Veterinary Public Health

Veterinary Public Health is the sum of all contributions to the **physical, mental and social well-being of humans** through an understanding and application of **veterinary science**[1]. This discipline covers a vast array of concerns linking animal and human health, and is primarily concerned with reducing exposure to **hazards** brought about by **interactions with animals**, **animal products** and **animal habitats**. This discipline includes **zoonoses**, **food-borne illnesses, toxicities**, **injuries and hazards related to the use of veterinary drugs and chemicals**. Antimicrobial resistance (AMR) is a significant public health issue of both human and veterinary concern, and AMR fostered by drug use in animals can certainly impact human health. In order to mitigate the emergence and spread of AMR, trained physicians and veterinarians exercise their professional responsibility to preserve antibiotic efficacy by assuring that antimicrobial products are not used indiscriminately. This particular learning module will highlight the veterinarians' indispensable local and global roles in mitigating the increasing prevalence of AMR in bacteria that infect both humans and animals.

Module Objectives:

1. Understand the public health Impact of imprudent antimicrobial usage in animals.
2. Understand the global impact of AMR and the means by which its emergence and transmission can be mitigated.
3. Understand the environmental impact of antibiotics used in agriculture.
4. Understand the global health impact of animal-related AMR.

Veterinary Public Health And Antimicrobial Resistance

The control and prevention of AMR is becoming a public health priority as reports of AMR emergence and spread increase from around the world. Veterinarians are medical professionals, and have a public health responsibility to ensure that antimicrobials are used appropriately and prudently to preserve the efficacy of antibiotics for both animals and humans. The bottom line is that we do not want our grandchildren to suffer the ill effects of antibiotic treatment failure because we squandered the efficacy of antibiotics when good alternative options were only slightly less convenient. Cost-benefit analysis of antimicrobial use policy must consider future costs as well as present costs.

Animals, Humans And Antimicrobials.

Epidemiological and molecular observations have shown that AMR, as fostered by extensive antibiotic usage in animals, can increase AMR problems among human populations. For example, vancomycin resistant enterococci (VRE) in both animals and people have become prevalent in countries that used a glycopeptide growth promotant called avoparcin, which is structurally similar to vancomycin. Vancomycin is a very important antibiotic in human medicine that is often used a last line of defense for several types of infectious agents. Consequent discontinuation of avoparcin's use in animals was followed by a rapid subsequent decline in the incidence of VRE in both human and animal populations. However, VRE in Europe has not disappeared.

Genes encoding resistance to antibiotics used only for animals have been found in increasing prevalence among animal pathogens, in the commensal flora of humans, in zoonotic pathogens like *Salmonella* and in strictly human pathogens like *Shigella*. This indicates the clonal spread of resistant strains and the shared transfer of resistance genes among bacteria infecting both humans and animals.[2]

The introduction of enrofloxacin in veterinary medicine was quickly followed by the emergence of fluoroquinolone resistance among *Campylobacter* isolates from broilers, and in humans shortly thereafter. As was the case with avoparcin, resistance to fluoroquinolones in human and animal populations remained rare in countries that had not used fluoroquinolones in food animals[3]

An increase in AMR to third-generation cephalosporins in *Salmonella* and *E.coli* was also observed following the increased usage of these antibiotics in animals. Furthermore, its withdrawal and re-introduction were subsequently followed by a decline and resurgence, respectively, in AMR among animal and human *Salmonella* isolates.

Examples Of Important Antimicrobials In Humans Used In Animals For Treatment, Metaphylaxis Or Growth Promotion[3,4]

Because a wide array of antimicrobials important for animal health and production are also important for preserving human health, use of these antibiotics in animal populations may negatively impact human health. While all AMR is a potential human health hazard, the preserved efficacy of some antibiotics is more critical to human health. Below is a list of antimicrobials used in both animals and humans, classified by the World Health Organization according to their importance to human health

A. Classified By The World Health Organization As CRITICALLY IMPORTANT For Humans

Antibiotic classes	ANIMALS				Humans
	Species	Disease treatment	Disease Prevention	Growth promotion	
Aminoclycosides: gentamicin, neomycin, streptomycin	Beef cattle, goats, poultry, sheep, swine, certain plants	Yes	Yes		Yes
Penicillins: amoxicillin, ampicillin	Beef cattle, dairy cows, fowl, poultry, sheep, swine	Yes	Yes	Yes	Yes
Cephalosporins, third generation: ceftiofur	Beef cattle, dairy cows, poultry, sheep, swine	Yes	Yes		Yes
Glycopeptides: Avoparcin, vancomycin	Poultry, swine			Yes	Yes
Macrolides: erythromycin, tilmicosin, tylosin	Beef cattle, poultry, swine	Yes	Yes	Yes	Yes
Quinolones: (fluoroquinolones) sarafloxacin, enrofloxaxin	Beef cattle, poultry	Yes	Yes		Yes
Streptogramins: Virginiamycin, quinupristin-dalfopristin	Beef cattle, poultry, swine	Yes	Yes	Yes	Yes
Carbapenems, lipopeptides, oxazolidinones, cycloserine, ethambutol, ethionamide, isoniazid, para-aminosalicyclic acid, pyrazinamide					Yes

