1928
Discovery of penicillin

1936
First release of sulphonamide

1944
First aminoglycoside: Streptomycin

1946
First amphenicol: Chloramphenicol

1948
First tetracycline: Chlortetracycline

1948
First polypeptide: Bacitracin

1952
First macrolide: Erythromycin

1956
First glycopeptide: Vancomycin

1960
Penicillinase-resistant penicillin: Methicillin

1963
Gentamicin: Aminoglycoside – anti-Pseudomonas

1966
First extended-spectrum penicillin: Ampicillin

1966
First cephalosporin: Cephalothin

The rise (and fall) of anti

Antibiotics have been used for many years with success. Is the increasing resistance against the use of these therapeutic drugs the result of wrong use in animal production or in human health care? An historical overview of an experienced veterinarian.

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A swine farm fridge including a wide range of veterinary tools, wi

Over 40 years ago when I qualified as a veterinarian, antibiotics played already a key role in the production of healthy animals, whether it was for meat production, eggs or milk and dairy produce. They were used as growth promoters, preventive medications and as therapeutics and had almost 'magical' properties. However, even as far back as 1969, the time of the Swann Report, there was controversy over their use, particularly as growth promoters and it concluded "the administration of antibiotics to farm livestock, particularly at sub-therapeutic levels, poses certain hazards to human and animal health." Has the debate really moved on over the last forty years? Are we really any wiser regarding how antimicrobial drugs work, how their use selects for resistance and have we quantified how much resistance in man has actually come indirectly from antimicrobial use in animals in comparison with the selection of resistance in man by the direct medical use of antibiotics, albeit, primarily to treat disease?

One of the finest quotes was from the House of Lords Report (1997-98) 'Resistance to Antibiotics' regarding the diversity of opinion about the link between antibiotic use in animals and resistance in man "*The argument is being conducted in conditions of some heat and inadequate light.*" Nothing has really changed or has it?

Brief history of antibiotics

Antibiotics are naturally occurring substances produced by bacteria and fungi to aid in their normal, competitive survival with other organisms. Antimicrobial resistance is a natural response by an organism to allow it to survive and compete, so it has been going on for millions of years. Harnessing the microbes production of antibiotics by the pharmaceutical industry, resulted in the discovery and production by fermentation of a number of antibiotics such as the penicillins, tetracyclines, chloramphenicols, peptides, macrolides, aminoglycosides, lincosamides, pleuromutilins and ionophores over the years. Semisynthetic antibiotics were also made by altering the side-chains to give improved antimicrobial activity, stability or absorption etc. The penicillins or beta lactam antibiotics were typical resulting in methicillin, aminobenzylpenicillins such as amoxycillin, cephalosporins and carbapenems. Purely synthetic antimicrobial drugs such as the sulphonamides, diaminopyrimidines, nitrofurans, nitroimidazoles, quinolones and fluoroquinolones were also discovered and produced. There had been an almost endless stream of new antibiotics from the 40s to the 80s, primarily for human but also animal medicine. Then the flow slowed in the 90s and now has become a trickle of new products, but usually based on the original families of antimicrobials.

Growth promotion the rise

The use of antibiotics as growth promoters reportedly arose following the discovery over 60 years ago that chlortetracycline fermentation waste actually enhanced the growth of poultry, pigs and other species. At that time the intensification of livestock was taking place and the use of broad spectrum antibiotics was shown to control increasing enteric and respiratory problems, hence their increase in popularity too. Many of these antibiotics used in feed in the 60s were not on prescription from the vet but under the control of the feed compounder. This is still largely the case in the US but their inclusion level is regulated. Some products can be used for growth promotion, prevention or treatment of disease usually at increasing levels.

The mode of action of growth promoters is not fully understood but is thought to be associated with suppressing commensal bacteria in the gut, such as *Enterococcus spp*, which diverted nutrition away from the animal and by maintaining a more effective and absorptive gut lining. It was noticed that the gut wall was thinner in chicks on growth promoters and this led to better

biotics in pig production

ols, with vaccines and antibiotics.

absorption of nutrients and the use of the term 'digestive enhancers'.

