in their food (see Figs. 6 and 7).



Figs 6 and 7: Pictures taken by the author during vacation trips

To meet the demands for animal welfare, animals in these production chains which get infected and need antimicrobial treatment, must be treated (and then be removed from the “drug-free” production line for using them in a regular production line). The incentive to keep the animals in a healthy environment and get a higher price for those animals without an antimicrobial treatment, contributes to the overall aim to reduce any unnecessary use of antibiotics.

This trend towards food with certain characteristics such as “sustainable”, “animal-friendly”, “drug-free” etc. has the potential to have an impact on the international trade with food in the near future.

7. Recommendations

The already mentioned ***Global Action Plan on Antimicrobial Resistance (2015)*** states: Antimicrobial resistance is occurring everywhere in the world, compromising our ability to treat infectious diseases. The goal of this global action plan is to ensure, for as long as possible, continuity of successful treatment and prevention of infectious diseases with effective and safe medicines that are quality-assured, used in a responsible way, and accessible to all who need them. To achieve this goal, the global action plan sets out five strategic objectives:

- to improve awareness and understanding of antimicrobial resistance;
- to strengthen knowledge through surveillance and research;
- to reduce the incidence of infection in order to reduce the necessary use of antimicrobials;

- to optimise the use of antimicrobial agents (antimicrobial stewardship); and
- to develop the economic case for sustainable investment that takes account of the needs of all countries, and increase investment in new medicines, diagnostic tools, vaccines and other interventions.

These very general recommendation issued by the United Nations require a multitude of targeted actions at the local, regional, national, and international level.

It is recommended that BMEL through DCZ enters into a dialogue with relevant institutions and agencies in China to address this increasingly important topic. A translation into Chinese of this basic study and introduction can possibly serve as basis and first step for this dialogue.

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