B. Classified By The World Health Organization As HIGHLY IMPORTANT For Humans

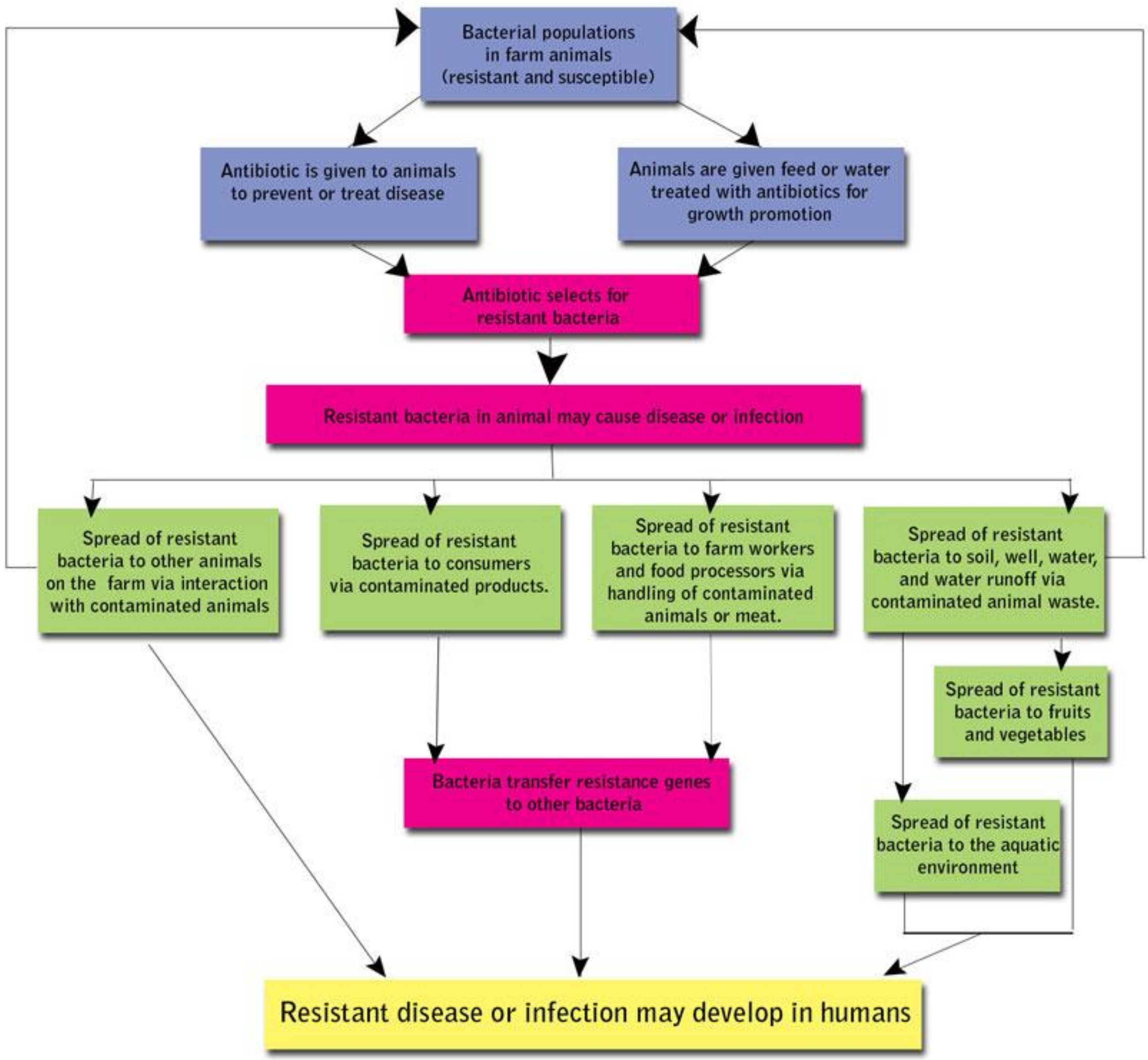
Antibiotic classes	ANIMALS				Humans
	Species	Disease treatment	Disease Prevention	Growth promotion	
Cephalosporins, first generation: cefadroxil					Yes
Cephalosporins, second generation: cefuroxime					Yes
Spectinomycin	Poultry, swine		Yes		Yes
Sulfonamides: sulfadimethoxine, sulfamethazine, sulfisoxazole	Beef cattle, dairy cows, fowl, poultry, swine, catfish, trout, salmon	Yes		Yes	Yes
Tetracyclines: Chlortetracycline, oxytetracycline, tetracycline	Beef cattle, dairy cows, honey bees, poultry, sheep, swine, catfish, trout, salmon, lobster	Yes	Yes	Yes	Yes
Cephamycins, dofazimine, monobactams, amino-penicillins, antipseudomonal penicillins, sulfones					Yes

C. Classified By The World Health Organization As IMPORTANT For Humans

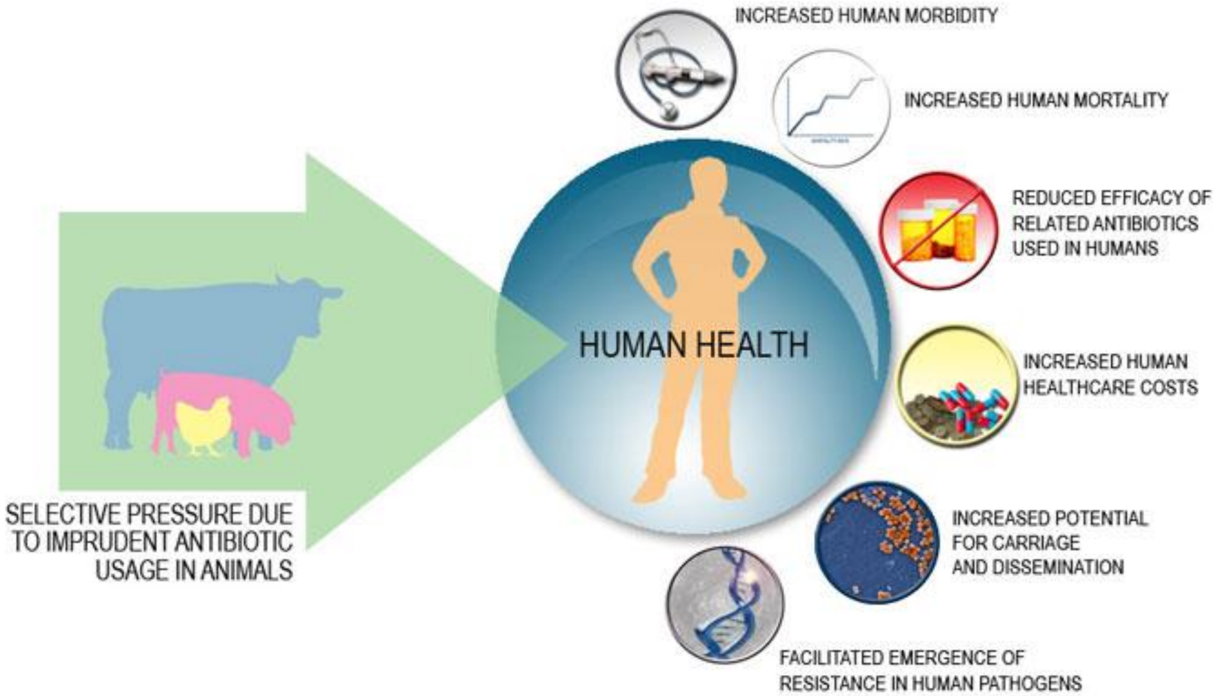
Antibiotic classes	ANIMALS				Humans
	Species	Disease treatment	Disease Prevention	Growth promotion	
Polypeptides: Bacitracin	Fowl, poultry, swine	Yes	Yes	Yes	Yes
Lincosamides: Lincomycin	Poultry, swine	Yes	Yes		Yes

D. Not known to be used in humans

Antibiotic classes	ANIMALS				Humans
	Species	Disease treatment	Disease Prevention	Growth promotion	
Babermycin: Flavomycin	Beef cattle, poultry, swine		Yes	Yes	
Ionophores: monensin, salinomycin, semduramicin, lasalocid	Beef cattle, fowl, goats, poultry, rabbits, sheep		Yes	Yes	


Bacterial populations in farm animals (resistant and susceptible)
Antibiotic is given to animals to prevent or treat disease
Animals are given feed or water treated with antibiotics for growth promotion
Antibiotic selects for resistant bacteria
Resistant bacteria in animal may cause disease or infection
Spread of resistant bacteria to other animals on the farm via interaction with contaminated animals
Spread of resistant bacteria to consumers via contaminated products.
Spread of resistant bacteria to farm workers and food processors via handling of contaminated animals or meat.
Spread of resistant bacteria to soil, well, water, and water runoff via contaminated animal waste.
Spread of resistant bacteria to fruits and vegetables
Bacteria transfer resistance genes to other bacteria
Spread of resistant bacteria to the aquatic environment
Resistant disease or infection may develop in humans

II. The Human Health Impact Of Antimicrobial Resistance In Animal Populations



Animal production practices have evolved over the years to meet the food protein needs of the growing human population. Some farms became very large, and used modern production practices to push food animal growth rates to their maximum. Disease prevention, husbandry, genetics and nutrition have greatly improved the efficiency of many food animal production facilities.