The Swann Report (1969) recommended that antibiotics which "have little or no application as therapeutic agents in man or animals and will not impair the efficacy of a prescribed therapeutic drug or drugs through the development of resistant strains of organisms" should be usable for growth promotion. The list of unsuitable antibiotics at that time was chlortetracycline, oxytetracycline, penicillin, tylosin (a macrolide related to erythromycin) and the sulphonamides. In the UK and most of Europe, these antimicrobials were put under veterinary control on prescription. Only tylosin had a dual role as growth promoter and prescription product.

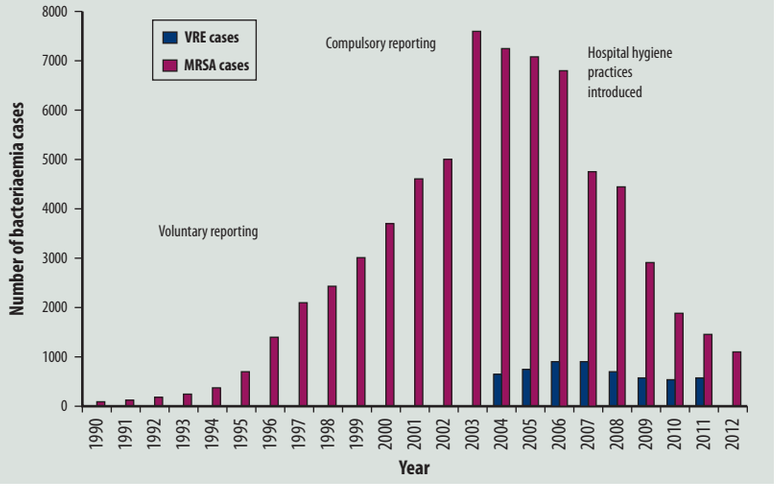
Over time the list of growth promoters grew to include carbadox, olaquindox, avilamycin, avoparcin, flavophospholipol, oleandomycin, salinomycin, monensin, tylosin, virginiamycin and bacitracin, mostly drugs not considered of importance in human medicine. Many of these antimicrobials had activity against certain diseases, and could be used for prevention of disease as well (see *Table 1*.) It was only when these products were banned in the EU from 1997 (avoparcin) to 2006, it was realised what a significant role they played in gut health, reducing/preventing enteric diseases such as swine dysentery, ileitis, colitis, salmonellosis, colibacillosis and particularly in poultry, necrotic enteritis caused by *Clostridium perfringens*. So as well as growth promotion they prevented disease i.e. they exerted an inhibitory effect on bacteria that could infect and colonise the gut. This made pigs grow faster and convert their feed more efficiently by 3-10% depending on the age of the pig and its health status. The presence of enteric disease in the pigs allowed growth promoters to give even higher performance up to 20% and better financial returns. The health and thereby the welfare of the pigs could be considered good they did not have diarrhoea and the farmer and feed compounder were happy too.

Concern about resistance in man

The drive to ban growth promoters in the EU came from the concern regarding the development of vancomycin resistance in man particularly in enterococci (VRE). Vancomycin was a glycopeptide and related to the growth promoter avoparcin and under the '*precautionary principle*' it was decided to ban its use, as avoparcin resistant enterococci had been determined in pigs and in case this resistance could be transferred to man. This sounded reasonable and logical at the time but the link or the extent of the risk was never quantified. In the US, avoparcin, a glycopeptides, was not approved for use in animals, yet they had the most severe VRE problems in man, mainly in hospitals in the 90s. Could this be because they were using a lot of vancomycin in human patients to combat methicillin resistant Staphylococcus aureus (MRSA) and enterococcal infections, following the massive increase in immuno-compromised patients with human immunodeficiency virus (HIV) or being treated with chemotherapy for cancer or to stop organ transplant rejection (see *Figure 1*).