To some degree, the industrialization of animal production was made possible by the availability of antibiotics for livestock and poultry. Although antibiotic usage has clearly benefited the animal industry and helped provide affordable animal protein to the growing human population, the use of antibiotics in food production also contributed to the emergence and spread of AMR. Along with antibiotics used for human medicine, antibiotics used for animal treatment, prophylaxis and growth promotion exerts an inestimable degree of selective pressure toward the emergence and propagation of resistant bacterial strains.

Antibiotic usage in veterinary practice may impact human health because animals can serve as mediators, reservoirs and disseminators of resistant strains and/or AMR genes. Consequently, imprudent use of antimicrobials in animals may unnecessarily result in increased human morbidity, increased human mortality, reduced efficacy of related antibiotics used for human medicine, increased healthcare costs, increased potential for carriage and dissemination of pathogens within human populations and facilitated emergence of resistant human pathogens.

A. Increased human morbidity

Due to their enhanced survivability in the presence of antibiotic concentrations, infectious agents possessing AMR traits gain an enhanced potential for transmission, incidence and persistence. This can result in their dominance over the prevailing microflora within mammalian host populations, leading to higher rates of transmission as compared to the susceptible bacterial strains. This is particularly important for zoonotic agents present in animal carriers in which the bacteria have gained the ability to resist antibiotics important for their treatment, control and prevention. Their enhanced ability to survive, thrive, prevail and resist treatment allows these resistant bacteria to be carried and maintained in their host animals, and therefore facilitates their spread to other susceptible hosts, including humans.

An example is the increasing frequency of quinolone resistance among *Salmonella* Enteritidis[5] and *Campylobacter spp* isolated from animals and people[6,7] and the multiple resistance of *Salmonella* Typhimurium for ampicillin, chloramphenicol, streptomycin, sulfonamides and tetracycline (ACSSuT)[8].

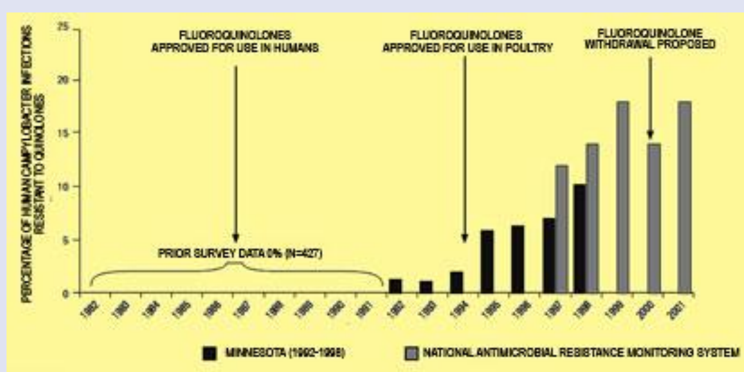
AMR In Foodborne Pathogens

Although resistance in strictly human pathogens such as *Shigella* spp. and *Salmonella typhi* is primarily attributed to the use of antibiotic agents in human populations, the use of antibiotics in agriculture is thought to be the principal driver of increasing resistance for many enteric zoonotic infectious agents for which animal populations serve as the principal epidemiological reservoir. The Department of Health and Human Services (HHS), Food and Drug Administration (FDA) and Centers for Disease Control and Prevention (CDC) believe that resistant strains of three major bacterial pathogens in humans – *Salmonella*, *Campylobacter* and *E. coli* - are linked to the use of antibiotics in foodborne animals[9]. These organisms are three of the top five major foodborne agents that account for an estimated 90% of deaths resulting from infection with foodborne pathogen in the United States[10] .

Increasing frequency of quinolone resistance among human and animal isolates has been shown in *Salmonella* Enteritidis and *Campylobacter* spp (see graph). Multiple resistance of *Salmonella* Typhimurium against ampicillin, chloramphenicol, streptomycin, sulfonamides and tetracycline (ACSSuT) have also been observed. Most reports relate these increasing trends to the subtherapeutic use of antimicrobials in livestock and poultry.

Campylobacter Resistance and Fluoroquinolones

The emergence of fluoroquinolone resistance among domestically acquired human infections with *Campylobacter jejuni* and *E. coli* is an example of AMR thought to have resulted from the use of antimicrobial agents in food animals and subsequent transmission of resistant bacteria to humans via the food supply[7]. Both molecular and epidemiological evidence indicate that the resulting AMR prevalence among humans was triggered by the introduction of enrofloxacin in poultry, prompting FDA to withdraw its approval for use in poultry in 2005[11]

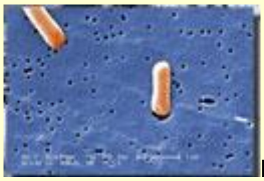


This graph shows that from 1982-2001 Campylobacter isolates from human infections were increasingly becoming resistant to quinolone in the USA.

B. Increased human mortality

Higher case fatality rates are seen for patients infected with AMR organisms compared with those infected with antibiotic sensitive organisms[12].

Multi-drug Resistant Salmonella



Helms et al. (2002) found that patients infected with pansusceptible *Salmonella* Typhimurium were 2.3 times more likely to die within 2 years after infection than persons in the general Danish population, and that patients infected with strains resistant to ampicillin, chloramphenicol, streptomycin, sulfonamide and tetracycline were 4.8 times (95% CI 2.2 to 10.2) more likely to die within 2 years. Furthermore, they established that quinolone resistance in this organism was associated with a mortality rate 10.3 times higher than the general population[13]. Evidence is also mounting that, for some pathogens, increases in virulence often accompany acquisition of resistance.

Physicians rely on empirical antibiotic treatments when therapy is urgent and cannot wait for laboratory testing, but empirical treatments may fail when the pathogen has gained resistance. Empirical treatments are experience-based, therapeutic regimens generally administered prior to confirmatory diagnosis Examples are the failure of quinolones in treating invasive salmonellosis or the failure of vancomycin in managing infection with nosocomial vancomycin-resistant enterococci (VRE).

While some antibiotics are used empirically as the “first line of defense”, other more toxic, more expensive or narrow spectrum antibiotics are reserved for use as the ”last line of defense” against infections due to resistant pathogens. However, resistance to even the newest and most expensive “last defense” antibiotics has now been documented., e.g. vancomycin failure in treating for methicillin-resistant *Staphylococcus aureus* (MRSA).

Additionally, the acquisition of AMR traits by some pathogens may be accompanied by additional pathogenicity and virulence genetic factors that increase the probability of patient death.

In some instances, death may occur due to therapeutic failure of the antibiotic of last resort. These types of drugs are usually reserved as the last choice when other less toxic, less expensive or broad spectrum drugs have been ineffective. There are cases however, in which resistance to these antibiotics of last resort have been documented. An example is vancomycin failure in treating for methicillin-resistant Staphylococcus aureus (MRSA).

The Impact Of Antimicrobial Resistance In The Developing World

The impact of AMR to the older and cheaper antibiotics is probably greater in developing countries where more expensive treatment alternatives are unavailable or unaffordable. It is impossible to quantify the increased human morbidity and mortality occurring in developing countries due to treatment failure with older antibiotics such as tetracyclines and penicillins that may be the only antibiotics available to people living in poverty.

C. Reduced efficacy to related antibiotics used in human medicine

Antimicrobial resistance due to a particular antibiotic used in food animals may result in reduced efficacy of most or all members of that same antibiotic class, some of which may be extremely important for human medicine. This occurs because of the similarity of the antibiotic's related structural components, which causes cross-recognition and cross-resistance for all or most of the antibiotics within the same antibiotic class. An example is the emergence and spread of vancomycin resistant enterococci (VRE) in hospitals following the extensive use of avoparcin in animals, a glycopeptide antimicrobial agent that is structurally similar to vancomycin. Another example is virginiamycin resistance cross-reacting with resistance to the human streptogramin, quinupristin-dalfopristin[14].

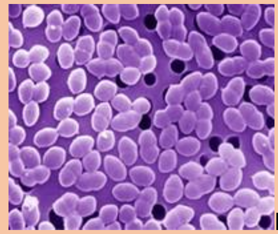
Streptogramin Resistance:

Streptogramins were developed for use in animals at a time when there was no interest in using this class of antibiotics for human medicine. Virginiamycin had been used subtherapeutically for growth promotion in livestock and poultry since 1974, However, after using virginiamycin in animals for many decades, researchers went back and re-visited the streptogramin class of antibiotics and developed quinupristin-dalfopristin for human usage. It was very disheartening in 1999 when this newly licensed human antibiotic was immediately met with AMR to *Enterococcus faecium* due to many years of using virginiamycin in animals.

The Avoparcin-Vancomycin Story

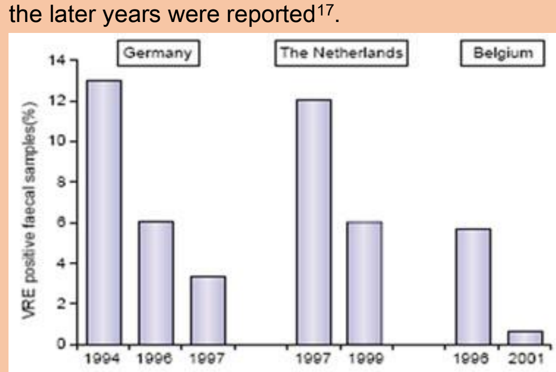
Avoparcin is a glycopeptide antibiotic like vancomycin. Although structurally related, these two antibiotics differ in usage and application. Vancomycin is clinically important for humans and often serves as a drug of last resort for Gram-positive infections. Avoparcin, however, was used in animals as a growth promotant in Europe and elsewhere (but not in the US). Strong evidence later linked vancomycin resistance with subtherapeutic usage of avoparcin in food animals, which led to the banning of the use of avoparcin in the EU in 1997.

Vancomycin-resistant Enterococci (VRE)



Enterococci are members of the normal gut flora for most warm-blooded animals, including humans. However, they are sometimes problematic nosocomial infections in hospital settings where the use of antibiotics is believed to contribute to the emergence of multiple antibiotic resistant genes in this organism. Vancomycin is considered the treatment of choice for many resistant organisms, so the emergence and subsequent spread of VRE became a significant public health concern.

Before the 1990s, it was thought that VRE were present only in hospitals where vancomycin had been used for many years[15]. However, epidemiological and molecular studies have shown that the use of avoparcin in farm animals can result in carriage and dissemination of VRE by these animals and in humans in close contact with these animals[15, 16]. Because of public health concerns about resistance to these glycopeptide antibiotics, avoparcin was banned in Denmark in 1995, in Germany in 1996, and eventually by all EU member states[15]. Subsequent reduction in prevalence of VRE in poultry, swine and humans in the later years were reported[17].



Although vancomycin is frequently used in the hospital setting in the USA, avoparcin was never used in livestock and poultry in the US. This may be the reason why, in spite of the relatively high rates of VRE in U.S. hospitals, there is less evidence of a community reservoir for VRE in this country[18].

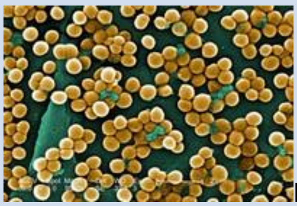
D. Increased human healthcare costs

An increased healthcare cost is another important consequence of antimicrobial resistance. Increased costs may be due to the need for additional antibiotic treatments, longer hospitalization, more diagnostic tests, higher professional costs and more pain management. In 1998, the Institute of Medicine estimated the annual cost of infections caused by antibiotic-resistant bacteria to be US$ .4 to 5 million[19]. With the increase in incidence and prevalence of AMR in the last few years, the current actual cost is now likely to be much higher. Again, increased health costs have more profound repercussions in poorer countries where resources are more limited and the lost efficacy of the older, lower-cost antibiotics is a more significant determinant of human morbidity and mortality.

E. Increased carriage and dissemination

Because of their survival advantage, resistant bacteria may remain viable for longer periods in the environment and in animal reservoirs where they can eventually be transmitted to humans. Acquisition of resistant bacteria from farm animals has been shown to occur either via ingestion of foods of animal origin[20] or via direct contact with infected animals[21, 22].