Virginiamycin, a streptogramin, is related to quinupristin/dalfopristin another product used in man for MRSA, and was withdrawn on the same basis that resistance might be transferred via faecal enterococci. Tylosin reverted back to being a prescription only medicine; monensin and salino-

Figure 1. MRSA epidemic and VRE resistance in England (HPA data).



1968
Methicillin resistant *Staphylococcus aureus* (MRSA)

1968
Gentamicin resistant Pseudomonas

1969
Amikacin: Aminoglycoside against GRP

1971
1st generation cephalosporin: Cephalexin

1973
First anti-Pseudomonas beta lactam: Carbenicillin

1976
First ionophore anticoccidial: Monensin

1978
Cefoxitin: First cephamycin – beta lactamase resistant

1978
First Lincosamide: Lincomycin

1979
First pleuromutilin for vet medicine: Tiamulin

1980
Cefotaxime: third generation cephalosporin

1983
Clavulanic acid: First betalactamase inhibitor + amoxicillin

1983
HIV: AIDS epidemic starts

1984
Imipenem: First carbopenem

1985
Norfloxacin: First fluoroquinolone

1986
Aztreonam: First monobactam

1988
New fluoroquinolones: Ciprofloxacin

1991
Improved macrolide introduced: Azithromycin

1993
First veterinary fluoroquinolone: Enrofloxacin

1994
Quinupristin/dalfopristin: First human streptogramin product for VRE

1995
Vancomycin resistant Enterococci (VRE)

1996
Tiamulin: *Brachyspira hyodysenteriae* resistance

1996
Multi-drug resistant *Mycobacterium tuberculosis*

1997
Penicillin resistant *Streptococcus pneumoniae*

Figure 2. Gut concentrations of virginiamycin in relation to the MICs against *C. perfringens*.

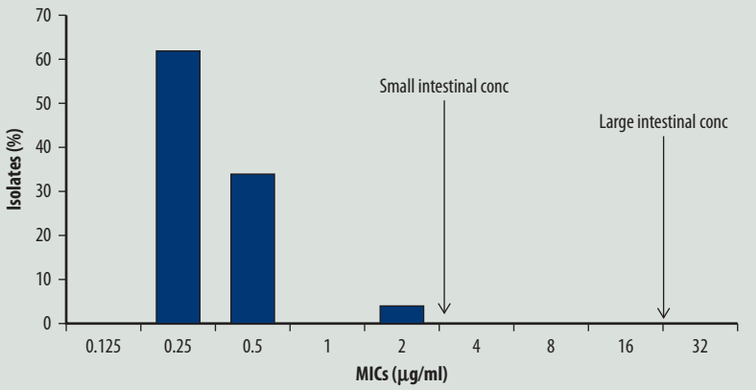


Table 1. Disease prevention activity of growth promoters plus additional activities.t

Growth promoter	GP	SD	CP	*S. Choleraesuis*	*E. coli*	Ileitis
Virginiamycin	+++	+	+++	-	-	+++
Tylosin	+++	+	+++	-	-	+++
Bacitracin	+++	+	+++	-	-	-
Flavophospholipol	++	-	-	-	-	?
Avilamycin	++	-	?	-	-	?
Carbadox	+++	+++	+++	++	++	+++
Salinomycin	+++	++	+++	-	-	?

Key: GP = growth promotion; SD = swine dysentery prevention; *Clostridium perfringens* activity

mycin, both ionophore antibiotics, were removed as growth promoters but are still widely used in poultry production as coccidiostats. Carbadox, virginiamycin, flavophospholipol, avilamycin and bacitracin are still used in the US. The early ban on growth promoters in Denmark caused a dramatic increase in the use of therapeutic antibiotics in response to increased enteric disease such as colibacillosis and ileitis.