Methicillin-resistant Staphylococcus Aureus (MRSA)



MRSA was first reported in 1961, and emerged as a sporadic problem in US hospitals. By the 1990s, MRSA was recognized as a serious worldwide nosocomial infection. MRSA strains are resistant to beta-lactam antibiotics, including those that are not affected by penicillinase. The resistance is mediated by a *mec*A gene which codes for a penicillin-binding protein (PBP2a) that has low affinity for beta-lactam antibiotics. In the last few years, animals have been implicated in the maintenance, spread and transmission of some types of MRSA among humans. There is evidence that transmission of MRSA strains can occur from animals to humans, and vice-versa. MRSA has been found in humans closely associated with carrier animals; among pet owners[23], veterinarians and veterinary personnel[24, 25, 26] as well as pig and cattle farmers[27, 28]. Studies identified both livestock and companion animals as potential sources of MRSA for humans, and close contact with these animals was identified as a risk factor for their carriage in people.

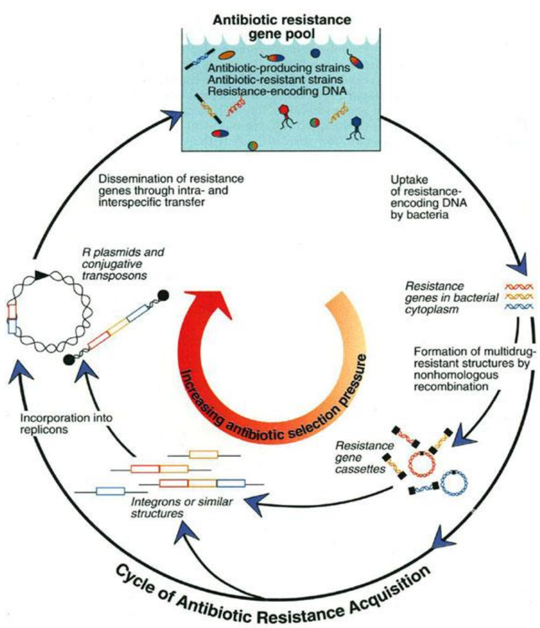
F. Facilitated emergence of resistance in human pathogens

Using mathematical models, Smith[29] demonstrated that the use of animal agricultural antibiotics can hasten the appearance of AMR bacteria in humans, with the greatest impact occurring soon after the first emergence of resistance. Although it is true that such changes and adaptations can occur independently of antimicrobial use in animals, the existence of resistance genes in animal populations can expedite the process by contributing a pool of resistant genes and resistant bacteria in the environment and reservoir hosts. This phenomena is illustrated in the resistance gene cycle depicted by Davies[53] which shows that resistance gene acquisition by various microorganisms could contribute to the environmental antibiotic resistance gene pool (seen at the top of the accompanying diagram) which then become a source of resistance genes for other types of bacteria.

Horizontal Gene Transfer In The Alimentary Tract

For foodborne pathogens, the gastrointestinal tract has been the most important environment for gene transfer. Referred to as "The Reservoir Hypothesis", many believe that numerous species of intestinal bacteria have a significant role in storing and transmitting AMR genes. Several authors have also reported transfer of genes in the rumen, in foodstuffs and in biofilms present on food processing equipment[30]. Acquisition of resistance genes via conjugation or transformation in these environments may pose a serious health issue when a pathogen acquires resistance genes from the surrounding flora in the gastrointestinal tract.

Several findings *in vitro* and *in vivo* have demonstrated the occurrence of gene transfer in the alimentary tract. For example, tetracylcine and erythromycin genes encoded on transposons were shown to be transferable from *Enterococcus faecalis* to *E. coli* and *L. monocytogenes* in the digestive tract of mice[31]. An epidemic R plasmid from *Salmonella enteritidis* moving to *Escherichia coli* of the normal human gut flora has also been observed[32]. Several epidemiologic and molecular studies involving antimicrobial resistance of human and animal pathogens also support this hypothesis.



Davies, J. 1994. Inactivation of antibiotics and the dissemination of resistance genes. *Science*, 264 (5157): 375-381.

III. The environmental impact of imprudent antimicrobial use in animals

Another area of human health concern is the effect of antibiotic residues in the environment. Although human antimicrobial usage may be the primary source for aquatic and terrestrial antibiotic contamination, antibiotic applications in livestock, poultry and aquaculture also contribute significantly to this growing problem.

A varying proportion of administered antibiotics may remain active in excreted biological matter (generally feces or urine) after passing through the animal. Along with antimicrobials used for humans, the livestock, poultry and aquaculture sectors are important contributors to aquatic and terrestrial contamination with antibiotics. Antibiotics and their metabolites (degradation products) reach the environment via the application of antibiotic-laden manure or slurry on agricultural lands, or direct deposition of manure by grazing animals. This can be followed by surface run-off, driftage or leaching into deeper layers of the earth[33]. A proportion of the antibiotics that reach the environment will remain biologically active. Low subtherapeutic concentrations of antibiotics that accumulate over time may have profound effects on some ecosystems. Environmental antibiotic concentrations may exert selective pressure on environmental bacteria and may also foster the transfer of resistance genes, helping create the "resistome" mixing pot.

A. Veterinary antibiotics in soil

The concentration of antibiotics in various soil layers is termed "***terracumulation***" [34]. Terracumulation will occur if an antibiotic is deposited in the soil at a rate that exceeds the rate of degradation.

How do veterinary antibiotics reach the soil?

Antibiotics administered to animals are not completely absorbed by the animals to which they are administered. Depending on the antibiotic, 30-90% of the antibiotic can be excreted via urine or feces as intact bioactive substances or as antibiotic metabolites that may still have some antimicrobial activity. The excretion rate varies greatly, and depends on the pharmacokinetics of the administered antimicrobial, the route of application and the animal species involved. Antibiotics can also reach the soil through medical wastes, improper drug disposal or via dust from pens or barns.

Has it been proven that active forms of veterinary antibiotics are indeed present in the soil?

A growing number of studies worldwide provide evidence of the presence of many of veterinary antibiotics in the soil at concentrations reaching as high as 9,990ug kg^{-1}. Examples include: oxytetracycline and sulfachlorpyridazine[35], sulfamethazine and chlortetracycline[36].

What happens to antibiotics in the soil?

Excreted compounds can be adsorbed, leached, degraded (through biotic or abiotic processes) and in some cases may revert back to the parent compound[37]. Degradation in soil is mainly from microbial action on the antibiotic. Although antimicrobials may remain in the upper layer of the soil, sorptive affinity and other properties of the antibiotic and soil may cause the antibiotic to reach the groundwater layer.

Do antibiotics in the soil remain active?

Once in the environment, any continued antibiotic efficacy depends on its physical-chemical properties (molecular structure, size, shape, solubility and hydrophobicity), prevailing climatic conditions, soil types and other environmental factors[33]. Antibiotic potency is mostly decreased by dilution, sorption and fixation, but antimicrobial activity may persist for long periods of time[38]. No one answer is correct for all types of antibiotics.

B. Veterinary antibiotics in water

How do veterinary antibiotics reach the aquatic environment?