Only tylosin was evaluated for the risk of treatment failure in man, associated with macrolide resistant *Enterococcus faecium* from pigs and was considered very small with a probability of 1 in 21 billion. Using macrolide resistance as a marker, the risk of *Campylobacter coli* infection and any resistance being spread to man was also low to zero.

Sub-therapeutic levels of antibiotics

The use of growth promoters and the use of antibiotics for prevention are considered to be at sub-therapeutic levels and therefore more likely to develop resistance. Is this really the case? If one looks at virginiamycin at 10ppm in feed, it is at a low level, but concentrations well above the minimum inhibitory concentration (MIC) are achieved, which inhibit the growth of *C. perfringens* (see *Figure 2*).

It explains its antimicrobial activity and effect and could be used to justify the claim of prevention of necrotic enteritis. It is not sub-therapeutic but perfectly therapeutic based on pharmacokinetic / pharmacodynamic (PK / PD) relationships for that drug against that bug.

Prevention is better than cure?

When there are low concentrations of organisms, lower concentrations of drug is required to inhibit them. When high concentrations of a bug are present often much higher concentrations of a drug are required to inhibit them or actually kill them. This is also linked to resistance development and mutant selection. Higher numbers of bugs $>10^6$ are more likely to select for mutant strains than low concentrations of $\leq 10^2$ and enhance potential resistance development. It is a numbers game. So it is actually worse, from a likely resistance development point of view, to keep on treating recurring infections with high numbers of bacteria. This is what vets and medical doctors, especially in hospital situations, frequently face and why resistance issues in hospitals are such a major issue. Prevention can be better than cure, providing the bacterial numbers are low. If the immune system is intact then it also gives an opportunity for immunity to develop to the infection, for example in the case of ileitis.

The ionophore anticoccidials have also been used for over 35 years, without the levels of resistance associated with earlier chemical products. Their use has enabled the broiler industry to grow and develop over this time and help feed the world.

In addition, the use of high levels of antibiotic to treat predictable disease or early outbreaks of disease is also highly effective, as the infection levels are low, and in some cases the infection can be eliminated. Metaphylaxis is a very important strategic approach to preventing diseases on farm.

Kill or inhibit bugs?

Many of the antimicrobials used in veterinary medicine are considered bacteriostatic, especially the tetracyclines, the most popular one used in pig medicine. The macrolides, lincosamides, pleuromutilins are also bacteriostatic and like the tetracyclines they primarily work by inhibiting the growth of the bacteria by working on their ribosomes and stops them producing proteins. As the drug concentration increases they start to kill the bacterium more quickly but the minimum bactericidal concentration (MBC) may be from 2-50 times the MIC depending on the drug and the bug. Hence the use of bacteriostatic antimicrobials is primarily in patients with an intact, functioning immune system, as it may have to be relied up on to destroy the bacteria.

Some bactericidal drugs kill bacteria much more quickly, within hours, especially the concentration-dependent aminoglycosides and the fluoroquinolones and therefore they are key compounds for immuno-compromised

patients, which doctors frequently encounter. The aminoglycosides are used less in man now because of patient toxicity issues (see *Figure 3*). The use of these compounds led to new concepts of treatment instead of using drug concentration above MIC they looked at concentrations that prevented mutations i.e. the mutant prevention concentration (MPC) which killed any mutants as well as susceptible bacteria, to reduce the risk of resistance development. This is more difficult to apply to bacteriostatic compounds as higher concentrations are required.

The penicillins (or beta lactams) are also bactericidal but are more time dependent but generally of low toxicity, so they have become widely used in man. The 3rd and 4th generation cephalosporins have been a mainstay in human medicine for many years as safe and effective products, so it is understandable that doctors are concerned about their use in veterinary medicine now and the potential risk of selecting plasmid carrying antimicrobial resistance genes, extended spectrum beta lactamases (ESBLs) that might be passed from animal *E. coli* to human *E. coli*.