Contamination of the soil may be followed by surface run-off, driftage or leaching into the surface and/or the ground water. Also, antibiotics used for aquaculture may directly affect the aquatic environment, particularly when pens are placed in natural seawaters[39].

Have there been findings that confirm antibiotic presence in ground or surface water?

Antibiotics that have been reported in ground and surface water include macrolides, sulfonamides, tetracycline, chloramphenicol, chlortetracycline, sulfamethazine, lincomycin, trimethoprim, sulfadimethoxine and sulfamethazine. The veterinary and human antibiotic sulfamethoxazole was found in 23% of the 47 groundwater sites tested across the United States, and is one of the most frequently detected chemical compounds as determined by a national survey of wastewater contaminants. A large proportion of aquatic antibiotic contamination is thought to be from human antibiotic usage, i.e. hospital effluents and municipal sewage and wastewater that eventually ends up in the environment [40].

C. Effects on other ecosystems

What are the effects of antibiotic residues on bacterial organisms in soil and water?

Veterinary antibiotics are designed to affect bacterial pathogens found in animals and people, but they certainly can also be hazardous to many types of non-targeted environmental microorganisms[41]. High “therapeutic” concentrations of antibiotics tend to be quickly lethal to susceptible bacterial strains, providing limited opportunity for selection of subpopulations that have low or intermediate resistant traits. In contrast, low-level antibiotic concentration in soil and water may be more likely to lead to the selection of resistant environmental microorganisms fueling the environmental resistant gene pool or “resistome”.

What are the effects of antibiotic residues on plants and invertebrates?

The overall ecologic impacts of residual antibiotics in the environment are largely unknown. However, antibiotics have been reported to markedly affect plant growth and development, causing inhibition of germination, inhibition of root growth and inhibition of shoot growth[42]. It has also bee shown to exhibit toxic effects to aquatic organisms such as freshwater crustacean *Daphnia magna*[43] and *Artemia spp*. [44].

Antimicrobial resistance: a global problem

Antibiotic resistance was initially viewed as only being a human medical problem in hospital-acquired infections, and usually only in critically ill and immunosuppressed patients. Today, the AMR phenomena has spread to the point that the general population is considered to be at risk, bringing about an era where many common infections are becoming increasingly difficult to treat. One of the significant contributing factors to this changing trend is the spillover of AMR from excessive and imprudent antibiotic use in poultry and livestock.

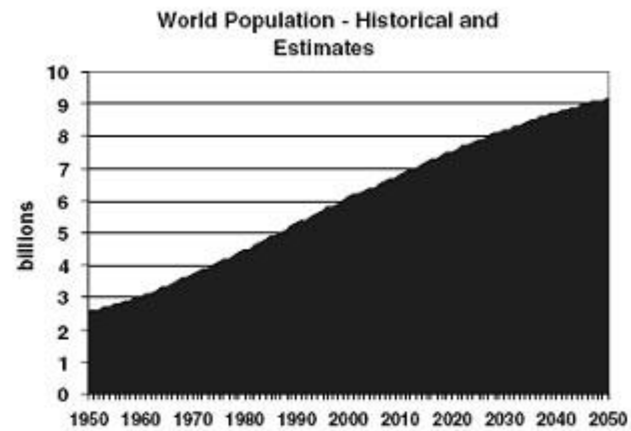
The AMR phenomenon has become a global concern as geographic borders among countries and continents have become less distinct due to increasing global trade, expanding human and animal populations, societal advances and technological developments. Because of this increasing global connectivity, we now see rapid transport of infectious agents and their AMR genes. This means that AMR, in any obscure microscopic niche anywhere in the world, may consequently exert an impact on the rest of the world.

Veterinary-related Factors Influencing the Global Spread of AMR

Veterinary-related factors that influence the global spread of AMR include the following:

1. Increase in population, demand for food animal protein and global changes in animal production systems.

The Center for Strategic and International Studies estimates that the world population increases by about 8,700 people every hour, 146 people every minute or 2.5 people every second. From 1950 to the year 2000, the population roughly doubled from 3 billion to 6.3 billion (Figure 2) and is projected to continue to increase in the years to come[45].



Understandably, food production must also increase to meet these increased nutritional demands. However, because of urbanization and industrialization, available agricultural lands continue to shrink and livestock production has become compromised in many regions, including the EU[45].

In reaction to the increasing demand for food and the decreasing available agricultural land, most livestock and poultry are now raised in smaller spaces at the least possible cost and pushed to the fastest possible rate of gain. This often requires reliance on antibiotics for treatment, metaphylaxis or growth promotion; thereby creating concomitant increased rates of AMR.



2. Changing trends in animal trading and increased movement of animals and animal byproducts.

The international trade in livestock and livestock products is a growing business, accounting for about one sixth, by value, of all agricultural trade[46]. To liberalize international trade, the General Agreement for Tariffs and Trade (GATT) was established in 1947. Recognizing that animal health and food safety standards can be nontariff barriers to international free trade, the World Trade Organization (WTO) also incepted Sanitary and Phytosanitary (SPS) measures. The Office International des Epizooties (OIE) was tasked to set appropriate global standards for animal health, while the Codex Alimentarius Commission sets standards for food safety[47].

These standards facilitated safer international movement of animals and animal by-products around the world. However, they do little to prevent the spread of AMR across the globe due to resistant bacterial organisms that may be hitchhiking in animal products and healthy animals.

Increased movement of animals and animal by-products has also been facilitated by technological improvements in travel and transport systems. It used to be that food products with short shelf lives could not be moved to distant markets, but what used to take weeks and months to transport can now be moved within a day or even less. This rapid movement increases the likelihood that bacteria will remain viable while in transit, further increasing the risk that AMR genes can quickly spread around the world.

3. Lack of Global Initiative Regarding AMR

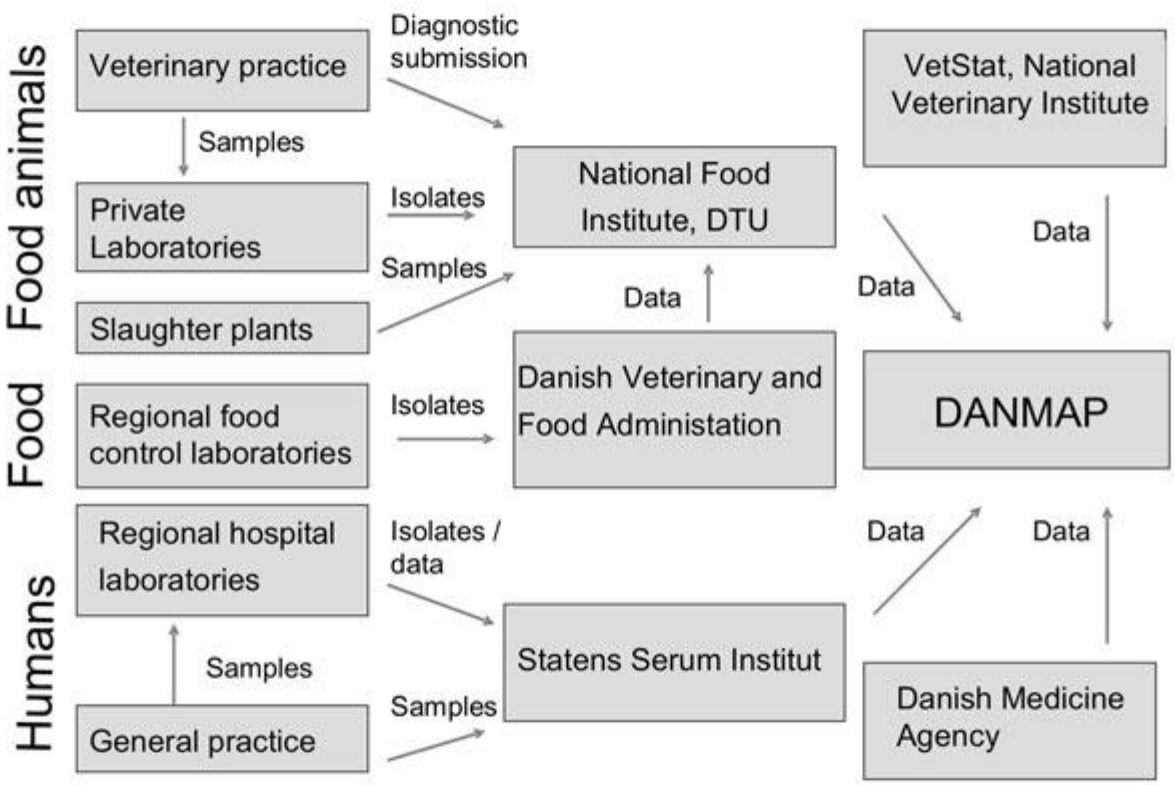
In many countries there is little surveillance information regarding rates of antimicrobial usage or AMR in food or food animals. Such programs are expensive, and may also require a strong political will to counter the influence of some in the private sector who may not want information revealed that might scare consumers, jeopardize pharmaceutical sales or negatively affect exports or imports. Also, many countries have much more pressing issues such as feeding their people, fighting wars and developing their economies.

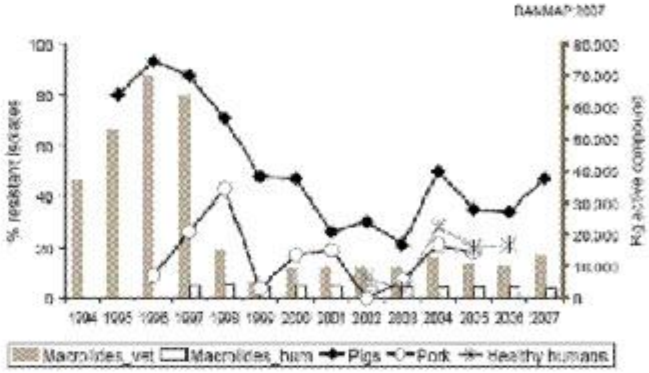
National and International AMR Programs

Today, AMR is no longer considered an unusual phenomenon as it was when first observed in the 1950. Many national and international agencies are taking action to mitigate AMR and keep antibiotics effectively working to maintain the health of human and animal populations.

a. Monitoring antibiotic usage

Denmark has become an international leader in the fight against AMR. Antibiotic sales for humans and animals are monitored annually, as are rates of AMR in bacteria from food animals, food and people by the Danish Integrated Antimicrobial Resistance Monitoring and Research Program (DANMAP). The component that monitors antibiotic usage in veterinary practice is VetStat, which collects data from pharmacies, veterinarians and feed mills[48]. The general data flow is shown in the figure below[49] along with an example of a trend for an antimicrobial consumption compared against resistance for the year 2007[50].





Trends in erythromycin resistance among Enterococcus faecium from pigs, pork and healthy humans in the community and the total consumption of macrolides, both as growth promoters in animals and therapeutics in animals and humans, Denmark (DANMAP, 2007)

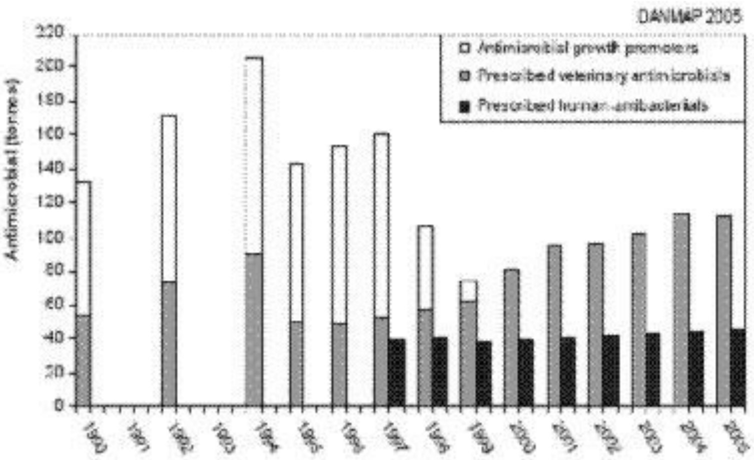


Figure. Consumption of prescribed antimicrobial and growth promoters in animal production and prescribed antibacterials in humans, Denmark (DANMAP Report, 2005)

In the U.S. and many other countries, pharmaceutical companies are not required to report information regarding antibiotic sales. There are published approximations of antibiotic sales in the U.S., however these estimates differ greatly. The Union of Concerned Scientists estimated contemporary non-therapeutic usage of antimicrobials in cattle, swine and poultry at 24.6 million pounds (cattle: 3.7 million pounds; swine: 10.3 million pounds; poultry: 10.5 million pounds), basing their calculations from the number of animals, recommended uses and dosage. The Animal Health Institute's 2000 report estimated that antimicrobials used for growth promotion was at about 3.1 million pounds, with 14.7 million attributed to therapeutic use and disease prevention[51].

However, monitoring the total pounds of antibiotics used per year encourages us to equate the AMR pressure from all types of antibiotics, whereas it is much more important to conserve the efficacy of those antibiotics that are most important for human health. For example, the impact of a pound of tetracycline should in no way be equated with the impact of a pound of 3rd generation cephalosporin or fluoroquinolone.

A review by Sarmah[37] summarized a list of animal antibiotics registered for use as growth promoters and/or feed efficiency in Australia, European Union (EU), Canada and the USA (Table 1).