Resistance transmission to man

Transmission may be by close contact with animals and pets, by food/meat contamination and possibly environmental contamination. The same could be considered for human to human transmission, close contact, unhygienic environments in hospitals and kitchens and environmental contact from sewage. Carbapenems are the next generation of beta-lactam antimicrobials in human use, which are almost the last resort drugs for gram-negative infections and are an example of this. Resistance has appeared in India and is now arriving in the EU mainly in hospital cases but this is primarily a human resistance issue, as these antibiotics are not currently used in animals.

The risks of resistance transfer from animals to man have not been fully assessed and need to be properly made before any decisions are implemented regarding their restriction or suspension of use from animal production, like the unfortunate 'precautionary' ban on growth promoters. These antimicrobials have also become valuable and relied upon in veterinary medicine both in farm and pet animals, so it would be a major decision both on animal health and welfare grounds to ban them.

David Burch: "We all need to work together to prolong the efficacy of antimicrobial therapy."

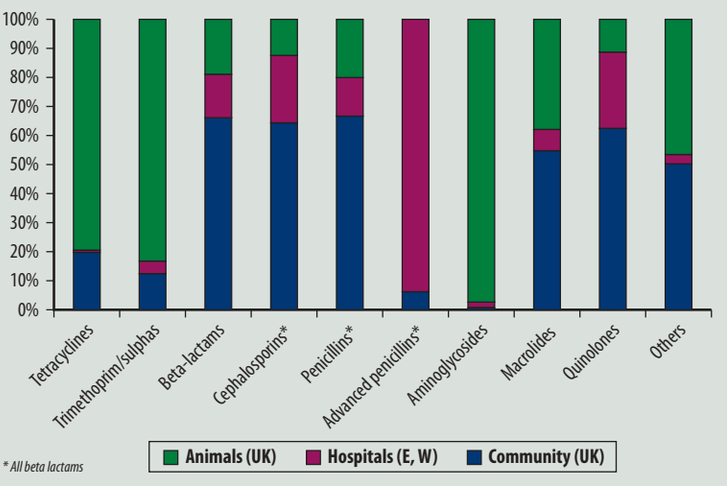
Conclusions

The use of antibiotics in agriculture did rise dramatically. With the bans on growth promoters in the EU and other countries and the early discussions taking place in the US, we can see their use diminish. Will the alternative replacement products be equally effective? Preventive use of antimicrobials is also being discussed in the EU, but it is hoped that sensible decisions on science rather than the precautionary principle be made.

The US is talking about approving prevention claims for growth promoters, so there is a difference of views internationally as well. The banning of certain therapeutic substances, like the oral use of fluoroquinolones for poultry in the US was a major change, although injections are still permitted in pigs and cattle. Putting all antimicrobial use under veterinary control / prescription is also being advocated in some countries. It is already the case in the EU. Banning veterinary medicines is thought not to be advisable, as it is widely felt that improved education and '*responsible use*' is the way forward, providing vets take head of this.

The human doctors are in a much more difficult position as they are treating individuals, even more so than in veterinary medicine but vet use sometimes appear to be made the easy scapegoat for poor hospital hygiene controls. However, we all need to work together to prolong the efficacy of antimicrobial therapy, as it has been the saviour of so many lives for so many years. They cannot be allowed to fall. PP

Figure 3. Comparison of human (community UK and hospital England and Wales) use with animal use (VMD, 2010)



1997
Avoparcin (glycopeptide) banned

1997
Cefotaxime CTX-M ESBLs

1997
Third generation cephalosporin for animals: Ceftiofur

1998
HIV: Antiviral drugs introduced

1998
Linezolid: First oxazolidinone For VRE & MRSA

1999
Second pleuromutilin for vet use: Valnemulin

2002
Carbapenemase resistance

2003
First lipopeptide: Daptomycin

2005
First glycylcycline: Tigecycline

2006
MRSA in pigs described

2007
First human pleuromutilin: Retapamulin

2012
Tildipirosin: New macrolide for pigs (injection)