Table 1. Animal antibiotics registered for use as growth promoters/feed efficiency in Australia, EU, Canada, and the USA[37]

ANTIBIOTIC GROUP	COUNTRIES USING	ANTIBIOTIC	USAGE
Arsenicals	Australia	3-Nitro-arsonic acid	Pigs, poultry
	USA	Arsenilic acid, Roxarsone, cabarsone	Poultry Poultry
Aminoglycosides	Canada	Neomycin	Cattle
Elfamycine	USA	Efrotomycin	Swine
Glycolpids	Canada	Babermycin	Breeder, turkey
	USA	Babermycin	Swine , poultry
Ionophores/Polyethers	Australia	Lasalocid, Monensin,	Cattle
		Narasin	Cattle
		Salinomycin	Pigs, cattle
	Canada	Lasolocid sodium	Cattle
		Monensin	Cattle
		Narasin	Swine
		Salinomycin sodium	Swine, cattle
	European Union	Monensin	Cattle
		Salinomycin	Pigs
	USA	Monensin, Lasalocid	Cattle
Lincosamides	Canada	Lincomycin hydrchloride	Breeder
Macrolides	Australia	Kitasamycin	Pigs
		Oleandomycin	Cattle
		Tylosin	Pigs
	Canada	Erythromycin	Breeder, broiler
		Tylosin	Sheep

		Erythromycin	Cattle
		Oleandomycin	Chicken, turkey
	USA	Tylosin	Cattle, swine, chicken
		Tiamulin	Swine
		Lincomycin	Swine
Oligosaccharides	EU	Avilamycin	Pigs, chickens, turkeys
Penicillins	Canada	Penicillin G potassium	Chicken, turkey
		Penicillin G procaine	Chicken, turkey, sheep
	USA	Penicillin	Poultry
		Arsanilic acid	Poultry
Polypeptides	Australia	Bacitracin	Meat, poultry
	Canada	Bacitracin	Chicken, swine, turkey, chicken
Quinoxalines	Australia	Olaquindox	Pigs
	Canada	Carbadox	Swine
	USA	Carbadox	Swine
Streptogramins	Australia	Virginiamycin	Pigs, poultry
Sulfonamides	Canada	Sulfamethazine	Swine, catlte
	USA	Sulfamethazine	Cattle, swine
		Sulfathiazole	Swine
Tetracyclines	Canada	Chlortetracycline	Chicken
		Oxytetracycline	Turkey, swine, cattle, sheep
	USA	Tetracycline	Swine
		Chlortetracycline	Cattle, swine, poultry
		Oxytetracycline	Cattle, swine

b. Agencies Involved in AMR monitoring

Some countries have national agencies charged with monitoring antimicrobial usage and rates of AMR in food animals, food and/or people. Examples of such national agencies include:

- National Antimicrobial Resistance Monitoring System (NARMS) in the USA ,
- Canadian Integrated Program for Antimicrobial Resistance (CIPARS) in Canada
- Observatoire National de Epidémiologie de la Résistance Bactérienne aux Antibiotiques (ONERBA) in France
- The Danish Integrated Antimicrobial Resistance Monitoring and Research Programme (DANMAP) in Denmark
- Japanese Veterinary Antimicrobial Resistance Monitoring System in Japan

There are also international collaborations that monitor AMR of specific pathogens, such as the WHO Global Salm-Surv, an international Salmonella surveillance program for Salmonella surveillance, serotyping and AMR testing throughout the world

c. WHO Recommendations for Mitigating AMR in Animals

The World Health Organization (WHO), developed the *WHO Global Strategy for Containment of Antimicrobial Resistance*[52]. Key recommendations to address the need for mitigating AMR were listed as follows:

Key recommendations emanating from the 25 expert reports:

- Increase awareness of the antibiotic resistance problem
- Improve surveillance of antibiotic resistance
- Improve antibiotic use in people
- Regulate antibiotic use in animals
- Encourage new product development
- Increase resources to curb antibiotic resistance in the developing world
- Increase funding for surveillance, research and education

Of particular interest for veterinarians is the recommendation to regulate antibiotic use in animals. The experts further identified key stakeholders and each of their respective potential contributions to support this particular recommendation:

National and municipal organizations:

- Increase awareness of the antibiotic resistance problem
- Regulate antibiotic prescriptions
- Restrict growth promoter use in animals
- Regulate antibiotic use in animals [Note: this means veterinary prescriptions]
- Set risk standards for resistance
- Consider human and non-human uses simultaneously
- Monitor advertising

Veterinarians:

- Promote the prudent use of antibiotics in animals
- Develop local guidelines for antibiotic use

Food animal producers:

- Improve farm hygiene
- Reduce use of antibiotics as growth promoters
- Improve animal husbandry

Researchers

- Conduct a risk-benefit analysis of growth promoter use
- Evaluate the environmental impact of antibiotic use
- Evaluate food processing and distribution methods.

The significance of the emergence and continued spread of AMR is sometimes met with skepticism by some stakeholders. Some argue that there is not sufficient evidence to prove that AMR may some day bring animal and human medicine back to pre-antibiotic days, and that restrictive regulations on antimicrobial usage are therefore unnecessarily harmful to the animal industries. What is indisputable, however, is that excessive antibiotic usage is known to exert selective pressure on some bacterial populations, that gene swapping among bacteria does occur, and an expanding number of people and food shipments transverse the globe much more quickly than ever before. In addition, development and approval of newer antibiotics has reached a plateau and novel antibiotics are rarely being introduced in the market today. These factors put us all at risk for increasing global AMR problems in future years. Evidence of the trend toward increasing rates of AMR is clear from reports in the literature regarding many previously susceptible pathogens. Taking action at this critical point in our history is important to avoid wasting the efficacy of antibiotics for frivolous purposes whenever good disease control alternatives exist. Veterinarians must do their part to preserve antibiotic efficacy for future generations.

Summary

- Veterinarians must understand their significant professional responsibility in preventing AMR by mitigating the emergence and spread of AMR.
- Several epidemiological and molecular evidence have shown that AMR, as fostered by extensive antibiotic usage in animals, can increase AMR problems among human populations.
- Animal-related AMR can impact human health via increased in human morbidity, increased human mortality, reduced efficacy of related antibiotics used for people, increased human healthcare costs, increased carriage and dissemination and facilitated emergence of resistance in human pathogens
- Imprudent and excessive use of veterinary antibiotics can contaminate the soil and acquatic environment.
- Antimicrobial resistance is a global problem, in that AMR resistance anywhere in the world can rapidly spread internationally.
- Some factors that contribute to AMR include: global changes in production systems brought about by increasing demand for food, changing trends in animal trading, increased movement of animals and animal by-products and the lack of global initiative regarding AMR.
- In response to this growing health concern, a number of national and international agencies are monitoring antimicrobial usage and rates of AMR in animals, food and people. These agencies are also enacting regulations aims at mitigating the growing AMR problem.

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